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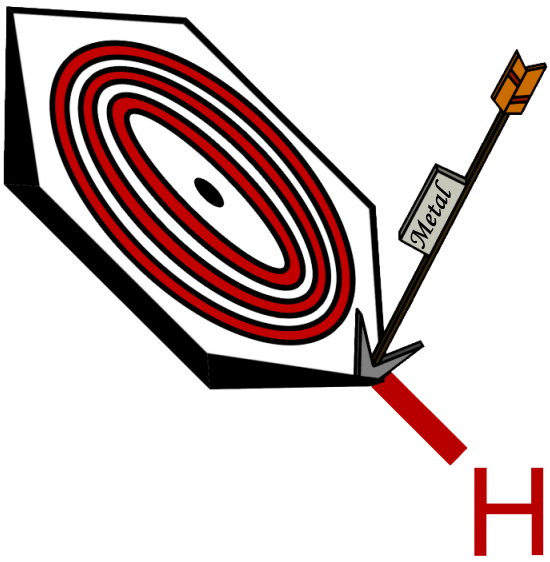
Universidad del País Vasco Euskal Herriko Unibertsitatea

Transition-Metal-Catalyzed C-H Activation Reactions onto Alkenes for the Synthesis of Heterocycles



MEMORIA PRESENTADA POR

ASIER CARRAL MENOYO

PARA OPTAR AL GRADO DE DOCTOR CON "MENCIÓN INTERNACIONAL"

Leioa, 2021

“Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less”

Marie Curie

“Lo bueno de la ciencia es que es cierta creas o no en ella”

Neil deGrasse Tyson

“Zientziaren helburu nagusia ez da ikustea beste inork ikusi ez duena, baizik eta pentsatzea beste inork pentsatu ez duena guztiek ikusten ari garen gauza bati buruz”

Erwin Schrödinger

Quisiera expresar mi más sincero agradecimiento a las Dras. Esther Lete y Nuria Sotomayor, directoras de este trabajo, por darme la oportunidad de realizar esta Tesis Doctoral bajo su supervisión y por su dedicación en la realización de la misma.

Me gustaría, asimismo, agradecer al Profesor Igor Larrosa la oportunidad concedida para llevar a cabo la estancia predoctoral de tres meses en sus laboratorios de la Universidad de Manchester.

También me gustaría dar las gracias al Gobierno Vasco por la concesión de la beca predoctoral, dentro del Programa Predoctoral de Formación de Personal Investigador No Doctor, así como al antiguo Ministerio de Economía y Competitividad, al actual Ministerio de Ciencia e Innovación, al Gobierno Vasco y a la Universidad del País Vasco/Euskal Herriko Unibertsitatea por la financiación recibida para la realización de los proyectos descritos en esta memoria.

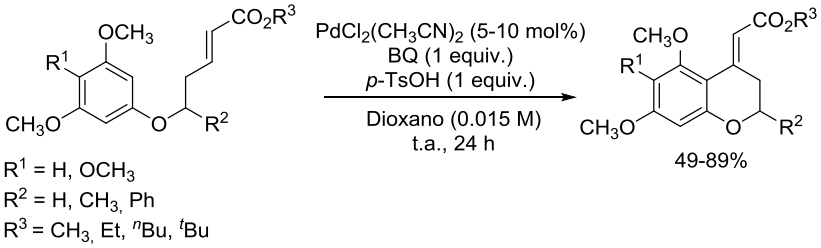
Gracias al Departamento de Química Orgánica II, en especial a mis compañeros de laboratorio, por toda la ayuda y compañía prestada a lo largo de estos años.

Quisiera agradecer a Olatz Orayen la cesión de la maravillosa fotografía que da portada a esta Tesis Doctoral.

Resumen

El trabajo que se recoge en la presente memoria se centra en el desarrollo de nuevos métodos para la formación de enlaces carbono-carbono mediante reacciones de activación C-H catalizadas por metales de transición, orientadas a la síntesis de diferentes heterociclos oxigenados y nitrogenados.

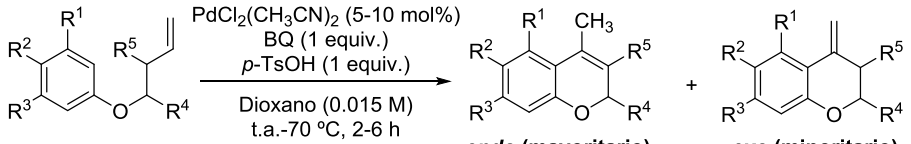
En el segundo capítulo de esta tesis doctoral, tomando como base la experiencia previa del grupo en la reacción intramolecular de Fujiwara-Moritani, una reacción de alquenilación C-H catalizada por paladio(II), se describe la ciclación de diferentes sustratos para la síntesis de compuestos heterocíclicos. En el primer apartado de este capítulo se detalla la aplicación del mencionado acoplamiento intramolecular sobre una variedad de aril butenil éteres con grupos atractores de electrones en la posición terminal del alqueno. De esta manera, mediante un proceso 6-*exo*-trig, se obtuvieron los correspondientes cromanos con rendimientos de moderados a buenos (Esquema I).



Esquema I

A continuación, se supuso que al eliminar el grupo deficiente de electrones del sustrato, responsable de la estabilización del doble enlace exocíclico del producto, dicho enlace sufriría una isomerización a la posición endocíclica más estable, dando lugar a la formación de cromenos. Esta hipótesis se demostró correcta, posibilitando la obtención de una amplia variedad de estos compuestos (Esquema II). Sin embargo, en la mayoría de los casos, se obtuvieron pequeñas cantidades de los correspondientes 4-metilencromanos (con el doble enlace en la posición exocíclica) como subproductos. Curiosamente, el uso de sustratos con anillos aromáticos 3,4-dialcoxi-sustituidos, proporcionó los correspondientes cromenos selectivamente. Esta completa regioselectividad también se observó usando aril butenil éteres con sustitución en la posición C-2, dando lugar a cromenos con alquenos endocíclicos tetrasustituidos, confiriéndole una mayor estabilidad al producto. Es digno de mención el

efecto beneficioso de la presencia de una vasta gama de sustituyentes en la posición C-1 de los productos de partida, dando lugar a mayores rendimientos, probablemente debido al efecto Thrope-Ingold.

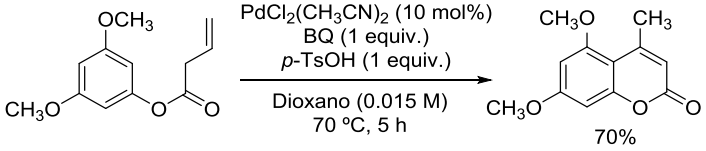


R^1 = H, OCH_3; R^2 = H, OCH_3
R^3 = OCH_3; R^2 = R^3 = -OCH_2O-
R^4 = H, CH_3, Pr, Ph, 3(OBn)C_6H_4, 3-furyl...
R^5 = H, CH_3, Ph, 4(F)C_6H_4, 4(Cl)C_6H_4

55-91%
endo:exo = (83:17)-(100:0)

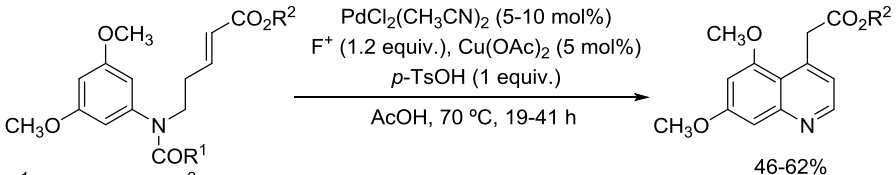
Esquema II

La reacción también pudo extenderse a la síntesis del núcleo de la cumarina usando el correspondiente butenoato de arilo como sustrato (Esquema III).



Esquema III

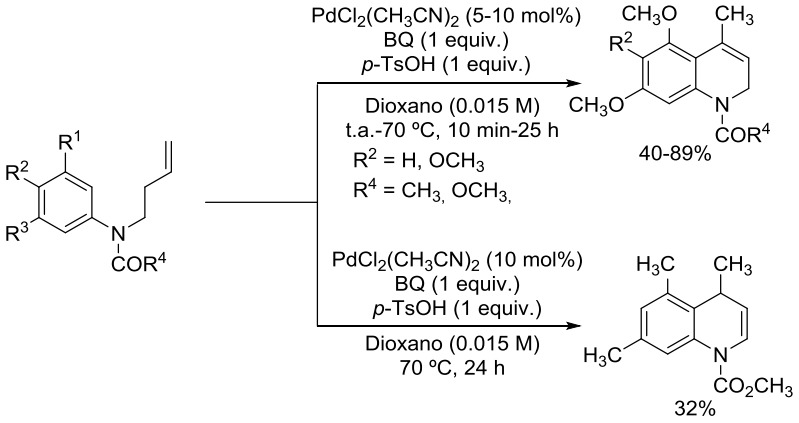
En el segundo apartado del segundo capítulo, se describe la extensión de la reacción intramolecular de Fujiwara-Moritani al uso de butenilanilinas *N*-protegidas como sustratos. De esta manera, al someter dichos compuestos, que incorporaban grupos deficientes de electrones en la posición terminal de la olefina, a condiciones previamente desarrolladas en el grupo para reacciones de alquenilación catalizadas por Pd(II), se obtuvieron las correspondientes quinolinas con rendimientos de moderados a buenos (Esquema IV).



R^1 = OCH_3, CH_3; R^2 = CH_3, $(CH_2)_{11}CH_3$, CH_2CF_3, Bn

Esquema IV

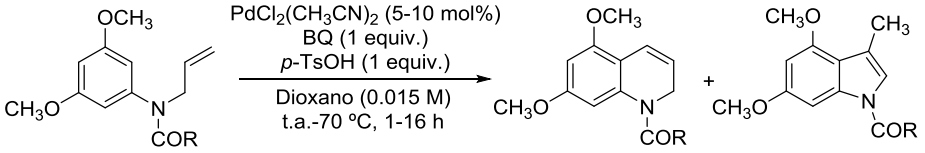
La formación de estos productos transcurre mediante una ciclación 6-*exo*-trig, seguida de la isomerización del doble enlace exocíclico a la posición interna y aromatización del intermedio obtenido, evento que implica la eliminación del grupo protector del nitrógeno. Se propuso que este último paso, responsable de producir las quinolinas, podría evitarse empleando condiciones de reacción más suaves. Con dicho objetivo en mente, se sometió a diferentes butenilanilinas *N*-protegidas, portando olefinas terminales, a las condiciones de reacción previamente usadas para la síntesis de cromanos. De esta forma, se obtuvieron las correspondientes 1,2-dihidroquinolinas con rendimientos de moderados a buenos (Esquema V). Curiosamente, al emplear un sustrato con un anillo aromático 3,5-dimetil-sustituido, se obtuvo la correspondiente 1,4-dihidroquinolina con un rendimiento bajo (Esquema V). Sin embargo, cuando se usaron *N*-butenilanilinas con arenos 3,4-dialcoxi-sustituidos, la reacción no procedió. Al contrario que la reacción empleada para la síntesis de quinolinas, esta alquenilación intramolecular no tolera la presencia de grupos atractores de electrones unidos a los alquenos de los sustratos. Tanto para la preparación de quinolinas como de dihidroquinolinas, se observó que los sustratos *N*-protegidos como carbamatos ofrecían mejores resultados que las correspondientes amidas.



Esquema V

También se intentó llevar a cabo, partiendo de butenilanilinas *N*-protegidas, una reacción en cascada que implicase la previamente expuesta alquenilación intramolecular catalizada por Pd(II), seguida de un proceso de carbonilación, empleando $Mo(CO)_6$ como la fuente de monóxido de carbono. Sin embargo, este proceso sólo condujo a la formación de la correspondiente 1,2-dihidroquinolina, indicando que la etapa de carbonilación no había sido exitosa.

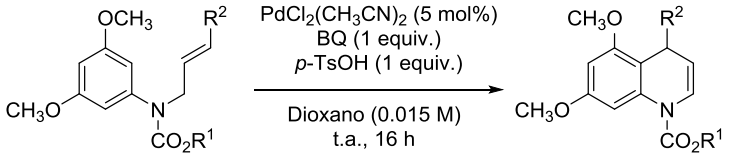
Como se indica en el tercer (y último) apartado del segundo capítulo, con el objetivo de estudiar la posibilidad de efectuar procesos de ciclación 6-*endo*-trig para la síntesis de dihidroquinolinas, se decidió utilizar alilanilinas *N*-protegidas como sustratos en la reacción intramolecular de Fujiwara-Moritani. Al usar *N*-alilanilinas con olefinas terminales, se obtuvieron las correspondientes 1,2-dihidroquinolinas con rendimientos de buenos a muy buenos. Sin embargo, la presencia del grupo 3,5-dimetoxifenilo en el sustrato era necesaria y la reacción no admitía sustituyentes en la parte interna del alqueno. Se observó una fuerte influencia del grupo protector del nitrógeno, viéndose reducida la eficacia de la transformación conforme menor era la capacidad coordinante del previamente mencionado grupo funcional. Por ejemplo, el uso de la acetamida y el carbamato de *tert*-butilo como grupos *N*-protectores trajo consigo la reducción de la regioselectividad de la ciclación, formándose, además de las esperadas 1,2-dihidroquinolinas, pequeñas cantidades de los correspondientes indoles (Esquema VI), generados a partir de un proceso 5-*exo*-trig. Cuando se introdujo un grupo metilo en el nitrógeno, debido a su falta de habilidad coordinante, la reacción no procedió, observándose descomposición del sustrato.



R = OCH_3	85%	0%
R = OBn	67%	0%
R = O^{t}Bu	58%	16%
R = CH_3	85%	10%

Esquema VI

Cabe resaltar que al introducir diferentes sustituyentes en la posición externa del alqueno de los sustratos, la ciclación proporcionó las correspondientes 1,4-dihidroquinolinas; es decir, variaba la regioselectividad de la β-eliminación (Esquema VII).



R^1 = CH_3, ^{t}Bu

R^2 = CH_3, Ph, 4(CH_3)C_6H_4, 4(F)C_6H_4, 4(OCH_3)C_6H_4...

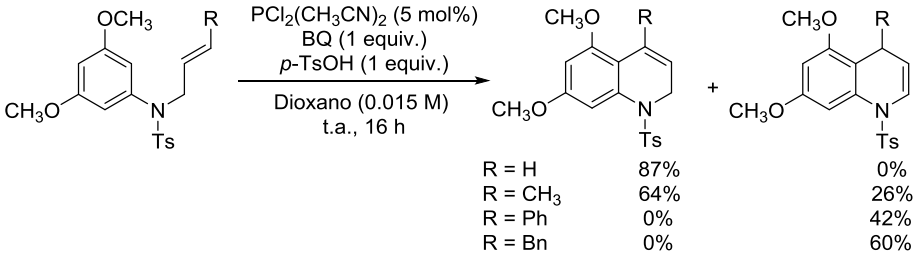
57-92%

Esquema VII

La transformación toleraba una amplia gama de grupos en dicha posición, proporcionando diversas 1,4-dihidroquinolinas con muy buenos rendimientos.

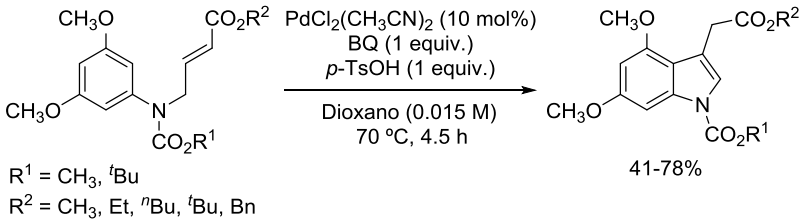
La adición de cantidades subestequiométricas del aminoácido *N*-monoprotegido Boc-Val-OH resultó ser beneficiosa para la reacción cuando se empleaban cinamilanilinas *N*-protegidas como sustratos. Al usar *N*-alilanilinas (sin sustituyentes en el doble enlace) o *N*-crotilanilinas, la adición de dicho ligando no tuvo ningún tipo de efecto positivo ni negativo.

Bajo las condiciones de reacción óptimas, la ciclación de diferentes *N*-alilanilinas *N*-tosil-protegidas proporcionó las correspondientes dihidroquinolinas con rendimientos de moderados a muy buenos. Curiosamente, en contraposición a lo observado anteriormente, cuando la *N*-crotilanilina *N*-tosil-protegida fue utilizada como sustrato, se obtuvo la 1,2-dihidroquinolina como producto mayoritario junto con una menor cantidad de la 1,4-dihidroquinolina (Esquema VIII).



Esquema VIII

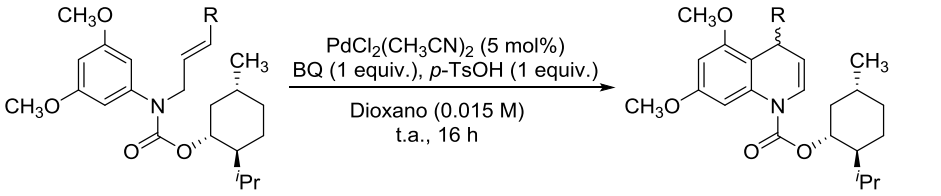
Al instalar ésteres en la posición terminal de la cadena alílica de los sustratos, la regioselectividad de la ciclación cambió completamente, obteniendo varios indoles 3-sustituidos debido a procesos 5-*exo*-trig. No obstante, hubo que aumentar tanto la carga de catalizador a 10 mol%, como la temperatura a 70 ºC (Esquema IX).



Esquema IX

Para racionalizar todos estos resultados y comprender mejor el mecanismo que operaba en este acoplamiento, se llevaron a cabo cálculos DFT en colaboración con el Profesor Enrique Gómez-Bengoa y Lía Sotorríos. Según dichos estudios, la regioselectividad de la ciclación está gobernada por el grupo protector/director unido al nitrógeno y la reacción comienza por la activación del alqueno (debido a la coordinación del centro de paladio). Después, la inserción del areno sobre la olefina ocurre en 6-*endo*-trig, siendo la coordinación del Pd(II) al grupo *N*-protector la responsable de dicha selectividad posicional. Tras la β-eliminación, cuya regioselectividad está guiada por la facilidad de abstracción de cada hidruro, se forma la correspondiente dihidroquinolina. Aunque no se estudió computacionalmente, se propone que la introducción de grupos electrón-atractores en el alqueno impide la coordinación entre el centro de paladio y el grupo *N*-protector, ya que el catalizador se coordina preferentemente al grupo éster de la olefina, debido a su mayor cercanía. Este efecto causa un cambio en la selectividad posicional de la ciclación, obteniéndose diferentes indoles 3-sustituidos mediante procesos 5-*exo*-trig.

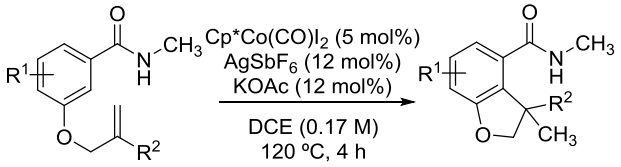
Con el propósito de probar experimentalmente la coordinación del paladio al grupo director, se emplearon *N*-alilanilinas con un grupo protector quiral y enantiopuro derivado del (-)-mentol. De esta manera, la ciclación tomó lugar con niveles moderados de diastereoselectividad, que no podrían haber sido obtenidos sin la ayuda del mencionado efecto coordinante (Esquema X).



Esquema X

Aunque el paladio ha demostrado ser un metal más que capaz para llevar eficientemente a cabo reacciones de activación C-H/formación de enlaces C-C, nuestro interés se desplazó a la utilización de metales de transición de la primera serie, ya que son más baratos y menos tóxicos. Por ello, se decidió estudiar el empleo de catalizadores de Cp*Co(III) para realizar la hidroarilación intramolecular de olefinas, tal como se muestra en el tercer capítulo de esta memoria. Con este objetivo en mente, se optimizaron las condiciones de reacción para la síntesis de 2,3-dihidrobenzofuranos partiendo de los correspondientes alil fenil éteres y

usando una amida como grupo director. Una vez se determinaron las condiciones óptimas para llevar a cabo esta ciclación 5-*exo*-trig, se estudió el alcance de la transformación, obteniendo los correspondientes dihidrobenzofuranos con rendimientos de moderados a muy buenos (Esquema XI). Se observó que este acoplamiento intramolecular es altamente sensible hacia la tensión estérica, ya que al introducir sustituyentes en la posición *orto* a la cadena aliloxi del sustrato, se observaron en algunos casos pronunciados descensos en el rendimiento.



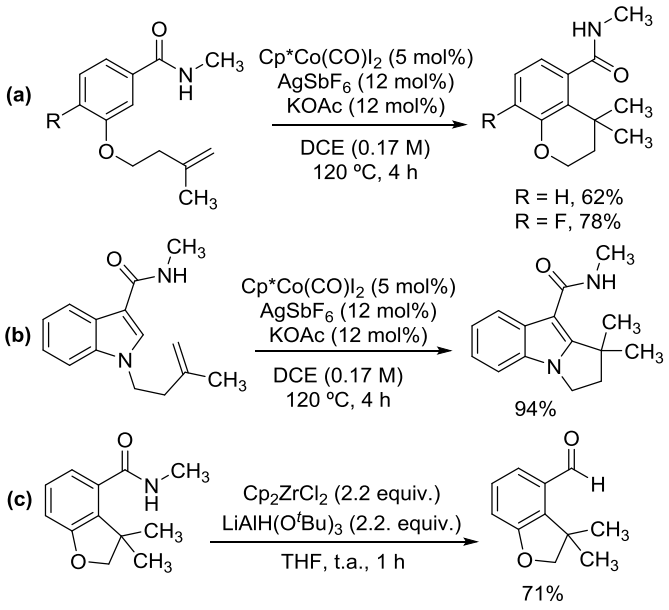
R^1 = H, 4-F, 4-OCH_3, 4,5-(OCH_2O),
4,5-$(OCH_3)_2$, 5-NO_2, 5-OCH_3...
R^2 = CH_3, Et, Ph

Esquema XI

Debido a la formación selectiva de 2,3-dihidrobenzofuranos 3,3-disustituidos, que poseen centros cuaternarios, se estudió la posibilidad de llevar a cabo el acoplamiento intramolecular de forma enantioselectiva. Para ello, se sintetizaron diferentes ácidos carboxílicos quirales y se emplearon como aditivos en la reacción. Lamentablemente, ninguno de ellos fue capaz de inducir más que trazas de enanticontrol, además de proporcionar el correspondiente producto en bajos rendimientos.

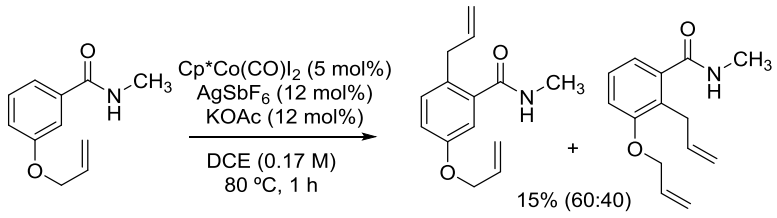
Aunque la reacción no procedía cuando se empleaban sustratos con olefinas internas, la ausencia de todo sustituyente en el doble enlace llevaba a la descomposición del producto de partida bajo las condiciones de reacción. Asimismo, se probó que la presencia de un N-H en el grupo director era necesaria.

Al aumentar la longitud de la cadena en el sustrato; es decir, al emplear butenil fenil éteres en la reacción, se sintetizaron los correspondientes cromanos con buenos rendimientos a través de procesos 6-*exo*-trig (Esquema XIIa). La hidroarilación intramolecular de olefinas también ocurría al emplear un indol en lugar de derivados de benceno, dando lugar a la síntesis del correspondiente pirroloindol (Esquema XIIb). Finalmente, es digno de mención que el grupo director pudo reducirse a un aldehído gracias a la generación *in situ* del reactivo de Schwartz, facilitando su derivatización (Esquema XIIc).



Esquema XII

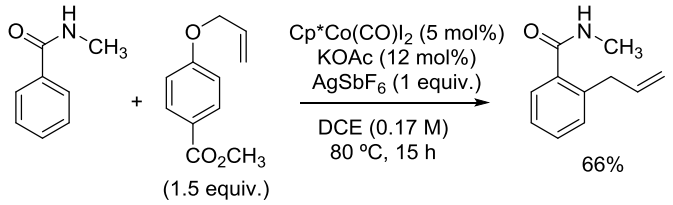
Como se ha mencionado con anterioridad, el empleo del alil fenil éter sin ningún sustituyente en el doble enlace dio lugar a la descomposición del sustrato en las condiciones óptimas para la hidroarilación intramolecular de olefinas (120 ºC durante 4 h). No obstante, al reducir la temperatura a 80 ºC y el tiempo de reacción a 1 h, se obtuvo el correspondiente producto de alilación con un rendimiento bajo y como una mezcla de regioisómeros, siendo el mayoritario aquel funcionalizado en la posición estéricamente menos congestionada (Esquema XIII).



Esquema XIII

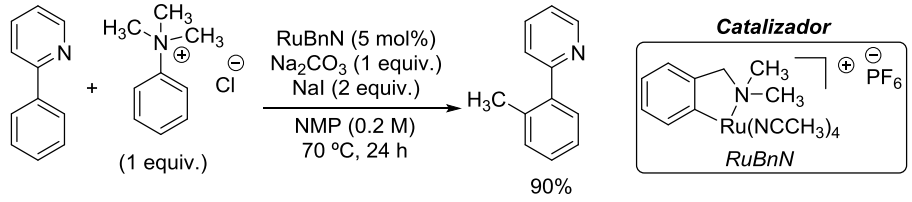
Así, estos resultados nos llevaron a pensar que los alil fenil éteres podrían ser utilizados como agentes alilantes bajo catálisis de Cp*Co(III). Usando *N*-metilbenzamida como el

sustrato modelo y 4-(aliloxi)benzoato de metilo como agente alilante, se comenzó la búsqueda de las condiciones de reacción óptimas. De esta forma, se consiguió obtener la 2-alil-*N*-metilbenzamida con un buen rendimiento del 66% (Esquema XIV). Este estudio queda abierto para posteriores trabajos.



Esquema XIV

Finalmente, en el cuarto capítulo se muestran los resultados obtenidos durante la estancia de tres meses realizada en el grupo del Profesor Igor Larrosa (Universidad de Manchester). A lo largo de ese tiempo se llevó a cabo la optimización de las condiciones de reacción para la *orto*-mono-metilación catalizada por Ru(II) de la 2-fenilpiridina, usando sales de ariltrimetilamonio como agentes metilantes. Se encontraron las condiciones de reacción idóneas para llevar a cabo dicha transformación, obteniendo la correspondiente 2-(*o*-tolil)piridina con un 90% de rendimiento, a 70 ºC y utilizando cloruro de feniltrimetilamonio como agente de acoplamiento (Esquema XV). Con la intención de reducir la temperatura de la reacción, se realizaron diferentes pruebas empleando yoduros de ariltrimetilamonio con anillos deficientes de electrones. De esa forma, aunque aún ha de llevarse a cabo una extensa optimización de las condiciones, se observaron resultados prometedores para la realización de dicho acoplamiento a 35 ºC.



Esquema XV

Summary

The research work described in this Ph.D. Thesis is focused on the development of novel methodologies based on transition-metal-catalyzed C-H activation/C-C bond formation reactions for the synthesis of a variety of oxygen- and nitrogen-containing heterocycles.

The intramolecular Fujiwara-Moritani reaction has been extended to the synthesis of a number of heterocyclic compounds. The chromane and quinoline cores have been efficiently constructed *via* 6-*exo*-trig processes, while 1,2- and 1,4-dihydroquinolines could be regioselectively obtained through 6-*endo*-trig cyclizations. The synthesis of indoles by means of the 5-*exo*-trig intramolecular Fujiwara-Moritani reaction has also been achieved. After carrying out all those transformations, confirming the outstanding efficacy of palladium to accomplish C-H activation/C-C bond formation couplings, the interest was focused on cobalt, which is a less toxic, cheaper and earth-abundant first-row transition metal. In this regard, we have been able to apply for the first time the Cp*Co(III)-catalyzed intramolecular hydroarylation of unactivated olefins to the synthesis of 3,3-disubstituted-2,3-dihydrobenzofurans, pyrroloindoles and chromanes through 5-*exo*-trig and 6-*exo*-trig cyclization processes, using amide-based directing groups. Moreover, it was found that allyl phenyl ethers could be used as allylating agents under Cp*Co(III) catalysis.

Besides, a three-month stay was carried out at the University of Manchester under the supervision of Professor Igor Larrosa. During this period, the optimization of the reaction conditions for the Ru(II)-catalyzed *ortho*-mono-methylation of 2-phenylpyridine was performed, using readily available aryltrimethylamonnium salts as the methylation agents.

Laburpena

Doktore-tesi honetan azaldutako lana heteroziklo oxigenatu zein nitrogenatuen sintesirako metodologia berrien garapenean oinarritzen da, trantsizio-metalen bidez katalizatutako C-H aktibazio/C-C lotura formazio erreakzio ezberdinez baliatuz.

Fujiwara-Moritani erreakzio intramolekularra hainbat konposaturen sintesirako aplikatu ahal izan da. Kromano eta kinolina nukleoak 6-*exo*-trig prozesuen bitartez prestatu egin dira, eta 1,2- zein 1,4-dihidrokinolinak erregioselektiboki sintetizatu ahal izan dira 6-*endo*-trig ziklazioen bidez. Zenbait indolen prestaketarako metodo bat garatzea ere posible izan da 5-*exo*-trig Fujiwara-Moritani erreakzio intramolekularrari esker. Eraldaketa horiek burutu ostean, zeintzuk paladioa C-H aktibazio/C-C lotura formazioan oinarritutako erreakzioak katalizatzeko metal oso eraginkorra dela erakusten duten, kobaltoaren bidez katalizatutako erreakzioen garapenean jarri genuen arreta, metal hori paladioa baino merkeagoa, toxikotasun gutxiagokoa eta ugariagoa baita. Modu horretan, Cp*Co(III)-ren bitartez katalizatutako lehenengo olefinen hidroarilazio intramolekularra garatu dugu eta erreakzio horretaz baliatuz, 2,3-dihidrobenzofurano 3,3-diordezkatuak, pirroloindolak eta kromanoak sintetizatu ahal izan ditugu, amidan oinarritutako talde zuzentzaileak erabiliz. Gainera, Cp*Co(III) konplexuek *N*-metilbenzamidaren alilazioa ahalbidetzen dutela aurkitu da, alil fenil eterrak agente alilatzaile bezala erabiliz.

Horretaz gain, Manchesterreko Unibertsitatean Igor Larrosa Irakaslearen zuzendaripean egindako hiru hilabeteko egonaldian, Ru(II)-an oinarritutako katalizatzaileak erabiliz, 2-fenilpiridinaren *orto*-mono-metilazioa lortzeko erreakzio baldintzen optimizazioa burutu zen, ariltrimetilamonio gatz ezberdinak erabilita.

ABCB1	ATP-Binding Cassette sub-family B member 1
Ac-Gly-OH	*N*-Acetylglycine
Ac-Phe-OH	*N*-Acetyl-L-phenylalanine
Ac-Val-OH	*N*-Acetyl-L-valine
1-AdCO$_2$H	1-Adamantanecarboxylic acid
^{t}Am	2-Methyl-2-butyl
aq.	Aqueous
Ar	Aryl
Ar^F	1,2,3,4,5-Pentafluorophenyl
Ar^N	2-(*o*-Tolyl)pyridyl
ATR	Attenuated Total Reflection
BHTL	*N*-(*endo*-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboximido)-*tert*-leucine
BIES	Base-Assisted Intramolecular Electrophilic Substitution
BINOL	1,1´-Bi(2-naphthol)
Boc-Pro-OH	*N*-(*tert*-butoxycarbonyl)-L-proline
Boc-Val-OH	*N*-(*tert*-butoxycarbonyl)-L-valine
BQ	*para*-Benzoquinone
Bz-Hpg-OH	*N*-Benzoyl-D-*para*-hydroxy-phenylglycine
c	Concentration
Calcd.	Calculated
Cat.	Catalyst
CB2	Cannabinoid receptor type 2
CCA	Chiral Carboxylic Acid
CI	Chemical ionization
CMD	Concerted Metalation-Deprotonation
COD	1,5-Cyclooctadiene
COSY	Correlated Spectroscopy
Cp	Cyclopentadienyl
Cp*	1,2,3,4,5-Pentamethyl-cyclopentadienyl
Cp*^{tBu}	1-*tert*-Butyl-2,3,4,5-tetramethylcyclopentadienyl
DAF	4,5-Diazafluoren-9-one
***o*-DCB**	*ortho*-Dichlorobenzene
DCC	*N,N´*-Dicyclohexyl-carbodiimide
DCE	1,2-Dichloroethane
DEPT	Distorsionless Enhancement by Polarization Transfer
DEAD	Diethyl azodicarboxylate
DFT	Density Functional Theory
DG	Directing Group
DHQ	Dihydroquinoline
DIAD	Diisopropyl azodicarboxylate
DMA	*N,N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
DNA-PK	DNA-Dependent Protein Kinase

d.r.	Diastereomeric ratio
Ed	Edition
Ed(s).	Editor(s)
ee	Enantiomeric excess
EEDQ	*N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
EI	Electronic impact
Equiv.	Equivalent
ESI	ElectroSpray Ionization
EWG	Electron-Withdrawing Group
EZH2	Enhancer of Zeste Homologue 2
F^+	N-Fluoro-2,4,6-trimethyl-pyridinium triflate
FID	Free Induction Decay
FT	Fourier Transform
Gen.	Generation
h	Hexaplet
H_2-BHTL	*(S)*-2-((3a*R*,4*R*,7*S*,7a*S*)-1,3-dioxooctahydro-2*H*-4,7-methanoisoindol-2-yl)-3,3-dimethylbutanoic acid
HCVNS5B	Hepatitis C Virus NonStructural protein 5B
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSAB	Hard and Soft Acids and Bases
HSQC	Heteronuclear Single Quantum Coherence
IR	Infrared
KIE	Kinetic Isotope Effect
L	Ligand
LLHT	Ligand-to-Ligand Hydrogen Transfer
LC	Liquid Chromatography
m	*meta*
M	Metal
M^+	Molecular Ion (MS)
m.p.	Melting point
MPAA	*N*-MonoProtected Amino Acid
MS	Mass Spectrometry
MS	Molecular Sieves
MW	Microwave
m/z	Mass to charge ratio
Naphth	Naphthyl
NHC	*N*-Heterocyclic Carbene
NMP	*N*-Methylpyrrolidone
NMR	Nuclear Magnetic Resonance
NS5B	NonStructural protein 5B
[O]	Oxidant
o	*ortho*
ORTEP	Oak Ridge Thermal Ellipsoid Plot
p	Page
p	*para*
Pc	Phthalocyanine

PA	Picolinamide	**Subst.**	Substrate
Phth	Phthaloyl	**t**	Time
Pin	Pinacolate	**T**	Temperature
PMB	*para*-Methoxybenzyl	**T**	Template
PMP	*para*-Methoxyphenyl	**TBAB**	Tetrabutylammonium bromide
Prod.	Product		
PTS	Polyoxyethanyl α-tocopheryl sebacate	**TBAI**	Tetrabutylammonium iodide
QTOF	Quadrupole Time-Of-Flight	**TBS**	*tert*-Butyldimethylsilyl
quant.	Quantitative	**TFA**	Trifluoroacetic acid
ROS	Reactive Oxygen Species	**TFE**	2,2,2-Trifluoroethanol
rt	Room temperature	**THF**	Tetrahydrofuran
SAR	Structure-Activity Relationship	**TLC**	Thin Layer Chromatography
		TOF	Time-Of-Flight
S_EAr	Electrophilic Aromatic Substitution	**TRPV1**	Transient Receptor Potential Vanilloid type 1
SEM	2-(Trimethylsilyl)-ethoxymethyl	**UPLC**	Ultra Performance Liquid Chromatography
SET	Single Electron Transfer	**UV**	Ultraviolet
SPINOL	1,1´-Spirobiindane-7,7´-diol	**Vol**	Volume

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I

Background and Aims of the Thesis

1. BACKGROUND OF THE THESIS

In organic synthesis, the construction of complex molecules has been usually attained through the conversion of functional groups already present in the starting compound, being palladium-catalyzed cross-coupling transformations and the Mizoroki-Heck reaction[1] common and widely used examples. For these couplings, the presence of a carbon-(pseudo)halide (C-X) bond is required in the substrate, which is cleaved in the course of the reaction, leading to the formation of carbon-carbon bonds. Although these transformations are powerful strategies capable of effectively constructing valuable C-C bonds, their main disadvantage lies on the necessity of pre-installing certain functionalities in the molecule that is to be modified. Therefore, longer synthetic pathways are required, what comes with the unavoidable consequence of the formation of larger amounts of waste.

Transition-metal-catalyzed C-H activation, which is a powerful tool consisting of taking advantage of C-H bonds (ubiquitous in organic molecules) for the functionalization of compounds, arises as an attractive alternative to the aforementioned reactions for the construction of C-C bonds. As its name suggests, those transformations involve the cleavage of C-H bonds instead of C-X bonds, what makes this approach more environmentally benign and atom economical. The usefulness of the herein presented strategy has already been proved, for example, in organic synthesis,[2] specifically for the synthesis of natural products,[3] in material sciences[4] and in medicinal chemistry.[5] However, what makes C-H activation so attractive also often comes as its main drawback. The presence of several carbon-hydrogen

[1] *Science of Synthesis. Cross Coupling and Heck-Type Reactions*; Molander, G.A., Wolfe, J.P., Larhed, M., Ed.; Thieme: Stuttgart, 2013; Vol. 1-3.

[2] Fore selected reviews, see: a) Bergman, R.G. *Nature* **2007**, *446,* 391; b) Giri, R.; Shi, B.-F.; Engle, K.M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242; c) Wang, F.; Yu, S.; Li, X. *Chem. Soc. Rev.* **2016**, *45*, 6462; d) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787; e) Gandeepan, P.; Ackermann, L. *Chem.* **2018**, *4*, 199.

[3] For selected reviews, see: a) Chen, D.Y.-K.; Youn, S.W. *Chem. Eur. J.* **2012**, *18*, 9452; b) Qiu, Y.; Gao, S. *Nat. Prod. Rep.* **2016**, *33*, 562; c) Genovino, J.; Sames, D.; Hamann, L.G.; Touré, B.B. *Angew. Chem. Int. Ed.* **2016**, *55*, 14218; d) Brady, P.B.; Bhat, V. *Eur. J. Org. Chem.* **2017**, 5179; e) Karimov, R.R.; Hartwig, J.F. *Angew. Chem. Int. Ed.* **2018**, *57*, 4234.

[4] For selected reviews, see: a) Schipper, D.J.; Fagnou, K. *Chem. Mater.* **2011**, *23*, 1594; b) Mercier, L.G.; Leclerc, M. *Acc. Chem. Res.* **2013**, *46*, 1597; c) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 66; d) Pouliot, J.-R.; Grenier, F.; Blaskovits, J.T.; Beaupré, S.; Leclerc, M. *Chem. Rev.* **2016**, *116*, 14225; e) Zhang, J.; Kang, L.J.; Parker, T.C.; Blakey, S.B.; Luscombe, C.K.; Marder, S.R. *Molecules* **2018**, *23*, 922.

[5] For selected examples, see: a) Ackermann, L. *Org. Process Res. Dev.* **2015**, *19*, 260; b) Seki, M. *Org. Process Res. Dev.* **2016**, *20*, 867.

bonds in organic molecules makes it troublesome to achieve site-selectivity efficiently. This problem may be solved by utilizing substrates bearing C-H bonds with different reactivities, which is often the strategy employed when heteroaromatic scaffolds are to be functionalized.[6] Nevertheless, in the case of benzene derivatives, the reactivity between the different C-H bonds present in the molecule is not usually different enough to completely overcome regioselectivity issues.

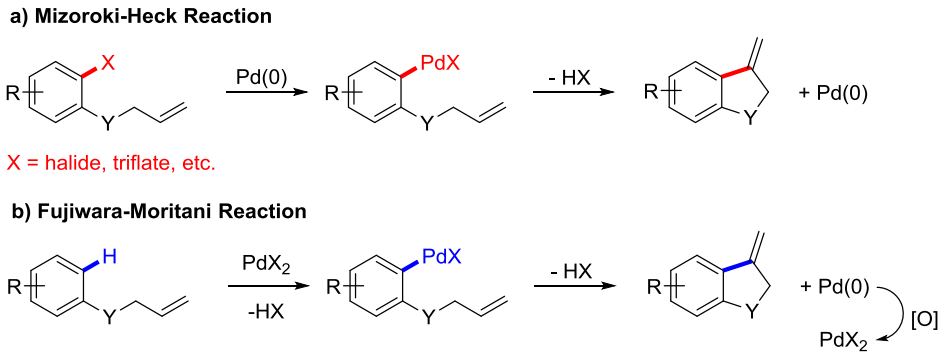
Therefore, in those cases, other methods are needed to control positional selectivity, such as the use of directing groups, which is the most efficacious one. A pioneering work on this approach was reported by Lewis and Smith for the Ru-catalyzed formation of C-C bonds[7] and the methodology became popular after the works of Murai and Chatani.[8] Due to the presence of Lewis basic atoms, directing groups are capable of coordinating to the metal center, bringing it close to the target C-H bond, which is usually *ortho* to the director. This causes an increase of the effective concentration of the catalyst at that position, what leads to augmented reactivity and selectivities.

During the last decade, palladium has been the most exploited transition metal to achieve C-H activation/C-C bond formation couplings. Among them, the intermolecular Fujiwara-Moritani reaction has recently gained much attention. This transformation consists of the oxidative coupling between an unfunctionalized arene and an alkene, allowing the construction of alkenylated aromatic rings, similarly to the Mizoroki-Heck reaction, but avoiding the use of prefunctionalized substrates (Scheme 1.1). Due to this, the Fujiwara-Moritani reaction is widely known as the oxidative Heck or dehydrogenative Heck reaction.[9] An important downside of the present coupling is the requirement for a stoichiometric oxidant in order to reoxidize the Pd(0) species obtained in the course of the reaction to the catalytically active Pd(II) species.

Although the intermolecular Fujiwara-Moritani reaction has been widely studied, the potential of its intramolecular variant for the synthesis of carbocyclic and heterocyclic frameworks remains relatively underexplored, and has been mainly applied to electron-rich

[6] a) Cho, S.H.; Kim, J.Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068; b) Bugaut, X.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7479.
[7] Lewis, L.N.; Smith, J.F. *J. Am. Chem. Soc.* **1986**, *108*, 2728.
[8] a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature*, **1993**, *366*, 529; b) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698.
[9] Suna, E.; Shubin, K. Metal-Catalyzed Heck-Type Reactions and C-C Cross Coupling via C-H Activation. In *Science of Synthesis. Cross Coupling and Heck-Type Reactions;* Larhed, M., Ed.; Thieme: Stuttgart, 2013; Vol. 3, p 643.

heteroarenes, such as indoles and pyrroles.[10] The potential of these Pd(II)-catalyzed alkenylations has also been shown in the synthesis of pyrrole-containing natural products, such as (±)–rhazinal[10e] or dragmacidins.[10c] Depending on the structural features of the substrate and the experimental conditions, different mechanistic pathways can operate (*i.e.*, arene metalation/alkene insertion or alkene activation/arene insertion), which may lead to different regioisomeric products.



Scheme 1.1

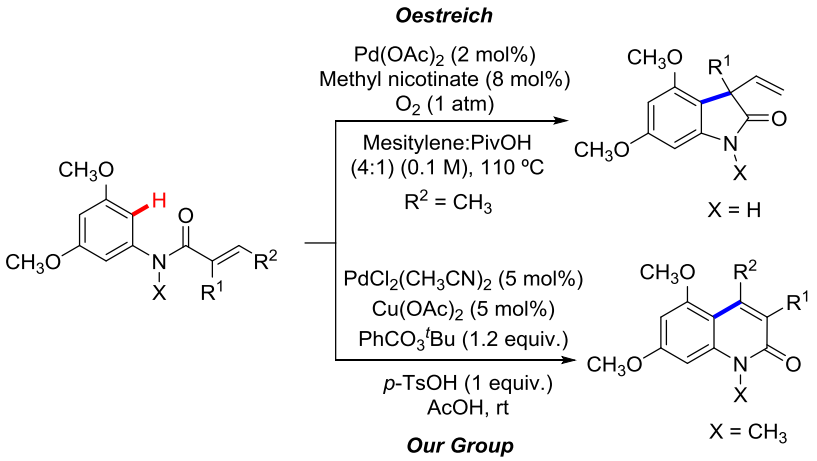
Those cyclizations usually consist of *exo* processes rather than their *endo* homologues, due to the strain involved in the approach of the arene to the intramolecular coupling partner, being the regioselective obtainment of the two possible products (*endo* and *exo*) utterly interesting. In this regard, Oestreich reported in 2011 that *N*-arylacrylamides, under Pd(II) catalysis and aerobic oxidative conditions, underwent intramolecular 5-*exo*-trig C-H alkenylation, furnishing the corresponding oxindoles selectively (Scheme 1.2).[11]

Curiously, in contrast to this observation, closely related substrates afforded different 2-quinolones *via* 6-*endo*-trig Fujiwara-Moritani cyclizations, when being subjected to the reaction conditions developed in our group (Scheme 1.2).[12]

[10] a) Ferreira, E.M.; Stoltz, B.M. *J. Am. Chem. Soc.* **2003**, *125*, 9578; b) Abbiati, G.; Beccalli, E.M.; Broggini, G.; Zoni, C. *J. Org. Chem.* **2003**, *68*, 7625; c) Garg, N.K.; Stoltz, B.M.A. *Chem. Commun.* **2006**, 3769; d) Schiffner, J.A.; Machotta, A.B.; Oestreich, M. *Synlett* **2008**, 2271; e) Bowie, A.L.; Trauner, D. *J. Org. Chem.* **2009**, *74*, 1581; f) Schiffner, J.A.; Wöste, T.H.; Oestreich, M. *Eur. J. Org. Chem*. **2010**, 174; g) Donets, P.A.; Van der Eycken, E.V. *Synthesis* **2011**, 2147; h) Abozeid, M.A.; Sairenji, S.; Takizawa, S.; Fujita, M.; Sasai, H. *Chem. Commun.* **2017**, *53*, 6887.

[11] Schiffner, J.A.; Oestreich, M. *Eur. J. Org. Chem.* **2011**, 1148.

[12] Ortiz-de-Elguea, V.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2015,** *357*, 463.



Scheme 1.2

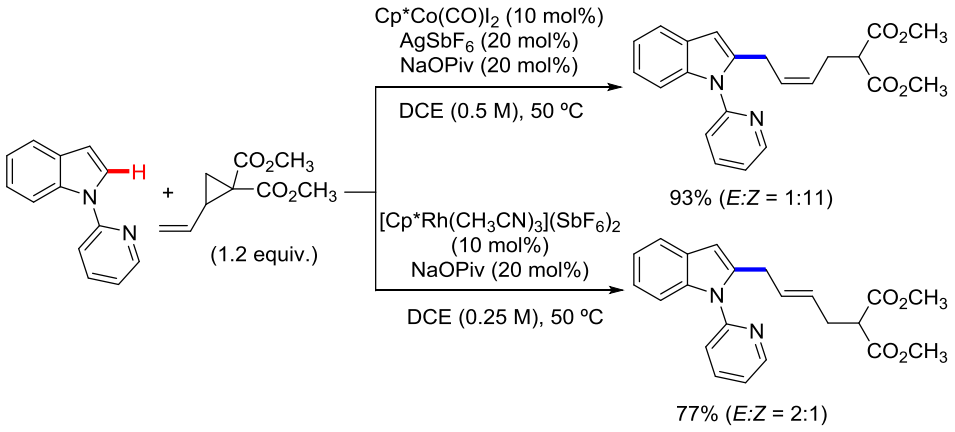
Despite palladium, as well as other noble 4d- and 5d-transition metals (such as iridium, rhodium and ruthenium), have unarguably proved to be able to promote C-H activation/C-C bond formation reactions efficiently, catalysts based on those elements are usually expensive and toxic. Therefore, the use of cheaper and more environmentally friendly 3d-transition-metal catalysts (copper, manganese, iron, nickel, cobalt…) has gained increasing popularity.

Among the first-row-transition metals available to carry out C-H activation reactions, cobalt-based complexes stand out. Cobalt is much less toxic than the abovementioned noble metals, and it is present in cobalamin (vitamin B12), thus playing an important role in mammals. Regarding its application in organic synthesis, cobalt catalysts bearing pentamethylcyclopentadienyl ligands (Cp*) have recently started to become popular since Matsunaga and Kanai published their seminal work (in 2013) on the utilization of these kind of high-valent-cobalt complexes for the C-H functionalization of the 2-phenylpyridine framework.[13] Those catalysts were initially designed to be used as cheap homologues of related Cp*Rh(III) complexes; however, cobalt has proved to possess unique reactivity.[14]

One example, among many, of this fact was observed by Ackermann and co-workers in the ring-opening reaction of vinylcyclopropanes using indole as the aromatic coupling partner under Cp*Co(III) catalysis. They saw that the corresponding allylation products were

[13] Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2207.
[14] Yoshino, T.; Matsunaga, S. *Adv. Synth. Catal*. **2017**, *359*, 1245.

obtained selectively as the *Z*-diastereomer; whereas the utilization of Cp*Rh(III) led to almost no selectivity, being the *E*-diastereoisomer slightly favored (Scheme 1.3).[15] In order to rationalize this, DFT calculations were accomplished, showing that the ring-opening process was not only the rate-determining event, but also the diastereoselectivity-determining one. According to the computational results, under Co(III) catalysis, the *Z*-isomer was clearly the preferred one, while the energy barrier of the two possible products was similar with Rh(III) catalysts, being the reaction somewhat favored towards the formation of the *E*-configured products. This was proposed to occur due to the shorter Co-C bonds, leading to more compact organometallic intermediates.



Scheme 1.3

When it comes to the formation of C-C bonds after C-H activation under Cp*Co(III) catalysis, alkynes are one of the most utilized coupling partners, although olefins are also quite popular. Several methodologies have been employed in order to couple those unsaturated compounds with different (hetero)arenes in an intermolecular manner. The intramolecular version of these C-H activation/C-C bond formation reactions; nevertheless, remains underexplored, existing (to the best of our knowledge) only two examples, involving both of them the use of alkynes as the intramolecular reaction partners.[16] Thus, the development of new approaches for the Cp*Co(III)-catalyzed synthesis of heterocyclic frameworks taking advantage of the intramolecular reaction of an arene with an alkene would expand the limits of the existing synthetic procedures in this area.

[15] Zell, D.; Bu, Q.; Feldt, M.; Ackermann, L. *Angew. Chem. Int. Ed.* **2016**, *55*, 7408.
[16] a) Bera, S.S.; Debbarma, S.; Jana, S.; Maji, M.S. *Adv. Synth. Catal.* **2018**, *360*, 2204; b) Lerchen, A.; Knecht, T.; Koy, M.; Daniliuc, C.G.; Glorius, F. *Chem. Eur. J.* **2017**, *23*, 12149.

2. AIMS OF THE THESIS

The overall aim of this research lies on the development of novel and powerful methodologies for the construction of carbon-carbon bonds by means of transition-metal-catalyzed intramolecular C-H activation reactions and their application to the synthesis of a variety of heterocycles.

Bearing in mind the previous experience of our group regarding the intramolecular Fujiwara-Moritani reaction,[12,17] in Chapter 2 of this Ph.D. Thesis, the application of this coupling to the synthesis of nitrogen- and oxygen-containing heterocyclic frameworks, such as chromanes, chromenes, quinolines, dihydroquinolines and indoles will be disclosed.

Moreover, in Chapter 3, the use of Cp*Co(III) complexes will be studied as viable alternatives to catalysts based on noble metals. In this case, their efficiency in promoting the intramolecular hydroarylation of olefins will be tested, along with the possibility of accomplishing this transformation in an enantioselective manner.

Finally, in Chapter 4, the work carried out during the three-month stay in the laboratories of Professor Igor Larrosa, at the University of Manchester, will be described. During this stay, the optimization of the reaction conditions for the Ru(II)-catalyzed *ortho*-mono-methylation of 2-phenylpyridines was addressed.

Thus, stages followed towards the achievement of these aims are depicted below:

2.1. Palladium(II)-catalyzed intramolecular C-H alkenylation for the synthesis of chromanes

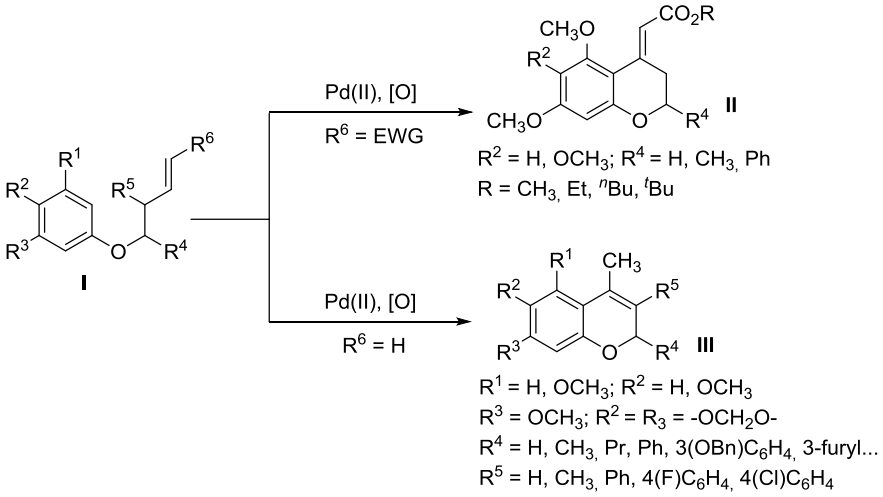
Our group has previously developed appropriate reaction conditions to attain the synthesis of the chromane core by means of the intramolecular Fujiwara-Moritani reaction.[18] Based on that and driven by the aim of synthesizing a range of chromanes **II**, our first objective was to expand the scope of this transformation by studying the possibility of employing this coupling over differently-substituted butenyl phenyl ethers **I** bearing ester moieties attached to the alkene terminus. Furthermore, the tolerance of the transformation towards

[17] For a recent review written by our group on the Pd-catalyzed synthesis of quinolines, see: Carral-Menoyo, A.; Sotomayor, N.; Lete, E. *Catal. Sci. Technol.* **2020**, *10*, 5345.

[18] Misol, A. Reacciones de Alquenilación Intramolecular Catalizadas por Pd(II) en la Síntesis de Cromanos y Cromenos. Master Thesis, UPV/EHU, September 2015.

placing different substituents at the C-1 position of the alkenyl chain of the substrates will be tested, along with the effect of using different aromatic rings (Scheme 1.4).

It was envisioned that by simply removing the electron-withdrawing group from the terminal position of the alkene, the exocyclic double bond would possibly isomerize to the more stable endocyclic olefin in the course of the reaction, allowing the formation of the corresponding chromenes **III**. Thus, with the aim of checking the viability of this hypothesis, different butenyl phenyl ethers **I**, bearing terminal alkene moieties, will be subjected to the intramolecular oxidative Heck reaction. During this investigation the effect of adding substituents to the C-1 and C-2 positions of the substrates will also be studied (Scheme 1.4).



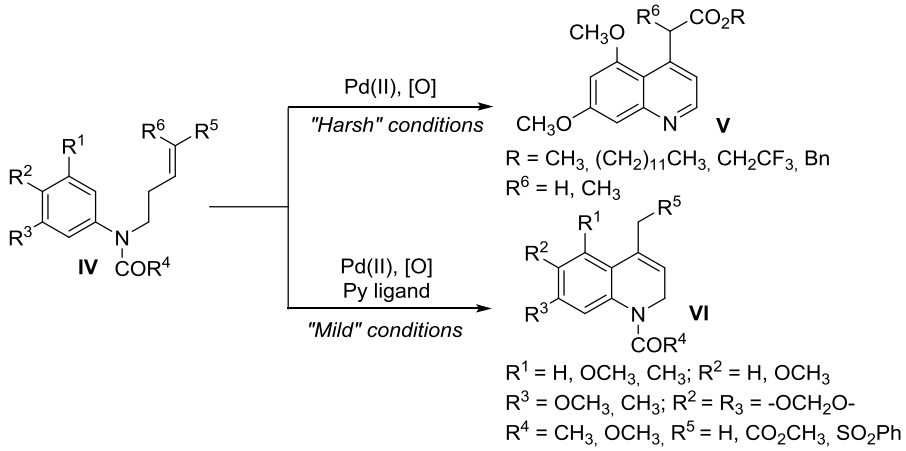
Scheme 1.4

2.2. Palladium-catalyzed dehydrogenative coupling. An efficient synthetic strategy for the construction of the quinoline core

Our group has formerly utilized *N*-protected butenyalanilines **IV** as viable substrates for the intramolecular Fujiwara-Moritani reaction, releasing the corresponding quinolines after a 6-*exo*-trig cyclization, followed by isomerization of the exocyclic double bond to the endocyclic position and further oxidation of the product upon deprotection of the nitrogen atom.[19] The reaction worked not only with terminal alkenes, but also with olefins possessing

[19] Ortiz-de-Elguea, V. Ready Access to Quinoline and Coumarin Scaffolds via Palladium.Catalyzed Alkenylation Reactions. Ph.D. Thesis, UPV/EHU, November 2014.

phenyl sulfone in the external position. Encouraged by the possibility of accomplishing the reaction with other electron-withdrawing groups on the alkene terminus, different esters will be placed at that position in order to synthesize the corresponding 4-substituted quinolines **V**. Besides, the effect of the protecting group on the nitrogen atom in the outcome of the reaction will be studied (Scheme 1.5).



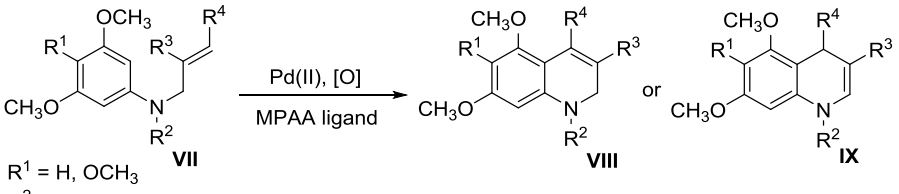
Scheme 1.5

As it has been mentioned above, the formation of the corresponding quinolines is proposed to involve extrusion of the *N*-protecting group and oxidation. Thus, the viability of avoiding this last step will be studied by employing softer reaction conditions (milder oxidants, non-acidic solvents…). That way, the utilization of *N*-protected butenylanilines **IV** as substrates in this intramolecular alkenylative coupling would lead to the obtainment of different 1,2-dihydroquinolines **VI**, preserving their *N*-protecting groups. Moreover, the impact of changing both the *N*-protecting group and the aromatic ring will be studied. (Scheme 1.5). The possibility of enhancing the efficiency of the reaction taking advantage of pyridine ligands will be tested.

2.3. Intramolecular palladium(II)-catalyzed 6-*endo* C-H alkenylation directed by the remote *N*-protecting group. Mechanistic insight and application to the synthesis of dihydroquinolines

After exploiting the efficacy of the Pd(II)-catalyzed intramolecular 6-*exo*-trig alkenylation reaction for the synthesis of both, oxygen- and nitrogen-containing heterocycles, the possibility of performing 6-*endo*-trig cyclizations over related substrates will be studied. In

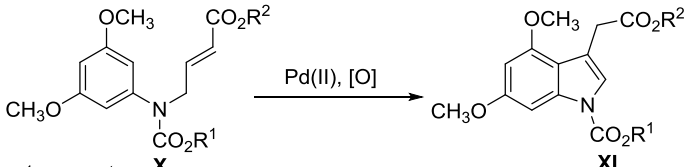
this context, our group has previously applied this intramolecular alkenylative coupling over different *N*-allylanilines; however, in those cases quinolines were furnished due to loss of the *N*-protecting group and over-oxidation.[19] As stated before, we thought that the aromatization process could be prevented by the utilization of softer reaction conditions. Thus, different *N*-protected allylanilines **VII** will be subjected to a "mild" intramolecular Fujiwara-Moritani reaction, with the aim of obtaining the corresponding 1,2- and/or 1,4-dihydroquinolines (**VIII** and **IX**, respectively) and studying the regioselectivity of the transformation, being this dependent on which of the two available hydride units is abstracted in the β-hydride elimination step. Furthermore, the behavior of both terminal and internal alkenes under the reaction conditions will be tested, as well as the impact of the addition of mono-protected amino acids as ligands and the utilization several *N*-protecting groups possessing different coordinative abilities (Scheme 1.6). Experimental and DFT studies will be accomplished in order to understand the mechanism operating in the reaction.



R^1 = H, OCH_3
R^2 = CO_2CH_3, $COCH_3$, CO_2(-)-Menthyl, Boc, Ts, CH_3
R^3 = H, CH_3
R^4 = H, CH_3, Ph, 4(CH_3)C_6H_4, 3(CH_3)C_6H_4, 4(OCH_3)C_6H_4, 4(Ph)C_6H_4, Bn...

Scheme 1.6

Besides, electron-withdrawing functionalities will be placed in the alkene terminus to check the feasibility of directing the cyclization towards the 5-*exo*-trig process, precluding the 6-*endo* pathway (Scheme 1.7).



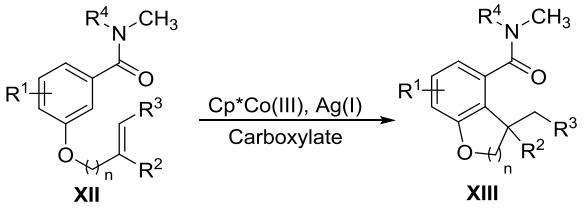
R^1 = CH_3, ^{t}Bu
R^2 = CH_3, Et, ^{n}Bu, ^{t}Bu, Bn

Scheme 1.7

2.4. Amide-directed intramolecular Co(III)-catalyzed C–H hydroarylation of alkenes for the synthesis of dihydrobenzofurans with a quaternary center

Encouraged by the experience of the group in Pd(II)-catalyzed intramolecular C-H activation reactions with alkenes, we decided to change this noble metal for cobalt, which is cheaper, more earth-abundant and less toxic. Several intermolecular Cp*Co(III)-catalyzed reactions between arenes and alkenes or alkynes have been developed throughout the last decade; however, intramolecular C-H activation/C-C bond formation reactions remain underexplored.[20] With this fact in mind, we were determined to study the possibility of carrying out the first intramolecular hydroarylation of olefins under Cp*Co(III) catalysis. To achieve this purpose, allyl phenyl ethers **XII**, possessing an amide directing group, will be utilized as substrates, leading to the formation of the corresponding 2,3-dihydrobenzofurans **XIII**, bearing a quaternary center. With the aim of optimizing the reaction conditions, different Cp*Co(III)-based catalyst will be studied, along with a range of carboxylate bases in the presence of $AgSbF_6$ as the Lewis-acidic silver salt. We will also seek for the optimal reaction time and temperature (Scheme 1.8).

Once the reaction is optimized, the effect of placing a variety of substituents on distinct sites of the aromatic ring and on the internal position of the alkene will be studied. The length of the alkenyl chain tethered to the arene will also be changed (Scheme 1.8). Moreover, an array of chiral carboxylic acids will be screened and utilized in this intramolecular coupling instead of the optimal carboxylate in order to try to induce enantioselectivity in the reaction.



XII **XIII**

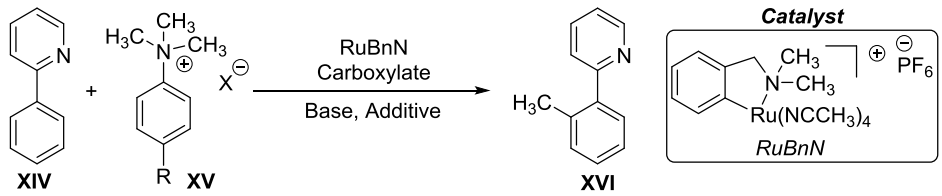
R^1 = H, 5-NO_2, 5-Br, 4,5-$(OCH_3)_2$, 5-Ph, 4-OCH_3, 4-F...
R^2 = H, CH_3, Ph, Et; R_3 = H, CH_3; R_4 = H, CH_3
n = 1, 2

Scheme 1.8

[20] For a recent review written by our group on this matter, see: Carral-Menoyo, A.; Sotomayor, N.; Lete, E. *ACS Omega* **2020***, 5,* 24974.

2.5. Ru(II) catalysis for the *ortho*-mono-methylation of 2-phenylpyridine utilizing bench-stable ammonium salts

During the three-month stay carried out in the Larrosa Group, at the University of Manchester, a new project was started, which consisted of the *ortho*-mono-methylation of the 2-phenylpyridine scaffold **XIV** under Ru(II) catalysis and using aryltrimethylammonium salts **XV** as methylating agents. The aim of the work was to optimize the reaction conditions in order to achieve the mentioned transformation efficiently. For that purpose, the different variables of the reaction were carefully studied in order to select the best methylating agent, base, carboxylate, additive, reaction time and temperature; however, the Ru(II) catalyst (RuBnN) remained untouched. The optimal amounts of all the reagents employed in the reaction were also investigated (Scheme 1.9).



XIV **XV** **XVI**

R = H, CF_3, CO_2Et
X = I, Br, Cl

Scheme 1.9

II

Intramolecular Fujiwara-Moritani Reaction

3.1.1. Synthesis of the substrates

*3.1.2. Palladium(II)-catalyzed cyclization of aryl homoallyl ethers **1aa-1db**, as well as esters **2aaa-2bba** and aryl butenoate **1ao**. Synthesis of chromanes **3aaa-3bba**, chromenes **4aa-4db** and coumarin **4ao***

3.2. Palladium-catalyzed dehydrogenative coupling. An efficient synthetic strategy for the construction of the quinoline core

3.2.1. Synthesis of the substrates

*3.2.2. Palladium(II)-catalyzed intramolecular alkenylation of N-protected butenylanilines **6aa-6ba** and **7aa-7bf**. Synthesis of quinolines **8a-8d** and dihydroquinolines **9aa-9ba** and **10ae***

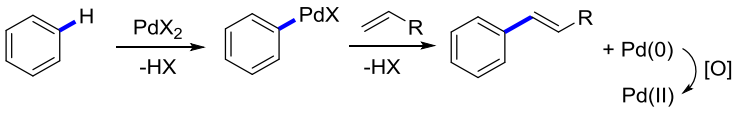
3.3. Intramolecular palladium(II)-catalyzed 6-endo C-H alkenylation directed by the remote N-protecting group. Mechanistic insight and application to the synthesis of dihydroquinolines

3.3.1. Synthesis of the substrates

*3.3.2. Intramolecular oxidative Heck reaction of N-protected allylanilines **11aa-11gl** and **12aa-12ba**. Synthesis of 1,2-dihydroquinolines **14aa-14da**, 1,4-dihydroquinolines **16ab-16gl** and indoles **17aa-17ba***

1. INTRODUCTION OF THE CHAPTER

The Fujiwara-Moritani reaction consists of the transition-metal-catalyzed alkenylation of C(sp^2)-H bonds, which can be efficiently employed for the synthesis of highly functionalized aromatic molecules in an atom-economical and an environmentally friendly way.[1] In this transformation, the oxidative coupling of an unfunctionalized arene and an alkene takes place *via* palladium(II)-catalysis, *i.e.* a C-C bond is formed starting from two inert C-H bonds. Thus, minimization of the waste typically delivered in the preparation of the prefunctionalized substrates required for classical cross-coupling reactions, such as the Mizoroki-Heck coupling, is achieved (Scheme 2.1).

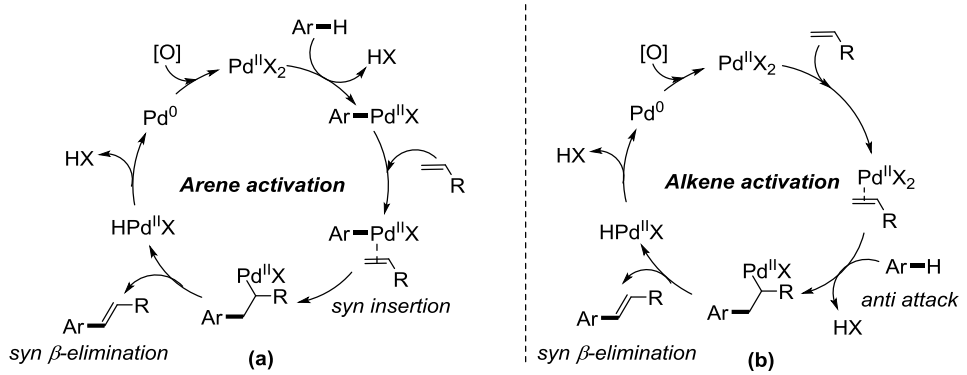


Scheme 2.1

For this oxidative Heck coupling, two different mechanisms have been proposed for the initial palladation: arene metalation-alkene insertion or alkene activation-arene insertion. In the first case, the reaction is thought to proceed through C-H activation of the aryl ring to form a σ-aryl-Pd(II) intermediate. Then, the olefin partner would coordinate to the Pd(II) species, followed by 1,2-migratory insertion to the Pd(II)-aryl bond (arene activation, Scheme 2.2a). In the second pathway, the first step consists of the coordination of the Pd(II) catalyst to the olefin, followed by subsequent nucleophilic attack of the arene ring (alkene activation, Scheme 2.2b). In both cases, the alkyl-Pd(II) species formed after the insertion

[1] For selected reviews, see: a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633; b) Beccalli, E.M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318; c) Ferreira, E.M.; Zhang, H.; Stoltz, B.M. Oxidative Heck-Type Reactions (Fujiwara-Moritani Reactions). In *The Mizoroki-Heck Reaction;* Oestreich, M., Ed.; Wiley-VCH: Chichester, 2009; p 345; d) Chen, X.; Engle, K.M:; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; e) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170; f) Suna, E.; Shubin, K. Metal-Catalyzed Heck-Type Reactions and C-C Cross Coupling via C-H Activation. In *Science of Synthesis. Cross Coupling and Heck-Type Reactions;* Larhed, M., Ed.; Thieme: Stuttgart, 2013; Vol. 3, p 643; g) Zhou, L.; Lu, W. *Chem. Eur. J.* **2014**, *20*, 634; h) Odell, L.R.; Sävmarker, J.; Lindh, J.; Nilsson, P.; Larhed, M. Addition Reactions with Formation of Carbon-Carbon Bonds: (v) The Oxidative Heck Reaction. In *Comprehensive Organic Synthesis*, 2nd Ed; Odell, L.R., Ed.; Elsevier: Amsterdam, 2014; Vol. 7, p 492; i) Kitamura, T.; Fujiwara, Y. Dehydrogenative Heck-Type Reactions: The Fujiwara-Moritani Reaction. In *From C-H to C-C Bonds: Cross-Dehydrogenative-Coupling;* Li, C.-J., Ed.; RSC: London, 2015; p 33; j) Gensch, T.; Hopkinson, M.N.; Glorius, F.; Wencel-Delord, J. *Chen. Soc. Rev.* **2016**, *45*, 2900; k) Li, Y.; Xu, S. *Chem. Eur. J.* **2018**, *24*, 16218; l) Kancherla, S.; Jørgensen, K.B.; Fernández-Ibáñez, M.A. *Synthesis* **2019**, *51*, 643.

event undergoes β-hydride elimination to give the alkenylated arene. The Pd(II)-hydride generated in that process is transformed into a Pd(0) species after reductive elimination, so an oxidant is required in order to recover the catalytically active Pd(II) species



Scheme 2.2

Organic molecules possess a wide range of C-H bonds, what makes the Fujiwara-Moritani reaction a very attractive method for their functionalization. However, this advantage can turn to be a huge disadvantage in synthetic chemistry, as it makes very challenging the achievement of high site-selectivity towards just one C-H bond among all the others present in the molecule. During the past decades, distinct mechanisms have been proposed for the C-H metalation step, each of which would proceed through one of the three different transition states depicted in Figure 2.1.[2] The first mechanism involves the formation of an aryl-Pd(II) species through the electrophilic palladation of the aromatic ring (Figure 2.1a).[3] In this case, the C-H activation step would take place *via* an electrophilic aromatic substitution, followed by a fast deprotonation that leads to rearomatization. That way, the aryl-Pd(II) species is formed by the transference of a proton to an acetate bonded to the palladium(II) center. For this C-H activation mechanism, the electronic properties of the arene substrate play a fundamental role. The second mechanism proposed (Figure 2.1b)[4] consists of a proton abstraction that takes place by means of a concerted and intramolecular transfer of a hydrogen atom to a base (concerted metalation-

[2] Engle, K.M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137.
[3] Ryabov, A.D.; Sakodinskaya, I.K.; Yatsimirsky, A.K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629.
[4] a) Gómez, M.; Granell, J.; Martinez, M. *Organometallics* **1997**, *16*, 2539; b) Gómez, M.; Granell, J.; Martinez, M. *J. Chem. Soc., Dalton Trans*. **1998**, 37; c) Davies, D.L.; Donald, S.M.A.; Macgregor, S.A. *J. Am. Chem. Soc.* **2005**, *127*, 13754.

deprotonation). The last mechanism (Figure 2.1c)[5] is based on the oxidative addition of the C-H bond to the Pd(II) center and involves the formation of a Pd(IV) species, which provides the aryl-Pd(II) species after reductive elimination.

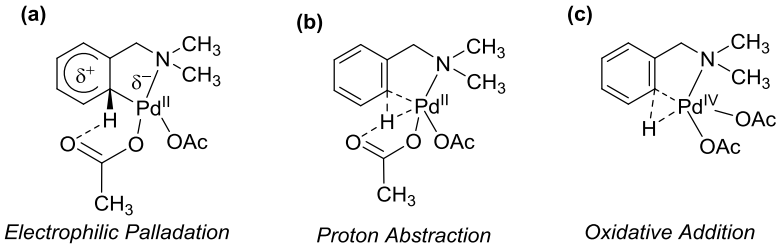


Figure 2.1

Irrespective of the mechanism operating in the C-H activation process, three main strategies for the control of regioselectivity are utilized,[6] involving substrate-control and/or catalyst-system-control (Figure 2.2):[7]

1) Advantage can be taken of the electronic properties of the arene. Typically, when this approach is utilized, a palladium(II) source ($Pd(OAc)_2$, commonly) is employed without the aid of directing groups and/or ligands. Usually, high loadings of the aryl coupling partner are required, being even used in some cases as the solvent or co-solvent. When this strategy is operating, the alkenylation reaction is thought to occur through electrophilic palladation or concerted metalation-deprotonation (CMD), functioning the acetate ligand as a base[8] (Figure 2.2a).

2) Functional groups can be attached to the substrate to act as auxiliary groups that are able to coordinate to the Pd(II) center, approaching it to a specific C-H site (in those cases the arene is usually used as the limiting reagent). In this approach, palladation of the C-H bond usually takes place *via* acetate-ligand-mediated CMD (Figure 2.2b).

3) The last approach consists of the use of ligands to tune the properties of the Pd(II) catalyst, being pyridine-based ligands and mono-protected amino acids (MPAA) the most

[5] Canty, A.J.; van Koten, G. *Acc. Chem. Res*. **1995**, *28*, 406.
[6] Neufeldt, S.R.; Sanford, M.S. *Acc. Chem. Res.* **2012**, *45*, 936.
[7] Chen, H.; Wedi, P.; Meyer, T.; Tavakoli, G.; van Gemmeren, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 2497.
[8] a) Ref. 4c; b) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118; c) Zhang, S.; Shi, L.; Ding, Y. *J. Am. Chem. Soc.* **2011**, *133*, 20218.

common ones. In this sense, when pyridine ligands are employed, the dehydrogenative coupling is usually proposed to proceed through a similar scenario as that one described in Figure 2.2a, although with higher catalytic efficiency (Figure 2.2c).[8c] On the other hand, it has been reported that *N*-acetyl amino acids can enhance the selectivity and reactivity of the system depicted in Figure 2.2b.[9] The ligand would replace the acetate, being its *N*-acetyl group responsible for the proton abstraction (Figure 2.2d).[9d,e]

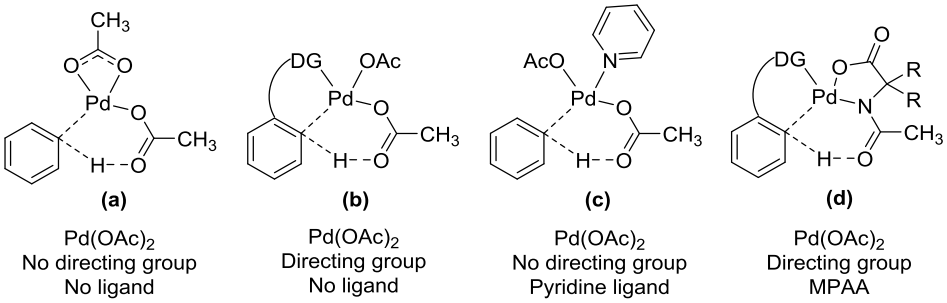


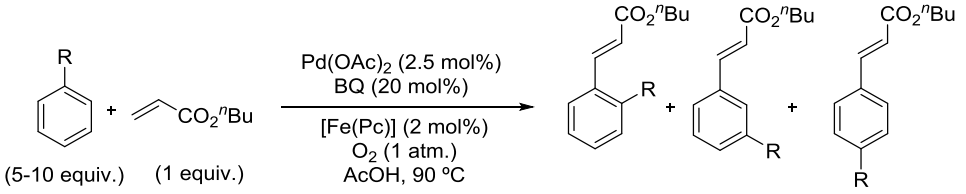
Figure 2.2

[9] a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882; b) Wang, D.-H.; Engle, K.M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315; c) Ref. 2; d) Cheng, G.-J.; Yang, Y.-F.; Liu, P.; Chen, P.; Sun, T.-Y.; Li, G.; Zhang, X.; Houk, K.N.; Yu, J.-Q.; Wu, Y.-D. *J. Am. Chem. Soc.* **2014**, *136*, 894; e) Yang, Y.-F.; Hong, X.; Yu, J.-Q.; Houk, K.N. *Acc. Chem. Res.* **2017**, *50*, 2853.

1.1. Regioselectivity driven by the electronic properties of the arene

When the Fujiwara-Moritani reaction is carried out over simple arenes, a common proposal is that the C-H activation step takes place *via* electrophilic metalation. That can be formally considered as an aromatic electrophilic substitution and thus, leads to mixtures of regioisomers. This issue can be overcome through the adjustment of the electronic properties of the aromatic ring by tuning its substituents, making is possible to control the site-selectivity of the olefination reaction.[10] Nevertheless, the possibility of a CMD mechanism operating in the C-H activation step cannot be ruled out, since depending on the substitution pattern of the aromatic ring, both pathways would lead to similar (if not the same) regioselectivities. Positional control ruled by the electronic nature of the aromatic ring is a very common approach when heteroaromatic substrates are utilized (quinolones, indoles…), since they possess very active C-H sites.[11]

Taking advantage of the electronic properties of the arene, in 2013, Bäckvall and co-workers were able to carry out the Pd(II)-catalyzed intermolecular alkenylation of different arenes using acrylates as coupling partners (Scheme 2.3).[12]



Scheme 2.3

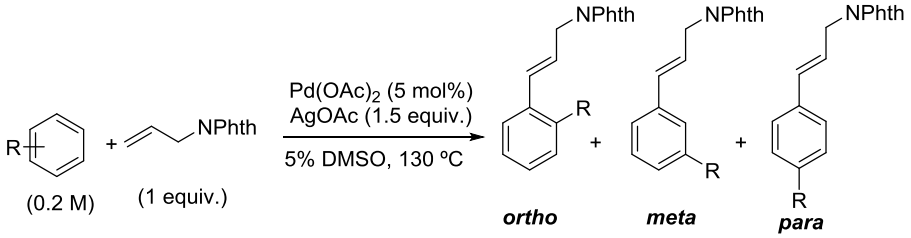
[10] a) Fujiwara, Y.; Moritani, I.; Asano, R.; Tanaka, H.; Teranishi, S. *Tetrahedron* **1969**, *25*, 4815; b) Fujiwara, Y.; Asano, R.; Moritani, I.; Teranishi, S. *J. Org. Chem.* **1976**, *41*, 1681; c) Jia, C.; Lu., W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097; d) Pan, D.; Yu, M.; Chen, W.; Jiao, N. *Chem. Asian J.* **2010**, *5*, 1090; e) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc*. **2010**, *132*, 4506.

[11] a) Hirota, K.; Isobe, Y.; Kitade, Y.; Maki, Y. *Synthesis* **1987**, 495; b) Li, Z.; Ma, L.; Tang, C.; Xu, J.; Wu, X.; Yao, H. *Tetrahedron Lett*. **2011**, *52*, 5643; c) Liu, W.; Yu, X.; Kuang, C. *Org. Lett.* **2014**, *16*, 1798; d) Le Bras, J.; Muzart, J. *Adv. Synth. Catal.* **2018**, *360*, 2411; e) Koubachi, J.; El Brahmi, N.; Guillaumet, G.; El Kazzouli, S. *Eur. J. Org. Chem.* **2019**, 2568.

[12] Babu, B.P.; Meng, X.; Bäckvall, J.-E. *Chem. Eur. J.* **2013**, *19*, 4140.

In order to achieve this transformation, they employed a biomimetic approach, in which iron phtalocyanine [Fe(Pc)] was utilized as an electron-transfer mediator to facilitate the aerobic reoxidation of the palladium catalyst.

In 2015, Xu and Deng disclosed the alkenylation of a range of simple aromatic rings employing allylamines.[13] To carry out this coupling the arene was used as solvent, along with a 5% of DMSO, what proved to be necessary for the reaction to take place smoothly. Several benzene derivatives were employed in the transformation, and as in the previous example, it was observed that the regioselectivity completely depended on their electronic properties: when electron-rich arenes were employed, *ortho*- and *para*-products were obtained predominantly, while when an electron-deficient aryl ring was utilized, the *meta*-product was selectively achieved (Scheme 2.4). To explain the γ-selectivity of the reaction, the authors proposed that the Pd(II) center was coordinated to the oxygen atom of the carbonyl of the *N*-protecting group during the reaction.

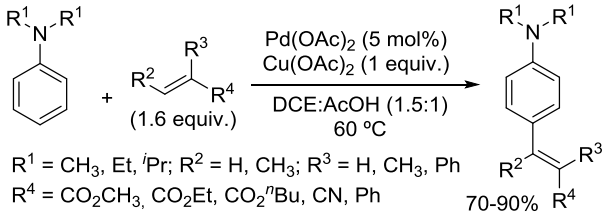


Scheme 2.4

Achieving complete site-selectivity taking advantage of the electronic properties of the arene may become a major challenge depending on the substrate. In this context, Karimi and co-workers were capable of overcoming the present disadvantage and they reported the *para*-selective palladium(II)-catalyzed alkenylation of tertiary anilines (Scheme 2.5).[14] It is worth to mention that in this work, the amine moiety did not act as a chelating/directing group to activate the *ortho* C-H site. The AcOH (used as co-solvent in the reaction) might have been responsible for that, since it tuned the concentration of the free aniline, thus avoiding the coordination of palladium(II) to the nitrogen atom. DFT calculations were run to elucidate the mechanism operating in this transformation and according to them, the

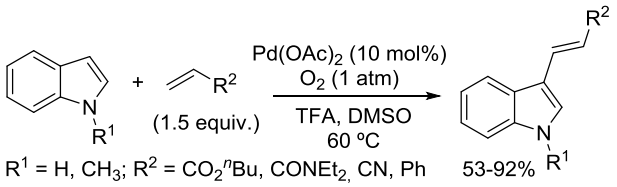
[13] Lei, Y.; Qiu, R.; Zhang, L.; Xu, C.; Pan, Y.; Qin, X.; Li, H.; Xu, L.; Deng, Y. *Chem.Cat.Chem.* **2015***, 7*, 1275.
[14] Moghaddam, F.M.; Pourkaveh, R.; Karimi, A. *J. Org. Chem.* **2017**, *82*, 10635.

reaction would start with an electrophilic metalation process towards the *para*-position of the arene. The activation of the three different possible sites was computationally studied. In this context, the results indicated that the metalation of the *ortho* position would involve the formation of a four-membered ring, which is more unstable that the six-membered ring formed when metalation occurs at the *para* position. Besides, the low electronic density present at the *meta* position makes the palladation unlikely to take place at that site.



Scheme 2.5

As it has been mentioned in the beginning of this section, the method to achieve regioselectivity herein disclosed is very popular when heteroarenes are used as substrates, since they have active C-H sites.[11] In this regard, the indole core is one of the most used hetereoaryl moieties in the intermolecular Fujiwara-Moritani reaction,[15] being the corresponding C-3 alkenylation products expected due the more-nucleophilic character of that site, thus undergoing there the electrophilic palladation. That fact was observed, for example, by Wang and co-workers, who used oxygen as the sole oxidant (Scheme 2.6).[16]

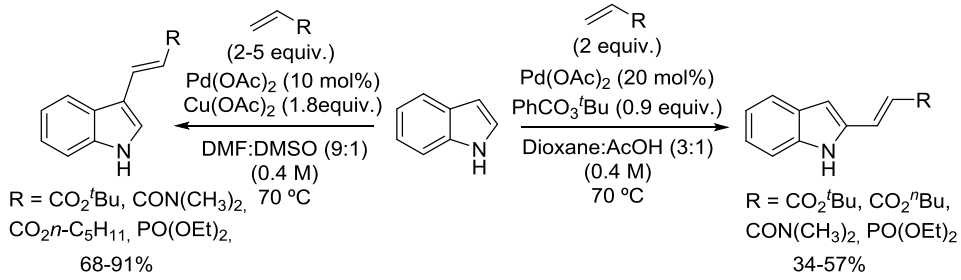


Scheme 2.6

[15] a) Beck, E.M.; Gaunt, M.J. *Top. Curr. Chem*. **2010**, *292*, 85; b) Broggini, G.; Beccalli, E.M.; Fasana, A.; Gazzola, S. *Beilstein J. Org. Chem*. **2012**, *8*, 1730; c) Ozaki, K.; Zhang, H.; Ito, H.; Lei, A.; Itami, K. *Chem. Sci.* **2013**, *4*, 3416; d) Saunthwal, R.K.; Patel, M.; Kumar, S.; Danodia, A.K.; Verma, A.K. *Chem. Eur. J.* **2015**, *21*, 18601; e) Laha, J.K.; Dayal, N. *Org. Lett.* **2015**, *17*, 4742; f) Verma, A.K.; Danodia, A.K.; Saunthwal, R.K.; Patel, M.; Choudhary, D. *Org. Lett.* **2015**, *17*, 3658; g) An, Y.-L.; Yang, Z.-H.; Zhang, H.-H.; Zhao, S.-Y. *Org. Lett.* **2016**, *18*, 152; h) Guo, L.; Xu, M.; Jian, Y.; Liu, S.; Pan, W.; Duan, L. *Chem. Res. Chinese U.* **2019**, *35*, 621.

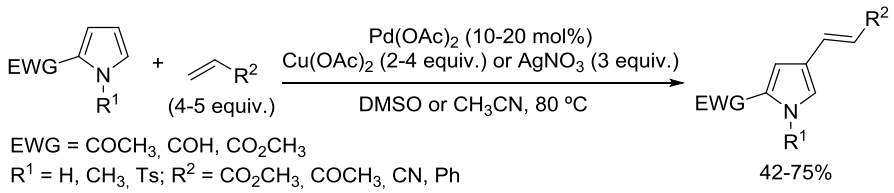
[16] Chen, W.-L.; Gao, Y.-R.; Mao, S.; Zhang, Y.-L.; Wang, Y.-F.; Wang, Y.-Q. *Org. Lett.* **2012**, *14*, 5920.

However, in 2005 Gaunt *et. al* could effectively accomplish the regioselective functionalization of indoles at the C-3 or C-2 position, just by changing the nature of the solvent employed, as well as the oxidant. That way, when acidic solvents were utilized, the site-selectivity of the alkenylation switched from the C-3 to the C-2 site (Scheme 2.7).[17]



Scheme 2.7

On the other hand, pyrroles, due to their instability in acidic and oxidative conditions, have a limited application to the Fujiwara-Moritani reaction. Despite that, some examples involving the alkenylation of this privileged framework have been reported.[18] For example, in 2017, Mule and co-workers were able to furnish 4-alkenylated pyrroles without the use of directing groups or specific *N*-protecting groups. The reaction proceeded efficiently with a free NH or with electronically diverse *N*-substituents, and they could use electron-deficient alkenes or styrenes as coupling partners (Scheme 2.8).[19]



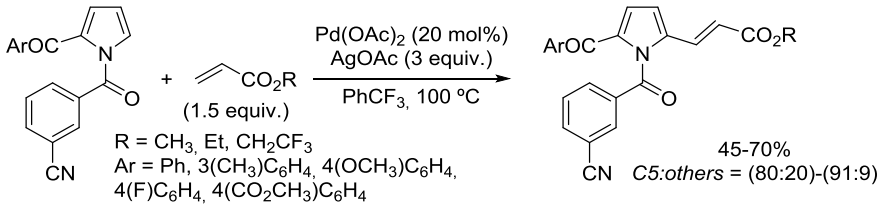
Scheme 2.8

The only requirement for this reaction to proceed site-selectively, was the presence of an electron-withdrawing group at the C-2 position. It was envisioned that the mentioned

[17] Grimster, N.P.; Gaunlett, C.; Godfrey, C.R.A.; Gaunt, M.J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3125.
[18] a) Beck, E.M.; Grimster, N.P.; Hatley, R.; Gaunt, M.J. *J. Am. Chem. Soc.* **2006**, *128*, 2528; b) Su, Y.; Zhou, H.; Chen, J.; Xu, J.; Wu, X.; Lin, A.; Yao, H. *Org. Lett.* **2014**, *16*, 4884; c) Su, Y.; Gao, S.; Huang, Y.; Lin, A.; Yao, H. *Chem. Eur. J.* **2015**, *21*, 15820.
[19] Laha, J.K.; Bhimpuria, R.A.; Mule, G.B. *ChemCatChem* **2017**, *9*, 1092.

functionality could increase the electron density on C-4, thus making that C-H site more prompt to undergo electrophilic palladation while avoiding C-5 alkenylation. When carrying out the reaction without the presence of the electron-withdrawing group at C-2, the corresponding 2-alkenylated pyrroles were achieved.

In contraposition to that work, later, Zhou and Sun reported a method for the selective C-5-alkenylation of 2-acylpyrroles, obtaining small amounts of other regioisomeric compounds (Scheme 2.9).[20]

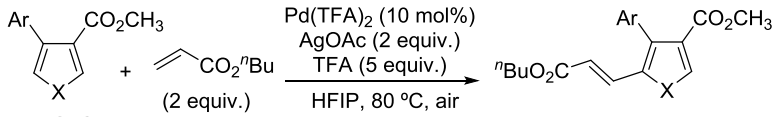


Scheme 2.9

To achieve such site-selectivity, different *N*-protecting groups were tested, observing that *N*-[3(CN)C_6H_4CO] was the optimal one. According to the mechanistic proposal provided by the authors, the metalation event takes place *via* electrophilic palladation. Nevertheless, they stated that although it should not be dominant in the present transformation, the coordinating (or directing) effect of the *N*-protecting group cannot be ignored.

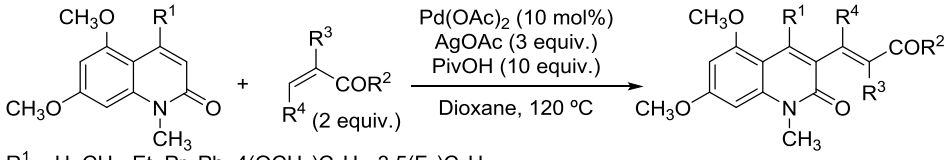
Related heterocycles, such as furans and thiophenes, [21] have been successfully employed in the oxidative Heck reaction. For instance, Yao and Lin developed the palladium(II)-catalyzed alkenylation of the furan and thiophene cores at the C-5 position using acrylates as the coupling partners (Scheme 2.10).[22] Although they also tried to switch the selectivity to the C-2 position taking advantage of the directing effect of the ester group present at C-3, it was impossible for them to achieve such regiocontrol under Pd(II) catalysis, and [$RuCl_2$(*p*-cymene)]$_2$ had to be used.

[20] Duan, J.-H.; Mi, R.-J.; Sun, J.; Zhou, M.-D. *Org. Chem. Front.* **2018**, *5*, 162.
[21] a) Zhao, J.; Huang, L.; Cheng, K.; Zhang, Y. *Tetrahedron Lett.* **2009**, *50*, 2758; b) Jiang, Z.; Zhang, L.; Dong, C.; Cai, Z.; Tang, W.; Li, H.; Xu, L.; Xiao, J. *Adv. Synth. Catal.* **2012**, *354*, 3225; c) Shang, Y.; Jie, X.; Zhou, J.; Hu, P.; Huang, S.; Su, W. *Angew. Chem. Int. Ed.* **2013**, *52*, 1299; d) Morita, T.; Satoh, T.; Miura, M. *Org. Lett.* **2015**, *17*, 4384.
[22] Gao, S.; Wu, Z.; Wu, F.; Lin, A.; Yao, H. *Adv. Synth. Catal.* **2016**, *358*, 4129.



Scheme 2.10

Despite electron-rich heteroarenes have been popular motifs to be functionalized *via* the intermolecular Fujiwara-Moritani reaction, their electron-deficient counterparts have also been successfully utilized as substrates in this Pd(II)-catalyzed alkenylation reaction. An interesting example was developed by our group, as we reported a method for the C-3 alkenylation of a variety of 2-quinolones through the intermolecular oxidative Heck coupling, using electron-deficient alkenes as the coupling partners (Scheme 2.11).[23]



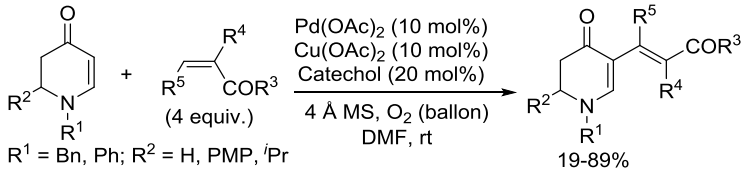
Scheme 2.11

In the last decade, those heterocycles bearing carbonyl groups have been widely alkenylated taking advantage of the transformation herein disclosed.[24] Among all the examples available, Georg and co-workers reported an interesting work on the C-3 alkenylation of 4-enaminones employing a biomimetic approach that utilized catechol as the electron-transfer mediator (Scheme 2.12).[25]

[23] Ortiz-de-Elguea, V.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2015,** *357*, 463.

[24] a) Li, M.; Li, L.; Ge, H. *Adv. Synth. Catal.* **2010**, *352*, 2445; b) Yu, Y.-Y.; Niphakis, M.J.; Georg, G.I. *Org. Lett.* **2011**, *13*, 5932; c) Kim, D.; Hong, S. *Org. Lett.* **2011**, *13*, 4466; d) Moon, Y.; Kwon, D.; Hong, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 11333; e) Moon, Y.; Hong, S. *Chem. Commun.* **2012**, *48*, 7191; f) Chen, Y.; Wang, F.; Jia, A.; Li, X. *Chem. Sci.* **2012**, *3*, 3231; g) Yu, Y.-Y.; Georg, G.I. *Chem. Commun.* **2013**, *49*, 3694; h) Min, M.; Kim, Y.; Hong, S. *Chem. Commun.* **2013**, *49*, 196; i) Liu, W.; Wang, S.; Zhang, Q.; Yu, J.; Li, J.; Xie, Z.; Cao, H. *Chem. Asian. J.* **2014**, *9*, 2436.

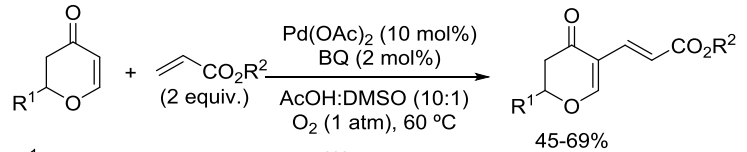
[25] Yu, Y.-Y.; Georg, G.I. *Adv. Synth. Catal.* **2014**, *356*, 1359.



R^1 = Bn, Ph; R^2 = H, PMP, ^{i}Pr
R^3 = OCH_3, O^tBu, $N(CH_3)_2$, O^nBu, OBn
R^4 = H, CH_3; R_5 = H, CH_3

Scheme 2.12

Regarding their oxygenated counterparts, Xia´s group reported the C-3 alkenylation of a range of dihydropyranones with acrylates (Scheme 2.13).[26]



R^1 = Ph, 2-naphth, Cy, *n*-C_7H_{15}, ^{sec}Bu, $4(Cl)C_6H_4$, $4(CH_3)C_6H_4$
R^2 = CH_3, Et, ^{n}Bu, ^{t}Bu, Ph

Scheme 2.13

[26] Chen, S.; Chang, X.; Tao, Y.; Chen, H.; Xia, Y. *Org. Biomol. Chem.* **2015**, *13*, 10675.

1.2. Regioselectivity driven by the use of directing groups

Another strategy for the achievement of site-selectivity in the C-H bond activation step consists of the incorporation of directing groups to the substrate. Those motifs are auxiliary groups (σ-chelating groups) that contain Lewis basic heteroatoms, which are capable of coordinating to the Pd(II) center and of bringing it close to a specific C-H bond (usually *ortho* to the directing group) forming palladacycles.[27]

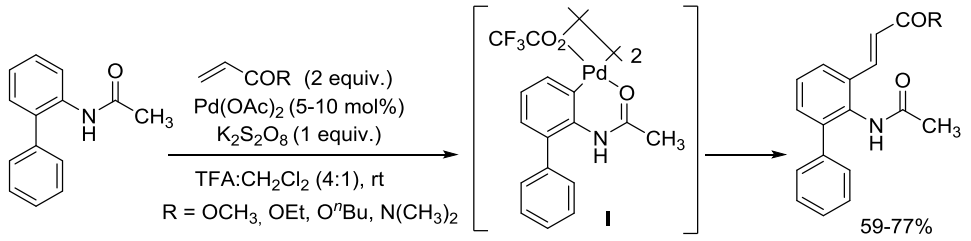
The major drawback of this strategy for the control of positional selectivity lies on the presence of an undesired functionality in the final product. Therefore, the use of directing groups that can be easily removed once the reaction has taken place or that can further react with the alkenylation product in a cascade fashion are utterly desirable.

A very common directing group used in intermolecular Pd(II)-catalyzed alkenylatyion reactions is the acetamido group.[28] Taking advantage of the directing ability of this functionality, in 2010, Youn *et al.* were able to carry out the alkenylation of 2-pheylacetanilides at the C-6 position, *ortho* to the director (Scheme 2.14).[29] Interestingly, they could isolate palladacylce **I**, which was proved to be an intermediate in the reaction.

[27] For selected reviews, see: a) Ref. 1c; b) Ref. 1d; c) Lyons, T.W.; Sanford, M.S. *Chem. Rev.* **2010**, *110*, 1147; d) Cho, S.H.; Kim, J.Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev*. **2011**, *40*, 5068; e) Ref. 1e; f) Yeung, C.S.; Dong, V.M. *Chem. Rev.* **2011**, *111*, 1215; g) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780; h) Engle, K.M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788; i) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107; j) Gensch, T.; Hopkinson, M.N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900; k) Bag, S.; Maiti, D. *Synthesis* **2016**, *48*, 804; l) Ma, W.; Gandeepan, P.; Li, J.; Ackermann, L. *Org. Chem. Front.* **2017**, *4*, 1435; m) Tomberg, A.; Muratore, M.E.; Johansson, M.J.; Terstiege, I.; Sköld, C.; Norrby, P.-O. *iScience,* **2019**, *20*, 373.

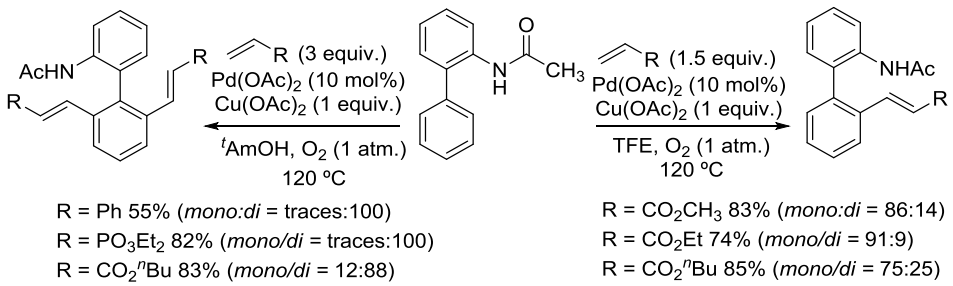
[28] a) Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, *46*, 4416; b) Boele, M.D.K.; van Strijdonck, G.P.F.; de Vries, A.H.M.; Kamer, P.C.J.; de Vries, J.G.; van Leeuwen, P.W.N.M. *J. Am. Chem. Soc*. **2002**, *124*, 1586; c) Zaitsev, V.G.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 4156; d) Amatore, C.; Cammoun, C.; Jutand, A. *Adv. Synth. Catal*. **2007**, *349*, 292; e) Rauf, W.; Thompson, A.L.; Brown, J.M. *Chem. Commun*. **2009**, 3874; f) Nishikata, T.; Lipshutz, B. *Org. Lett.* **2010**, *12*, 1972; g) Rauf, W.; Thompson, A. L.; Brown, J.M. *Dalton Trans.* **2010**, *39*, 10414; h) Wasa, M.; Engle, K.M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680; i) Liu, X.; Hii, K.K.M. *J. Org. Chem*. **2011**, *76*, 8022; j) Ferlín, F.; Santoro, S.; Ackermann, L.; Vaccaro, L. *Green Chem.* **2017**, *19*, 2510.

[29] Kim, B.S; Jang, C.; Lee, D.J.; Youn, S.W. *Chem. Asian J*. **2010**, *5*, 2336.



Scheme 2.14

In contrast to the tendency observed by Youn and co-workers, Chuang´s group has recently developed the alkenylation of 2-phenylacetanilides at the C-2´ position, in the secondary aryl ring (Scheme 2.15). [30]



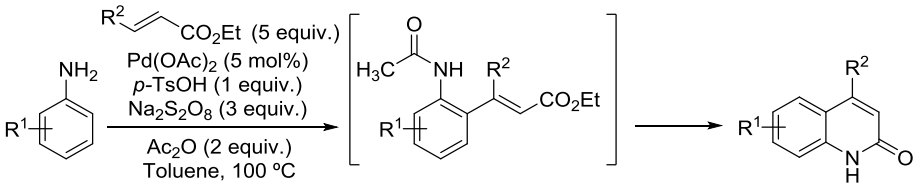
Scheme 2.15

The authors proposed that C-H activation at the C-6 site (primary arene) is favored in acidic solvents (TFA), since they make the Pd(II) center more electrophilic, thus favoring the coordination between the metal and the carbonyl oxygen. On the other hand, they stated that the use of less acidic solvents (^{t}AmOH, TFE…) leads to an increase of the coordinating ability of the nitrogen atom, driving the C-H activation towards the C-2´ position (secondary arene). They were able to selectively obtain the mono- and di-alkenylated products just by changing the solvent and the amount of the olefin coupling partner.

Furthermore, it has also been possible to use the acetamide director as a transient and traceless auxiliary group. Liu and co-workers developed an interesting intermolecular Fujiwara-Moritani coupling/intramolecular amidation cascade reaction for the synthesis of quinolones, starting from different anilines and acrylates and taking advantage of an *in situ*

[30] Annamalai, P.; Hsu, K.-C.; Raju, S.; Hsiao, H.-C.; Chou, C.-W.; Lin, G.-Y.; Hsieh, C.-M.; Chen, P.-L.; Liu, Y.-H.; Chuang, S.-C. *J. Org. Chem.* **2018**, *83*, 3840.

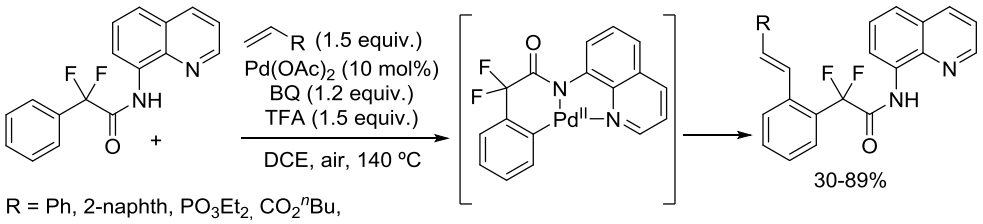
formed acetamide directing group, which could be eliminated in the course of the reaction (Scheme 2.16).[31]



R^1 = H, 2-CH_3, 4-CH_3, 4-^{t}Bu, 4-F, 4-OCH_3, 3-CF_3
R^2 = H, Ph, 4-$(OCH_3)C_6H_4$, 4-$(F)C_6H_4$, CH_3

Scheme 2.16

Bidentate amide directing groups, such as those ones derived from 8-aminoquinoline, can also be used as efficient directors in the Fujiwara-Moritani reaction. Zhang could employ that scaffold to carry out the intermolecular oxidative Heck coupling between α,α-difluorophenylacetic acid derivatives and different olefins. In this case, not only electron-deficient alkenes could smoothly furnish the olefinated arenes, but also styrenes and non-activated olefins could be employed as coupling partners; although the last ones provided the products in moderate yields (Scheme 2.17).[32]



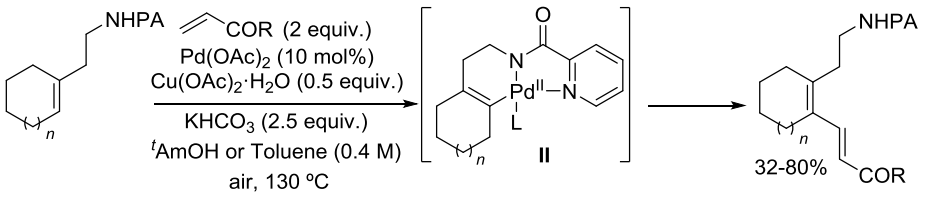
R = Ph, 2-naphth, PO_3Et_2, $CO_2{}^n$Bu, SO_2Ph, n-$C_{10}H_{21}$, CH_2OAc, BPin

Scheme 2.17

The use of directing groups has also allowed to carry out the Pd(II)-catalyzed C-H alkenylation over non-aromatic substrates bearing C(sp^2)-H bonds.[33] In this sense, Cai and co-workers reported the Fujiwara-Moritani reaction of cycloalkenes with electron-deficient

[31] Wu, J.; Xiang, S.; Zeng, J.; Leow, M.; Liu, X.-W. *Org. Lett.* **2015**, *17*, 222.
[32] Shao, C.; Shi, G.; Zhang, Y. *Eur. J. Org. Chem.* **2016**, 5529.
[33] a) Liu, M.; Yang, P.; Karunananda, M.K.; Wang, Y.; Liu, P.; Engle, K.M. *J. Am. Chem. Soc.* **2018**, *140*, 5805; b) Shen, C.; Lu, X.; Zhang, J.; Ding, L.; Sun, Y.; Zhong, G. *Chem. Commun.* **2019**, *55*, 13582.

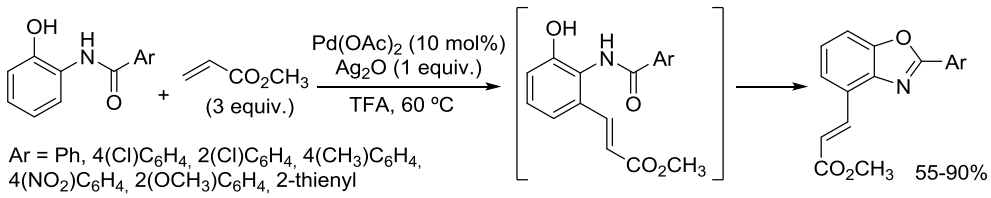
olefins utilizing a picolinamide director (Scheme 2.18).[34] After running different control experiments, it was concluded that the picolinamide moiety was necessary for the reaction to proceed and the transformation was proposed to take place *via* palladacycle **II**.



Scheme 2.18

As it has been mentioned before, a careful design of the reaction conditions may allow directing groups to undergo cascade reactions once the coupling with the olefin partner has occurred.

In this sense, in 2019, Panda and Sahoo developed a procedure for the benzamide-directed olefination of several 2-amidophenols with electron-deficient alkenes. Once the alkenylative coupling took place, the product obtained underwent an acid-catalyzed condensation reaction between the hydroxyl group and the amide director providing the corresponding 4-alkenyl benzoxazoles smoothly (Scheme 2.19).[35]



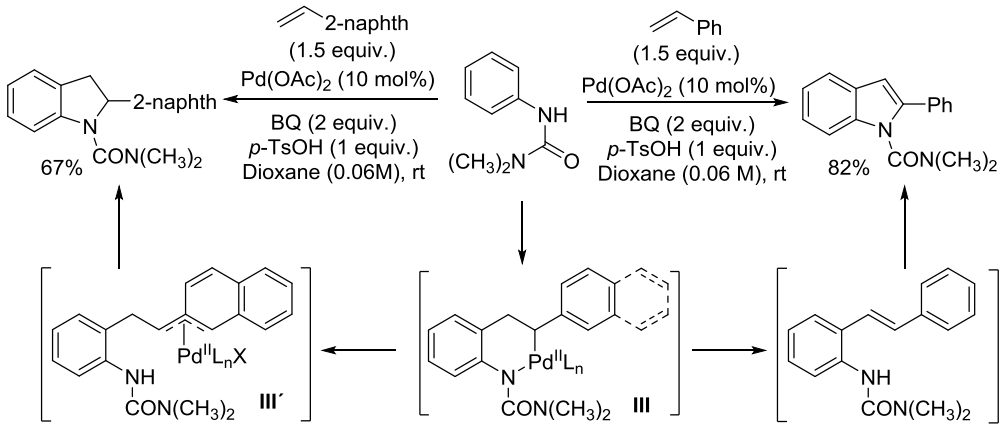
Scheme 2.19

Urea-derived auxiliary groups can also be applied to cascade reactions involving the Pd(II)-promoted alkenylation of aryl rings, followed by a subsequent reaction with the directing group.[36] For example, in 2015, Jana *et al.* disclosed the Pd(II)-catalyzed reaction between

[34] Mao, C.-L.; Zhao, S.; Zang, Z.-L.; Xiao, L.; Zhou, C.-H.; He, Y.; Cai, G.-X. *J. Org. Chem.* **2020**, *85*, 774.
[35] Panda, N.; Sahoo, K. *Adv. Synth. Catal.* **2019**, *361*, 617.
[36] Houlden, C.E.; Bailey, C.D.; Ford, J.G.; Gagné, M.R.; Lloyd-Jones, G.C.; Booker-Milburn, K.I. *J. Am. Chem. Soc.* **2008**, *130*, 10066.

different vinyl arenes and *N,N*-dimethyl-*N´*-pheylureas. They observed that when styrenes were used, the corresponding indoles were obtained due to the Fujiwara-Moritani coupling, followed by a 5-*exo*-trig aza-Wacker-type cyclization (Scheme 2.20).[37]

On the other hand, when vinyl naphthalenes were employed, indoline products were provided *via* capture of the σ-alkyl-Pd(II) intermediate **III** formed after the urea-directed C-H palladation and the migaratory insertion process (Scheme 2.20).[37] This was proposed to occur due to the formation of a stabilized π-benzyl-Pd species (**III´**), which would be responsible for the suppression of the β-hydride elimination step.

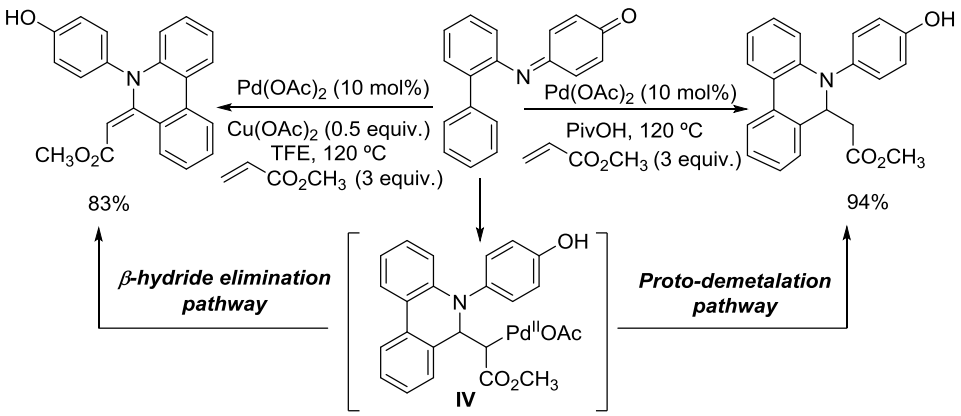


Scheme 2.20

In 2017, Chuang disclosed the use of iminoquinone as a directing group and internal oxidant or cooxidant for the synthesis of dihydrophenanthridines and phenanthridines, starting from the corresponding iminoquinone 2-aminobiaryls and different electron-deficient alkenes (Scheme 2.21).[38]

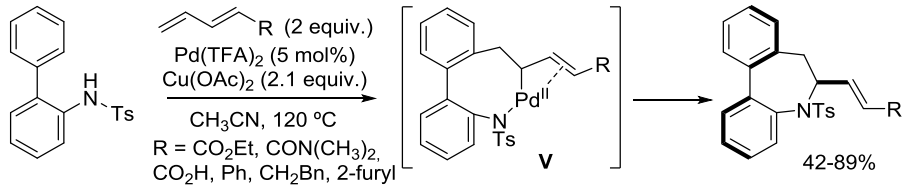
It was observed that when an acidic solvent (PivOH) was utilized without the addition of an oxidant, the corresponding dihydrophenanthridines were furnished due to proto-demetalation of intermediate **IV**. Besides, in the case of employing TFE with an external oxidant, the phenanthridine products were provided after evolution of **IV** to the corresponding product *via* β-hydride elimination.

[37] Manna, M.K.; Hossian, A.; Jana, R. *Org. Lett.* **2015**, *17*, 672.
[38] Raju, S.; Annamalai, P.; Chen, P.-L.; Liu, Y.-H.; Chuang, S.-C. *Org. Lett.* **2017**, *19*, 4134.



Scheme 2.21

Sulfonamide-based auxiliary groups have been efectively used as directors for intermolecular Fujiwara-Moritani/cyclization cascade reactions.[39] To put an example, Luan and coworkers described the reaction between *N*-tosyl-protected *ortho*-arylanilines and different dienes for the diastereoselective synthesis of dibenzo[*b,d*]azepines. The transformation is proposed to take place through migratory insertion of the aryl-Pd(II) species (formed after C-H palladation of the arene) to the diene, followed by reductive elimination of palladacycle **V** (Scheme 2.22).[40]



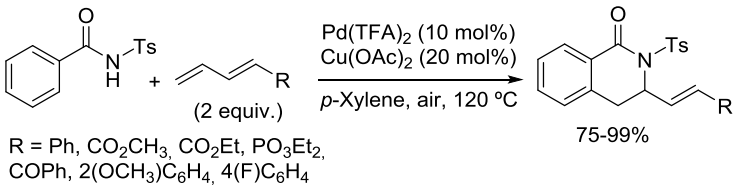
Scheme 2.22

A similar transformation was reported by Wang for the Pd(II)-catalyzed annulation of aryl carboxamides with dienes for the obtainment of the corresponding 3,4-dihydroisoquinolones (Scheme 2.23).[41]

[39] a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211; b) Kim, B.S.; Lee, S.Y.; Youn, S.W. *Chem. Asian J.* **2011**, *6*, 1952.

[40] Bai, L.; Wang, Y.; Ge, Y.; Liu, J.; Luan, X. *Org. Lett.* **2017**, *19*, 1734.

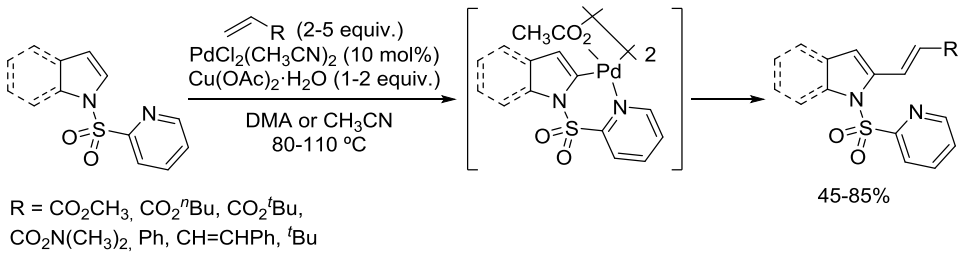
[41] Sun, M.; Li, J.; Chen, W.; Wu, H.; Yang, J.; Wang, Z. *Synthesis* **2020**, *52*, 1253.



Scheme 2.23

Following with the use of sulfonamide-based directors, an interesting functionality that has been widely employed was reported by Carretero and co-workers to be an efficient directing group for the Fujiwara-Moritani reaction: the (2-pyridyl)sulfonyl framework. The versatility and usefulness of this moiety lies not only on its capability of efficiently coordinating the palladium center, but also on the fact that it can be easily removed and derivatized.

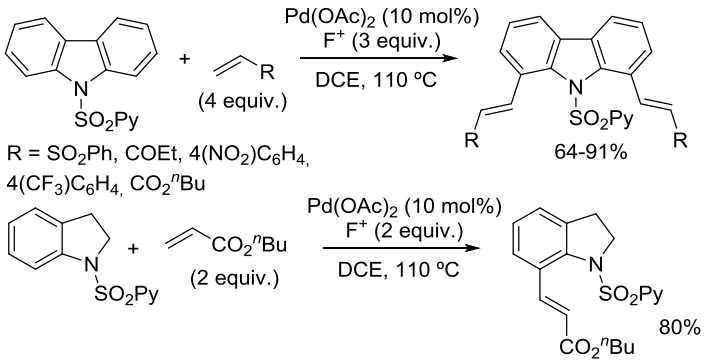
They initially utilized this group in the intermolecular Fujiwara-Moritani reaction with the aim of carrying out the directed C-2 alkenylation of indoles with different olefin coupling partners.[42] The methodology was also found effective for the mono- and di-alkenylation of the pyrrole nucleus (Scheme 2.24).



Scheme 2.24

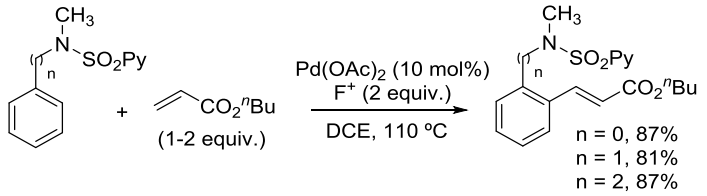
Furthermore, in 2013 they could apply this *N*-protecting/directing group to the *ortho*-di-olefination of different carbazole units. In this work they also proved to be capable of functionalizing the indoline framework (Scheme 2.25).[43]

[42] a) García-Rubia, A.; Gómez-Arrayás, R.; Carretero, J.C. *Angew. Chem. Int. Ed.* **2009**, *48*, 6511; b) García-Rubia, A.; Urones, B.; Gómez-Arrayás, R.; Carretero, J.C. *Chem. Eur. J.* **2010**, *16*, 9676.
[43] Urones, B.; Gómez-Arrayás, R.; Carretero, J.C. *Org. Lett.* **2013**, *15*, 1120.



Scheme 2.25

However, the herein commented scaffold is not limited to allowing the directed olefination of heteroaromatic rings. In this context, it has been possible to alkenylate *via* the intermolecular oxidative Heck reaction different benzene derivatives with the aid of the (2-pyridyl)sulfonyl group.[44] The present functionality could be used as the *N*-protecting group of a variety of anilines, acting as the director for the C-H olefination event and providing the corresponding *ortho*-alkenylated arenes. The transformation could be further extended to the functionalization of benzylamines and β-arylethylamines (Scheme 2.26).[45]



Scheme 2.26

Recently, this framework has been utilized as the *N*-protecting/directing group in different 2-arylpyrrolidines, promoting the alkenylation of the arene attached to the pyrrolidine scaffold at the *ortho* position (Scheme 2.27).[46]

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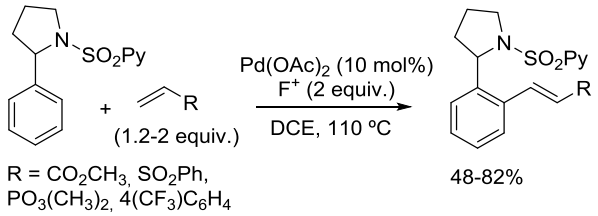
[44] a) García-Rubia, A.; Laga, E.; Cativiela, C.; Urriolabeitia, E.P.; Gómez-Arrayás, R.; Carretero, J.C. *J. Org. Chem.* **2015**, *80*, 3321; b) Legarda, P.D.; García-Rubia, A.; Gómez-Arrayás, R.; Carretero, J.C. *Adv. Synth. Catal.* **2016**, *358*, 1065.

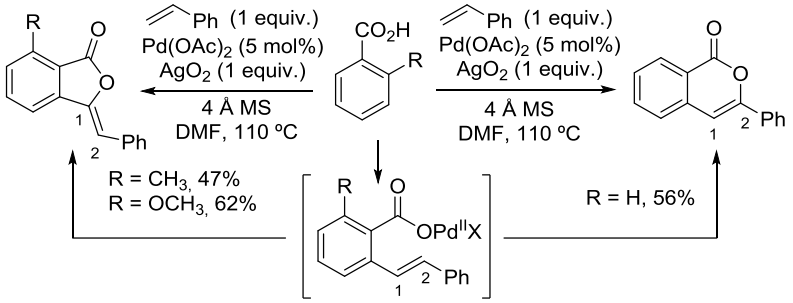
[45] García-Rubia, A.; Urones, B.; Gómez-Arrayás, R.; Carretero, J.C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10927.

[46] Legarda, P.D.; García-Rubia, A.; Gómez-Arrayás, R.; Carretero, J.C. *Tetrahedron* **2018**, *74*, 3947.



Scheme 2.27

There are other several directors beyond those amide-based auxiliary groups that can be efficiently utilized for the site-selective functionalization of a variety of (hetero)arenes. One of those privileged moieties are carboxylic acids. These scaffolds have been widely used in the transition-metal catalyzed functionalization or aromatic rings, sometimes as traceless directing groups.[47] For instance, Lee *et al.* could carry out the Pd(II)-catalyzed alkenylation of different benzoic acids with styrenes, followed by *in situ* lactonization of the obtained products through intramolecular Wacker reactions. It was seen that in the case of *ortho*-substituted benzoic acids, a 5-*exo*-trig intramolecular Wacker reaction took place (attack to the C1 carbon on the olefin) to form the corresponding 3-benzylidenephthalides. Otherwise, when no *ortho*-substituent was placed on the benzoic acids, the Wacker reaction proceeded *via* a 6-*endo*-trig cyclization (attack to the C2 carbon on the olefin) to give different isocoumarins (Scheme 2.28).[48] This was reasoned to happen due to the steric hindrance between the carboxylate directing group and the adjacent substituent, which precludes the attack towards the distal C2 carbon of the newly inserted alkene moiety.

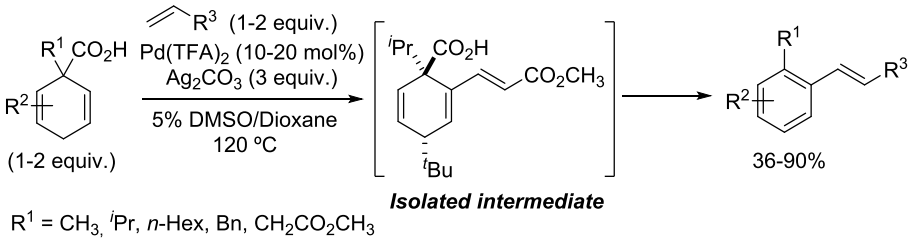


Scheme 2.28

[47] a) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett*. **2008**, *10*, 1159; b) Drapeau, M.P.; Gooßen, L.J.; *Chem. Eur. J.* **2016**, *22*, 18654; c) Font, M.; Quibell, J.M.; Perry, G.J.P.; Larrosa, I. *Chem. Commun.* **2017**, *53*, 5584.

[48] Nandi, D.; Gosh, D.; Chen, S.-J.; Kuo, B.-C.; Wang, N.M.; Lee, H.M. *J. Org. Chem.* **2013**, *78*, 3445.

In 2018, Chou, Huang and Tsai reported a procedure for the carboxylate-directed olefination of a range of dearomatized benzoic acids with acrylates and styrenes, to provide the corresponding vinylarenes after a Fujiwara-Moritani coupling followed by rearomatization upon decarboxylation (Scheme 2.29).[49] They observed that in all the cases the corresponding mono-alkenylated products were obtained.



R^1 = CH_3, ^{i}Pr, *n*-Hex, Bn, $CH_2CO_2CH_3$
R^2 = H, 2-CH_3, 3-CH_3, 4-^{t}Bu
R^3= CO_2CH_3, $CO_2{}^i$Bu, Ph, 4$(OCH_3)C_6H_4$, 4$(NO_2)C_6H_4$

Scheme 2.29

Different experiments were conducted to elucidate which of the two metals present in the reaction was responsible for the decarboxylation/aromatization step. The results obtained showed that both of them were necessary for that event, suggesting that the Pd/Ag bimetallic system played a key role in the tandem decarboxylative C-H olefination process followed by rearomatization.

[49] Tsai, H.-C.; Huang, Y.-H.; Chou, C.-M. *Org. Lett.* **2018**, *20*, 1328.

1.3. Regioselectivity driven by ligand assistance

As it can be observed in the examples given throughout this section, some of the greatest problems of the Fujiwara-Moritani coupling are: 1) in the case of electronic control, the low regioselectivity provided by the arene substrate and the narrow scope of the aromatic coupling partners, and 2) in the case of directing-group control, not all the directors can be completely and efficiently removed, leading to the presence of undesired moieties in the products. In this sense, the development of ligands for the oxidative Heck reaction is very interesting, since, although in some cases directing groups are required, they are able to help chemists address site-selectivity, reactivity and scope issues.[50] Two main classes of ligands are mostly used nowadays: pyridine-based ligands and mono-protected amino acids (MPAA), both of which can be efficiently used in the non-directed (without directing groups) or directed (with directing groups) Fujiwara-Moritani reaction and examples of those cases will be herein disclosed.

1.3.1. Non-directed ligand-assisted Fujiwara-Moritani reaction

In the past decade, many efforts have been devoted to the development of methods for the olefination of different arenes under ligand assistance without the aid of directing groups.[51] With this in mind, Sanford and co-workers studied the use of simple pyridine derivatives as ligands for the Pd(II) center to modulate reactivity and site-selectivity.[52] In 2012, they applied those additives to the Pd(II)-catalyzed intermolecular alkenylation of simple arenes, and found that those type of ligands had influence not only in the efficiency and the rate of the reaction, but also in the positional selectivity of the C-H activation step.[53] In this work, the use of different pyridines was studied, observing that the effect of these ligands in the reactivity of the metal center can highly depend on the oxidant utilized.

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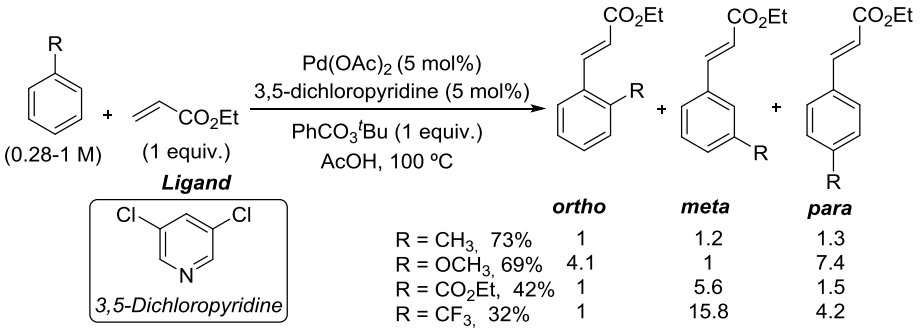
[50] Engle, K.M.; Yu, J.-Q. *J. Org. Chem.* **2013**, *78*, 8927.

[51] a) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072; b) Cong, X.; Tang, H.; Wu, C.; Zeng, X. *Organometallics* **2013**, *32*, 6565; c) Piotrowicz, M.; Zakrzewski, J. *Organometallics* **2013**, *32*, 5709; d) Lee, W.-C.; Wang, T.-H.; Ong, T.-G. *Chem. Commun.* **2014**, *50*, 3671; e) Huang, Q.; Zhang, X.; Qiu, L.; Wu, J.; Xiao, H.; Zhang, X.; Lin, S. *Adv. Synth Catal.* **2015**, *357*, 3753; f) Piotrowicz, M.; Zakrzewski, J.; Métivier, R.; Brosseau, A.; Makal, A.; Woźniak, K. *J. Org. Chem.* **2015**, *80*, 2573; g) Han, S.J.; Kim, H.T. ; Joo, J.M. *J. Org. Chem.* **2016**, *81*, 689; h) Kim, H.T.; Ha, H.; Kang, G.; Kim, O.S.; Ryu, H.; Biswas, A.K.; Lim, S.M.; Baik, M.-H.; Joo, J.M. *Angew. Chem. Int. Ed.* **2017**, *56*, 16262; i) Yu, J.; Yang, X.; Wu, C.; Su, W. *J. Org. Chem.* **2020**, *85*, 1009.

[52] Emmert, M.H.; Cook, A.K.; Xie, Y.J. Sanford, M.S. *Angew. Chem. Int. Ed.* **2011**, *50*, 9409.

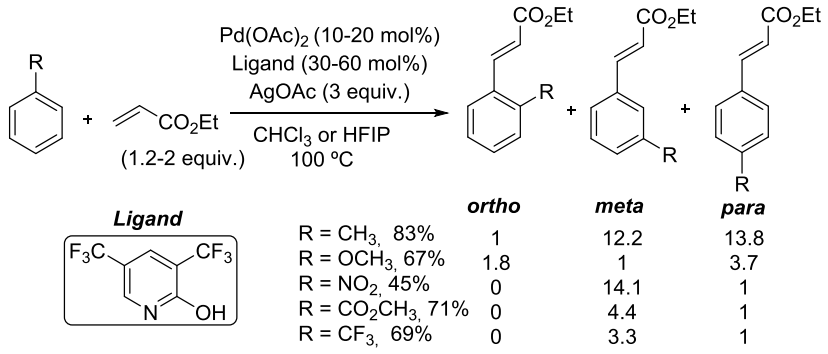
[53] Kubota, A.; Emmert, M.H.; Sanford, M.S. *Org. Lett.* **2012**, *14*, 1760.

According to their studies, the ideal palladium to ligand ratio was 1:1 and, as it was expected, the regioselectivity observed for those couplings was consistent with that one observed in the electrophilic aromatic substitution (Scheme 2.30).



Scheme 2.30

Following with the use of this kind of ligands, Yu and co-workers made an outstanding contribution to the field of the non-directed ligand-assisted Fujiwara-Moritani coupling. In 2017, they disclosed the employment of 2-pyridone-based ligands for the non-directed site-selective Pd(II)-catalyzed C-H alkenylation of simple arenes and heteroarenes, utilizing the aromatic substrate as the limiting reagent and electron-deficient alkenes as the coupling partners. The corresponding olefinated products were obtained in good yields even when highly electron-deficient arenes were used (Scheme 2.31).[54]



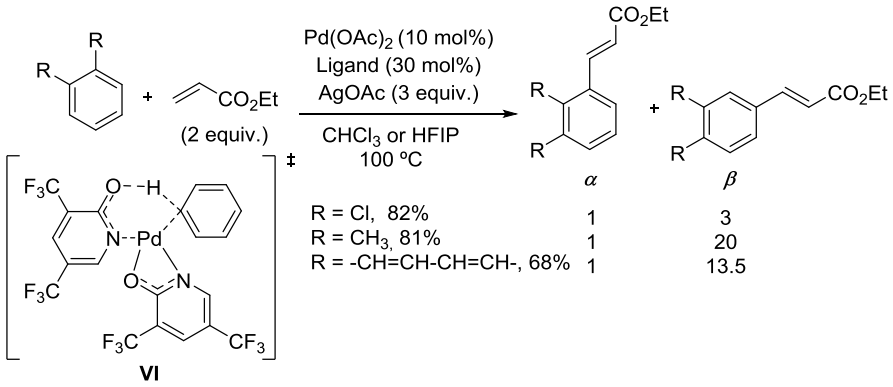
Scheme 2.31

[54] Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J.X.; Tao, S.; Cheng, P.T.W.; Poss, M.A.; Farmer, M.E.; Yeung, K.-S.; Yu, J.-Q. *Nature* **2017**, *551*, 489.

In all the cases the mono-olefinated products were provided; however, when highly reactive substrates were subjected to the reaction conditions, small quantities of the di-olefinated products were obtained. In those cases, they observed that changing the solvent from HFIP to $CHCl_3$ could reduce the amount of di-alkenylated product obtained. Apart from that, it was seen that the site-selectivity was mainly governed by the electronic and steric effects of the arene starting material, being the influence of sterics enhanced by the pyridone ligand.

In order to understand the role of the ligand, they carried out a deep study (kinetic-isotope effect, DFT…) and it was found that two pyridone ligands would coordinate to the Pd(II) in the C-H activation event, which is the rate-limiting step, one of them acting as an internal base (**VI**) in a CMD mechanism. The experiments carried out suggested that the ligand has two different roles in the reaction: 1) it increases the initial reaction rate and 2) stabilizes the metal center by forming more stable complexes, preventing catalyst decomposition. This stabilization is thought to be crucial to maintain the efficiency of the catalytic system.

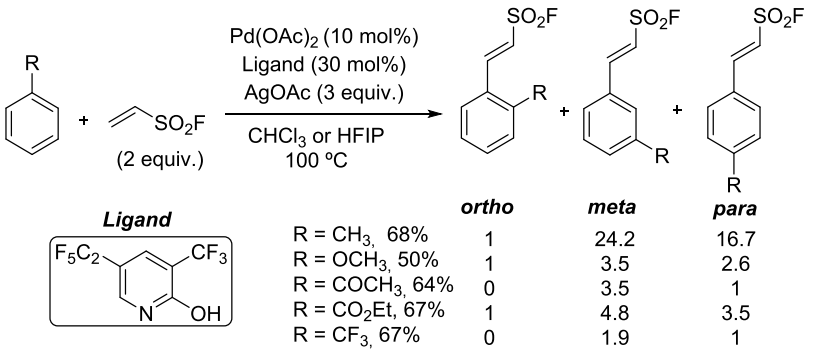
This ligand was also utilized in the coupling between di-substituted arenes and ethyl acrylate. Curiously, when naphthalene was used as the substrate, a considerable site-selectivity was appreciated towards the β position instead of the α one, what is in contraposition to the usual regioselectivity of the classic Friedel-Crafts reaction (Scheme 2.32).[55]



Scheme 2.32

[55] Li, B.; Gao, L.; Bian, F.; Yu, W. *Tetrahedron Lett.* **2013**, *54*, 1063.

Based on this work, they used those newly-developed ligands to tackle the synthesis of β-arylethenesulfonyl fluorides (Scheme 2.33).[56]



Scheme 2.33

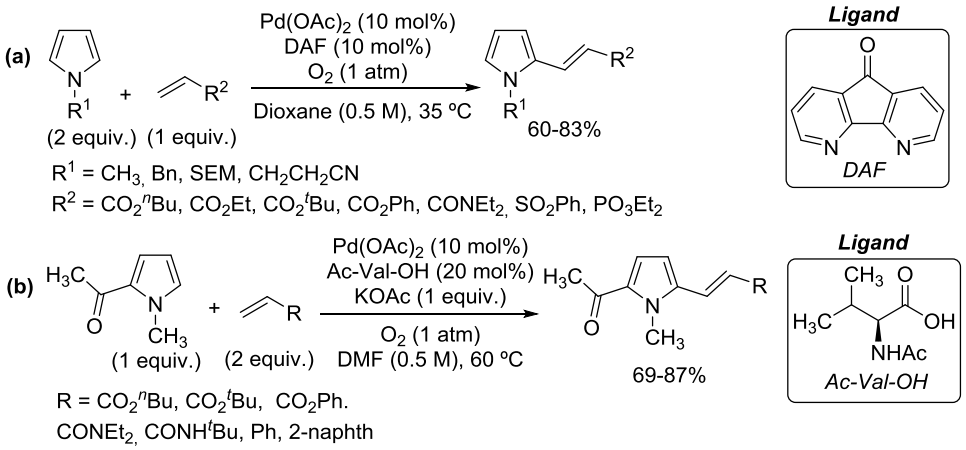
With that purpose in mind, they were able to develop a method for the non-directed ligand-driven alkenylation of arenes using ethane-sulfonyl fluoride as the olefin coupling partner. After an optimization of the reaction conditions and a study of different ligands, they observed that the olefination, in most cases, took place preferentially at the *meta*-position, even when electron-donating substituents were present. This unnatural regioselectivty is thought to be due to the unique properties of ethane-sulfonyl fluoride, which may be acting as a ligand. Poly-functionalized aromatic rings and even some heterocycles could be functionalized employing this method.

The use of ligands for the non-directed oxidative Heck coupling can also be applied to the functionalization of heterocycles. In 2018, Joo and co-workers reported the regioselective alkenylation of pyrroles at C-2 or C-5, using a different ligand for each case.[57] They observed that DAF (4,5-diazafluoren-9-one) additive could efficiently promote a highly selective C-2 mono-alkenylation of differently *N*-substituted pyrroles (Scheme 2.34a); while, when employing 2-acylpyrroles as substrates, the use of a MPAA, along with a stoichiometric base, allowed them to carry out the transformation selectively at C-5 (Scheme 2.34b).

They based the explanation for the different site-selectivity provided by the ligands on the electronic properties of the initial pyrrole: when the substrate is a simple *N*-substituted pyrrole, due to its electron-rich nature, an electron-deficient ligand (DAF) that is capable of

[56] Chen, X.-Y.; Wu, Y.; Zhou, J.; Wang, P.; Yu, J.-Q. *Org. Lett.* **2019**, *21*, 1426.
[57] Kim, H.T.; Lee, W.; Kim, E.; Joo, J.M. *Chem. Asian J.* **2018**, *13*, 2418.

making the Pd(II) center more electrophilic would be beneficial, promoting functionalization at the most nucleophilic C-2 position. Besides, the presence of an electron-withdrawing functionality within the pyrrole nucleus at C-2 would increase the acidity of the C(5)-H bond. Thus, the utilization of bases as ligands (Ac-Val-OH and a stoichiometric amount of KOAc) would promote the site-selective C-H activation at that position.



Scheme 2.34

1.3.2. Directed ligand-assisted Fujiwara-Moritani reaction

This is the most common scenario when ligand-aided Pd(II)-catalyzed alkenylations are carried out, and thus, several ligands have been utilized combined with different directing groups. In those cases, the ligand has to be carefully designed:[2] if the substrate contains a too-strongly-coordinating directing group, the coordination of the ligand to the metal center would be avoided (Figure 2.3a).

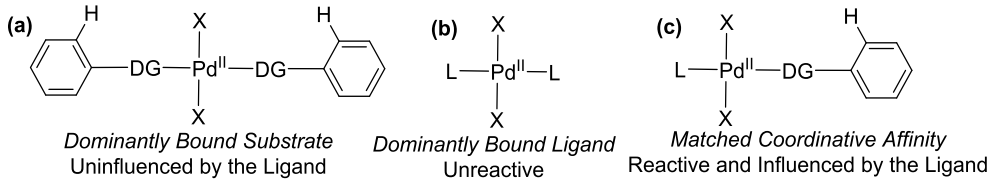


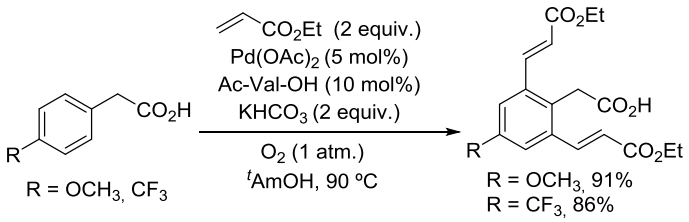
Figure 2.3

However, if the ligand is coordinated too strongly to the palladium, the directing group would not be able to perform its work (Figure 2.3b). Therefore, the design of a ligand that is capable of generating a pre-transition state where the Pd(II) is coordinated to one molecule of the ligand and one molecule of the substrate is utterly desirable (Figure 2.3c).

With these precepts in mind, several procedures have been developed for the alkenylation of a variety of arenes.[58] For instance, Yu´s group developed a wide variety of *N*-monoprotected amino acids[9b] that are capable of coordinating to the Pd(II) center in the C-H activation step, enhancing its efficiency and the rate of the process.[59]

When trying to prepare unsymmetrically di-alkenylated phenylacetic acids taking advantage of the Fujiwara-Moritani reaction, they realized that after the first C-H olefination event low conversions were achieved for the second functionalization process under the same reaction conditions. This reactivity issue could be addressed by developing more efficient catalytic systems, utilizing for that purpose MPAA ligands.[60]

They studied the effect of several of those additives and found that they could smoothly promote the di-alkenylation of phenylacetic acids containing not only electron-donating substituents, but also electron-withdrawing functionalities, using *N*-acetylvaline (Ac-Val-OH) as the optimal ligand (Scheme 2.35).[60]



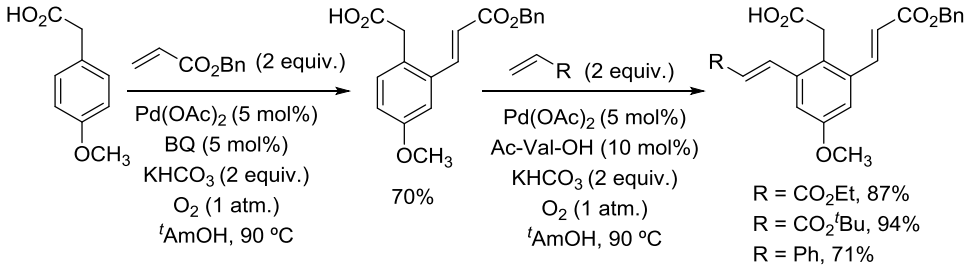
Scheme 2.35

[58] For selected examples, see: a) Huang, C.; Chattopadhyay, B.; Gevorgyan, V. *J. Am. Chem. Soc.* **2011**, *133*, 12406; b) Pi, C.; Li, Y.; Cui, X.; Zhang, H.; Han, Y.; Wu, Y. *Chem. Sci.* **2013**, *4*, 2675; c) Cong, X.; You, J.; Gao, G.; Lan, J. *Chem. Commun.* **2013**, *49*, 662; d) Li, S.; Ji, H.; Cai, L.; Li, G. *Chem. Sci.* **2015**, *6*, 5595; e) Kim, K.; Vasu, D.; Im, H.; Hong, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 8652; f) Liang, Q.-J.; Jiang, B.; Xu, Y.-H.; Loh, T.-P. *J. Org. Chem.* **2018**, *83*, 8265; g) Chen, J.; Xu, J.; Zhou, Y.; Xie, S.; Gao, F.; Xu, X.; Xu, X.; Jin, Z. *Org. Lett.* **2019**, *21*, 7928; h) Fu, X.; Yang, J.; Deng, K.; Shao, L.; Xia, C.; Ji, Y. *Org. Lett.* **2019**, *21*, 3505.

[59] For selected reviews, see: a) Ref. 9; b) Ref. 50; c) Engle, K.M. *Pure Appl. Chem.* **2016**, *88*, 119; d) Shao, Q.; Wu, K.; Zhuang, Z.; Qian, S.; Yu, J.-Q. *Acc. Chem. Res*. **2020**, *53*, 833.

[60] Engle, K.M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2010**, *49*, 6169.

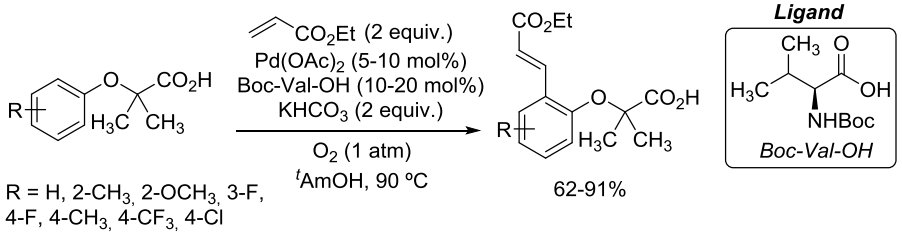
Besides, they were also able to design a sequential protocol for the installation of two different alkenes, utilizing bezoquinone as ligand in the first step and Ac-Val-OH in the second one (Scheme 2.36).[60]



Scheme 2.36

In 2013, this same group disclosed an interesting method for the olefination of α-phenoxyacetic acids that, upon removal of the acetic acid directing group, could be formally considered as an efficient *ortho*-functionalization of phenols. Despite the problems associated to this kind of substrates (coordination of the Pd(II) center to both the carboxylate and the α-oxygen, as well as the long distance between the carboxylate coordination point and the *ortho* C-H site), Yu´s group was able to develop a procedure to carry out the *ortho* mono-functionalization reaction using ethyl acrylate as the coupling partner (Scheme 2.37).[61]

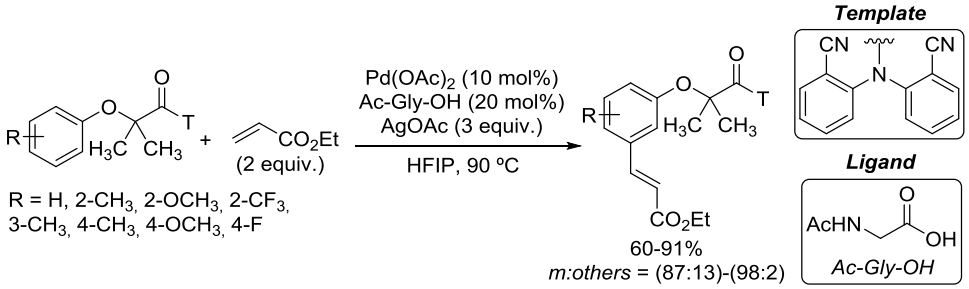
It was observed that the mono-selectivity was due to the bulkiness provided by the α,α-dimethyl groups of the director. Besides, their absence heavily hampered the outcome of the reaction, owing to the fact of losing the favorable Thorpe-Ingold effect.



Scheme 2.37

[61] Dai, H.-X.; Li, G.; Zhang, X.-G.; Stepan, A.F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 7567.

Encouraged by those results, they decided to accomplish the *meta*-functionalization of those substrates by changing the tethered CO_2H directing group with a removable nitrile-based template. That way, the substrates underwent *meta*-mono-alkenylation (irrespective of the electronic properties of the arene) with a high selectivity, although in some cases a small amount of the di-olefinated product was obtained (Scheme 2.38). In conclusion, in this work, Yu´s group was able to design a method for the formal *ortho*- and *meta*-selective functionalization of phenols.[61]



Scheme 2.38

Throughout the last years, beyond the development of several *meta*-selective functionalization reactions,[62] *para*-directed olefinative couplings have also been reported using different directing groups, with the aid of MPAAs.[63] In this sense, Maiti and co-workers could achieve the formal *para*-olefination of phenol derivatives with relatively high selectivity (employing electron-deficient olefins as coupling partners) by designing a removable silyl-biphenyl template (Scheme 2.39).[64]

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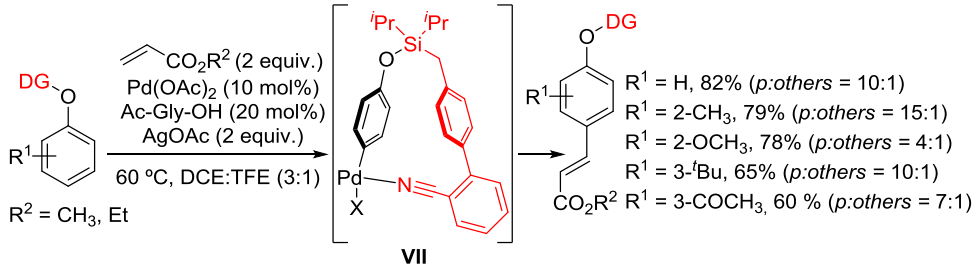
[62] a) Bera, M; Modak, A.; Patra, T.; Maji, A.; Maiti, D. *Org. Lett.* **2014**, *16*, 5760; b) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 10807; c) Bera, M.; Maji, A.; Sahoo, S.K.; Maiti, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 8515; d) Chu, L.; Shang, M.; Tanaka, K.; Chen, Q.; Pissarnitski, N.; Streckfuss, E.; Yu, J.-Q. *ACS Cent. Sci.* **2015**, *1*, 394; e) Li, S.; Cai, L.; Ji, H.; Yang, L.; Li, G. *Nat. Commun* **2016**, *7*, 10443; f) Maity, S.; Hoque, E.; Dhawa, U.; Maiti, D. *Chem. Commun.* **2016**, *52*, 14003; g) Patra, T.; Watile, R.; Agasti, S.; Naveen, T.; Maiti, D. *Chem. Commun.* **2016**, *52*, 2027; h) Bera, M.; Sahoo, S.K.; Maiti, D. *ACS Catal.* **2016**, *6*, 3575; i) Zhang, L.; Zhao, C.; Liu, Y.; Xu, J.; Xu, X.; Jin, Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 12245; j) Dutta, U.; Modak, A.; Bhaskararao, B.; Bera, M. Bag, S.; Mondal, A.; Lupton, D.W.; Sunoj, R.B.; Maiti, D. *ACS Catal.* **2017**, *7*, 3162; k) Bag, S.; Jayarajan, R.; Mondal, R.; Maiti, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 3182; l) Yang, G.; Zhu, D.; Wang, P.; Tang, R.-Y.; Yu, J.-Q. *Chem. Eur. J.* **2018**, *24*, 3434.

[63] a) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D. *J. Am. Chem. Soc.* **2015**, *137*, 11888; b) Ref. 27l.

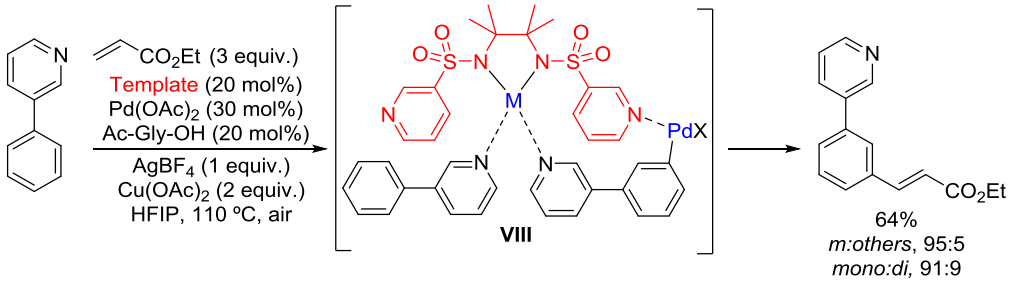
[64] Patra, T.; Bag, S.; Kancherla, R.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A.; Maiti, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 7751.

This directing group proved to be capable of overriding the site selectivity driven by the electronic properties of the substrate: to prove so, electron-withdrawing functionalities were placed in the *meta*-position relative to the -ODG group, also affording the *para*-alkenylated products. Furthermore, *para*-selective olefination could also be accomplished when bulky substituents were placed in the *meta*-site. This class of reaction is proposed to proceed through palladacycle **VII**.[65]



Scheme 2.39

Although this type of templates provide an effective method for the functionalization of distal C-H bonds, the main drawback lies on the fact that they are covalently bonded to the substrate, meaning that a specific functional group is required to anchor those directing groups to the starting molecule. With the aim of overriding this disadvantage, Yu´s group developed a template capable of directing the *meta*-C-H functionalization through a reversible coordination with an heterocyclic substrate (Scheme 2.40).[66]

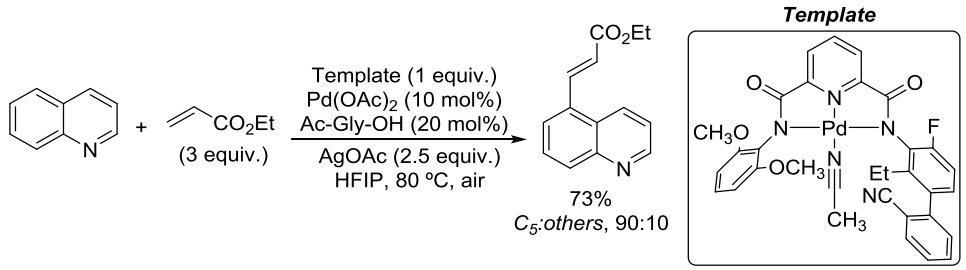


Scheme 2.40

[65] Maji, A.; Guin, S.; Feng, S.; Dahiya, A.; Singh, V.K.; Liu, P.; Maiti, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 14903.
[66] Zhang, Z.; Tanaka, K.; Yu, J.-Q. *Nature* **2017**, *543*, 538.

To achieve this, a bifunctional template, which was able to coordinate two different metal centers, was designed. Thus, one metal center could allow the binding of the template with the substrate and the other one could promote the C-H cleavage (**VIII**). Employing this directing backbone they were able to carry out the intermolecular *meta*-olefination of different 3-phenylpyridine derivatives with electron deficient alkenes, using a MPAA as ligand.

On the other hand, they also tried to carry out the C-5 alkenylation of quinolines using the optimized protocol, but it proved to be inefficient. The design of new templates was found to be necessary and stoichiometric amounts of the preassembled complex had to be added instead of catalytic quantities of the free template. That way, the corresponding 5-alkenylated quinolines were obtained in moderate to good yields (Scheme 2.41).[66] This method could also be applied to the remote functionalization of quinoxaline, benzoxazole and benzothiazole. The preassembled template could be recovered upon treatment with first, DMAP and then, methanesulfonic acid in acetonitrile. Furthermore, Maiti and co-workers were able to employ this methodology for the C-5 olefination of thiazoles.[67]

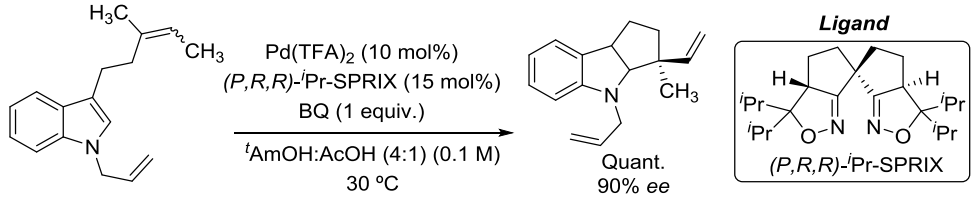


Scheme 2.41

[67] Achar, T.K.; Biswas, J.P.; Porey, S.; Pal, T.; Ramakrishna, K.; Maiti, S.; Maiti, D. *J. Org. Chem.* **2019**, *84*, 8315.

1.4. Enantioselective Fujiwara-Moritani reaction

Although it is beyond the scope of this thesis, the ligand-mediated Fujiwara-Moritani reaction has also been employed to achieve the enantioselective alkenylation of different framenworks.[68] For instance, with regard to the non-directed ligand-mediated oxidative Heck coupling, in 2017 Sasai *et al.* developed an optimization of the reaction conditions for the previously reported enantioselective cyclization of 3-alkenylindole, which had been disclosed by Oestreich.[69] It was found that the use of a SPRIX ligand, with two isoxazoline moieties that act as weak coordination sites, could generate an electrophilic Pd(II)-SPRIX catalytic system, which was able to promote the intramolecular C-H alkenylation process with good yields and enantiomeric excesses (Scheme 2.42).[70]



Scheme 2.42

During the study of the reaction, it was observed that the presence of an allyl functionality as the *N*-protecting group was necessary for the obtainment of high enantioselectivities in an efficient manner. Furthermore, when that group was changed with a *N*-propyl group, the corresponding product was furnished in lower yields and enantiomeric excesses. Poor results were also achieved using homoallyl and prenyl groups attached to the nitrogen atom. This could mean that the allyl moiety provides a weak and reversible coordination for

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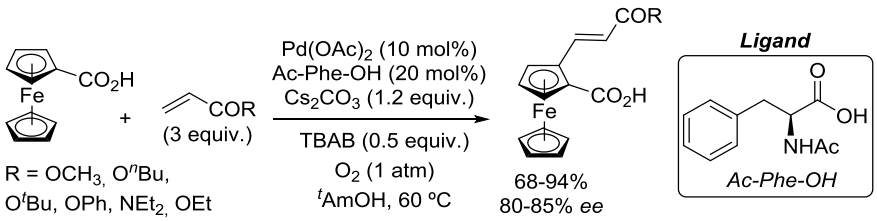
[68] a) Mikami, K.; Hatano, M.; Terada, M. *Chem. Lett*. **1999**, *28*, 55; b) Shi, B.-F.; Zhang, Y.-H.; Lam, J.K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460; c) Wang, S.-G.; You, S.-L. Asymmetric Cross-Dehydrogenative Coupling (CDC) Reactions. In *Asymmetric Functionalization of C-H Bonds*; You, S.-L., Ed.; RSC: London, 2015; p 67; d) Li, S.-X.; Ma, Y.-N.; Yang, S.-D. *Org. Lett.* **2017**, *19*, 1842; e) Zhu, Y.-C.; Li, Y.; Zhang, B.-C.; Zhang, F.-X.; Yang, Y.-N.; Wang, X.-S. *Angew. Chem. Int. Ed.* **2018**, *57*, 5129; f) Sun, Q.-Y.; Ma, W.-Y.; Yang, K.-F.; Cao, J.; Zheng, Z.-J.; Xu, Z.; Cui, Y.-M.; Xu, L.-W. *Chem. Commun.* **2018**, *54*, 10706; g) Lin, Y.; Ma, W.-Y.; Xu, Z.; Zheng, Z.-J.; Cao, J.; Yang, K.-F.; Cui, Y.-M.; Xu, L.-W. *Chem. Asian J.* **2019**, *14*, 2082; h) Song, H.; Li, Y.; Yao, Q.-J.; Jin, L.; Liu, L.; Liu, Y.-H.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2020**, *59*, 6576; i) Zhan, B.-B.; Wang, L.; Luo, J.; Lin, X.-F.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2020**, *59*, 3568.

[69] a) Schiffner, J.A.; Machotta, A.B.; Oestreich, M. *Synlett* **2008**, 2271; b) Schiffner, J.A.; Wöste, T.H.; Oestreich, M. *Eur. J. Org. Chem*. **2010**, 174.

[70] Abozeid, M.A.; Sairenji, S.; Takizawa, S.; Fujita, M.; Sasai, H. *Chem. Commun.* **2017**, *53*, 6887.

the palladium center. Besides, it was found that both reactivity and enantioselectivity were highly influenced by the geometry of the starting olefin. When a *Z*-enriched substrate was subjected to the reaction conditions, better results were obtained compared to those ones provided when an *E*-enriched starting material was employed. Finally, the kinetic isotope experiments run, suggested that the C-H activation of the indole framework was the rate-determining step.

Moving to an example of directed ligand-assisted Fujiwara-Moritani reaction, Wu and co-workers have recently disclosed an elegant method for the enantioselective oxidative Heck alkenylation of ferrocenecarboxylic acid, employing the carboxylate group present in the molecule as director and *N*-acetyl-L-phenylalanine as the optimal ligand. Under the optimized reaction conditions, the corresponding olefinated ferrocenecarboxylic acids were provided in good yields and good enantiomeric excesses (Scheme 2.43).[71]



Scheme 2.43

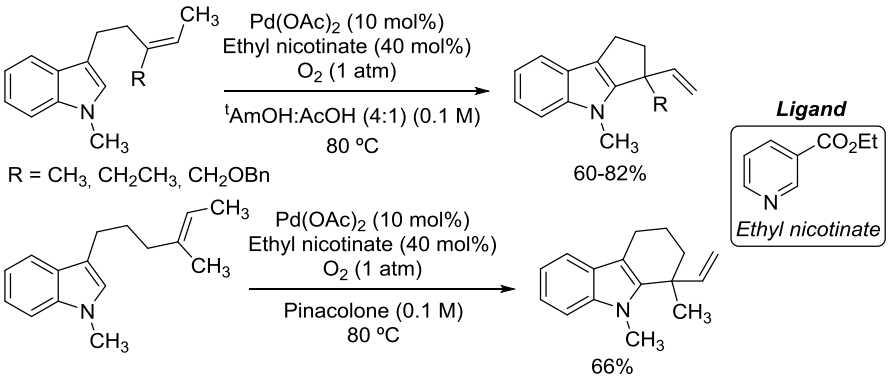
When carrying out the screening of the MPAA additive, they found out that the *N*-protecting group played a crucial role in the reactivity and selectivity of this transformation, observing that bulky functionalities led to lower yield and enantioselectivities.

Apart from that, after running some experiments, they observed that an oxygen atmosphere was necessary for the reaction to proceed well, since when the coupling was run under nitrogen atmosphere, the product was obtained in a lower yield. Furthermore, ferrocenium carboxylic acid was detected through high-resolution ESI-FTMS. This two findings suggest that oxygen reacts with ferrocene to give the detected species, which is thought to be the responsible for reoxidating the Pd(0) formed in the course of the reaction to the catalytically active Pd(II).

[71] Huang, Y.; Pi, C.; Cui, X.; Wu, Y. *Adv. Synth. Catal.* **2020**, *362*, 1385.

1.5. Intramolecular Fujiwara-Moritani reaction

Although the intermolecular Fujiwara-Moritani reaction has been extensively studied and investigated in the last decades, its intramolecular variant is still relatively underexplored and mainly focused on the use of electron-rich heteroaromatic rings, such as indoles.[72] In this regard, in 2003, Ferreira and Stoltz combined the use of this framework, bearing a butenyl chain tethered to the C-3 position, with the utilization of pyridine-based ligands to achieve an intramolecular aerobic Pd(II)-catalyzed C-H alkenylation reaction, leading to the formation of 5-membered rings *via* 5-*exo*-trig processes (Scheme 2.44).[73]



Scheme 2.44

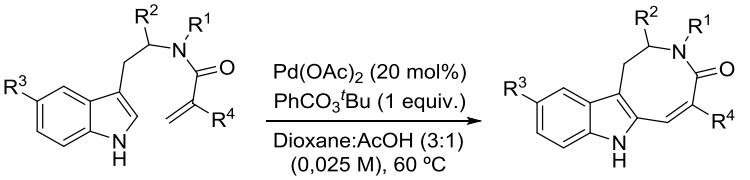
Interestingly, when the length of the alkenyl chain was increased, the corresponding 6-*exo*-trig cyclization could be attained for the construction of a 6-membered ring having a quaternary center (Scheme 2.44).

Additionally, thanks to the versatility of the intramolecular oxidative Heck coupling, the assembly of bigger cycles has also been possible. In 2019, Liu and co-workers described an interesting method for the synthesis of eight-membered rings, allowing the construction of

[72] a) Baran, P.S.; Corey, E.J. *J. Am. Chem. Soc.* **2002**, *124*, 7904; b) Abbiati, G.; Beccalli, E.M.; Broggini, G.; Zoni, C. *J. Org. Chem.* **2003**, *68*, 7625; c) Liu, C.; Widenhoefer, R.A. *J. Am. Chem. Soc*. **2004**, *126*, 10250; d) Kong, A.; Han, X.; Lu, X. *Org. Lett*. **2006**, *8*, 1339; e) Han, X.; Lu, X. *Org. Lett*. **2009**, *11*, 2381; f) Donets, P.A.; Van der Eycken, E.V. *Synthesis* **2011**, *13*, 2147; g) Kandukuri, S.R.; Schiffner, J.A.; Oestreich, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 1265; h) Agy, A.C.; Rodrigues, M.T.; Zeoly, L.A.; Simoni, D.A.; Coelho, F. *J. Org. Chem.* **2019**, *84*, 5564.

[73] a) Ferreira, E.M.; Stoltz, B.M. *J. Am. Chem. Soc.* **2003**, *125*, 9578; b) Ferreira, E.M.; Zhang, H.; Stoltz, B.M. *Tetrahedron* **2008**, *64*, 5987.

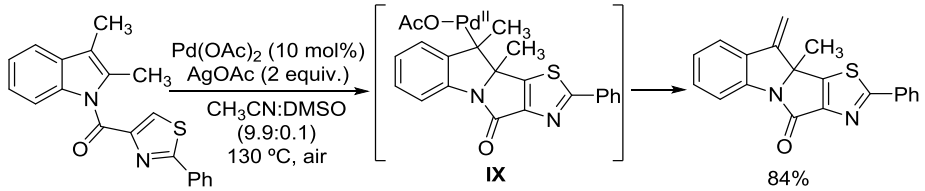
the indoloazocine framework. This coupling occurred *via* an unusual 8-*endo*-trig cyclization starting from acrylated tryptamides (Scheme 2.45).[74]



R^1 = CH_3, Bn, PMB; R^2 = H, CO_2CH_3
R^3 = H, OCH_3, CH_3, Cl; R^4 = H, CH_3, Bn, $CH_2CO_2CH_3$

Scheme 2.45

In 2016, Yao and Lin described a curious intramolecular Fujiwara-Moritani reaction of indoles bearing a thiazole framework, in which the indole core did not act as the moiety to be alkenylated, but as the olefin counterpart. That way, a dearomative 5-*exo*-trig oxidative cyclization took place for the synthesis of thiazol-fused pyrrolidinones, which would proceed through intermediate **IX** to furnish the product after β-hydride elimination (Scheme 2.46).[75]

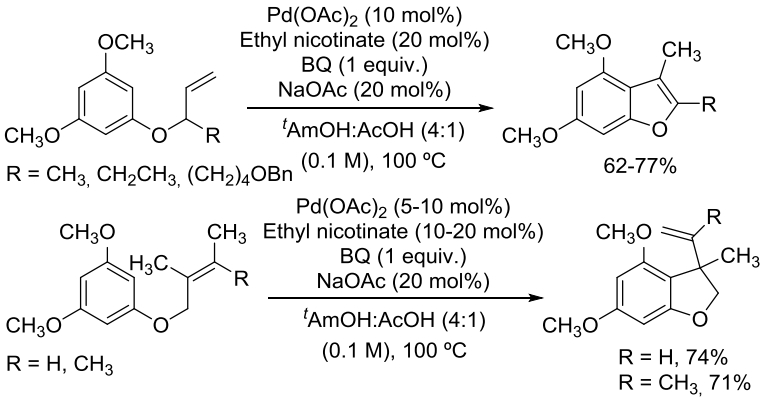


Scheme 2.46

Although heteroaromatic frameworks are common substrates in this intramolecular oxidative coupling, different benzene derivatives bearing electron-rich arenes have efficiently undergone the present alkenylative cyclization. For example, in 2005, following with their work on the intramolecular Fujiwara-Moritani reaction, Stoltz and co-workers carried out the Pd(II)-catalyzed 5-*exo*-trig oxidative cyclization of a variety of allyl phenyl ethers. With the assistance of pyridine ligands, they were able to synthesize a variety of benzofurans and 2,3-dihydrobenzofurans (Scheme 2.47).[76,73b] According to experiments

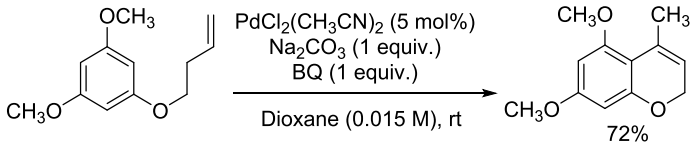
[74] Zhao, P.; Huang, Z.-Y.; Zhao, C.-S.; Liu, S. *J. Heterocyclic Chem.* **2019**, *56*, 108.
[75] Gao, S.; Yang, C.; Huang, Y.; Zhao, L. ; Wu, X.; Yao, H.; Lin, A. *Org. Biomol. Chem.* **2016**, *14*, 840.
[76] Zhang, H.; Ferreira, E.M.; Stoltz, B.M. *Angew. Chem. Int. Ed.* **2004**, *43*, 6144.

carried out by the authors, this transformation is proposed to proceed through arene palladation, followed by migratory insertion onto the olefin and β-hydride elimination.



Scheme 2.47

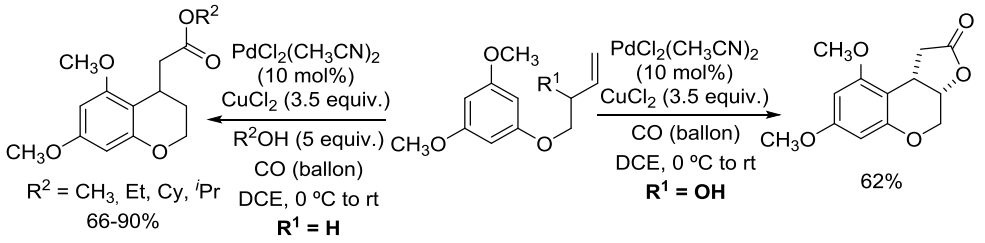
Similarly, Youn and Eom described the synthesis of different chromenes starting from the corresponding electron-rich phenyl homoallyl ethers (Scheme 2.48)[77] *via* an intramolecular 6-*exo*-trig oxidative Heck reaction, followed by isomerization of the double bond from the exocyclic to the endocyclic position. In this case, the reaction is proposed to proceed through the coordination of the palladium(II) center to the alkene, followed by the nucleophilic attack of the aromatic ring to the activated olefin moiety. The alkyl-Pd(II) species formed would evolve to the product by means of β-hydride elimination.



Scheme 2.48

In 2015, the carbonylative 6-*exo*-trig cyclization of different aryl butenyl ethers (R^1 = H) and aryloxybutenols (R^1 = OH) was described for the synthesis of electron-rich chromanes (Scheme 2.49)[78]. It was seen that when simple phenyl homoallyl ethers were employed, the corresponding chromane-type esters were obtained.

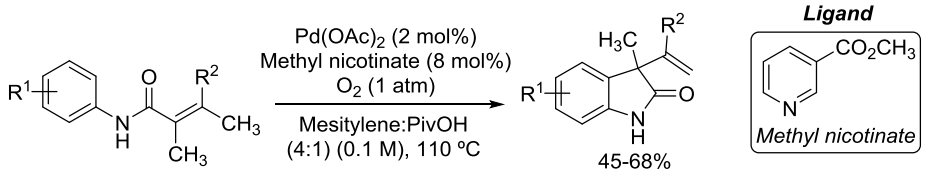
[77] Youn, S.W.; Eom, J.I. *Org. Lett.* **2005**, *7*, 3355.
[78] Li, S.; Li, F.; Gong, J.; Yang, Z. *Org. Lett.* **2015**, 17, 1240.



Scheme 2.49

On the other hand, the utilization of aryloxybutenols (R^1 = OH), in the absence of external alcohols, led to the diastereoselective formation of the corresponding *cis*-lactone-fused chromanes due to the reductive elimination between the carbonyl group introduced after the cyclization process and the oxygen atom initially present in the hydroxyl functionality of the substrate. This intramolecular alkenylative coupling is also proposed to take place by alkene activation-arene insertion.

Regarding the synthesis of nitrogen-containing heterocycles, in 2011, Oestreich´s group was able to carry out the synthesis of different oxindoles, bearing quaternary centers, *via* ligand-aided Pd(II)-catalyzed 5-*exo*-trig oxidative cyclizations of several *N*-arylacrylamides (Scheme 2.50). Interestingly, in this work oxygen was used as the sole oxidant. Besides, they saw that an electron-rich aromatic ring was essential for the reaction to take place, as well as a free N-H and a tri- or tetra-substituted olefin motif.[79]



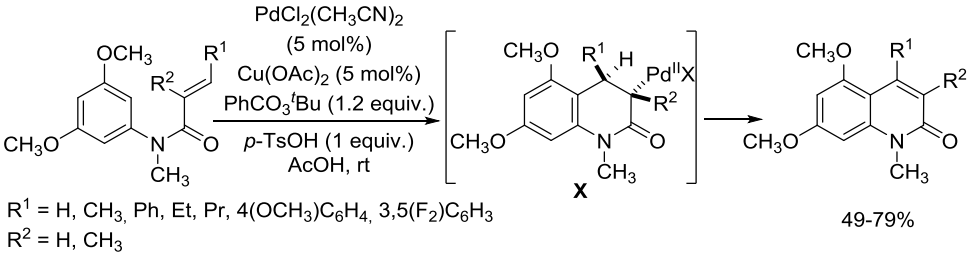
R^1 = 3,5-$(OCH_3)_2$, 3,4-$(OCH_3)_2$, 3,5-$(CH_3)_2$, 3,4,5-$(OCH_3)_3$
R^2 = H, CH_3

Scheme 2.50

According to the literature, Pd(II)-catalyzed cyclizations of *N*-arylacrylamides, prefer to proceed through 5-*exo*-trig processes to form oxindoles, even when β-hydride elimination

[79] Schiffner, J.A.; Oestreich, M. *Eur. J. Org. Chem.* **2011**, 1148.

is not allowed, the Pd(II)-alkyl intermediate prefers to capture a nucleophile[80] or to undergo C-H alkylation.[81] In contrast to the usual reactivity shown by these substrates under Pd(II) catalysis, our group was able to find the adequate catalytic system to switch the reaction to the β-position of the alkene (the most reactive position in the intermolecular reactions), generating 2-quinolones *via* an unprecedented 6-*endo*-trig cyclization process. The control of site-selectivity could be explained by the change in the steric and electronic properties around the metal center. Thus, we have developed an efficient method for the synthesis of 2-quinolones starting from *N*-arylacrylamides as substrates using $PdCl_2(CH_3CN)_2$ as catalyst and $PhCO_3{}^tBu/Cu(OAc)_2$ as the oxidant system. This Pd(II)-catalyzed intramolecular olefination takes place with high efficiency at room temperature (Scheme 2.51).[23]



Scheme 2.51

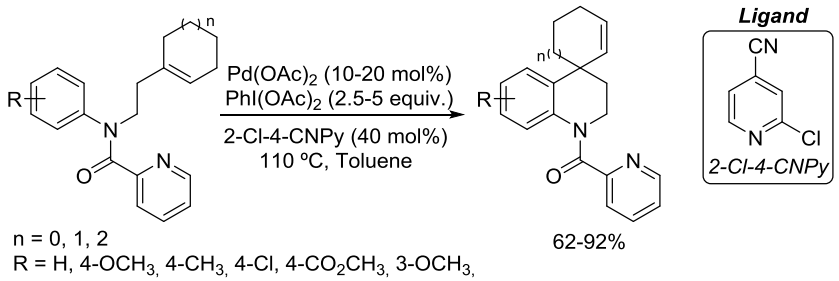
Furthermore, the reaction could be carried out not only in a 2% wt. aqueous solution of PTS, but also in water, obtaining the quinolones in good yields, though the cyclization required longer reaction times (24 h). Several substitution patterns in the alkene were well tolerated in this transformation; that way, both 4-substituted and 3,4-disubstituted 2-quinolones could be efficiently obtained. Nonetheless, alkenes bearing electron-deficient substituents did not perform well, probably due to acidic decomposition of the substrate.

The mechanistic pathway would involve a selective 6-*endo*-trig cyclization process that would provide intermediate **X**, leading to the corresponding quinolone after β-hydride elimination (Scheme 2.51). Although the reaction was initially proposed to occur through palladation of the aromatic ring followed by *syn* addition onto the olefin and isomerization to obtain **X**, an alkene activation-arene insertion mechanism cannot be discarded. In any case, either an electrophilic palladation of the arene or an electrophilic aromatic

[80] a) Jaegli, S.; Dufour, J.; Wei, H.-L.; Piou, T.; Duan, X.-H.; Vors, J.-P.; Neuville, L.; Zhu, J. *Org. Lett.* **2010**, *12*, 4498; b) Mu, X.; Wu, T.; Wang, H.-Y.; Guo, Y.-L.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878.
[81] Wu, T.; Mu, X.; Liu, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 12578.

substitution to the Pd(II)-activated alkene should take place, as the reaction only works well with *N*-(3,5-dimethoxyphenyl) acrylamides. This is probably the main drawback of the abovementioned procedure.

In 2017, He´s group demonstrated that directing groups can be utilized in the intramolecular Fujiwara-Moritani reaction, combining them with ligands. They developed a method for the intramolecular Pd(II)-catalyzed alkenylation reaction of different cycloalkene-bearing anilines, using picolinamide as the *N*-protecting group and a pyridine ligand. Those compounds were subjected to a 6-*exo*-trig cyclization to obtain the corresponding spiro-tetrahydroquinolines (Scheme 2.52).[82]



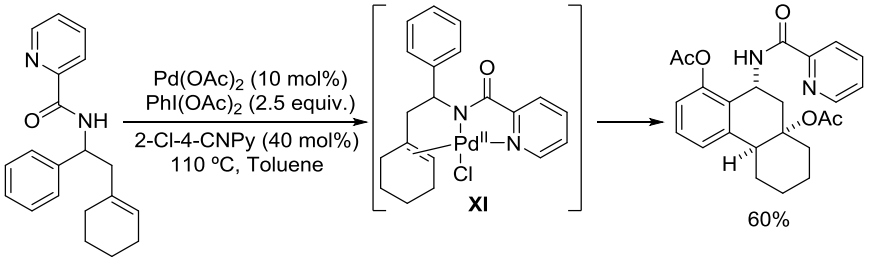
Scheme 2.52

The use of the pyridine ligand proved to be essential, since the yield decreased from 80% to 20% when it was removed. This reaction showed to be efficient and compatible not only with electron-rich substituents, but also with electron-withdrawing groups in the aniline ring. Nevertheless, in the last cases, the catalyst loading and the oxidant equivalents had to be doubled, probably due to the lower nucleophilicity of the aromatic ring. Furthermore, different ring-sizes were tolerated in the cycloalkene moiety.

The requirement for picolinamide as the *N*-protecting/directing group was also demonstrated. It was observed that when a free NH or a *N*-methyl group were used, the reaction did not take place. When coordinating protecting groups, such as Boc and tosyl, were utilized, the substrate underwent allylic acetoxylation. According to those results, the coordination of Pd(II) to the pyridine ring may be necessary for the reaction to proceed. In order to try to determine the mechanism operating in the reaction, kinetic isotope experiments were run, obtaining results that suggested that the aryl C(sp^2)-H activation was the rate-limiting step.

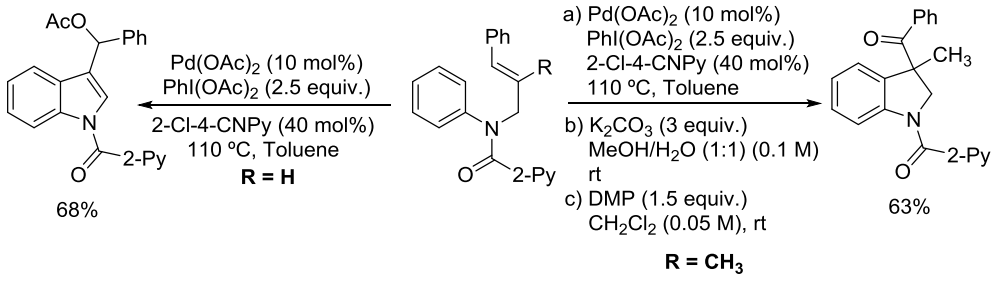
[82] Zang, Z.-L.; Karnakanti, S.; Zhao, S.; Hu, P.; Wang, Z.; Shao, P.-L.; He, Y. *Org. Lett.* **2017**, *19*, 1354.

When the reaction was carried out using α-aryl-substituted amines instead of the aniline substrates, oxidative arylation of the cycloalkene moiety took place, followed by double acetoxylation. This transformation proceeded in a highly diastereoselective manner, obtaining the corresponding octahydrophenanthrene products in moderate yields (Scheme 2.53). They independently synthesized the possible intermediate **XI** and subjected it to the reaction conditions, obtaining the corresponding product in a 26% yield, suggesting that the reaction might proceed *via* that palladacycle.



Scheme 2.53

The same group also reported that when picolinamide-*N*-protected cinnamyl anilines were subjected to the abovementioned reaction conditions, cyclization followed by acetoxylation took place to form the corresponding indoles (Scheme 2.54, R = H).[83]



Scheme 2.54

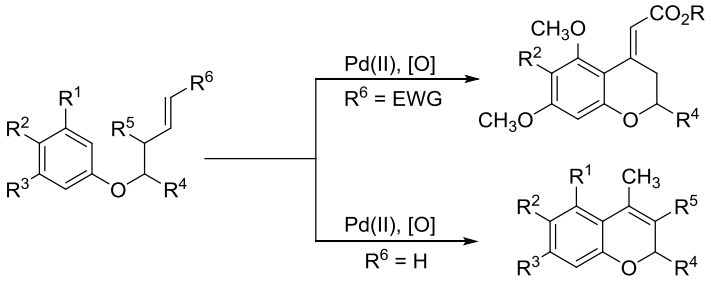
However, when a methyl group was placed in the internal position of the olefin moiety, the acetoxylated indolines were furnished. In this case, due to the obtainment of diastereomeric mixtures, the cyclization products were hydrolyzed and oxidized to furnish the corresponding ketones (Scheme 2.54, R = CH_3).

[83] Karnakanti, S.; Zang, Z.-L.; Zhao, S.; Shao, P.-L.; Hu, P.; He, Y. *Chem. Commun.* **2017**, *53*, 11205.

2. AIMS OF THE CHAPTER

Based on all the precedents commented throughout the introductory part of this chapter, we decided to develop an intramolecular Fujiwara-Moritani reaction for the synthesis of different oxygen- and nitrogen-containing heterocycles. With regard to the achievement of site selectivity in these desired transformations, we decided to take advantage of the electronic properties of the aromatic rings in the substrates, since although efficient, the use of directing groups many times involves the presence of undesired motifs in the final product.

Taking all this into account, the aim of the first section in this chapter consists of the utilization of different aryl butenyl ethers, bearing electron-withdrawing groups in the alkene terminus, as substrates for the Pd(II)-catalyzed intramolecular alkenylation reaction, leading to the corresponding chromanes with exocyclic double bonds (Scheme 2.55).

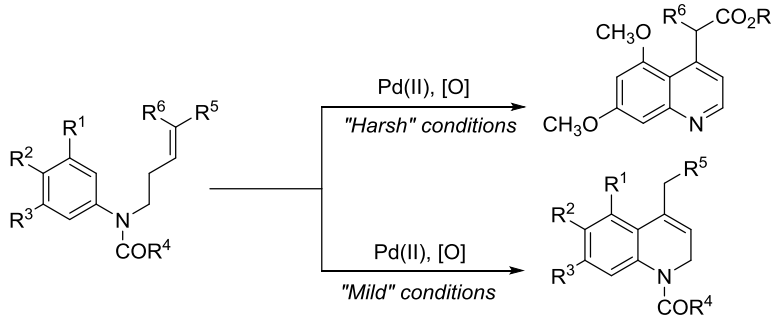


Scheme 2.55

With the aim of synthesizing the chromene core, having endocyclic double bonds, we hypothesized that the removal of the abovementioned electron-withdrawing groups from the olefin would induce the isomerization of the exocyclic alkene to the more stable internal position in the course of the reaction (Scheme 2.55).

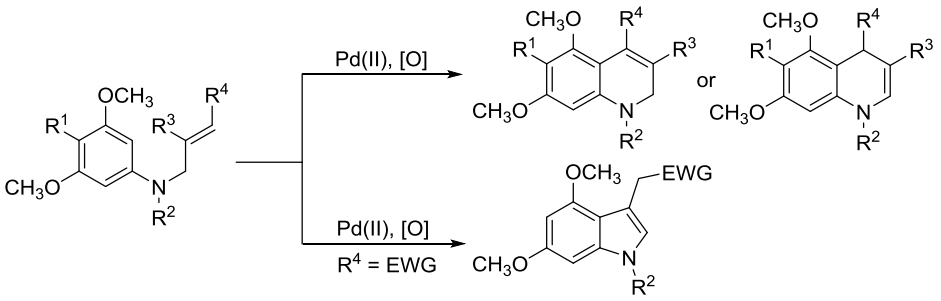
Moving to the second section, we decided to apply the 6-*exo*-trig Fujiwara-Moritani cyclization to the synthesis of the quinoline core. Based on previous results from the group, we proposed that it would be possible to subject *N*-protected butenylanilines (possessing different esters attached to the olefin terminus) to relatively strong acidic and oxidative conditions, obtaining the corresponding 4-substituted quinolines due to cyclization, followed by isomerization of the double bond to the endocyclic position and further oxidation upon extrusion of the protecting group. It was also envisioned that milder

reaction conditions would prevent the last aromatization step, thus providing the corresponding 1,2-dihydroquinoline products (Scheme 2.56).



Scheme 2.56

In the third and last section, the possibility of attaining the synthesis of dihydroquinolines by means of intramolecular 6-*endo*-trig alkenylation reactions over *N*-allylanilines will be explored. In this transformation, depending on the hydride abstracted during the β-elimination event, the obtainment of two different products should be possible, namely 1,2- or 1,4-dihydroquinolines. Thus, the site selectivity of this intramolecular coupling will be studied, performing, for that purpose, DFT and experimental studies to deeply investigate the mechanism operating in the transformation. Besides, it was thought that the addition of electron-withdrawing functionalities to the external position of the alkenes present in the substrates may lead to a change in the regioselectivity of the cyclization process, allowing the obtainment of 3-substituted indoles though 5-*exo*-trig intramolecular events. (Scheme 2.57).



Scheme 2.57

3. RESULTS AND DISCUSSION

3.1. Palladium(II)-catalyzed intramolecular C-H alkenylation for the synthesis of chromanes[84]

As stated in previous sections, depending on the experimental conditions and the structural features of the substrates, different mechanisms can operate in the Fujiwara-Moritani reaction (*i.e.* arene metalation-alkene insertion or alkene activation-arene insertion), which may lead to different regioisomeric products. For example, as commented in the introduction of this chapter, intramolecular reactions of *N*-phenylacrylamides in the presence of Pd(II) catalysts and oxidants have been reported to afford oxindoles.[79] Even when the subsequent β-hydride elimination is not permitted, those substrates have been observed to undergo 5-*exo* trig cyclizations followed by nucleophile capture[80] or C-H alkylation.[81] However, as stated before, the reaction can be directed to the β-position of the olefin, achieving the selective intramolecular 6-*endo* trig alkenylation of related *N*-alkyl-substituted *N*-phenylacrylamides to give 4-substituted or 3,4-disubstituted 2-quinolones (Scheme 2.51), as reported by our group.[23]

To expand the synthetic utility of this procedure, we decided to investigate C-H alkenylation reactions for the synthesis of oxygenated heterocycles, such as chromanes. The chromane and 2*H*-chromene moieties are important structural motifs present in a wide variety of bioactive natural products,[85] pharmaceuticals[86] and photochromic materials for different applications (laser dyes, fluorescence probes, etc.).[87] For example, 4-alkylidenechromanes have shown their potential as antagonists of transient receptor type 1 (TRPV1)[88] for pain relief[89] and as muscle relaxants.[90] Besides, they are used as building blocks in the synthesis

[84] The work described in this section has been published in: Carral-Menoyo, A.; Misol, A.; Gómez-Redondo, M.; Sotomayor, N.; Lete, E. *J. Org. Chem.* **2019**, *84*, 2048.
[85] Costa, M.; Dias, T.A.; Brito, A.; Proença, F. *Eur. J. Med. Chem.* **2016**, *123*, 487.
[86] Pratap, R.; Ram, V.J. *Chem. Rev.* **2014**, *114*, 10476.
[87] Paramonov, S.V.; Lokshin, V.; Fedorova, O.A. *J. Photochem. Photobiol., C* **2011**, *12*, 209.
[88] Uchida, H.; Kosuga, N.; Satoh, T.; Hotta, D.; Kamino, T.; Maeda, Y.; Amano, K.-I.; Akada, Y. (Mochida Pharmaceutical Co., Ltd., Japan) Preparation of Novel 2-(Bicyclic Heterocyclidene)-acetamide Derivatives as Antagonists of Transient Receptor Potential Type 1 (TRPV1). PCT Int. Appl. WO 2007010383 A1 20070125, Jan 25, 2007; *Chem. Abstr.* **2007**, *146*, 163039.
[89] Lee, Y.; Hong, S.; Cui, M.; Sharma, P.K.; Lee, J.; Choi, S. *Expert. Opin. Ther. Pat.* **2015**, *25*, 291.
[90] Kelley, J.L.; Rigdon, G.C.; Cooper, B.R.; McLean, E.W.; Musso, D.L.; Orr, G.F.; Selph, J.L.; Styles, V.L. (Glaxo Wellcome Inc., USA) Preparation of Indanylideneacetamides, Naphthylideneacetamides, and Benzopyranylideneacetamides as Muscle Relaxants. US 6124284 A 20000926, Sep 26, 2000; *Chem. Abstr.* **2000**, *133*, 252177.

of 6-oxasteroid derivatives.[91] On the other hand, flav-2-enes (2-aryl-2*H*-chromenes) have shown anticancer, anti-inflammatory and antiviral activity,[92] while isoflavenes (3-aryl-2*H*-chromenes) have been recently identified as novel potential osteogenic agents[93] (in Figure 2.4 some biologically active chromane and 2*H*-chromene derivatives can be seen). As a consequence, rapid access to the chromane nucleus bearing substituents at specific positions is of great interest to both synthetic and medicinal chemistry.

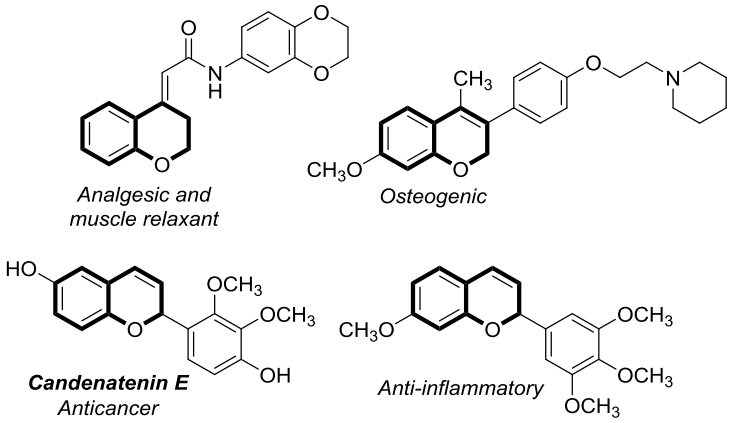


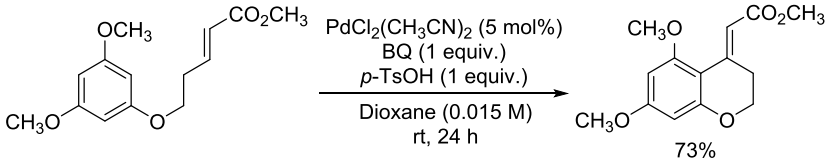
Figure 2.4

Chromenes have been prepared *via* intramolecular cyclization of advanced intermediates using metal-free Brönsted and Lewis acid/base catalysis and transition-metal-catalyzed transformations,[94] although only a few examples of oxidative C-H alkenylation reactions have been described for the synthesis of those motifs.

As it has been already mentioned in the introduction of this chapter, Youn and Eom described the Pd(II)-catalyzed oxidative cyclization of aryl homoallyl ethers to obtain the corresponding chromenes, after isomerization of the initially formed exocyclic double bond (Scheme 2.48).[77] Besides, the carbonylative cyclization of aryl homoallyl ethers has also been reported for the synthesis of 4-substituted chromanes (Scheme 2.49).[78]

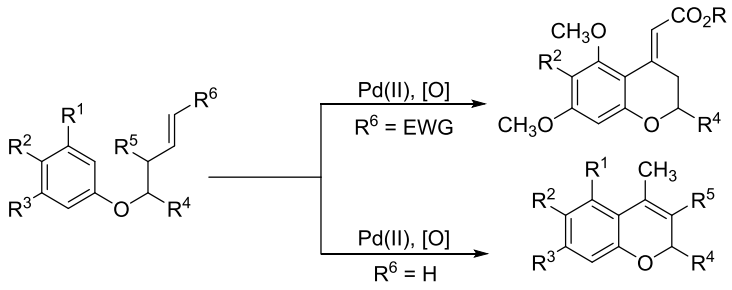
[91] Halskov, K.S.; Donslund, B.S.; Barfüsser, S.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* **2014**, *53*, 4137.
[92] Thomas, N.; Zachariah, S.M. *Asian J. Pharm. Clin. Res*. **2013**, *6* (Suppl 2), 11.
[93] Gupta, A.; Ahmad, I.; Kureel, J.; Hasanain, M.; Pandey, P.; Singh, S.; John, A.A.; Sarkar, J.; Singh, D. *J. Steroid Biochem. Mol. Biol.* **2016**, *158*, 63.
[94] Majumdar, N.; Paul, N.D.; Mandal, S.; de Bruin, B.; Wulff, W.D. *ACS Catal.* **2015**, *5*, 2329.

In this context, our group has formerly developed an efficient procedure that could be used to accomplish the intramolecular Fujiwara-Moritani coupling of methyl *(E)*-5-(3,5-dimethoxyphenoxy)pent-2-enoate, affording the corresponding chromane in a good yield and with complete diastereoselectivity towards the *E*-configured cyclization product (Scheme 2.58).[95] When the starting material was subjected to the reaction conditions utilized for the 6-*endo*-trig cyclization of *N*-arylcrylamides [$PdCl_2(CH_3CN)_2$ (5 mol%), $PhCO_3{}^tBu$ or F^+ (1.2 equiv.), $Cu(OAc)_2$ (5 mol%) and *p*-TsOH (1 equiv.) in ACOH],[23] decomposition products were observed, while the conditions developed by Youn and Eom for the synthesis of chromenes [$PdCl_2(CH_3CN)_2$ (5 mol%), BQ (1 equiv.), and Na_2CO_3 (1equiv.) in dioxane][77] led to no reaction. However, the addition of *p*-TsOH instead of Na_2CO_3, allowed the efficient and selective formation of the corresponding chromane.



Scheme 2.58

With this preliminary result in mind and as indicated in the aims of the chapter, we were committed to study the scope of the transformation, changing the substitution pattern present on the alkenyl chain, the aromatic ring, and the ester placed in the olefin moiety. Besides, the possibility of synthesizing different chromenes, bearing endocyclic double bonds, only by removing the electron-withdrawing group from the alkene terminus will be evaluated (Scheme 2.59).

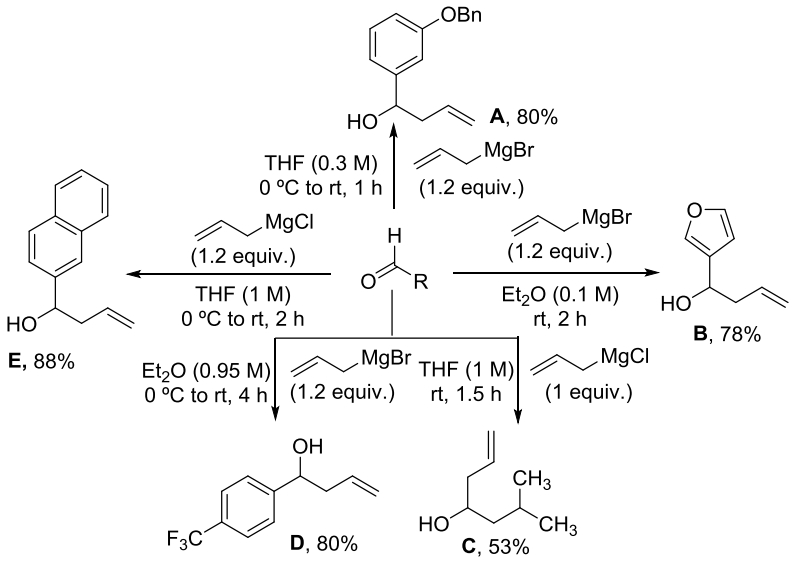


Scheme 2.59

[95] Misol, A. Reacciones de Alquenilación Intramolecular Catalizadas por Pd(II) en la Síntesis de Cromanos y Cromenos. Master Thesis, UPV/EHU, September 2015.

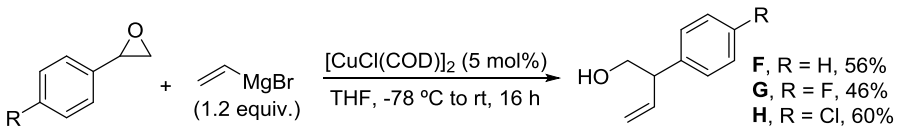
3.1.1. Synthesis of the substrates[96]

In this section, the preparation of aryl homoallyl ethers **1**, as well as esters **2** will be disclosed. We firstly performed the synthesis of ethers **1**, which bear a terminal olefin moiety, envisioning that they could be easily assembled *via* the Mitsunobu reaction starting from the corresponding phenols and homoallylic alcohols. Despite some of those 3-buten-1-ols were commercially available, most of them had to be prepared. Thus, alcohols **A**-**E** were obtained *via* the addition of allylmagnesium halides to aldehydes (Scheme 2.60).



Scheme 2.60

Besides, 2-substituted 3-buten-1-ols **F-H** were prepared in moderate yields by means of the nucleophilic attack of vinyl magnesium bromide to different epoxides using a bulky copper(I) catalyst (Scheme 2.61).

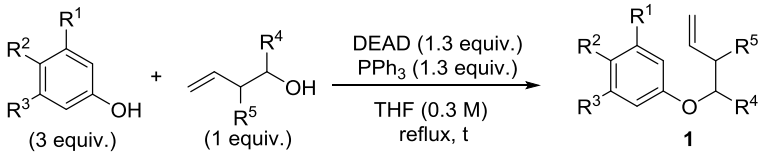


Scheme 2.61

[96] References of compounds already reported in the literature are shown in the experimental part.

With all the desired homoallylic alcohols in hand, we subjected them to the Mitsunobu reaction using different electron-rich phenols as coupling partners. That way, ethers **1aa-1db** were successfully synthesized (Table 2.1).

Table 2.1



Entry	R^1	R^2	R^3	R^4	R^5	t (h)	Prod.	Yield (%)[a]
1	OCH_3	H	OCH_3	H	H	4	**1aa**	83
2	OCH_3	H	OCH_3	CH_3	H	3	**1ab**	73
3	OCH_3	H	OCH_3	Pr	H	16	**1ac**	63
4	OCH_3	H	OCH_3	Ph	H	16	**1ad**	47
5	OCH_3	H	OCH_3	3(OBn)C_6H_4	H	16	**1ae**	50
6	OCH_3	H	OCH_3	3-furyl	H	16	**1af**	29
7	OCH_3	OCH_3	OCH_3	H	H	5.5	**1ba**	78
8	OCH_3	OCH_3	OCH_3	CH_3	H	6	**1bb**	78
9	OCH_3	OCH_3	OCH_3	Pr	H	16	**1bc**	63
10	OCH_3	OCH_3	OCH_3	Ph	H	16	**1bd**	41
11	OCH_3	OCH_3	OCH_3	3(OBn)C_6H_4	H	16	**1be**	45
12	OCH_3	OCH_3	OCH_3	3-furyl	H	16	**1bf**	27
13	OCH_3	OCH_3	OCH_3	^{i}Bu	H	16	**1bg**	36
14	OCH_3	OCH_3	OCH_3	4(CH_3)C_6H_4	H	16	**1bh**	42
15	OCH_3	OCH_3	OCH_3	4(CF_3)C_6H_4	H	16	**1bi**	68
16	OCH_3	OCH_3	OCH_3	2-naphth	H	16	**1bj**	31
17	H	OCH_3	OCH_3	CH_3	H	16	**1cb**	67
18	H	OCH_3	OCH_3	Ph	H	16	**1cd**	31
19	H	-OCH_2O-		CH_3	H	8	**1db**	86
20	OCH_3	H	OCH_3	H	CH_3	3.5	**1ak**	79
21	OCH_3	H	OCH_3	H	Ph	16	**1al**	30
22	OCH_3	H	OCH_3	H	4(F)C_6H_4	5	**1am**	30
23	OCH_3	H	OCH_3	H	4(Cl)C_6H_4	5	**1an**	23

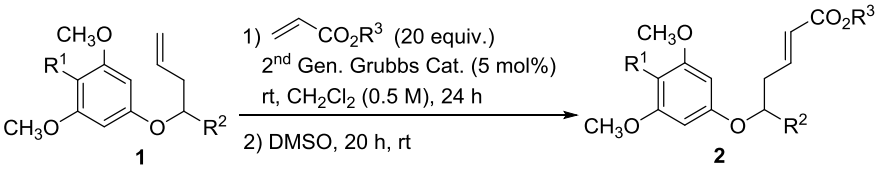
[a] Yield of the isolated pure compounds.

As it can be observed, the yield of the transformation was highly dependent on the substituent at C-1 (R^4). The reaction proceeded, in general, with moderate to good yields;

nonetheless, when bulky functionalities were employed at that position, low yields were obtained (**^{t}Bu**, Table 2.1, entry 13) and the same happened when utilizing electron-rich substituents (**3-furyl**, Table 2.1, entries 6 and 12). The reaction also furnished the corresponding ethers in low yields when 2-aryl-substituted homoallylic alcohols were employed (Table 2.1, entries 21-23). The use of 3,4-dimethoxyphenol also led to lower yields than its 3,5-dimethoxy and 3,4,5-trimethoxy counterparts (Table 2.1, entries 2, 4, 8 and 10 *vs* 17 and 18).

After synthesizing ethers **1**, some of them were selected and further subjected to a metathesis reaction, using the ruthenium-based 2nd generation Grubbs catalyst and different acrylates as coupling partners (Table 2.2). That transformation allowed us to install different electron-deficient groups on the alkene terminus, obtaining the corresponding esters **2aaa-2bba** with good to excellent yields, except for **2aba** and **2aab** (Table 2.2, entries 2 and 4, respectively). It is worth to mention that in all the cases the reaction is diastereoselective towards the formation of the *E* alkenes, obtaining just that diastereomer with the only exception of **2aaa** (Table 2.2, entry 1). When this compound was synthesized, a small amount of the *Z* isomer could be isolated in 6% yield.

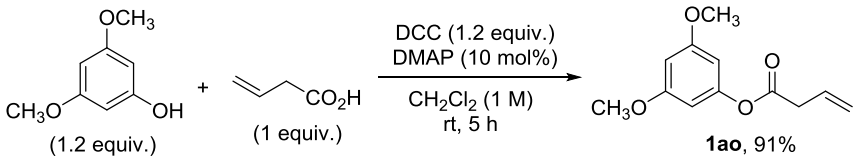
Table 2.2



Entry	Subst.	R^1	R^2	R^3	Prod.	Yield (%)[a]
1	**1aa**	H	H	CH_3	**2aaa**[b]	87
2	**1ab**	H	CH_3	CH_3	**2aba**	55
3	**1ad**	H	Ph	CH_3	**2ada**	75
4	**1aa**	H	H	Et	**2aab**	57
5	**1aa**	H	H	^{n}Bu	**2aac**	82
6	**1aa**	H	H	^{t}Bu	**2aad**	73
7	**1ab**	H	CH_3	^{t}Bu	**2abd**	87
8	**1bb**	OCH_3	CH_3	CH_3	**2bba**	83

[a] Yield of the isolated pure compounds. [b] 6% of the compound bearing a *(Z)*-alkene was obtained.

Finally, aryl butenoate **1ao** was prepared by means of a simple esterification reaction using *N,N´*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (4-DMAP), starting from 3,5-dimethoxyphenol and 3-butenoic acid (Scheme 2.62).

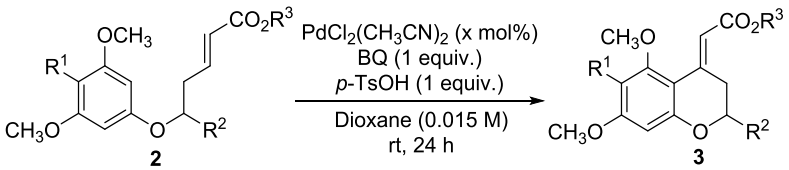


Scheme 2.62

*3.1.2. Palladium(II)-catalyzed cyclization of aryl homoallyl ethers **1aa-1db**, as well as esters **2aaa-2bba** and aryl butenoate **1ao**. Synthesis of chromanes **3aaa-3bba**, chromenes **4aa-4db** and coumarin **4ao**.*

Bearing in mind the aforementioned precedents in our group on the intramolecular Fujiwara-Moritani reaction, we commenced our study with the synthesis of differently substituted chromanes, bearing esters at the olefin terminus (Table 2.3).

Table 2.3

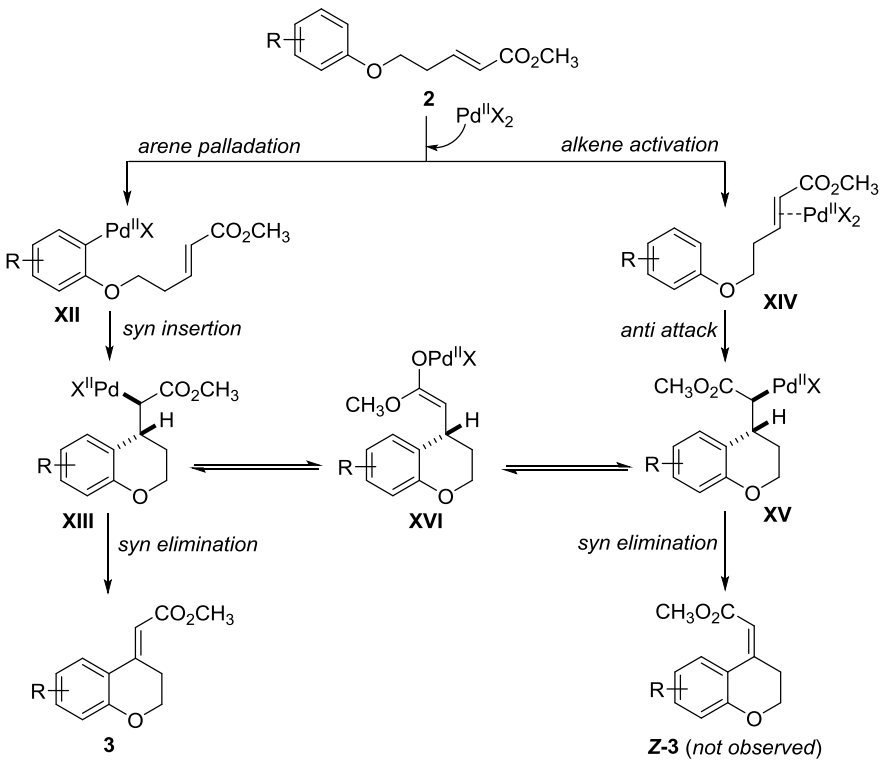


Entry	Subst.	R^1	R^2	R^3	Pd(II) (mol%)	Prod.	Yield (%)[a]
1	**2aba**	H	CH_3	CH_3	5	**3aba**	80
2	**2ada**	H	Ph	CH_3	5	**3ada**	59
3	**2aab**	H	H	Et	5	**3aab**	49
4	**2aab**	H	H	Et	10	**3aab**	77
5	**2aac**	H	H	^{n}Bu	5	**3aac**	44
6	**2aac**	H	H	^{n}Bu	10	**3aac**	70
7	**2aad**	H	H	^{t}Bu	5	**3aad**	35
8	**2aad**	H	H	^{t}Bu	10	**3aad**	59
9	**2abd**	H	CH_3	^{t}Bu	10	**3abd**	69
10	**2bba**	OCH_3	CH_3	CH_3	10	**3bba**	60

[a] Yield of the isolated pure compounds.

Interestingly, substitution at C-1 in the substrates was tolerated (Table 2.3, entries 1, 2, 9 and 10), and thus, flavan **3ada** could be accessed (Table 2.3, entry 2).

Different substitution patterns at the ester moiety were also allowed; however, the reactions did not proceed to full conversion in 24 h (Table 2.3, entries 3, 5 and 7), so the catalyst loading had to be increased (10 mol%) to obtain good yields within the same reaction time (Table 2.3, entries 4, 6 and 8). Besides, the methodology could also be extended to the synthesis of a 5,6,7-trimethoxysubstituted chormane, such as **3bba** (Table 2.3, entry 10). All the cyclization products **3aba-3bba** were obtained with complete stereoselectivity (as *E* diastereomers) and as single regioisomers, since no isomerization of the exocyclic double bond to the endocyclic position was observed. Two related reaction mechanisms could be proposed for this cyclization (Scheme 2.63).

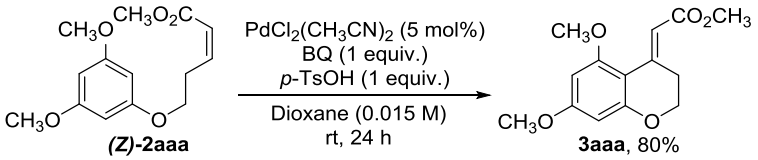


Scheme 2.63

On the one hand, C-H electrophilic palladation of the aromatic ring with a cationic palladium species (favored by the addition of *p*-TsOH)[28b,36] could occur to obtain an aryl-palladium(II) intermediate **XII**, which would undergo a *syn* olefin insertion to afford **XIII**. Subsequent *syn* β-hydride elimination is possible to give the corresponding product with the observed *E* configuration. This mechanism has been proposed for related alkenylations of electron-rich aromatic systems.[73b,76,97]

On the other hand, a Pd(II)-mediated alkene activation followed by *anti* nucleophilic attack of the aromatic ring to the Pd(II) π-complex (**XIV**)[77,72c,72g] would lead to a diastereomeric intermediate, such as **XV**. In this case, the alignment of the C(sp^3)-Pd(II) and C(sp^3)-H bonds required for the direct *syn* β-hydride elimination would give the *Z*-configured product (***Z*-3**), which is not detected in any case. An *anti* elimination would thus be required to furnish the observed chromane bearing an *E*-configured alkene. However, **XIV** could undergo epimerization at the α-carbon through the formation of an oxo-π-allylpalladium(II) intermediate **XVI**[72g] to form **XIII**, allowing the *syn* β-hydride elimination to afford the experimentally observed product.

To check if this was possible, we carried out the cyclization of ***(Z)*-2aaa**, and under the same reaction conditions, **3aaa** was obtained in a comparable yield with complete diastereoselectivity (Scheme 2.64). Therefore, the reaction is not diastereospecific. This does not rule out none of the abovementioned mechanisms, but shows that palladium enolate intermediate **XV** could epimerize, to give the more stable *E* isomer after *syn*-elimination.



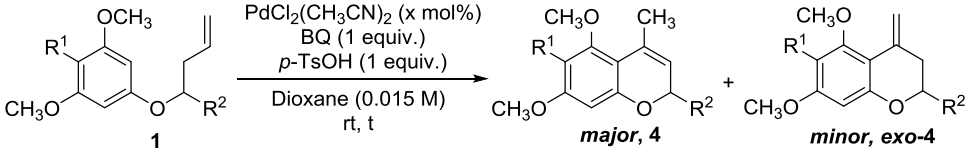
Scheme 2.64

We then envisioned that the removal of the electron-withdrawing group from the alkene moiety, would induce an *in situ* isomerization of the exocyclic double bond to the thermodynamically more stable endocyclic position.

[97] Gao, Y.; Gao, Y.; Wu, W.; Jiang, H.; Yang, X.; Liu, W.; Li, C.-J. *Chem. Eur. J.* **2017**, *23*, 793.

With this aim in mind, a series of aryl homoallyl ethers bearing unsubstituted olefin moieties **1** were subjected to the previously employed reaction conditions (Table 2.4). Firstly, the cyclization reaction of **1aa** was tested and, in this case, the reaction proved to be much faster, furnishing 2*H*-chromene **4aa** after 2 h and at rt with a good isolated yield (74%, Table 2.4, entry 1). However, the ^{1}H NMR and ^{13}C NMR spectra showed the presence of a minor amount of the regioisomeric methylenechromane, with an exocyclic double bond. A 93:7 *endo/exo* ratio was established by ^{1}H NMR.

Table 2.4

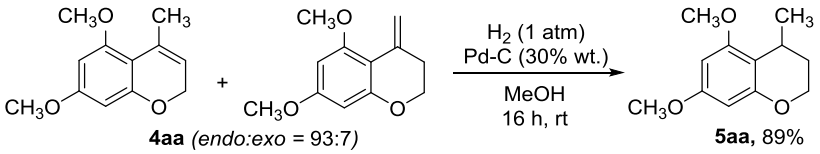


Entry	Subst.	R^1	R^2	t (h)	Pd(II) (mol%)	Prod.	Yield (%)[a]	*endo/exo*[b]
1	**1aa**	H	H	2	5	**4aa**	74	93:7
2	**1ab**	H	CH_3	2	5	**4ab**	83	83:17
3	**1ac**	H	Pr	2	5	**4ac**	85	93:7
4	**1ad**	H	Ph	2	5	**4ad**	83	9:1
5	**1ae**	H	3(OBn)C_6H_4	2	5	**4ae**	87	9:1
6	**1af**	H	3-furyl	2	5	**4af**	86	85:15
7	**1ba**	OCH_3	H	6	10	**4ba**	61	94:6
8	**1bb**	OCH_3	CH_3	2	10	**4bb**	88	92:8
9	**1bc**	OCH_3	Pr	2.5	10	**4bc**	86	96:4
10	**1bd**	OCH_3	Ph	2	10	**4bd**	79	94:6
11	**1be**	OCH_3	3(OBn)C_6H_4	2.5	10	**4be**	84	93:7
12	**1bf**	OCH_3	3-furyl	3	10	**4bf**	72	9:1
13	**1bg**	OCH_3	^{i}Bu	2.5	10	**4bg**	79	94:6
14	**1bh**	OCH_3	4(CH_3)C_6H_4	3	10	**4bh**	87	9:1
15	**1bi**	OCH_3	4(CF_3)C_6H_4	5.5	10	**4bi**	91	92:8
16	**1bj**	OCH_3	2-naphth	2.5	10	**4bj**	81	89:11

[a] Yield of the isolated pure compounds. [b] *Endo/exo* ratio determined by ^{1}H NMR.

Various 2-substituted chromenes **4**, including flavenes **4ad**, **4ae** or even their heteroaryl analog **4af**, were efficiently obtained under these reaction conditions (Table 2.4, entries 4, 5 and 6, respectively), in high isolated yields. The reaction could also be extended to different substitution patterns on the aromatic ring, obtaining 5,6,7-trimethoxy-substituted

chromenes **4ba**-**4bj**, although an increase of the catalyst loading was required to maintain reactivity (Table 2.4, entries 7-16). Thus, a series of both alkyl and aryl substituted 2*H*-chromenes were easily accessed. To unarguably confirm the formation of positional isomers, the mixture **4aa** was subjected to a hydrogenation reaction, obtaining chromane **5aa** in high yield and as a single product (Scheme 2.65).



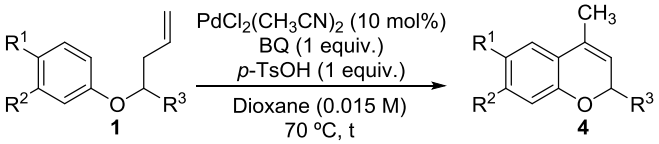
4aa *(endo:exo* = 93:7*)* **5aa,** 89%

Scheme 2.65

As it can be observed in Table 2.4, an outstanding increase of the yield was seen when different substituents were present at the C-1 position of the substrates (Table 2.4, entries 1 and 7 *vs* entries 2-6 and 8-16, respectively). This is thought to occur due to the Thorpe-Ingold effect provided by those substituents, although it is usually observed when two functionalities are placed instead of just one.[98]

According to previous observations in our group on related reactions,[23] the herein mentioned alkenylative coupling requires an activated electron-rich aromatic ring to provide the corresponding products. However, the transformation worked efficiently with different oxygenated substitution patterns on the aryl ring. Different 6,7-disubstituted chromenes **4cb**-**4db** were obtained as single regioisomers using this procedure (Table 2.5).

Table 2.5



Entry	Subst.	R^1	R^2	R^3	t (h)	Prod.	Yield (%)[a]
1	**1cb**	OCH_3	OCH_3	CH_3	1	**4cb**	61
2	**1cd**	OCH_3	OCH_3	Ph	3	**4cd**	55
3	**1db**	-OCH_2O-		CH_3	2.5	**4db**	60

[a] Yield of the isolated pure compounds.

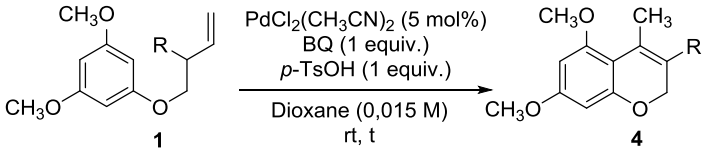
[98] a) Beesley, R.M.; Ingold, C.K.; Thorpe, J.F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080; b) Jung, M.E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735; c) Bachrach, S.M. *J. Org. Chem.* **2008,** *73*, 2466.

However, to achieve those transformations the palladium loading had to be doubled (10 mol%) and the temperature had to be increased to 70 ºC. This is interesting, since previous reports show that, under similar conditions, catalyst loadings up to 20 mol% or 25 mol% were needed to achieve comparable yields with this type of substitution on the aryl ring.[77]

When a substituent was placed at the C-2 position of the homoallyl ether (**1ak-1an**, R = CH_3, aryl), the reaction was completed in just 1-5 h with 5 mol% catalyst at room temperature. Employing those substrates, the selective obtainment of the double bond only in the endocyclic position of the product was favored due to its substitution pattern, since a tetrasubstituted olefin was formed upon isomerization.

On that basis, the corresponding 3-substituted 2*H*-chromenes, including isofavenes **4al-4an**, were furnished in high yields with complete regioselectivity (Table 2.6). In those cases, although not so evidently, the Thorpe-Ingold effect was also observed, since chromene products **4ak-4am** (Table 2.6, entries 1-3) were provided in higher yields than their unsubstituted homologue **4aa** (Table 2.4, entry 1). Nevertheless, **4an** was found to be an exception (Table 2.6, entry 4), since it was furnished with almost the same yield.

Table 2.6



Entry	Subst.	R	t (h)	Prod.	Yield (%)[a]
1	**1ak**	CH_3	1	**4ak**	83
2	**1al**	Ph	2.5	**4al**	87
3	**1am**	4(F)C_6H_4	4	**4am**	79
4	**1an**	4(Cl)C_6H_4	5.5	**4an**	73

[a] Yield of the isolated pure compunds.

The structure of the chromenes was unambiguously confirmed by single-crystal X-ray analysis of **4am**[99] (Figure 2.5).[100]

[99] CCDC 1872267 contains the supplementary crystallographic data for this structure.
[100] ORTEP plot of compound **4am** with thermal ellipsoids at the 50% probability level with the atomic nomenclature used.

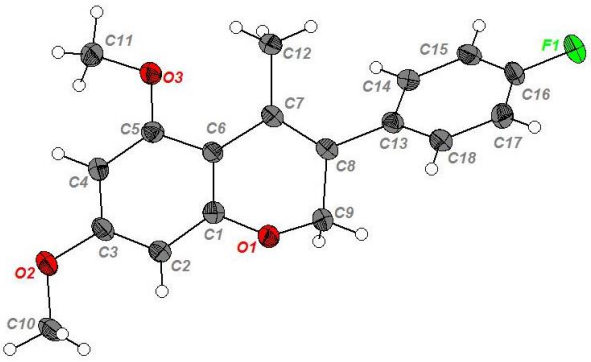
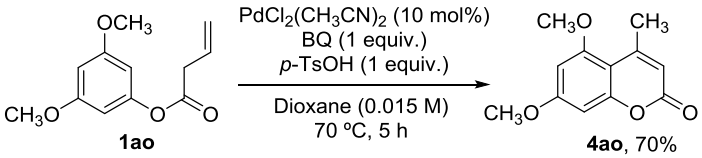


Figure 2.5

Finally, we tested this intramolecular alkenylation on aryl butenoate **1ao** to check the applicability of this procedure to the synthesis of coumarins. Thus, coumarin **4ao** was obtained, although heating to 70 ºC and an increase of the catalyst loading (10 mol%) was required to achieve full conversion in a reasonable reaction time (Scheme 2.66).



Scheme 2.66

In conclusion, an improved and mild protocol for the Pd(II)-catalyzed intramolecular C-H alkenylation of aryl homoallyl ethers has been developed. The use of *p*-TsOH as additive accelerates the reaction, probably generating more electrophilic Pd(II) species,[28b,36] and gives the procedure a significant improvement in substrate scope and reaction conditions. This is thought to occur through the replacement of ligands of the metal center with tosilate, what leads to a faster metalation. Thus, in most cases, the reactions could be run at room temperature using catalyst loadings of 5-10 mol%, depending on the aromatic substitution pattern.

Besides, the herein studied transformation employs benzoquinone, which is a usual oxidant in the Fujiwara-Moritani reaction, to recover the Pd(II) catalytically active species, delivering

hydroquinone as byproduct,[101] being this reaction known to be accelerated by acid.[102] It has been reported in previous works that the utilization of catalytic amounts of benzoquinone resulted in an enhancement of reactivity, obtaining better yields when its amount was increased.[10c] This compound is believed to stabilize Pd(0) species present during the catalytic cycle by the *in situ* formation of Pd(0)-benzoquinone complexes that prevent Pd(0) species from aggregation to Pd black and facilitate benzoquinone to oxidize Pd(0) to Pd(II).[10c,28b,72e] Therefore, benzoquinone could play two roles in palladium chemistry, serving as the oxidant of Pd(0) and acting as a ligand to stabilize the Pd species.

The methodology described throughout this section would be complementary to the Mizoroki-Heck reaction previously reported in the literature that led to the formation of 4-methylidenechromanes, bearing exocyclic double bonds,[103] with the advantage that it does not require the prior functionalization of the substrates. The procedure is very versatile, as it allows the synthesis of alkylidenechromanes **3** and 2*H*-chromenes **4** with different types of substituents (alkyl, electron-rich and electron-deficient aryl and heteroaryl) at C-2 or C-3 of the chromene moiety, therefore accessing relevant flavenes, isoflavenes and even coumarins. As a result, this strategy would be an efficient alternative to previously reported catalytic approaches,[94] which usually give access either to 2-substituted[104] or to 3-substituted chromane derivatives.[105]

[101] For a review, see: Popp, B.V.; Stahl, S.S. *Top. Organomet. Chem.* **2007**, *22*, 149.
[102] Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *Organometallics* **1993**, *12*, 1790.
[103] Hornillos, V.; van Zijil, A.W.; Feringa, B.L. *Chem. Commun.* **2012**, *48*, 3712.
[104] For selected examples of preparation of flavenes *via* transition-metal catalyzed methods, see: a) Pastine, S.J.; Youn, S.W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055; b) Scheidt, K.A.; Zeng, B.S. Catalytic Enantioselective Synthesis of 2-Arylchromenes and Related Phosphoramidite Ligands and Catalyst Compounds. U.S. Pat. Appl. 20150315168 A1 20151105, Nov 5, 2015; *Chem. Abstr.* **2015**, *163*, 676768; c) He, H.; Ye, K.-Y.; Wu, Q.-F.; Dai, L.-X.; You, S.-L. *Adv. Synth. Catal.* **2012**, *354*, 1084.
[105] See, for example: a) Erhardt, P.W.; Khupse, R.S.; Luniwal, A. (The University of Toledo, USA) Methods for Synthesizing Glycinols, Glyceollins I and II and Isoflavenes and Chromanes Using a Wittig Reaction, and Compositions made therewith. U.S. Pat. Appl. 20120115942 A1, May 10, 2012; *Chem. Abstr.* **2012**, *156*, 613224; b) Ma, L.; Li, W.; Xi, H.; Bai, X.; Ma, E.; Yan, X.; Li, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 10410; c) Ref. 93.

3.2. Palladium-catalyzed dehydrogenative coupling. An efficient synthetic strategy for the construction of the quinoline core[106]

With the encouraging results obtained in the synthesis of the chromane core *via* the Fujiwara-Moritnai cyclization of aryl homoallyl ethers,[84] we decided to study the utilization of their nitrogen counterparts (Figure 2.6) for the obtainment of the corresponding quinoline adducts. With that purpose in mind, we aimed to subject to an intramolecular 6-*exo*-trig oxidative Heck reaction different *N*-protected butenylanilines, bearing electron-withdrawing carbonyl-based *N*-protecting groups.

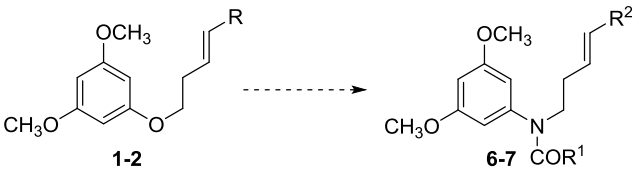


Figure 2.6

Quinolines are important motifs widely found in biologically active natural products, pharmaceuticals or agrochemicals,[107] such as antimalarial chloroquine or hydroxychloroquine (Figure 2.7),[108] which have recently attracted much attention regarding their use as anti-COVID-19. Quinoline derivatives have also been used in the manufacture of dyes and as organic optoelectronic materials.[109] Besides, Cinchona-alkaloid derivatives

[106] The work described in this section has been published in: Carral-Menoyo, A.; Ortiz-de-Elguea, V.; Martinez-Nunes, M.; Sotomayor, N.; Lete, E. *Mar. Drugs* **2017**, *15*, 276.

[107] For selected reviews, see: a) Fernandes da Silva, M.F.G.; Soares, M.S.; Fernandes, J.B.; Vieria, P.C. Alkyl, Aryl, Alkylarylquinoline, and Related Alkaloids. In *The Alkaloids: Chemistry and Biology*; Cordell, G.A., Ed.; Elsevier: Amsterdam, 2007; Vol. 64, p 139; b) Michael, J.P. *Nat. Prod. Rep.* **2008**, *25*, 166; c) Afzal, O.; Kumar, S.; Haider Md.R.; Ali, Md.R.; Kumar, R.; Jaggi, M.; Bawa, S. *Eur. J. Med. Chem.* **2015**, *97*, 871; d) Horta, P.; Secrieru, A.; Coninckx, A.; Cristiano, M.L.S. Quinolones for Applications in Medicinal Chemistry: Synthesis and Structure. In *Targets in Heterocyclic Systems*; Attanasi, O.A.; Merino, P.; Spinelli, D., Eds.; Società Chimica Italiana: Rome, 2018; Vol. 22, p 260.

[108] For their use as antimalarial, see: a) Kaur, K.; Jain, M.; Reddy, R.P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45,* 3245; for their use as anti-COVID-19, see: b) Cortegiani, A.; Ingoglia, G.; Ippolito, M.; Giarratano, A.; Einav, S. *J. Crit. Care* **2020**, *57*, 279; c) Yao, X.; Ye, F.; Zhang, M.; Cui, C.; Huang, B.; Niu, P.; Liu, X.; Zhao, L.; Dong, E.; Song, C.; Zhan, S.; Lu, R.; Li, H.; Tan, W.; Liu, D. *Clin. Infect. Dis.* **2020**, *71*, 732.

[109] Shi, C.; Guo, Z.; Yan, Y.; Zhu, S.; Xie, Y.; Zhao, Y.S.; Zhu, W.; Tian, H. *ACS Appl. Mater. Interfaces* **2013**, *5*, 192.

are important ligands and catalysts in asymmetric catalysis.[110] The quinoline core is also a common structural motif among many marine alkaloids;[107b,111] for example, the pyridoacridine family (ascididemin, for instance, Figure 2.7), a large class of marine alkaloids isolated from sessile organisms (sponges, corals, ascidians, bryozoans)[112] which display different types of biological activities, such as cytotoxicity, production of reactive oxygen species (ROS) and topoisomerase inhibition.[113]

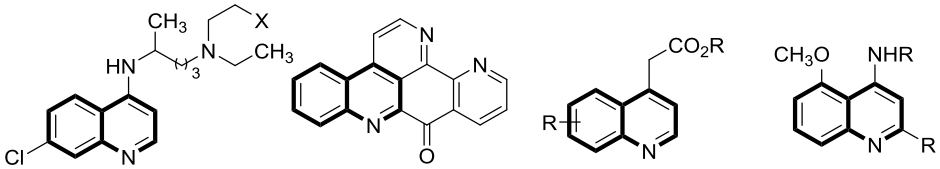


Figure 2.7

Furthermore, it has been claimed that synthetic 4-alkylcarbonylmethyl- or 4-alkoxycarbonylmethyl-substituted quinolines (Figure 2.7) show inhibitory activity against drug-resistant *Mycobacterium tuberculosis*[114] and potent antimicrobial activity against *Helicobacter pylori*.[115] More recently, based on SAR studies, it has been demonstrated that the presence of a methoxy group at C-5 position of the quinoline nucleus is a structural feature common to a new class of Enhancer of Zeste Homologue 2 (EZH2) inhibitors (Figure 2.7), which could be useful for the treatment of several cancer types (lymphoma, colon,

[110] Boratyński, P.J.; Zielińska-Błajet, M.; Skaržewski, J. *Cinchona* Alkaloids. Derivatives and Applications. In *The Alkaloids: Chemistry and Biology*; Knölker, H.-J., Ed.; Elsevier: Amsterdam, 2019; Vol. 82, p 29.

[111] Blunt, J.W.; Copp, B.R.; Hu, W.-P.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. *Nat. Prod. Rep.* **2007**, *24*, 31.

[112] a) Molinski, T.F. *Chem. Rev.* **1993**, *93*, 1825; b) Skyler, D.; Heathcock, C.H. *J. Nat. Prod.* **2002**, *65*, 1573.

[113] a) Delfourne, E.; Bastide, J. *Med. Res. Rev.* **2003**, *23*, 234; b) Pascual-Alfonso, E.; Avendaño, C.; Menéndez, J.C. *Tetrahedron Lett.* **2003**, *44*, 6003; c) Imperatore, C.; Aiello, A.; D´Aniello, F.; Senese, M.; Menna, M.L. *Molecules* **2014**, *19*, 20391; d) Melzer, B.; Plodek, A.; Bracher, F. *J. Org. Chem.* **2014**, *79*, 7239.

[114] Jain, R.; Singh, P.P.; Jain, M.; Sachdeva, S.; Misra, V.; Kaul, C.L.; Kaur, S.; Vaitilingam, B.; Nayyar, A.; Bhaskar, P.P. Ring-Substituted Quinoline Analogs as Anti-Tuberculosis Agents. Indian Patent 2002DE00628, 11 Mar, 2005.

[115] Khan, M.A.; Miller, K.; Rainsford, K.D.; Zhou, Y. *Molecules* **2013**, *18*, 3227.

prostate, breast and lung cancer).[116] Due to the wide array of applications of quinolines, there has been an increasing interest for the design of different strategies to synthesize derivatives of this privileged scaffold. Therefore, the development of new methodologies for the preparation of quinolines and their dihydro/tetrahydro counterparts is well documented in the literature.[117] Among the several methods for their synthesis, the palladium-mediated transformations[118] and, in particular, the intramolecular Mizoroki-Heck reaction[119] stand out as valuable synthetic protocols.

In our research program on quinoline synthesis,[120] we have previously reported an effective procedure for the synthesis of 2-substituted 4-alkylidenetetrahydroquinoline derivatives, which employs a 6-*exo*-trig Mizoroki-Heck cyclization of *N*-alkeny-substituted 2-haloanilines.[121] When non-substituted alkenes were used, the reaction could be directed towards the formation of an exocyclic or endocyclic carbon-carbon double bond, while 4-alkylidenetetrahydroquinolines were site-selectively obtained with substituted alkenes. In our group, the synthesis of quinolines *via* the intramolecular oxidative Heck reaction has

[116] Xiang, P.; Jie, H.; Zhou, Y.; Yang, B.; Wang, H.-J.; Hu, J.; Hu, J.; Yang, S.-Y. ; Zhao, Y.-L. *Molecules* **2015**, *20*, 7620.

[117] a) Kouznetsov, V.V.; Vargas Méndez, L.Y.; Meléndez Gómez, C.M. *Curr. Org. Chem.* **2005**, *9*, 141; b) Barluenga, J.; Rodríguez, F.; Fañanás, F.J. *Chem. Asian J.* **2009**, *4*, 1036; c) Alajarín, R.; Burgos, C. Six-Membered Heterocycles: Quinoline and Isoquinoline. In *Modern Heterocyclic Chemistry*; Álvarez-Builla, J., Vaquero, J.J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, 2011; p 1527; d) Ramann, G.A.; Cowen, B.J. *Molecules* **2016**, *21*, 986; e) Carral-Menoyo, A.; Sotomayor, N.; Lete, E. *Catal. Sci. Technol.* **2020**, *10*, 5345.

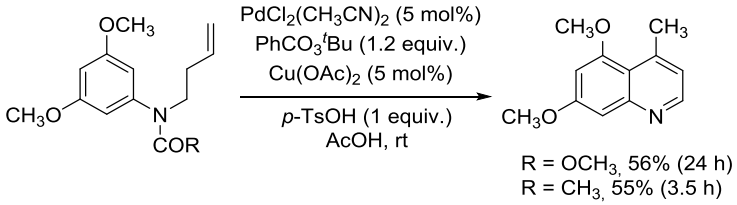
[118] a) Ahmad, N.M.; Li, J.J. Palladium in Quinoline Synthesis. In *Advances in Heterocyclic Chemistry*; Katritzky, A.R., Ed.; Elsevier: Amsterdam, 2003; Vol 84, p 1; b) *Metal-Catalyzed Cross-Coupling Reactions,* 2nd Ed; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; c) Wu, X.-E.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9047; d) Tymoshenko, D.; Jeges, G.; Gregg, B.T. Synthesis of Heterocycles by Palladium-Catalyzed Intramolecular Heteroarylation. In *Progress in Heterocyclic Chemistry*; Gribble, G.W., Joule, J.A., Eds.; Elsevier: Oxford, 2011; Vol. 23, p 27; e) Majumdar, K.C.; Samanta, S.; Sinha, B. *Synthesis* **2012**, *44*, 817.

[119] a) Zeni, G.; Larock, R.C. *Chem. Rev.* **2006**, *106*, 4644; b) *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, 2nd Ed; Li, J.J., Gribble, G.W., Eds.; Elsevier: Amsterdam, 2007; c) Muller, T.; Bräse, S. Formation of Heterocycles. In *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; Wiley-VCH: Chichester, 2009; p 215; d) Beletskaya, I.P.; Cheprakov, A.V. Modern Heck Reactions. In *New Trends in Cross-Coupling: Theory and Applications*; Colacot, T., Ed.; RSC: London, 2015; Vol. 21, p 355.

[120] a) Martínez-Estíbalez, U.; Sotomayor, N.; Lete, E. *Tetrahedron Lett.* **2007**, *48*, 2919; b) Martínez-Estíbalez, U.; Sotomayor, N.; Lete, E. *Org. Lett.* **2009**, *11*, 1237; c) García-Calvo, O.; Martínez-Estíbalez, U.; Lete, E.; Sotomayor, N. *Heterocycles* **2014**, *88*, 425.

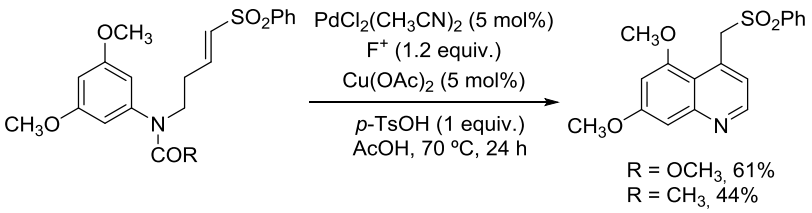
[121] Martínez-Estíbalez, U.; García-Calvo, O.; Ortiz-de-Elguea, V.; Sotomayor, N.; Lete, E. *Eur. J. Org. Chem.* **2013**, 3013.

previously been achieved using different *N*-protected butenylanilines as substrates,[122] employing for such transformation the conditions developed for the construction of 2-quinolones from the corresponding *N*-arylacrylamides.[23] The reaction proceeded through a 6-*exo*-trig cyclization process, followed by isomerization of the double bond to the endocyclic position and further deprotection and oxidation of the product formed (Scheme 2.67).



Scheme 2.67

When an electron withdrawing group, such as phenyl sulfone, was placed in the terminal position of the alkene, the reaction had to be carried out at 70 ºC and using a stronger stoichiometric oxidant, *N*-fluoro 2,4,6-trimethylpyridinium triflate (F^+), specifically (Scheme 2.68).[122] In this context, the use of $Cu(OAc)_2$ along with a stoichiometric oxidant is thought to facilitate the reoxidation of Pd(0) to Pd(II), therefore lowering the reductive decomposition of the catalyst to palladium black.[28i]



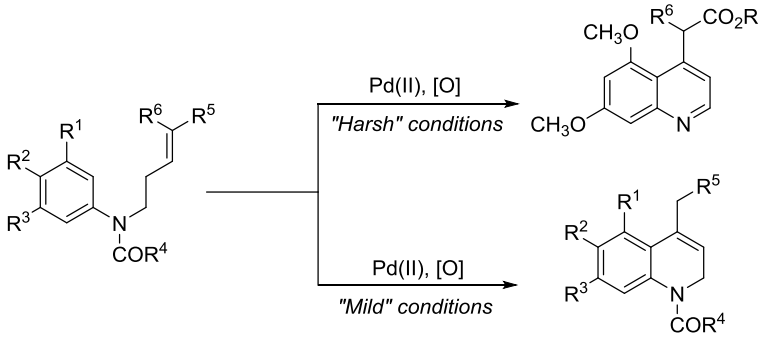
Scheme 2.68

As it can be observed in Scheme 2.67, the utilization of terminal *N*-protected butenylanilines as substrates led to the formation of the corresponding quinolines with almost the same yield regardless of the protecting group used on the nitrogen. However, the transformation proceeded faster when acetamide was employed (3.5 h), since 24 h were required for the reaction to achieve completion with the carbamate starting material. On the other hand,

[122] Ortiz-de-Elguea, V. Ready Access to Quinoline and Coumarin Scaffolds *via* Palladium-Catalyzed Alkenylation Reactions. Ph.D. Thesis, UPV/EHU, November 2014.

when the substrates bearing electron-deficient olefins were subjected to the reaction conditions (Scheme 2.68), the efficiency of the transformation was switched, as the carbamate-*N*-protected substrate afforded the corresponding quinoline in a higher yield than its acetamide counterpart (61% *vs* 44%).

With this encouraging former results in mind and as it has been stated in the aims of the chapter, we decided to investigate the feasibility of broadening the scope of the reaction to the synthesis of 4-substituted quinolines bearing different esters as the electron withdrawing groups (Scheme 2.69).



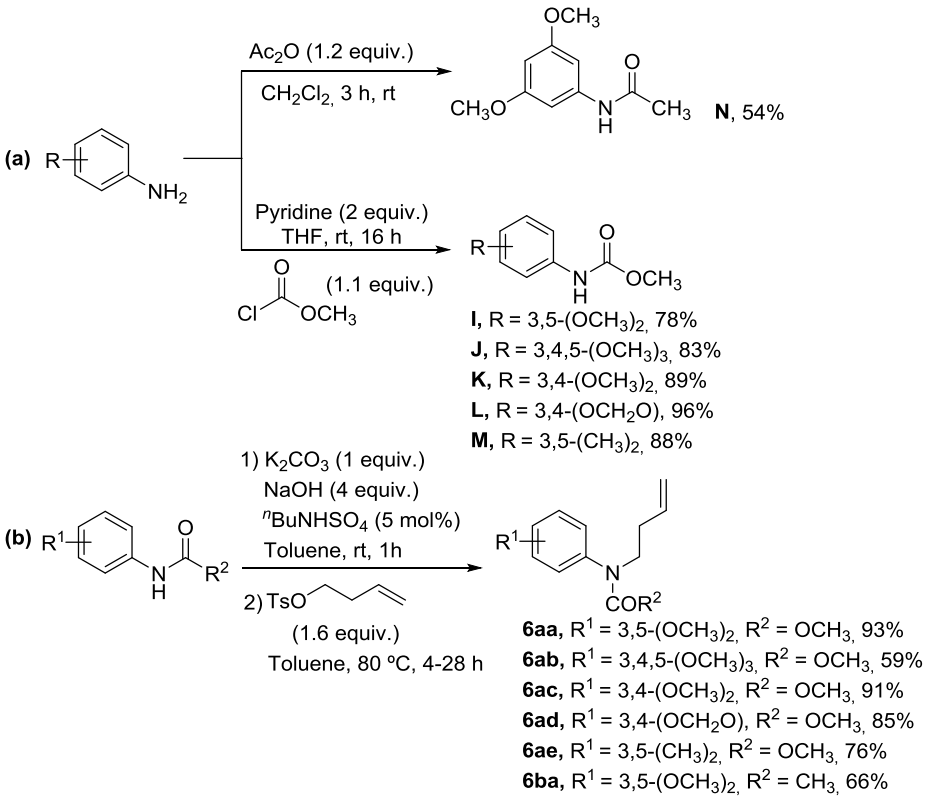
Scheme 2.69

Besides, we envisioned that the utilization of milder reaction conditions, such as those employed in the synthesis of the chromane core,[84] would prevent the last aromatization process from occurring, thus leading to the formation of 1,2-dihydroquinolines (Scheme 2.69).

3.2.1. Synthesis of the substrates[96]

Herein, the synthetic methodology employed for the preparation of substrates **6aa-6ba** and **7aa-7bf** will be disclosed. To start with, we prepared *N*-protected butenylanilines **6aa-6ba** in two simple steps: 1) protection of the corresponding aniline, and 2) incorporation of the homoallyl chain *via* alkylation in basic media. With this strategy in mind, different anilines were protected as methyl carbamates using methyl chloroformate to furnish **I**-**M** (Scheme 2.70a). Additionally, 3,5-dimethoxyaniline was also treated with acetic anhydride, yielding acetamide **N** (Scheme 2.70a). Afterwards, those *N*-protected electron-rich anilines **I-N** were subjected to an alkylation process under phase transfer conditions, employing but-3-en-1-yl 4-methylbenzenesulfonate, which was synthesized from commercially available 3-buten-

1-ol.[123] That way, the corresponding *N*-protected butenylanilines **6aa-6ba** were provided in good to excellent yields (Scheme 2.70b).

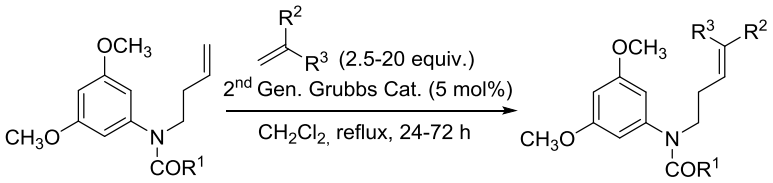


Scheme 2.70

Once substrates **6aa-6ba** bearing unsubstituted alkenes were synthesized, we next subjected **6aa** and **6ba** to cross metathesis reactions, using 2nd generation Grubbs catalyst, with the aim of installing electron-withdrawing functionalities on the terminus of the olefin moiety. Following this method, the corresponding products **7aa-7bf** were isolated in good to excellent yields for both carbamate and acetamide substrates (Scheme 2.71). All the acrylates utilized in the reaction were commercial except for benzyl acrylate, which was

[123] The synthesis of this alkylating agent was accomplished following the procedure described in Falb, E.; Nudelman, A.; Gottlieb, H.E.; Hassner, A. *Eur. J. Org. Chem.* **2000**, 645.

prepared from acryloyl chloride and benzyl alcohol.[124] It is worth to mention that in all the cases the corresponding *E*-configured products were obtained.



6aa, $R^1 = OCH_3$
6ba, $R^1 = CH_3$

7aa, $R^1 = OCH_3$, $R^2 = CO_2CH_3$, $R^3 = H$, 88%
7ba, $R^1 = CH_3$, $R^2 = CO_2CH_3$, $R^3 = H$, 91%
7ab, $R^1 = OCH_3$, $R^2 = CO_2(CH_2)_{11}CH_3$, $R^3 = H$, quant.
7ac, $R^1 = OCH_3$, $R^2 = CO_2CH_2CF_3$, $R^3 = H$, 94%
7ad, $R^1 = OCH_3$, $R^2 = CO_2Bn$, $R^3 = H$, 86%
7ae, $R^1 = OCH_3$, $R^2 = CO_2CH_3$, $R^3 = CH_3$, 92%
7af, $R^1 = OCH_3$, $R^2 = SO_2Ph$, $R^3 = H$, 71%
7bf, $R^1 = CH_3$, $R^2 = SO_2Ph$, $R^3 = H$, 77%

Scheme 2.71

*3.2.2. Palladium(II)-catalyzed intramolecular alkenylation of N-protected butenylanilines **6aa-6ba** and **7aa-7bf**. Synthesis of quinolines **8a-8d** and dihydroquinolines **9aa-9ba** and **10ae***

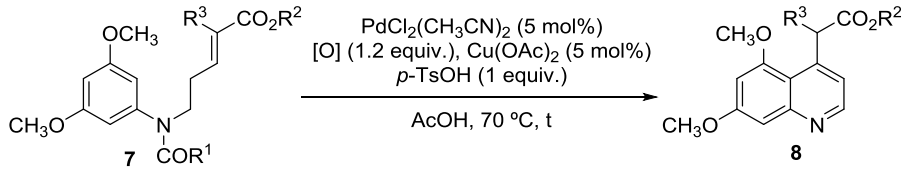
As it has been stated before, keeping in mind the previous results obtained in our group regarding the assembly of the quinoline core *via* the intramolecular Fujiwara-Moritani reaction,[122] we commenced our study by checking the possibility of using *N*-butenylanilines **7**, with ester groups attached to the alkene terminus, as substrates in the mentioned cyclization. That way, several 4-substituted quinolines could be obtained (Table 2.7).

When carbamate **7aa** was subjected to the reaction conditions shown in scheme 2.68, the corresponding quinoline **8a** was obtained in 54% percent yield after 19 h (Table 2.7, entry 1). Similarly to the tendency observed with the sulfone-substituted substrates (Scheme 2.68),[122] although the same yield of **8a** was achieved when employing the acetamide counterpart **7ba**, longer reaction times and higher catalytic loadings were required (Table 2.7, entry 2), indicating the lower efficiency of the acetamide-*N*-protected starting materials.

[124] The synthesis of benzyl acrylate was accomplished following the procedure described in Chanthamath, S.; Takaki, S.; Shibatomi, K.; Iwasa, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 5818.

The utilization of $PhCO_3{}^tBu$ as oxidant instead of F^+ in the cyclization of **7ba**, led to the formation of **8a** in a lower yield (32%) after 47 h (Table 2.7, entry 3). The scope of the reaction was further studied using substrates **7ab**-**7ae**, possessing carbamate-protecting groups, due to their higher reactivity. Thus, the reaction proceeded efficiently for the synthesis of quinolines **8b**-**8d** that bear different ester moieties (Table 2.7, entries 4-6), but failed when a trisubstituted olefin was used (Table 2.7, entry 7).

Table 2.7



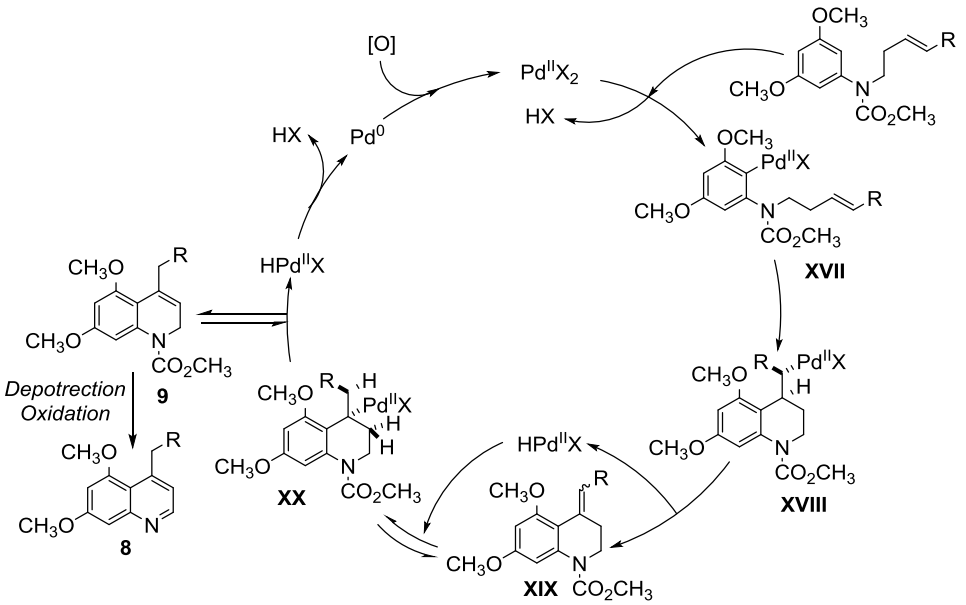
Entry	Subst.	R^1	R^2	R^3	[O]	t (h)	Prod.	Yield (%)[a]
1	**7aa**	OCH_3	CH_3	H	F^+	19	**8a**	54
2	**7ba**	CH_3	CH_3	H	F^+	41	**8a**	54[b]
3	**7ba**	CH_3	CH_3	H	$PhCO_3{}^tBu$	47	**8a**	32[b]
4	**7ab**	OCH_3	$(CH_2)_{11}CH_3$	H	F^+	21	**8b**	50
5	**7ac**	OCH_3	CH_2CF_3	H	F^+	21	**8c**	46
6	**7ad**	OCH_3	Bn	H	F^+	21	**8d**	62
7	**7ae**	OCH_3	CH_3	CH_3	F^+	21	-	-[c]

[a] Yield of the isolated pure compounds. [b] An additional amount of the catalyst (5 mol%) had to be added during the reaction. [c] Decomposition was observed.

Based on the results obtained, and the mechanism proposals given in previous works,[23] this reaction was thought to proceed as depicted in Scheme 2.72. First, aromatic metalation of the arene would take place through electrophilic palladation to form species **XVII**, favored by the electron-donor effect of the substituents on the aromatic ring. Subsequently, *syn* migratory insertion of the alkene in a 6-*exo*-trig fashion would take place, giving **XVIII**, which after β-hydride elimination would provide tetrahydroquinoline **XIX**, along with palladium hydride. However, despite those considerations, a pathway involving a prior activation of the alkene followed by arene insertion cannot be discarded,[72c,72g,125] since that route would also effectively lead to the formation of intermediate **XIX**.

[125] McDonald, R.I.; Liu, G.; Stahl, S.S. *Chem. Rev.* **2011**, *111*, 2981.

Irrespective of the mechanism operating in the first steps of the catalytic cycle, the exocyclic double bond of **XIX** could isomerize to form the 1,2-dihydroquinoline **9** (with an endocyclic double bond) *via* palladium(II) hydride migratory insertion to form intermediate **XX**, which would evolve to 1,2-dihydroquinoline **9** through β-hydride elimination. The obtained Pd(II) hydride undergoes reductive elimination to form a Pd(0) species that is afterwards reoxidized to the catalytically active Pd(II) species. The 1,2-dihydroquinoline **9** delivered from the catalytic cycle is then proposed to undergo deprotection and oxidation/aromatization, to furnish the corresponding quinoline **8**.



Scheme 2.72

As pointed out previously, after accomplishing this intramolecular coupling, we envisioned that it would be possible to obtain the corresponding 1,2-dihydroquinolines (1,2-DHQ) starting from the same substrates employed for the synthesis of quinolines (namely, *N*-protected butenylanilines **6-7**). This aim would be attained by avoiding deprotection of the nitrogen atom and thus, preventing further oxidation. Indeed, the synthesis of 1,2-DHQs is of high interest, as those compounds have proved to be privileged scaffolds which show

antibacterial,[126] antitrypanosomal[127] and antioxidant[128] activities, among others. They can also be employed as antidiabetic agents[129] and antijuvenile hormone insecticides.[130] Relevant examples include the antioxidant ethoxyquin, which is used as food preservative,[131] and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), that can act as D-2 dopamine receptor antagonist and irreversible α-adrenergic antagonist (Figure 2.8).[132]

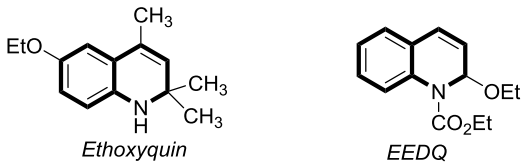


Figure 2.8

We envisioned that the development of an effective method to synthesize 1,2-DHQs would imply the use of milder reaction conditions, avoiding the utilization of acetic acid as solvent. In order to accomplish the proposed transformation, it was decided to employ the reaction conditions previously applied for the formation of the chromane core starting from the corresponding aryl homoallyl ethers.[84]

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[126] Johnson, J.V.; Rauckman, B.S.; Baccanari, D.P.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942.

[127] a) Fotie, J.; Kaiser, M.; Delfín, D.A.; Manley, J.; Reid, C.S.; Paris, J.-M.; Wenzler, T.; Maes, L.; Mahasenan, K.V.; Li, C.; Werbovetz, K.A. *J. Med. Chem.* **2010**, *53*, 966; b) Reid, C.S.; Patrick, D.A.; He, S.; Fotie, J.; Premalatha, K.; Tidwell, R.R.; Wang, M.Z.; Liu, Q.; Gershkovich, P.; Wasan, K.M.; Wenzler, T.; Brun, R.; Werbovetz, K.A. *Bioog. Med. Chem.* **2011**, *19*, 513.

[128] a) Lockhart, B.; Bonhomme, N.; Roger, A.; Dorey, G.; Casara, P.; Lestage, P. *Eur. J. Pharmacol.* **2001**, *416*, 59; b) Ramis-Ramos, G. Synthetic Antioxidants. In *Encyclopedia of Food Sciences and Nutrition*, 2nd Ed; Caballero, B., Ed.; Academic Press: San Diego, 2003; p 275.; c) Kumar, S.; Engman, L.; Valgimigli, L.; Amorati, R.; Fumo, M.G.; Pedulli, G.F. *J. Org. Chem.* **2007**, *72*, 6046.

[129] a) Takahashi, H.; Bekkali, Y.; Capolino, A.J.; Gilmore, T.; Goldrick, S.E.; Kaplita, P.V.; Liu, L.; Nelson, R.M.; Terenzio, D.; Wang, J.; Zuvela-Jelaska, L.; Proudfoot, J.; Nabozny, G.; Thomson, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5091; b) Kato, M.; Takai, M.; Matsuyama, T.; Kurose, T.; Hagiwara, Y.; Matsuda, M.; Mori, T.; Imoto, K.; Dota, A. (Santen Pharmaceutical Co., Ltd., Japan). Preparation of 2,2,4-Trimethyl-6-phenyl-1,2-dihydroquinoline Derivatives Having Substituted Oxy Group as Glucocorticoid Receptor Agonists. PCT Int. Appl. WO 2009139361 A1, May 12, 2009.

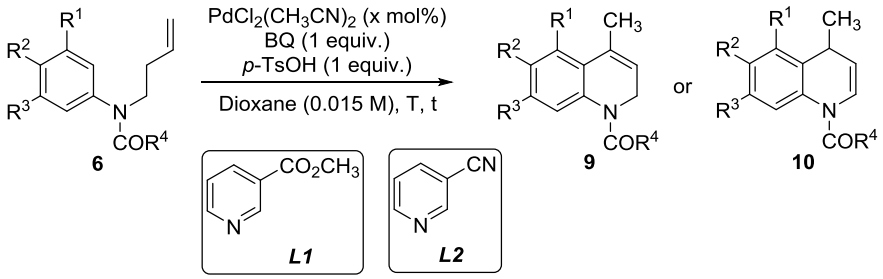
[130] Tsushima, K.; Hatakoshi, M.; Matsuo, N.; Ohno, N.; Nakayama, I. *Agric. Biol. Chem.* **1985**, *49*, 2421.

[131] a) Pryor, W.A.; Strickland, T.; Church, D.F. *J. Am. Chem. Soc.* **1988**, *110*, 2224; b) de Koning, A.J. *Int. J. Food Prop.* **2002**, *5*, 451; c) Błaszczyck, A.; Skolimowski, J. *Chem.-Biol. Interact.* **2006**, *162*, 70.

[132] Hamblin, M.W.; Creese, I. *Life Sci*. **1983**, *32*, 2247.

Thus, we found that the cyclization could be efficiently performed in dioxane at room temperature, using benzoquinone as the oxidant in the presence of *p*-toluenesulfonic acid (Table 2.8). Under these reaction conditions, both protecting groups **6aa** and **6ba** were stable, and dihydroquinolines **9aa** and **9ba** were obtained in good yields (Table 2.8, entries 1 and 3, respectively). Once again, the carbamate-protected aniline **6aa** was more reactive than acetamide **6ba**, leading to a good yield of **9aa** in a shorter reaction time (7.5 h *vs* 25 h).

Table 2.8



Entry	Subst.	R^1	R^2	R^3	R^4	T (ºC)	t (h)	Pd(II) (mol%)	Prod.	Yield (%)[a]
1	**6aa**	OCH_3	H	OCH_3	OCH_3	rt	7.5	5	**9aa**	74
2	**6aa**	OCH_3	H	OCH_3	OCH_3	70	10 min	5	**9aa**	89
3	**6ba**	OCH_3	H	OCH_3	CH_3	rt	25	5	**9ba**	62
4	**6ba**	OCH_3	H	OCH_3	CH_3	rt[b]	23	5	-	-[d]
5	**6ba**	OCH_3	H	OCH_3	CH_3	rt[c]	23	5	-	-[d]
6	**6ab**	OCH_3	OCH_3	OCH_3	OCH_3	rt	24	5	-	-[d]
7	**6ab**	OCH_3	OCH_3	OCH_3	OCH_3	70	2	5	**9ab**	33
8	**6ab**	OCH_3	OCH_3	OCH_3	OCH_3	70	2	10	**9ab**	40
9	**6ab**	OCH_3	OCH_3	OCH_3	OCH_3	70	7	10	**9ab**	11
10	**6ac**	H	OCH_3	OCH_3	OCH_3	70	24	10	-	-[d]
11	**6ad**	H	OCH_2O		OCH_3	70	24	10	-	-[d]
12	**6ae**	CH_3	H	CH_3	OCH_3	70	24	10	**10ae**	32

[a] Yield of the isolated pure compounds. [b] **L1** (5 mol%) was added. [c] **L2** (5 mol%) was added. [d] No reaction. Starting material recovered.

An increase of the reaction temperature to 70 ºC led to a more efficient reaction, obtaining **9aa** in high yield (89%) after only 10 minutes (Table 2.8, entry 2). The use of ligands for palladium to increase reactivity was also studied. In this context, pyridine ligands have been

shown to enhance not only the reaction rate, but also the site selectivity in Pd(II)-catalyzed reactions[52,53] and they have been used in intramolecular couplings, in combination with different oxidants.[72g,76,79] We selected two pyridine ligands: methyl nicotinate (**L1**) and 3-cyanopyridine (**L2**); however, the use of those ligands proved to be detrimental for the reaction, completely precluding the transformation (Table 2.8, entries 4 and 5, respectively).

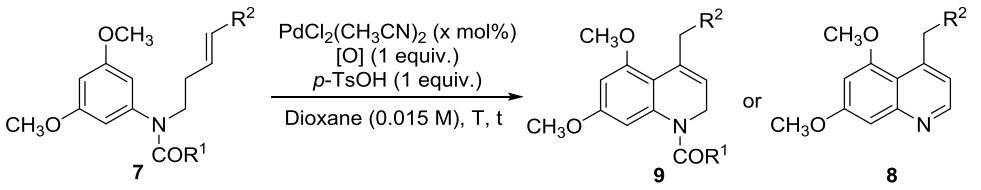
Then, the extension to other substitution patterns on the aromatic ring was studied. Interestingly, with a more electron-rich aromatic ring (**6ab**), the reaction was less efficient, and no cyclization was observed at room temperature after 24 h (Table 2.8, entry 6). An increase of the temperature was required to obtain **9ab** in a low yield (Table 2.8, entry 7), which could be improved increasing the catalyst loading (Table 2.8, entry 8). However, an increase of the reaction time led to decomposition, lowering the isolated yield of **9ab** (Table 2.8, entry 9).

An electron-donor group *ortho* to the cyclization position appears to be necessary, as no product was observed whatsoever, when the 3,4-disubstituted substrates **6ac** and **6ad** where employed (Table 2.8, entries 10 and 11, respectively). However, when weakly donor methyl groups were incorporated in 3,5-positions (**6ae**), the cyclization took place, but in this case, isomerization of the double bond led to the formation of the 1,4-dihydroquinoline **10ae** (Table 2.8, entry 12).

Furthermore, we decided to study the tolerance of the developed transformation towards the presence of electron-withdrawing groups tethered to the terminal position of the alkene (Table 2.9). When substrate **7af** with a sulfone group was subjected to the "mild" reaction conditions, the transformation did not proceed after 24 h (Table 2.9, entry 1), not even upon heating at 70 ºC for 72 h (Table 2.9, entry 2). When acetamide **7bf** was used at that temperature and the reaction time was increased to 96 h in the presence of 10 mol% of the catalyst (Table 2.9, entry 3), only traces of the cyclization product could be observed.

We then used *N*-butenylanilines **7aa** and **7ba** as substrates, bearing methoxycarbonyl-substituted alkenes. None of those substrates were able to furnish the corresponding dihydroquinolines regardless of the temperature (rt-70 ºC), time (24-48 h) and catalyst loading (5-10 mol%) (Table 2.9, entries 4-6). In order to try to improve those results, different oxidants were tested using acetamide **7ba** as the model substrate: $PhCO_3{}^tBu$ (Table 2.9, entry 7) and F^+ (Table 2.9, entry 8). However, in both cases traces of the aromatized cyclization product **8a** were observed.

Table 2.9



Entry	Subst.	R^1	R^2	[O]	T (ºC)	t (h)	Pd(II) (mol%)	Prod.	Yield (%)
1	**7af**	OCH_3	SO_2Ph	BQ	rt	24	5	-	-[a]
2	**7af**	OCH_3	SO_2Ph	BQ	70	72	5	-	-[a]
3	**7bf**	CH_3	SO_2Ph	BQ	70	96	10	**9bf**	-[b]
4	**7aa**	OCH_3	CO_2CH_3	BQ	rt	24	5	-	-[a]
5	**7aa**	OCH_3	CO_2CH_3	BQ	70	48	10	-	-[a]
6	**7ba**	CH_3	CO_2CH_3	BQ	70	48	10	-	-[a]
7	**7ba**	CH_3	CO_2CH_3	$PhCO_3{}^tBu$	70	60	10	**8a**	-[b]
8	**7ba**	CH_3	CO_2CH_3	F^+	70	48	10	**8a**	-[b]

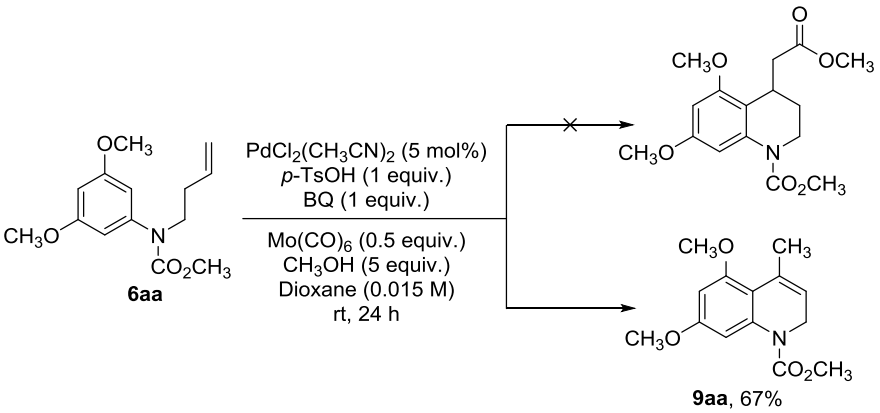
[a] No reaction. Starting material recovered. [b] Traces of the product were observed.

As stated in the introduction of this chapter, Yang and co-workers were able to carry out the synthesis of chromanes *via* a Fujiwara-Moritani cyclization of aryl homoallyl ethers followed by carbonylation using gaseous carbon monoxide.[78] Based on this and taking into account that Carretero and co-workers reported the use of $Mo(CO)_6$ as carbon monoxide source in Pd(II)-catalyzed C-H activation reactions,[133] with the aim of forming the corresponding tetrahydroquinoline, we attempted the Pd(II)-catalyzed cyclization followed by carbonylation of substrate **6aa**, using $Mo(CO)_6$ as carbon monoxide source and CH_3OH as the nucleophile. Nevertheless, the carbonylation step did not take place and only the usual 1,2-dihydroquinoline product was obtained in a good yield (Scheme 2.73).

In conclusion, it has been shown that both quinolines and 1,2-dihydroquinolines can be selectively obtained in moderate to good yields *via* palladium(II)-catalyzed intramolecular C-H alkenylative couplings, by the right choice of the reaction conditions. Thus, when the trasformations are carried out in acetic acid, deprotection and further oxidation leads to the one-pot formation of 4-substituted quinolines **8a-8d**. On the other hand, under mild reaction conditions, deprotection and over-oxidation can be avoided, leading to 1,2-

[133] Hernando, E.; Villalva, J.; Martínez, A.M.; Alonso, I.; Rodríguez, N.; Gómez-Arrayás, R.; Carretero, J.C. *ACS Catal.* **2016**, *6*, 6868.

dihydroquinolines **9aa**, **9ba** and **9ab**; nonetheless, the reaction does not tolerate electron-deficient alkenes. This procedure has proved to provide the corresponding 1,2-dihydroquinolines regioselectively, since not even small amounts of the 4-methylenetetrahydroquinoline counterparts (bearing exocyclic double bonds) have been observed. This fact is in contrast to the tendency seen in the Pd(II)-catalyzed alkenylation of aryl homoallyl ethers for the synthesis of chromenes, where substrate control had to be used to get complete site selectivity towards the product bearing the endocyclic double bond.[84]



Scheme 2.73

Furthermore, this method is complementary to the related Mizoroki-Heck reaction developed by our group, which led to the formation of 4-methylenetetrahydroquinolines,[121] with the advantage that the methodology described throughout this section does not require the prior functionalization of the substrates. However, the method is so far limited to the use of electron-rich aromatic rings.

3.3. Intramolecular palladium(II)-catalyzed 6-*endo* C-H alkenylation directed by the remote *N*-protecting group. Mechanistic insight and application to the synthesis of dihydroquinolines[134]

Following with the synthesis of quinoline derivatives, we envisioned the possibility of achieving the successful formation of a variety of dihydroquinolines using *N*-protected allyl-anilines as substrates instead of their homoallylic homologues (Figure 2.9). This reaction would proceed *via* a 6-*endo*-trig cyclization rather than through the 6-*exo*-trig process disclosed in the previous sections.

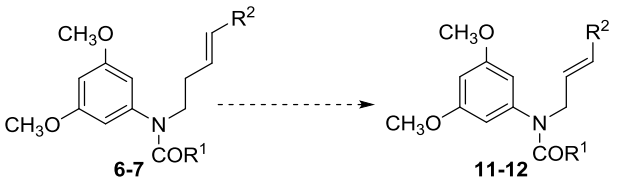


Figure 2.9

As in related Heck cyclizations, the regioselectivity of the intramolecular Fujiwara-Moritani reaction is determined by the ring size and the preferential *exo* processes, which has been attributed to the strain involved in the approach of the arene to the olefin. On the other hand, *endo*-trig cyclizations are rare and have been reported when the *exo* processes are blocked, and the palladium hydride elimination is not possible.[72d,72e] Nonetheless, as previously stated, our group has already reported the synthesis of several 2-quinolones *via* a 6-*endo*-trig intramolecular dehydrogenative Heck reaction, using *N*-arylacrylamides as substrates.[23] Since those compounds are similar to *N*-allylanilines **11**, we were encouraged by the possibility of extrapolating that method to the synthesis of dihydroquinolines.

Partially hydrogenated quinolines are important structural motifs present in a myriad of bioactive natural products and pharmaceuticals, and can be efficiently utilized as building blocks in organic synthesis.[135] Among them, 1,4-dihydroquinolines (1,4-DHQ) have attracted special attention, due to their important biological activities. For example, 4-aryl 1,4-

[134] The work described in this section has been published in: Carral-Menoyo, A.; Sotorríos, L.; Ortiz-de-Elguea, V.; Díaz-Andrés, A.; Sotomayor, N.; Gómez-Bengoa, E.; Lete, E. *J. Org. Chem.* **2020**, *85*, 2486.

[135] For selected reviews, see: a) Ref. 107b; b) Ref. 108a; c) Garrido Montalban, A. Quinolines and Isoquinolines. In *Heterocycles in Natural Product Synthesis*; Majumdar, K.C., Chattopadhyay, S.K., Eds.; Wiley-VCH: Weinheim, 2011; p 299; d) Ref. 107c.

dihydroquinoline derivatives (Figure 2.10) have been characterized as a novel class of ABCB1 inhibitors to reverse the multidrug resistance of anticancer drugs.[136] Azapodophyllotoxins (Figure 2.10), whose core is based on 1,4-dihydroquinolines, are known to be antiproliferative microtubule destabilizing agents and have expressed a very pronounced antitumor activity.[137] 1,4-DHQs can also be used as drug carriers for specific delivery to the central nervous system in the treatment of Alzheimer´s disease[138] or cerebral ischemia/reperfusion injury,[139] as well as in the targeting of positron emission tomography radioligands for brain imaging.[140] On the other hand, they are used as building blocks in the synthesis of pyridoacridones,[141] a family of marine alkaloids that exhibit an array of biological activities.[112b,113a]

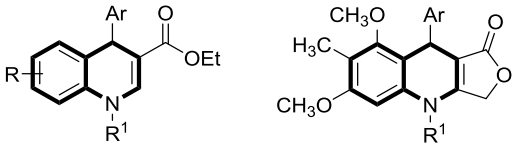


Figure 2.10

Although many examples of the catalytic synthesis of quinolines and tetrahydroquinolines have been reported,[142] there have been relatively few examples of the preparation of 1,4-

[136] For a review, see: a) Hilgeroth, A.; Baumert, C.; Coburger, C.; Seifert, M.; Krawczyk, S.; Hempel, C.; Neubauer, F.; Krug, M.; Molnar, J.; Lage, H. *Med. Chem.* **2013**, *9*, 487; For representative examples, see: b) Hemmer, M.; Krawczyk, S.; Simon, I.; Lage, H.; Hilgeroth, A. *Bioorg. Med. Chem*. **2015**, *23*, 5015; c) Hemmer, M.; Krawczyk, S.; Simon, I.; Hilgeroth, A. *Bioorg. Med. Chem. Lett*. **2015**, *25*, 3005.

[137] a) Kumar, A.; Kumar, V.; Alegria, A.E.; Malhotra, S.V. *Curr. Med. Chem.* **2011**, *18*, 3853; b) Chernysheva, N.B.; Tsyganov, D.V.; Philchenkov, A.A.; Zavelevich, M.P.; Kiselyov, A.S.; Semenov, R.V.; Semenova, M.N.; Semenov, V.V. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2590.

[138] a) Bodor, N.; Farag, H.H.; Barros, M.D.C.; Wu, W.-M.; Buchwald, P. *J. Drug. Target.* **2002**, *10*, 63; b) Ţînţaş, M.-L.; Foucout, L.; Petit, S.; Oudeyer, S.; Gourand, F.; Barré, L.; Papamicaël, C.; Levacher, V. *Eur. J. Med. Chem.* **2014**, *81*, 218.

[139] Dong, Y.; Dong, L.; Chen, J.; Luo, M.; Fu, X.; Qiao, C. *Med. Chem. Res.* **2018**, *27*, 1111.

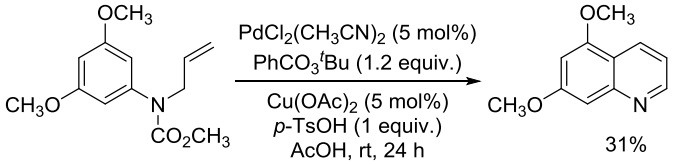
[140] a) Foucout, L.; Gourand, F.; Dhilly, M.; Bohan, P.; Dupas, G.; Costentin, J.; Abbas, A.; Marsais, F.; Barré, L.; Levacher, V. *Org. Biomol. Chem.* **2009**, *7*, 3666; b) Gourand, F.; Ţînţaş, M.-L.; Henry, A.; Ibazizène, M.; Dhilly, M.; Fillesoye, F.; Papamicaël, C.; Levacher, V.; Barré, L. *ACS Chem. Neurosci.* **2017**, *8*, 2457.

[141] Zhang, D.; Llorente, I.; Liebeskind, L.S. *J. Org. Chem.* **1997**, *62*, 4330.

[142] a) Ref. 117a; b) Ref. 117b; c) Sridharan, V.; Suryavanshi, P.A.; Menéndez, J.C. *Chem. Rev.* **2011**, *111*, 7157; d) Solomon, V.R.; Lee, H. *Curr. Med. Chem.* **2011**, *18*, 1488; e) Ref. 117c

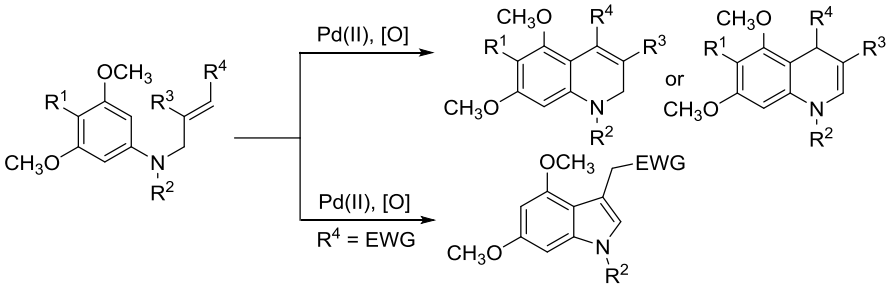
dihydroquinoline derivatives. In this context, we have been able to develop a 6-*endo*-trig cyclization of *N*-protected allylanilines that leads to the synthesis of 1,4-dihydroquinolines from simple and readily accessible substrates.

We supposed that we would be capable of synthesizing 6-membered rings upon cyclization of different *N*-protected allylanilines due to a preliminary result previously obtained in our group.[122] In this regard, when *N*-allyl-3,5-dimethoxyaniline, protected as a carbamate, was subjected to the reaction conditions reported for the cyclization of *N*-arylacrylamides,[23] it was observed that the transformation proceeded *via* a 6-*endo*-trig process, followed by aromatization, to furnish the corresponding quinoline (Scheme 2.74). That compound was provided in low yield (31%), together with decomposition products.



Scheme 2.74

Taking into account that we have previously succeeded in avoiding the last aromatization step for the synthesis of dihydroquinolines by means of 6-*exo*-trig cyclizations of *N*-protected butenylanilines,[106] we envisioned that the use of the same mild reaction conditions over *N*-protected allylanilines would allow us to obtain 1,2- or 1,4-dihydroquinolines through Pd(II)-promoted intramolecular 6-*endo*-trig alkenylative couplings, as disclosed in the aims of the chapter (Scheme 2.75).

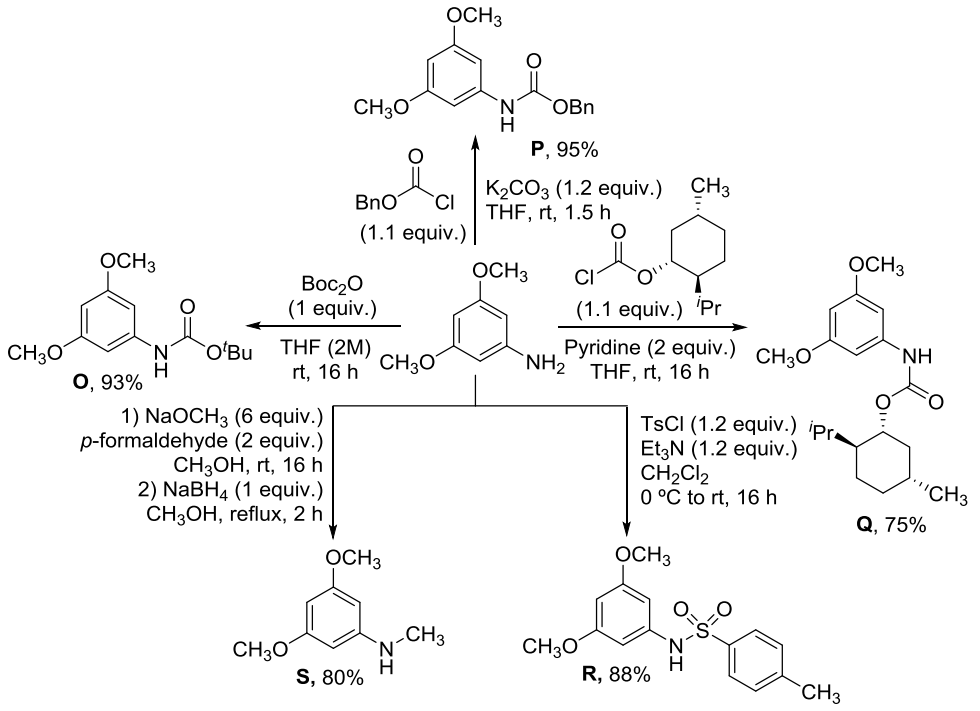


Scheme 2.75

Moreover, *exo* cyclizations are generally favored using activated alkenes (bearing an electron-withdrawing group). We therefore thought that the addition of electron-withdrawing functionalities to the alkene terminus would lead to a change in the regioselectivity of the cyclization, furnishing the corresponding 3-substiuted indoles due to 5-*exo*-trig processes (Scheme 2.75).

3.3.1. Synthesis of the substrates[96]

In this section the synthesis of *N*-protected allylanilines **11aa-11gl**, ***(Z)*-11ac**, esters **12aa-12ba** and carbamate **13aa** will be disclosed. First of all the installation of a variety of *N*-protecting groups on the corresponding anilines was carried out, using different functionalities for that purpose (Scheme 2.76).



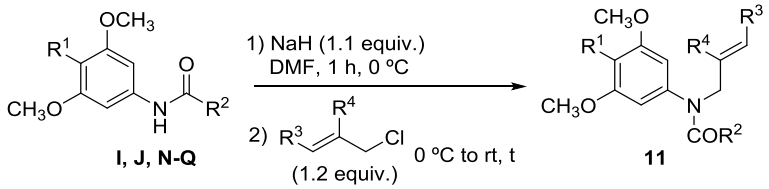
Scheme 2.76

Apart from methyl carbamates **I**, **J** and acetamide **N**, whose preparation has been previously commented (Scheme 2.70a), 3,5-dimethoxyaniline was also protected by treatment with

di-*tert*-butyl dicarbonate, benzyl chloroformate and (-)-menthyl chloroformate, furnishing carbamates **O**, **P** and **Q**, respectively (Scheme 2.76). Furthermore, that same aniline was protected as sulfone **R** (using *p*-toluenesulfonyl chloride) and even mono-methylated by reductive amination, to provide **S** (Scheme 2.76).

Those *N*-protected anilines were afterwards subjected to alkylation reactions to install different allyl moieties, obtaining substrates **11aa-11gc** (Table 2.10), as well as **11ea-11fn** (Scheme 2.77). In all the cases, the allylating agents employed were commercially available except for *(E)*-(4-bromobut-2-en-1-yl)benzene, that had to be prepared using an already described procedure.[143]

Table 2.10



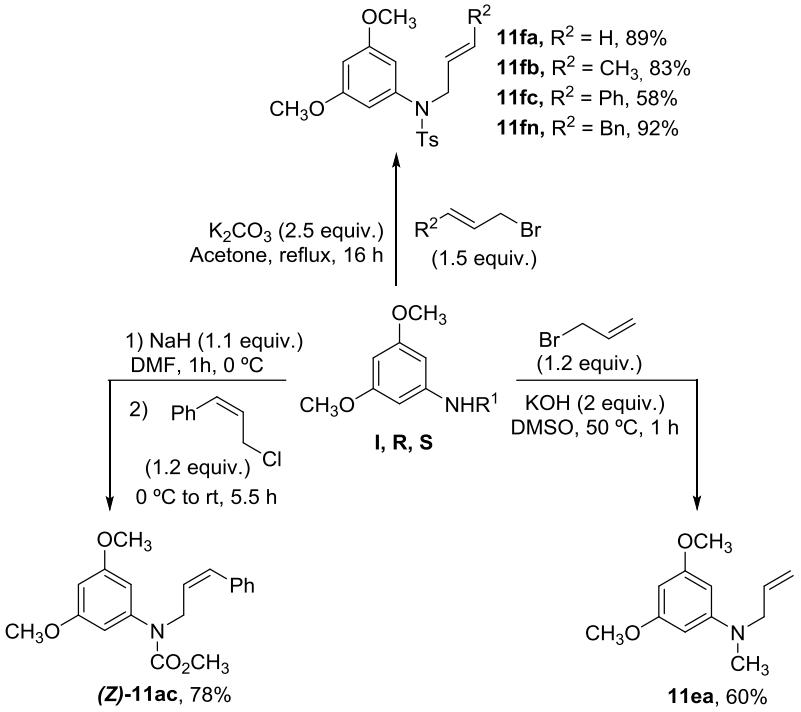
Entry	Subst.	R^1	R^2	R^3	R^4	t (h)	Prod.	Yield (%)[a]
1	**I**	H	OCH_3	H	H	3	**11aa**	91
2	**I**	H	OCH_3	CH_3	H	7	**11ab**	88
3	**I**	H	OCH_3	Ph	H	3	**11ac**	70
4	**I**	H	OCH_3	H	CH_3	3	**11am**	89
5	**J**	OCH_3	OCH_3	H	H	5	**11baa**	91
6	**O**	H	O^{t}Bu	H	H	4	**11ba**	72
7	**O**	H	O^{t}Bu	Ph	H	7.5	**11bc**	98
8	**P**	H	OBn	H	H	5	**11ca**	86
9	**N**	H	CH_3	H	H	3	**11da**	97
10	**Q**	H	O(-)Menth.	H	H	4	**11ga**	72
11	**Q**	H	O(-)Menth.	CH_3	H	7	**11gb**	82
12	**Q**	H	O(-)Menth.	Ph	H	7	**11gc**	71

[a] Yield of the isolated pure compounds.

The synthesis of ***(Z)*-11ac** (with a *Z*-configured olefin) was also accomplished by alkylation of carbamate **I**, using in this case *(Z)*-cinnamyl chloride (Scheme 2.77), which was prepared

[143] Race, N.J.; Bower, J.F. *Org. Lett.* **2013**, *15*, 4616.

through partial hydrogenation of commercial 3-phenyl-2-propyn-1-ol,[144] followed by chlorination of the *(Z)*-allyl alcohol obtained.[145]



Scheme 2.77

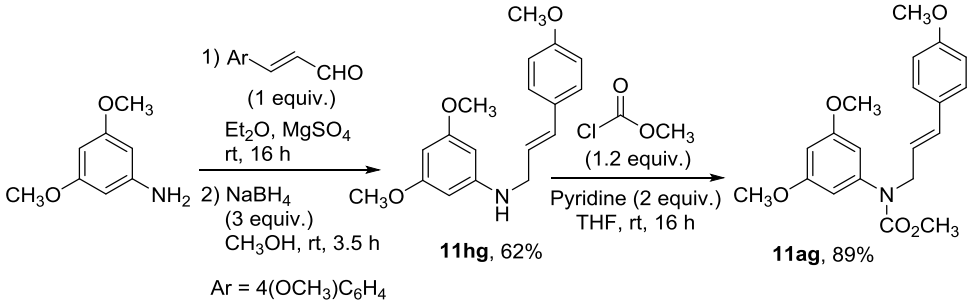
On the other hand, the synthesis of substrates **11ad-11gl** bearing different aryl groups at the alkene terminus proved to be much more troublesome, since the cinnamyl halides necessary for their preparation were not commercially available. Taking this into account, we envisioned that it could be possible to synthesize a variety of allyl chlorides with aryl substituents on the terminal position of the alkene and employ them to install those moieties in different *N*-protected anilines *via* the protocol disclosed in Table 2.10. To check the feasibility of this synthetic method, *(E)*-1-(3-chloroprop-1-en-1-yl)-3-methoxybenzene was prepared,[146] but when reacting it with carbamate **I**, the alkylation did not proceed to

[144] Rehbein, J.; Leick, S.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1531.
[145] Jiang, T.; Huynh, K.; Livinghouse, T. *Synlett* **2013**, *24*, 193.
[146] Meiβ, R.; Kumar, K.; Waldmann, H. *Chem. Eur. J.* **2015**, *21*, 13526.

completion, and to make matters worse, **11ah** was isolated as a mixture with the corresponding allyl chloride.

In the quest for a better methodology for the synthesis of those substrates, we supposed that it would be possible to prepare the desired compounds by reductive amination of different cinnamaldehydes with 3,5-dimethoxyaniline; followed by the protection of the free NH (Scheme 2.78).

The main drawback of this procedure was the fact that most of the cinnamaldehydes required were not commercially available, meaning that they had to be prepared *via* Mizoroki-Heck reaction (followed by one-pot hydrolysis) of acrolein diethyl acetal with different aryl halides.[147] Unfortunately, when subjecting those aldehydes to reductive amination in the presence of 3,5-dimethoxyaniline, low yields were achieved in general, except for **11hg** (Scheme 2.78).



Scheme 2.78

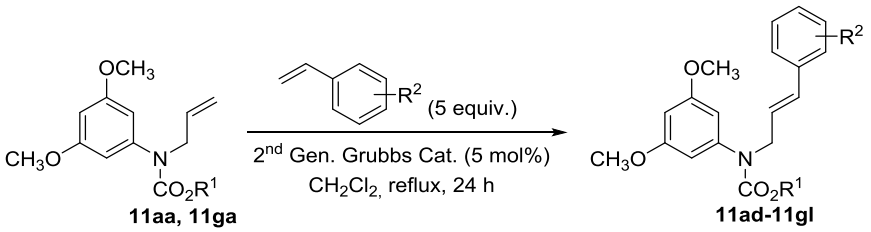
The discouraging results obtained in the aforementioned approach, together with the fact that almost all the aldehydes had to be synthesized, led us to find more efficient processes. With that aim in mind, we studied the possibility of subjecting substrates bearing unsubsituted alkenes to a cross metathesis reaction, utilizing different commercially available styrenes as coupling partners (Table 2.11).

After some experimentation to study the feasibility of the transformation, it was found that the reaction proceeded well with 5 equivalents of the styrene and 5 mol% of 2nd generation Grubbs catalyst, in CH_2Cl_2 at reflux for 24 h. Nonetheless, for the synthesis of **11ag**, the previous method based on the reductive amination process was found to be more efficient,

[147] Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777.

as the crude product obtained in the metathesis reaction proved to be tough to purify, and compound **11ag** was always isolated with small amounts of the styrene-homocoupling product.

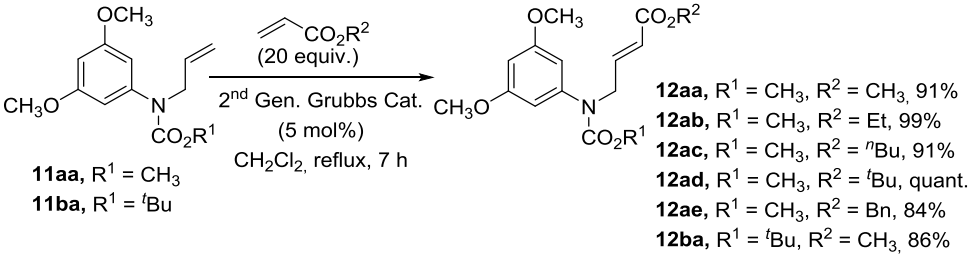
Table 2.11



Entry	Subst.	R^1	R^2	Prod.	Yield (%)[a]
1	**11aa**	CH_3	4-CH_3	**11ad**	70
2	**11aa**	CH_3	3-CH_3	**11ae**	61
3	**11aa**	CH_3	2-CH_3	**11af**	75
4	**11aa**	CH_3	3-OCH_3	**11ah**	61
5	**11aa**	CH_3	4-Ph	**11ai**	40
6	**11aa**	CH_3	4-^{t}Bu	**11aj**	67
7	**11aa**	CH_3	4-F	**11ak**	56
8	**11aa**	CH_3	2,3-(CH=CH-CH=CH)	**11al**	70
9	**11ga**	(-)Menth.	2,3-(CH=CH-CH=CH)	**11gl**	62

[a] Yield of the isolated pure compounds.

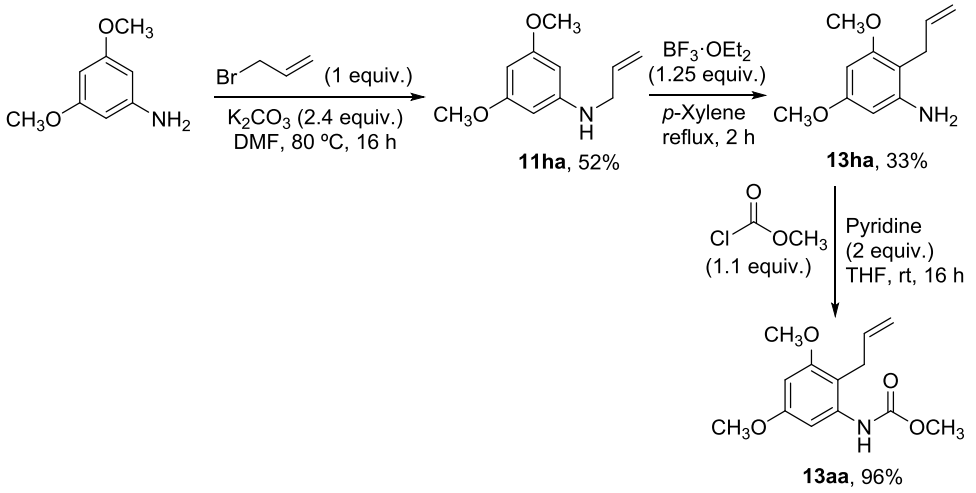
Substrates **12aa-12ba** bearing electron-withdrawing functionalities at the alkene terminus were also prepared *via* metathesis reaction (Scheme 2.79).



Scheme 2.79

In this case, acrylates were used as coupling partners, achieving **12aa-12ba** in high yields, employing the optimal conditions shown in the previous section for their homoallylic counterparts (Scheme 2.71). It is worth to mention that both of the protocols described in this section for the cross-metathesis reaction afforded selectively the corresponding *E*-configured alkenes.

Compound **13aa** was synthesized in three steps: 1) 3,5-dimethoxyaniline was subjected to a mono-allylation reaction, forming **11ha**, followed by 2) Claisen rearrangement to give **13ha** and 3) protection of the free amine group in **13ha** as the corresponding methyl carbamate under the usual reaction conditions, furnishing **13aa** (Scheme 2.80).



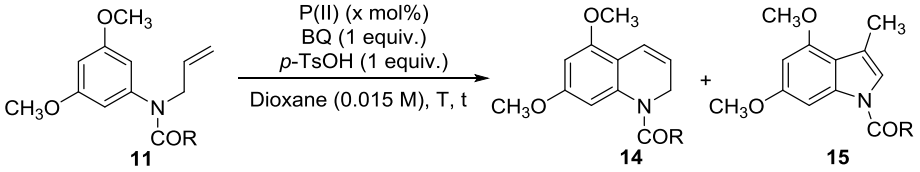
Scheme 2.80

*3.3.2. Intramolecular oxidative Heck reaction of N-protected allylanilines **11aa-11gl** and **12aa-12ba**. Synthesis of 1,2-dihydroquinolines **14aa-14da**, 1,4-dihydroquinolines **16ab-16gl** and indoles **17aa-17ba***

As stated previously, in order to avoid the aromatization event observed in Scheme 2.74, we studied the possibility of switching to the milder reaction conditions formerly used for the synthesis of chromanes, chromenes (Tables 2.3-2.6) and dihydroquinolines (Table 2.8) *via* 6-*exo* processes.[84,106] Therefore, dioxane was utilized as solvent, benzoquinone as the sole oxidant and *para*-toluenesulfonic acid as the additive, which is important to enhance the reactivity through the formation of a more electrophilic Pd(II) species (Table 2.12).[28b,36] Under these reaction conditions, the 6-*endo* cyclization took place with complete

regioselectivity towards the corresponding 1,2-dihydroquinoline, obtaining **14aa** in a high isolated yield (85%) after 16 h at room temperature (Table 2.12, entry 1). The formation of the indole counterpart **15aa**, *via* a 5-*exo*-trig cyclization process, was not detected whatsoever.

Table 2.12



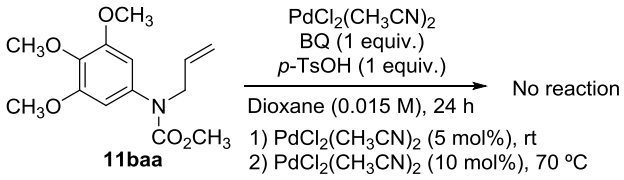
Entry	Subst.	R	Pd(II) (mol%)	t (h)	DHQ	Yield (%)[a]	Indole	Yield (%)[a]
1	**11aa**	OCH_3	$PdCl_2(CH_3CN)_2$ (5)	16[b]	**14aa**	85	-	-
2	**11ba**	O^{t}Bu	$PdCl_2(CH_3CN)_2$ (5)	16[b]	**14ba**	38	-	-
3	**11ba**	O^{t}Bu	$PdCl_2(CH_3CN)_2$ (10)	1.5[b]	**14ba**	58	**15ba**	16
4	**11ba**	O^{t}Bu	$PdCl_2(PhCN)_2$ (10)	1.5[b]	**14ba**	56	**15ba**	13
5	**11ba**	O^{t}Bu	$PdCl_2(PhCN)_2$ (10)[c]	2[b]	**14ba**	59	**15ba**	15
6	**11ba**	O^{t}Bu	$Pd(CH_3CN)_4(BF_4)_2$ (10)[c]	3[b]	**14ba**	16[d]	**15ba**	3[d]
7	**11ba**	O^{t}Bu	$Pd(OAc)_2$ (10)[c]	6[b]	**14ba**	21[e]	**15ba**	14[e]
8	**11ca**	OBn	$PdCl_2(CH_3CN)_2$ (10)	3[b]	**14ca**	67	-	-
9	**11da**	CH_3	$PdCl_2(CH_3CN)_2$ (5)	20[b]	-[f]	-	-	-
10	**11da**	CH_3	$PdCl_2(CH_3CN)_2$ (10)	1[g]	**14da**	85	**15da**	10

[a] Yield of the isolated pure compounds. [b] Room temperature. [c] Boc-Val-OH (20 mol%) was used as ligand. [d] Yield determined by ^{1}H NMR using DMAP as internal standard (55% conversion). [e] Yield determined by ^{1}H NMR using DMAP as internal standard (51% conversion). [f] No reaction. Starting material recovered. [g] 70 ºC.

Interestingly, when the protecting group was changed to a *t*-butyl carbamate (**11ba**, Table 2.12, entry 2), under the same reaction conditions, the transformation was sluggish, obtaining **14ba** in a much lower yield (38%), along with trace amounts of indole **15ba** (not isolated) and decomposition products. An increase of the catalyst loading to 10 mol% (Table 2.12, entry 3) resulted in a faster reaction (1.5 h at room temperature). However, although the dihydroquinoline **14ba** was obtained in a higher yield (58%), the reaction was not completely selective, isolating a significant amount of indole **15ba**, obtained through the 5-*exo*-trig process. The change of the palladium precatalyst (Table 2.12, entry 4) gave a similar result. The use of a MPAA (Boc-Val-OH) in this case did not accelerate the rate of the

coupling and also led to a nonselective reaction (Table 2.12, entry 5), even when the palladium source was changed trying to obtain more electrophilic palladium intermediates (Table 2.12, entries 6 and 7).The use of benzyl carbamate **11ca** also furnished 1,2-DHQ **14ca** site-selectively (Table 2.12, entry 8). A significant difference in reactivity was observed when the nitrogen was protected as an amide: acetyl-protected **11da** (Table 2.12, entry 9) did not react at all under the conditions used for **11aa** (Table 2.12, entry 1). It was necessary to increase the catalyst loading and heat the reaction to 70 ºC to achieve full conversion (Table 2.12, entry 10). Although the 6-*endo* cyclization was the major reaction pathway obtaining a good yield of **14da** (85%), indole **15da** was also isolated from the reaction mixture (10%). Thus, the protecting group used has a strong influence on both the reactivity and the regioselectivity of the reaction, obtaining the best results with the methyl carbamate.

As we have previously seen in related reactions, in all the cases an electron-rich aromatic ring (3,5-dimethoxyphenyl ring, specifically) was used, due to the fact that it was required to obtain good reactivity.[23,84,106] However, the utilization of substrate **11baa** bearing a 3,4,5-trimethoxyphenyl ring led to no reaction, recovering the starting material (Scheme 2.81) regardless of the temperature (rt-70 ºC) or the catalyst loading (5-10 mol%).



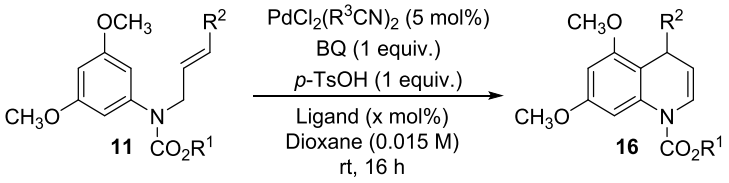
Scheme 2.81

Next, we extended the reaction to substrates bearing substituents on the alkene (Table 2.13). It is noteworthy that the corresponding 1,4-dihydroquinolines **16** were obtained with complete regioselectivity, not detecting the formation of the indoles or the corresponding 1,2-dihydroquinolines by NMR. In this context, 2-butenylaniline **11ab** ($R^1 = R^2 = CH_3$) gave only a moderate yield of **16ab** (57%, Table 2.13, entry 1), also in the presence of Boc-Val-OH (Table 2.13, entry 2). However, the reaction proved to be best suited for the synthesis of 4-aryl-substituted 1,4-dihydroquinolines, obtaining **16ac**-**16al** (Table 2.13, entries 3-18) with high yields and complete regioselectivity under the standard conditions.

When employing **11ac** as substrate, the corresponding 1,4-DHQ was obtained in a good yield (77%, Table 2.13, entry 3) and the change of the catalyst to $PdCl_2(PhCN)_2$ showed no significant increase of the efficiency of the transformation (79%, Table 2.13, entry 4).

However, the use of Boc-Val-OH as ligand led to a dramatic improvement of the outcome of the reaction (89%, Table 2.13, entry 5). That same ligand allowed us to improve the yield of some other cyclization products (Table 2.13, entries 7 *vs* 8 and entries 16 *vs* 17). In this case, the use of the *tert*-butyl carbamate as protecting group (**11bc**) did not imply a loss of selectivity nor reactivity, as **16bc** was obtained in a good yield, not detecting the formation of the indole in any case (Table 2.13, entries 7 and 8). The reaction could also be efficiently carried out in a 1 mmol scale, obtaining **16ac** in 85% yield (Table 2.13, entry 6).

Table 2.13



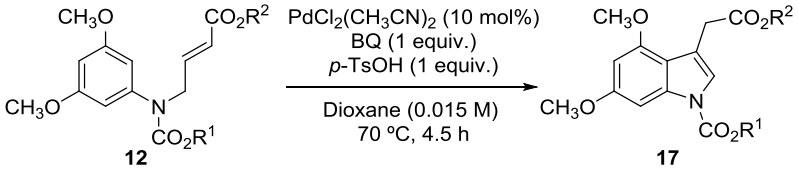
Entry	Subst.	R^1	R^2	R^3	L (mol%)	Prod.	Yield (%)[a]
1	**11ab**	CH_3	CH_3	CH_3	-	**16ab**	57
2	**11ab**	CH_3	CH_3	Ph	Boc-Val-OH (10)	**16ab**	56
3	**11ac**	CH_3	Ph	CH_3	-	**16ac**	77
4	**11ac**	CH_3	Ph	Ph	-	**16ac**	79
5	**11ac**	CH_3	Ph	Ph	Boc-Val-OH (10)	**16ac**	89
6	**11ac**[b]	CH_3	Ph	Ph	Boc-Val-OH (10)	**16ac**	85
7	**11bc**	^{t}Bu	Ph	CH_3	-	**16bc**	73
8	**11bc**	^{t}Bu	Ph	Ph	Boc-Val-OH (10)	**16bc**	86
9	**11ad**	CH_3	4(CH_3)C_6H_4	CH_3	-	**16ad**	82
10	**11ae**	CH_3	3(CH_3)C_6H_4	CH_3	-	**16ae**	92
11	**11af**	CH_3	2(CH_3)C_6H_4	CH_3	-	**16af**	82
12	**11ag**	CH_3	4(OCH_3)C_6H_4	CH_3	-	**16ag**	82
13	**11ah**	CH_3	3(OCH_3)C_6H_4	CH_3	-	**16ah**	81
14	**11ai**	CH_3	4(Ph)C_6H_4	CH_3	-	**16ai**	73
15	**11aj**	CH_3	4(^{t}Bu)C_6H_4	CH_3	-	**16aj**	87
16	**11ak**	CH_3	4(F)C_6H_4	CH_3	-	**16ak**	72
17	**11ak**	CH_3	4(F)C_6H_4	Ph	Boc-Val-OH (10)	**16ak**	85
18	**11al**	CH_3	1-naphth	CH_3	-	**16al**	82

[a] Yield of the isolated pure compounds. [b] The reaction was carried out in a 1 mmol scale.

The regioselectivity of the reaction completely changed when electron-withdrawing groups were introduced in the terminal position of the alkene (Table 2.14). Under the standard

conditions, no reaction was observed for **12aa**, and an increase of the catalyst loading to 10 mol% and heating to 70 ºC was required. Under these conditions, indole **17aa** was selectively obtained in a moderate yield (Table 2.14, entry 1).

Table 2.14



Entry	Subst.	R^1	R^2	Prod.	Yield (%)[a]
1	**12aa**	CH_3	CH_3	**17aa**	68
2	**12ba**	^{t}Bu	CH_3	**17ba**	41
3	**12ab**	CH_3	Et	**17ab**	68
4	**12ac**	CH_3	^{n}Bu	**17ac**	63
5	**12ad**	CH_3	^{t}Bu	**17ad**	54
6	**12ae**	CH_3	Bn	**17ae**	78

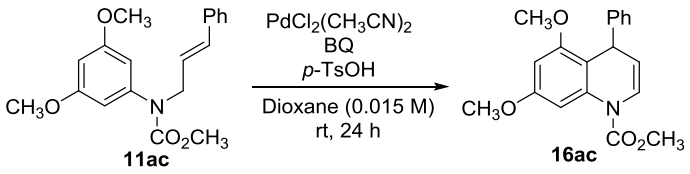
[a] Yield of the isolated pure compounds.

The same result was achieved with the Boc-protected substrate **12ba**, although indole **17ba** was isolated in a lower yield (Table 2.14, entry 2), observing decomposition of the substrate. The reaction could be extended to different esters **12ab**-**12ae**, obtaining selectively the indoles **17ab-17ae** with moderate to good yields (Table 2.14, entries 3-6).

The results obtained showed that the site selectivity of the reaction is strongly influenced on the one hand, by the protecting group on the nitrogen atom, and on the other hand, by the nature of the alkene, leading to 6-*endo* or 5-*exo* pathways.

At this point, additional experiments were carried out to establish the scope and limitations of the reaction and provide additional information on the possible reaction mechanism. Firstly, control experiments were carried out with **11ac** (Scheme 2.82).

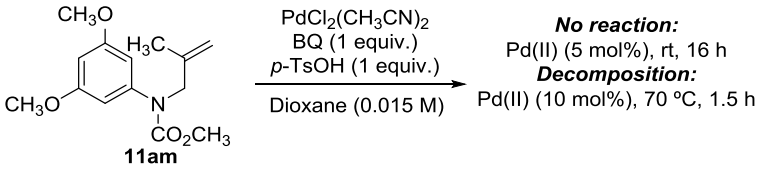
In the absence of the palladium source, the reaction did not take place and unreacted **11ac** was recovered after 24 h at room temperature. When removing *p*-TsOH, decomposition products were obtained. Finally, just a minor amount of **16ac** (<5%) was observed by ^{1}H NMR when the reaction was performed with no oxidant.



a) no $PdCl_2(CH_3CN)_2$, BQ (1 equiv.), *p*-TsOH (1 equiv.): no reaction
b) $PdCl_2(CH_3CN)_2$ (5 mol%), BQ (1 equiv.), no *p*-TsOH: decomposition
c) $PdCl_2(CH_3CN)_2$ (5 mol%), no BQ, *p*-TsOH (1 equiv.): <5%, **16ac**

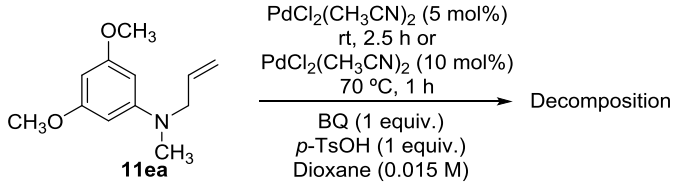
Scheme 2.82

The coupling was not compatible with substitution on the internal position of the alkene. Under the standard conditions, **11am** was unreactive, whereas only decomposition was achieved when the reaction was heated to 70 ºC with 10 mol% of the catalyst (Scheme 2.83).



Scheme 2.83

The influence of the protecting group on the nitrogen is clear, as only decomposition products were obtained when *N*-methyl aniline **11ea** was subjected to the standard reaction conditions at room temperature or at 70 ºC (Scheme 2.84).



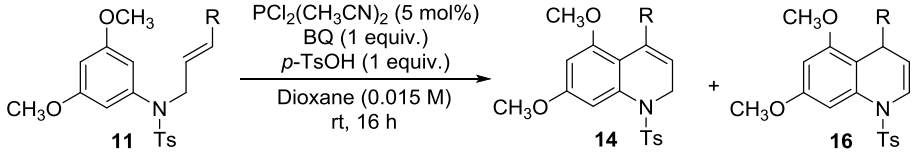
Scheme 2.84

In view of these results, we next studied the effect of the presence of a *p*-toluenesulfonyl group on the nitrogen under the previously established reaction conditions. Recently, *N*-allyl-arylsulfonamides have been used as precursors of tetrahydroquinolines in a palladium-

catalyzed cascade reaction with benzenesulfonyl chlorides.[148] The proposed mechanism involves the initial coordination of the alkene to an arylpalladium(II) intermediate formed by oxidative addition of the sulfonyl chloride to Pd(0). Although the reaction results in a formal 6-*endo* cyclization, the proposed mechanistic pathway does not involve the cyclization of a substituted alkene.

Under our reaction conditions, sulfonamide **11fa** gave 1,2-dihydroquinoline **14fa** with complete regioselectivity in an excellent yield (Table 2.15, entry 1), comparable to that one obtained with carbamate **11aa** (Table 2.12, entry 1).

Table 2.15



Entry	Subst.	R	1,2-DHQ	Yield (%)[a]	1,4-DHQ	Yield (%)[a]
1	**11fa**	H	**14fa**	87	**-**	-
2	**11fb**	CH_3	**14fb**	64	**16fb**	26
3	**11fc**	Ph	**-**	-	**16fc**	42
4	**11fn**	Bn	**-**	-	**16fn**	60

[a] Yields of the isolated pure compounds.

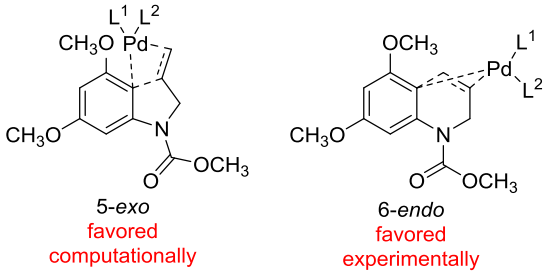
However, **11fb** afforded a regioisomeric mixture of 1,2- and 1,4-dihydroquinolines **14fb** and **16fb**, respectively (Table 2.15, entry 2). Curiously, in disagreement with what has been previously observed with substrates possessing internal alkenes, (Table 2.13), the corresponding 1,2-DHQ happened to be the major product. In addition, 1,4-DHQs **16fc** and **16fn** were selectively obtained from the corresponding *N*-allylanilines, although in moderate yields (Table 2.15, entries 3 and 4).

With this results in hand and based on previous mechanistic proposals for related transformations,[23,84,106] we hypothesized that the reaction could proceed *via* electrophilic palladation of the aromatic ring, followed by *syn* migratory insertion to the alkene in a 6-*endo*-trig fashion. Nonetheless, prior activation of the alkene and subsequent arene insertion cannot be discarded.

[148] Yuan, K.; Soulé, J.-F.; Dorcet, V.; Doucet, H. *ACS Catal.* **2016**, *6*, 8121.

At this point, we decided to examine the reactivity pattern computationally, in collaboration with Professor Enrique Gómez-Bengoa and Lía Sotorríos, to get a more precise insight into the mechanistic course of the reaction. Substrate **11aa** was considered as a useful starting point for DFT calculations, to explore the main role of the palladium catalyst in the C-H activation step (alkene activation or arene palladation), and the subsequent 5-exo/6-endo selectivity of the cyclization process. With this studies, three key features of the transformation were explained: the unusual 6-*endo* selectivity, the large influence of the *N*-protecting group on the outcome of the reaction and the preference for the formation of the corresponding 1,2- or 1,4-dihydroquinolines, depending on the nature of the substituents in the terminal position of the alkene.

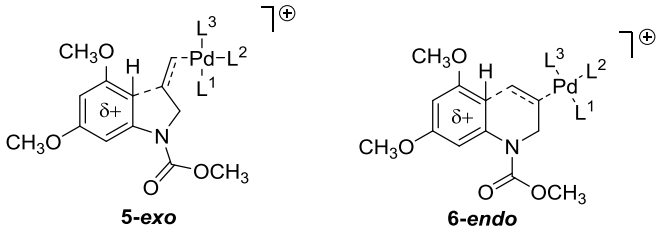
According to our mechanistic proposal, a hypothetical arene palladation would be followed by a *syn* migratory insertion of the alkene into the aryl-Pd(II) bond, which could occur through 5-*exo* or 6-*endo* pathways. Interestingly, the DFT-computed activation barriers for palladium complexes with different electronic properties show a general high preference towards 5-*exo* insertion (Figure 2.11) in disagreement with the experimental results. This observation presents no exception, being electron-rich complexes, like the anionic Pd(II) species in **TS1**, the ones which showed the largest *exo/endo* energy difference ($\Delta\Delta G^{\ddagger}$ = 10.7 Kcal/mol). Decreasing the electronic charge in the metal center reduces the *exo* preference, but even the dicationic Pd complex **TS5**, which lacks L1 and L2, is still unable to explain the positional selectivity observed experimentally ($\Delta\Delta G^{\ddagger}$ = 3.4 Kcal/mol). Thus, these data served to discard a mechanism involving cyclization after a previous arene palladation step.



	L_1	L_2	$\Delta G^{\ddagger}$(6-*endo*) - $\Delta G^{\ddagger}$(5-*exo*)
TS1	OAc	OAc	10.7
TS2	OAc	none	6.7
TS3	CH_3CN	CH_3CN	6.1
TS4	CH_3CN	none	5.9
TS5	none	none	3.4

Figure 2.11

On the other hand, low activation barriers were measured for palladaium complexes activating the alkene towards a cyclization driven by aromatic electrophilic substitution. However, once again, the indole was predicted to be the major product of the reaction, by a difference of 0.8 Kcal/mol when an acetate is coordinated to the metal center (**TS6**, Figure 2.12) and 2.2 Kcal/mol for the chloride derivative.

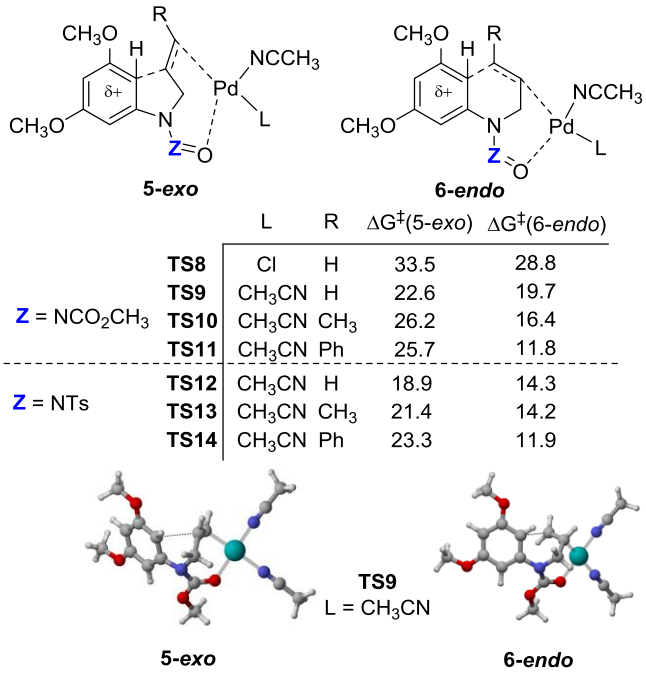


TS6, L^1 = OAc, L^2 = L^3 = CH_3CN $\Delta\Delta G^{\ddagger}$ (6-*endo* - *5-exo*) = 0.8 Kcal/mol
TS7, L^1 = Cl, L^2 = L^3 = CH_3CN $\Delta\Delta G^{\ddagger}$ (6-*endo* - *5-exo*) = 2.2 Kcal/mol

Figure 2.12

Noteworthy, if the coordination of the oxygen of the carbamate to the Pd(II) center is considered (Figure 2.13), the interesting effect of a complete inversion of the *endo/exo* selectivity is observed. In all the cases, the quinoline product becomes the preferred adduct (**TS8-TS11**), as experimentally noted. If a chloride is still coordinated to the palladium, as in **TS8**, the activation energies are high, over 28 Kcal/mol. The replacement of the chloride by a second molecule of acetonitrile reduces the values below 20 Kcal/mol, predicting a feasible reaction in the experimental conditions.

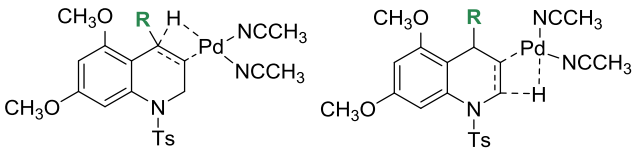
The regioselectivity towards the *endo* product is general for terminal (**TS9**) and substituted alkenes (**TS10** and **TS11**), and the energy difference with respect to the 5-*exo* counterparts is always high (3,0-10.0 Kcal/mol), ensuring a complete site selectivity. Furthermore, the tosylamide group can play a similar role, and the activation energies for the 6-*endo* approach are in the three cases (**TS12-TS14**) largely lower than those ones of the 5-*exo* transition states. This regioselectivity seems logical, since the coordination of the *N*-protecting group to the palladium induces a larger ring strain in the *exo* adducts. Besides, the participation of the *N*-protecting group in the reaction *via* intramolecular coordination to the metal can help explain the effect of the different substituents of the nitrogen (Table 2.12). For example, increasing the steric bulkiness of the carbamate (**O^{t}Bu**, Table 2.12, entries 2-7 and **OBn**, entry 8) or replacing the carbamate by an amide (Table 2.12, entries 9-10) can reduce their coordinative ability, affecting negatively the reactivity and/or selectivity of the process.



		L	R	ΔG‡(5-*exo*)	ΔG‡(6-*endo*)
Z = NCO_2CH_3	**TS8**	Cl	H	33.5	28.8
	TS9	CH_3CN	H	22.6	19.7
	TS10	CH_3CN	CH_3	26.2	16.4
	TS11	CH_3CN	Ph	25.7	11.8
Z = NTs	**TS12**	CH_3CN	H	18.9	14.3
	TS13	CH_3CN	CH_3	21.4	14.2
	TS14	CH_3CN	Ph	23.3	11.9

Figure 2.13

The formation of different amounts of 1,2 or 1,4-dihydroquinoline products depending on the substitution at the alkene terminus is difficult to rationalize at the first sight. Thus, we calculated the β-elimination of the H atoms at the C-2 and C-4 positions of the cyclized palladium complexes, to examine whether the adduct formation is operating under kinetic or thermodynamic control. Interestingly, the calculations showed that the 1,2-dihydro adduct **14** is slightly (ca. 1 Kcal/mol) more stable than **16** regardless of the presence of a substituent (hydrogen, methyl, phenyl) in the benzylic position, contrary to what has been observed experimentally (Table 2.15). Therefore, the regioselectivity is not directed by the relative stability of the two possible products. Gratifyingly, under kinetic conditions, the substrate bearing a terminal alkene (R = H, **TS15**, Figure 2.14) was predicted to be deprotonated preferentially ($\Delta\Delta G^{‡}$ = 2.4 Kcal/mol) at the benzylic position to afford the 1,2-dihydroquinoline product, in agreement with the experimental results (Table 2.15, entry 1).



1,2-dihydro ***1,4-dihydro***

$\Delta G^{\ddagger}(1,4) - \Delta G^{\ddagger}(1,2)$

TS15, R = H + 2.4

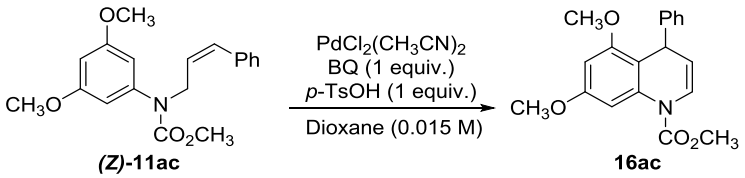
TS16, R = CH_3 - 2.1

TS17, R = Ph - 4.5

Figure 2.14

The conjugation of the forming double bond is probably responsible for this behavior. However, with a phenyl group as the substituent (**TS17**), the computed and experimental selectivities also matched, favoring the formation of the 1,4-dihydroquinoline as the major product. This phenomenon can be explained by the steric hindrance between CH_3O/Ph and Ph/Pd moieties, as this probably induces a dramatic increase of the activation barrier of the 1,2-dihydro transition state. The methyl group shows a mixed behavior: while **TS16** is energetically in between the two other cases, the reaction is experimentally nonselective (Table 2.15, entry 2). The calculations were not able to predict correctly the positional selectivity for this case, probably due to its borderline character.

Along these lines, we also found that the reaction is not stereospecific, and 1,4-dihydroquinoline **16ac** could be formed irrespective of the geometry of the double bond in the starting material. Despite substrate ***(Z)*-11ac** did not react at all under the optimal reaction conditions, when it was heated to 70 ºC in the presence of 10 mol% catalyst, 1,4-DHQ **16ac** was furnished with a good yield, not detecting the formation of the corresponding 1,2-dihydroquinoline (Scheme 2.85).

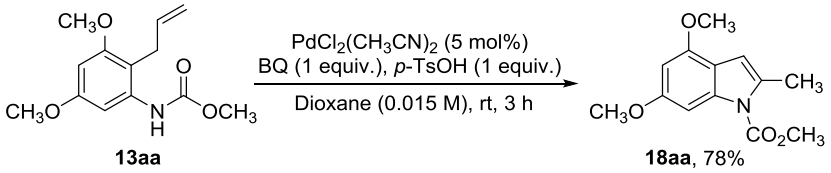


***(Z)*-11ac** **16ac**

a) $PdCl_2(CH_3CN)_2$ (5 mol%), rt, 16 h: no reaction
b) $PdCl_2(CH_3CN)_2$ (10 mol%), 70 ºC, 1 h: **16ac**, 76%

Scheme 2.85

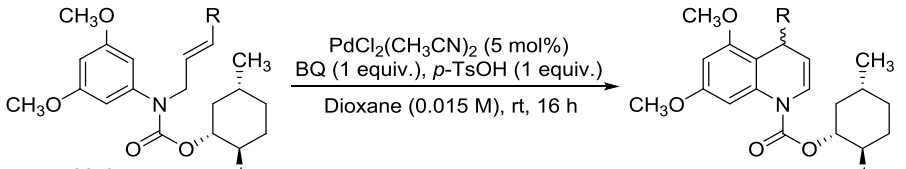
A mechanism involving a palladium-catalyzed Claisen rearrangement followed by a 5-*exo*-trig oxidative cyclization has been proposed for the obtainment of benzofurans from allyl aryl ethers.[77] In order to rule out a related mechanism for the formation of dihydroquinolines, the Claisen transposition product of **11aa** (*N*-protected *o*-allylaniline **13aa**) was prepared (Scheme 2.80). Under the standard reaction conditions, the intramolecular aza-Wacker coupling took place efficiently in only 3 h at room temperature, but exclusively through a 5-*exo* pathway, leading to 2-methylindole **18aa** in a high yield (Scheme 2.86).



13aa **18aa**, 78%

Scheme 2.86

Finally, we studied the cyclization reaction using a chiral non-racemic carbamate as protecting group on the nitrogen. For this purpose, we selected the carbamate derived from (-)-menthol as the protecting group. We reasoned that the coordination of the carbonyl with palladium in transition states such as those depicted in Figure 2.13 could favor a closer disposition of the auxiliary to the stereocenter being formed, allowing the obtainment of some extent of diastereoselectivity that would not be expected without the coordination effect. As shown in Scheme 2.87, the reaction took place in good yields and with modest, but appreciable, diastereoselectivity in the case of **16gc**. In all the cases, the 1,4-DHQ products were provided as inseparable mixtures of diastereomers and their ratio was determined by NMR. This modest 1,7-induction observed supports the proposal of the coordination of the remote *N*-protecting group with palladium in the transition state.

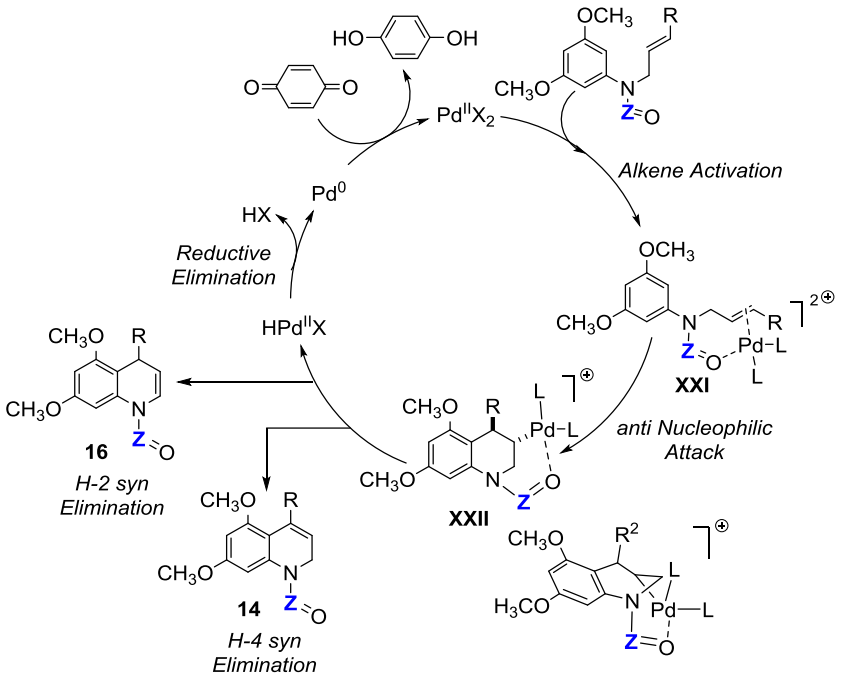


11gb R = CH_3
11gc R = Ph
11gl R = 1-naphth

16gb 67% (*d.r.* = 58:42)
16gc 78% (*d.r.* = 63:37)
16gl 79% (*d.r.* = 58:42)

Scheme 2.87

To sum up, a reaction pathway proposal in accordance with the computational and experimental data is shown in Scheme 2.88.

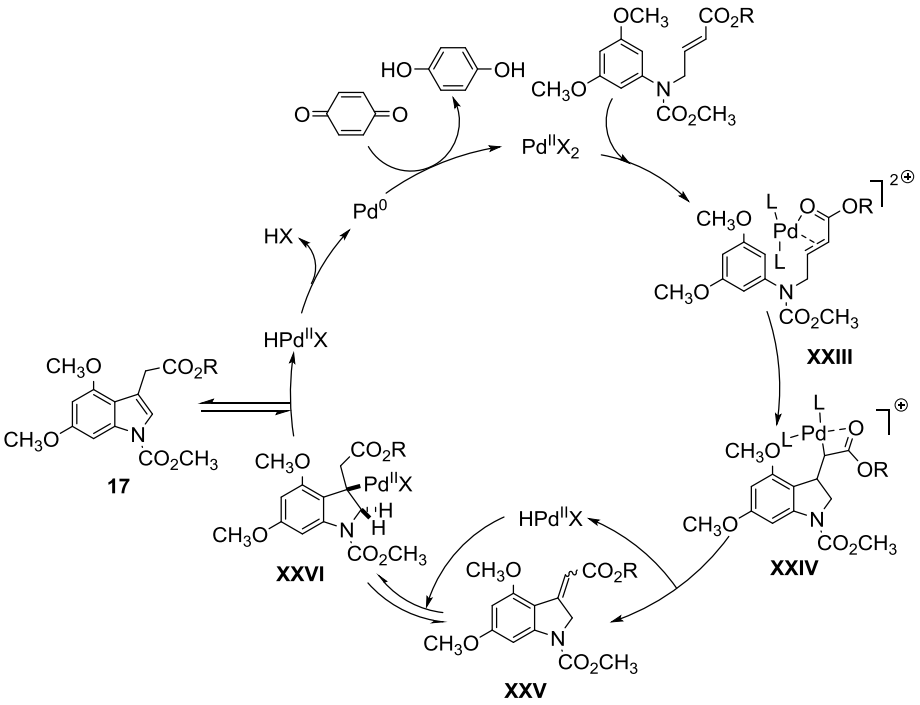


Scheme 2.88

In this context, the cyclization reaction would involve attack of the electron-rich aromatic ring onto the palladium-complexed olefin in **XXI**. As discussed earlier (Figure 2.12 and 2.13), the formation of intermediate **XXII** *via* a 6-*endo*-trig process would be energetically favored by the effect of the coordination of the Pd(II) center to the oxygen atom of the auxiliary group tethered to the nitrogen. Finally, *syn* β-hydride elimination of H-4 or H-2 would lead to the formation of 1,2- or 1,4-dihydroquinolines **14** or **16**, respectively. The formation of the more stable 1,2-DHQ is favored when R = H, whereas H-2 elimination is preferential when R = Ar (Figure 2.14).

As it has been shown in Table 2.14, when *N*-protected allylanilines bearing electron deficient alkenes were subjected to the reaction conditions, the corresponding indole products were furnished, due to a 5-*exo*-trig cyclization. This change of regioselectivity was hypothesized to happen due to the coordination of the palladium nucleus to the ester attached to the

olefin moiety, instead of to the *N*-protecting group, since the former is closer to the metal center than the latter (Scheme 2.89).



Scheme 2.89

Therefore, as the coordination of the Pd(II) to the protecting group is now precluded, the 5-*exo*-trig cyclization process is thought to be favored, forming intermediate **XXIV**. That species would undergo β-hydride elimination, furnishing **XXV**, that would easily aromatize *via* reinsertion of Pd(II) hydride followed by another β-hydride elimination, releasing indole **17**. The palladium hydride species formed evolves to Pd(0) through reductive elimination and is reoxidized to the catalytically active Pd(II) species. However, further DFT studies were not carried out to corroborate this proposal.

In conclusion, an efficient procedure for the selective synthesis of 1,2-dihydroquinolines and 4-substituted 1,4-dihydroquinolines by means of the Pd(II)-catalyzed 6-*endo*-trig intramolecular C-H alkenylation reaction of readily accessible *N*-allylanilines has been developed. The regioselectivity of the cyclization is controlled by the nature of the *N*-

protecting group and DFT studies, which are in agreement with the experimentally observed outcome, have provided understanding of the factors that govern this unusual 6-*endo* process. The reaction proceeds *via* prior activation of the alkene, being the coordination of the remote *N*-protecting group to the palladium center crucial for the formation of the six-membered ring. Interestingly, with electron-withdrawing groups tethered to the terminal position of the olefin, the regioselectivity changed, leading to the formation of the corresponding 3-substituted indoles.

III

Cp*Co(III)-Catalyzed Intramolecular Hydroarylation

*as well as N-homoallylindole **21**. Synthesis of 2,3-dihydrobenzofurans **22aa-22ca**, chromanes **23da-23dg** and pyrroloindole **24***

3.1.3. *Cp*Co(III)-catalyzed intramolecular enantioselective hydroarylation of 3-(allyloxy)benzamide **19ba** using chiral carboxylic acids **CCA1-CCA7***

3.1.4. *Cp*Co(III)-catalyzed allylation of N-methylbenzamide **27** using methyl 4-(allyloxy)benzoate **28** as the coupling partner. Synthesis of 2-allyl-N-methylbenzamide **29***

1. INTRODUCTION OF THE CHAPTER

As it can be deduced from the introductory section of Chapter 2, during the last two decades palladium has unarguably been in the limelight when accomplishing C-H bond activation reactions,[1] although other transition metals, such as rhodium,[2] ruthenium[3] and iridium,[4] have also been capable of efficiently carrying out this kind of transformations. Nonetheless, the use of the aforementioned second- and third-row-transition metals comes with the disadvantage of their toxicity and expensiveness. Therefore, with the aim of overcoming those issues, the use of more earth-abundant first-row transition metals (nickel, iron, manganese, copper and cobalt, for instance) has started to gain importance.[5]

Among them, cobalt catalysts bearing pentamethylcyclopentadienyl ligands (Cp*) have recently started to gain center stage,[6] after the publication of Matsunaga and Kanai´s pillar

[1] For selected reviews, see: a) Lyons, T.W.; Sanford, M.S. *Chem. Rev.* **2010**, *110*, 1147; b) Engle, K.M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788; c) Neufeldt, S.R.; Sanford, M.S. *Acc. Chem. Res.* **2012**, *45*, 936; d) Giri, R.; Thapa, S.; Kafle, A. *Adv. Synth. Catal.* **2014**, *356*, 1395; e) Zhou, L.; Lu, W. *Chem. Eur. J.* **2014**, *20*, 634; f) Kancherla, S.; Jørgensen, K.B.; Fernández-Ibáñez, M.A. *Synthesis* **2019**, *51*, 643.

[2] For selected reviews, see: a) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212; b) Patureau, F.W.; Wencel-Delord, J.; Glorius, F. *Aldrichim. Acta* **2012**, *45*, 31; c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651; d) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308; e) Rej, S.; Chatani, N. *Angew. Chem. Int. Ed.* **2019**, *58*, 8304; f) Zhu, W.; Gunnoe, T.B. *Acc. Chem. Res.* **2020**, *53*, 920.

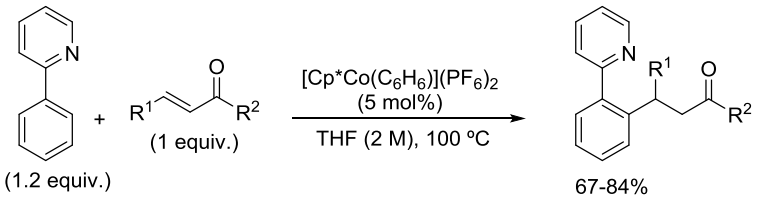
[3] For selected reviews, see: a) Arockiam, P.B.; Bruneau, C.; Dixneuf, P.H. *Chem. Rev.* **2012**, *112*, 5879; b) Sarkar, S.D.; Liu, W.; Kozhushkov, S.I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461; c) Leitch, J.A.; Frost, C.G. *Chem. Soc. Rev.* **2017**, *46*, 7145; d) Wang, Z.; Xie, P.; Xia, Y. *Chin. Chem. Lett.* **2018**, *29*, 47; e) Duarah, G.; Kaishap, P.P.; Begum, T.; Gogoi, S. *Adv. Synth. Catal.* **2019**, *361*, 654; f) Singh, K.S. *Catalysts* **2019**, *9*, 173.

[4] For selected reviews, see: a) Choi, J.; Goldman, A.S. *Top. Organomet. Chem.* **2011**, *34*, 139; b) Li, X.; Ouyang, W.; Nie, J.; Ji, S.; Chen, Q.; Huo, Y. *ChemCatChem* **2020**, *12*, 2358.

[5] For selected reviews, see: a) Moselag, M.; Li, J.; Ackerman, L. *ACS Catal*. **2016**, *6*, 498; b) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. *Chem. Rev.* **2019**, *119*, 2192.

[6] For recent reviews, see: a) Chirila, P.G.; Whiteoak, C.J. *Dalton Trans.* **2017**, *46*, 9721; b) Wang, S.; Chen, S.-Y.; Yu, X.-Q. *Chem. Commun.* **2017**, *53*, 3165; c) Yoshino, T.; Matsunaga, S. High-Valent Cobalt-Catalyzed C-H Bond Functionalization. In *Advances in Organometallic Chemistry*; Pérez, P.J., Ed.; Academic Press: San Diego, 2017; Vol. 68, p 197; d) Santhoshkumar, R.; Cheng, C.-H. *Beilstein J. Org. Chem.* **2018**, *14*, 2266; e) Planas, O.; Chirila, P.G.; Whiteoak, C.J.; Ribas, X. Current Mechanistic Understanding of Cobalt-Catalyzed C-H Functionalization. In *Advances in Organometallic Chemistry*; Pérez, P., Ed.; Academic Press: San Diego, 2018; Vol. 69, p 209; f) Planas, O.; Whiteoak, C.J.; Ribas, X. Recent Advances in Cobalt-Catalyzed Cross-Coupling Reactions. In *Non-Noble Metal Catalysis: Molecular Approaches and Reactions;* Gebbink, R.J.M.K., Moret, M.-E., Eds.; Wiley-VCH: Weinheim,

work, reported in 2013, on the utilization of high-valent Cp*Co(III). They demonstrated that a nucleophilic Co(III) organometallic species was generated *via* C-H activation, exemplified by the conjugate addition of 2-phenylpyridine to unsaturated ketones (Scheme 3.1).[7] For this reaction, complex $[Cp^*Co(C_6H_6)](PF_6)_2$ was utilized as catalyst, which is proposed to work similarly to Cp*Rh(III) catalysts on the addition of phenylpyridine to sulfonylimines: the benzene ligand is proposed to thermally dissociate, allowing the catalyst to undergo complexation with 2-phenylpyridine, followed by C-H activation/metalation *ortho* to the directing group.[8] The complex $[Cp^*CoCl_2]_2$ in the presence of $AgPF_6$ could also be used as catalyst for this transformation.



R^1 = CH_3, Ph, $4(OCH_3)C_6H_4$, $4(Cl)C_6H_4$
R^2 = CH_3, Et, Ph, $3(OCH_3)C_6H_4$, $4(Br)C_6H_4$

Scheme 3.1

Although that first Cp*Co(III) complex efficaciously catalyzed the aforementioned C-H activation reaction, a glovebox was required for its synthesis. Consequently, responding to the need of more bench-stable catalysts that could be easily synthesized without the need of an extremely inert atmosphere, Matsunaga reported the use of the $Cp^*Co(CO)I_2$ complex[9] as a precursor for cationic (pentamethylcyclopentadienyl)cobalt(III) catalysis and its application to the C-2 selective C-H amidation of indoles,[10a] as well as to the allylation of

2019; p 297. For a review on intramolecular reactions: g) Peneau, A.; Guillou, C.; Chabaud, L. *Eur. J. Org. Chem*. **2018**, 5777.

[7] Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2207.

[8] a) Tsai, A.S.; Tauchert, M.E.; Bergman, R.G.; Ellman, J.A. *J. Am. Chem. Soc.* **2011**, *133*, 1248; b) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 2115; c) Tauchert, M.E.; Incarvito, C.D.; Rheingold, A.L.; Bergman, R.G.; Ellman, J.A. *J. Am. Chem. Soc.* **2012**, *134*, 1482; d) Li, Y.; Zhang, X.-S.; Li, H.; Wang, W.-H.; Chen, K.; Li, B.-J.; Shi, Z.-J. *Chem. Sci.* **2012**, *3*, 1634.

[9] For the synthesis of the complexes, see: Frith, S.A.; Spencer, J.L.; Geiger, W.E.; Edwin, J. *Inorg. Synth.* **1990**, *28*, 273.

[10] a) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 1491; b) Suzuki, Y.; Sun, B.; Sakata, K.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 9944; c)

indoles,[10b] 6-arylpurines and aromatic amides.[10c] This Cp*Co(CO)I_2 complex has become the most widely utilized catalyst to achieve Cp*Co(III)-promoted C-H functionalization reactions. That same group also reported that complex [Cp*CoI_2]$_2$,[10d] which came from the thermal decomposition of Cp*Co(CO)I_2,[9] could also be an effective catalyst. However, it must be mentioned that, when using Cp*Co(CO)I_2 or [Cp*CoI_2]$_2$, the addition of cationic and Lewis-acidic silver salts is usually necessary, as they act as halide scavengers, activating the Cp*Co(III) precatalysts. They also provide the counter-anion of the cationic active Cp*Co(III) species, which usually has a dramatic effect on both the reactivity and stability of the catalytic system. Due to this, the fact that it can be easily tuned just by changing the silver additive comes as a huge advantage. Nevertheless, in order to avoid the use of expensive silver salts, acetonitrile-complex [Cp*Co(CH_3CN)$_3$](SbF_6)$_2$ was reported by Glorius to be able to catalyze this type of transformations.[11] During the last years, this compound has also become a very common catalyst, being at many times the complex of choice to promote efficiently C-H bond activation reactions.

As it will be commented later, Ellman's group reported several three-component reactions that required the utilization of a catalyst bearing an inert and non-coordinating counter-anion: [Cp*Co(C_6H_6)][B(C_6F_5)$_4$]$_2$, prepared by them in pervious reports from [Cp*Co(C_6H_6)](PF_6)$_2$.[12] In addition, they applied a variation of the method for the preparation of the precatalyst introduced by Matsunaga and Kanai in 2013, employing Cp*Co(CO)I_2 as the starting material.

In Cp*Co(III) catalysis, non- or weakly-coordinating solvents, such as 1,2-dichloroethane (DCE), hexafluoro-2-propanol (HFIP) and 2,2,2-trifluoroethanol (TFE), are usually employed. Besides, sometimes the addition of carboxylates is beneficial or even crucial to promote those reactions, probably because they enable or facilitate C-H bond activation *via* a concerted metalation-deprotonation (CMD)[13] or a base-assisted intramolecular electrophilic substitution (BIES)[14] mechanism.

Bunno, Y.; Murakami, N.; Suzuki, Y.; Kanai, M.; Yoshino, T.; Matsunaga, S. *Org. Lett*. **2016**, *18*, 2216; d) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Chem. Commun.* **2015**, *51*, 4659.

[11] For the preparation of the catalyst, see: Yu, D.-G.; Gensch, T.; de Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722.

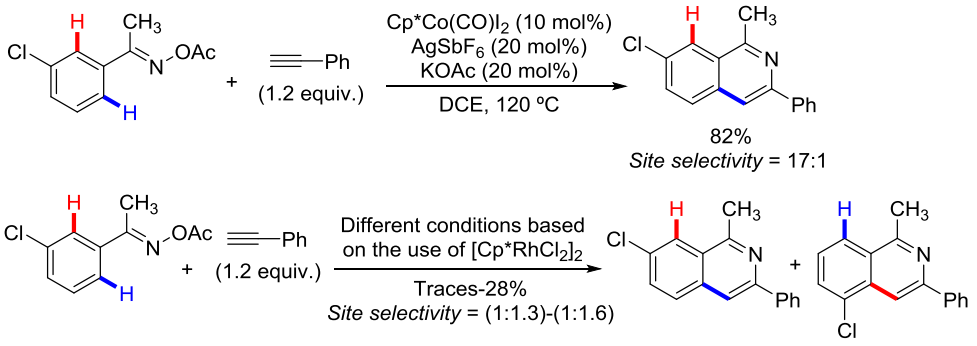
[12] Hummel, J.R.; Ellman, J.A. *J. Am. Chem. Soc.* **2015**, *137*, 490.

[13] a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118; b) Wei, D.; Zhu, X; Niu, J.-L.; Song, M.-P. *ChemCatChem* **2016**, *8*, 1242.

[14] a) Oxgaard, J.; Tenn III, W.J.; Nielsen, R.J.; Periana, R.A.; Goddard III, W.A. *Organometallics* **2007**, *26*, 1565; b) Ma, W.; Mei, R.; Tenti, G.; Ackermann, L. *Chem. Eur. J.* **2014**, *20*, 15248.

The Co(III) complexes herein mentioned were initially designed to act as homologues of their Cp*Rh(III) (and/or Cp*Ir) counterparts; however, cobalt has proved to possess unique reactivity,[15] as it will be shown in the incoming sections. For example, the ionic radius of Co(III) catalysts is much smaller than that of Rh(III) complexes. This fact has a dramatic effect on reactivity and selectivity, as under Cp*Co(III) catalysis the Cp* ligand is closer to the substituents of the coupling partners due to the smaller size of the metal.

Matsunaga and Kanai, who in 2015 accomplished an annulative reaction between unsymmetrically substituted *O*-acyloximes and alkynes featuring the formation of isoquinolines (Scheme 3.2), demonstrated the effect described above. They observed that, due to the mentioned steric hindrance between the Cp* "hat" and the substituents on the substrate, high regioselectivities were achieved towards the functionalization at the less sterically demanding position using $Cp^*Co(CO)I_2$ as catalyst, whereas $[Cp^*RhCl_2]_2$ led to no selectivity under various conditions.[16] Scheme 3.2 shows the different regioselectivities obtained with each complex for the reaction of phenylacetylene with the substrate bearing a chlorine atom at the *meta* position. Thus, in most of the examples that will be described throughout this chapter, when an unsymmetrically substituted substrate is used, the functionalization takes place at the less hindered position.

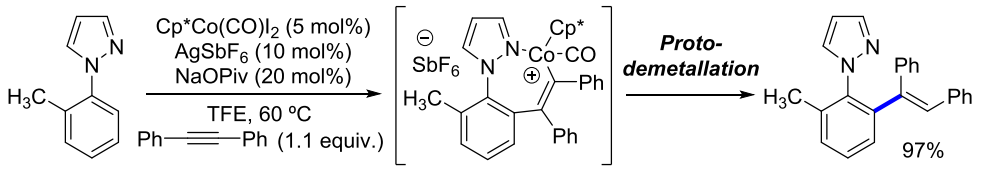


Scheme 3.2

Although it is beyond the scope of this thesis, alkynes have been very popular coupling partners to carry out Cp*Co(III)-catalyzed C-H activation/C-C bond formation reactions, since they allow the construction of a wide variety of cyclic or acyclic alkenylated aromatic

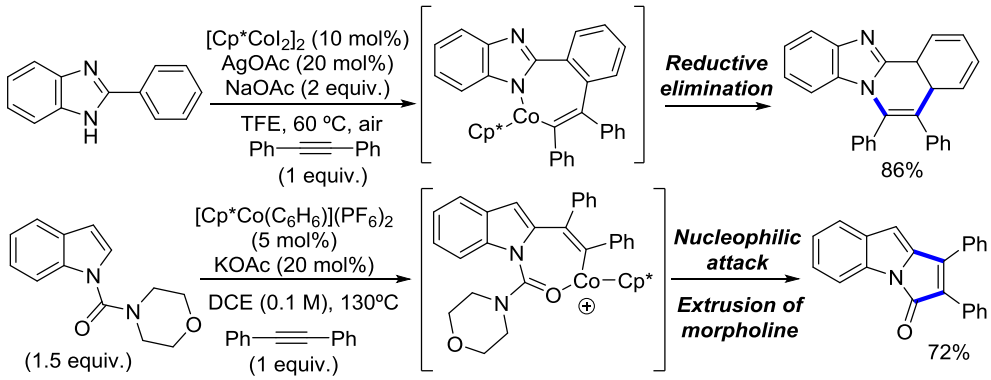
[15] Yoshino, T.; Matsunaga, S. *Adv. Synth. Catal*. **2017**, *359*, 1245.
[16] Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 12968.

frameworks, depending on the mechanism followed.[17] In this sense, the organocobalt intermediate formed after C-H activation of the arene and subsequent migratory insertion towards the alkyne, can undergo proto-demetalation, allowing the synthesis of several acyclic alkenylated aromatic rings (Scheme 3.3).[18]



Scheme 3.3

Regarding the formation of cyclic products, advantage can be taken of the linkage between the Cp*Co(III) center and the directing group, leading to a cyclized alkenyalted product upon reductive elimination (Scheme 3.4).[19] Besides, cobalt, due to its higher nucleophilicity, can accomplish a nucleophilic attack towards the director, also furnishing cyclic and olefinated arene derivatives (Scheme 3.4).[20]



Scheme 3.4

[17] For a recent review written by our group on this matter, see: Carral-Menoyo, A.; Sotomayor, N.; Lete, E. *ACS Omega* **2020**, *5*, 24974.

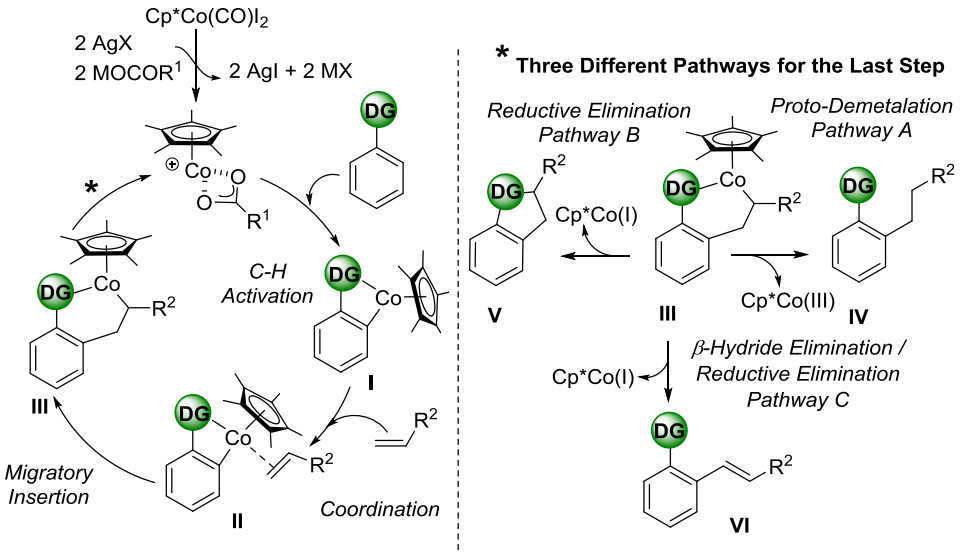
[18] Sen, M.; Rajesh, N.; Emayavaramban, B.; Premkumar, J.R.; Sundararaju, B. *Chem Eur. J.* **2018**, *24*, 342.

[19] Dutta, P.K.; Sen, S. *Eur. J. Org. Chem.* **2018**, 5512.

[20] Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424.

1.1. Alkenes as coupling partners under Cp*Co(III) catalysis

Despite they are not so widely employed as alkynes, the utilization of alkene coupling partners is common in Cp*Co(III) catalysis, since they usually grant access to the formation of alkylated or even alkenylated (hetero)arenes, being three the most common routes to achieve that goal, each of which would provide different products. The general catalytic cycle for this type of couplings is depicted in Scheme 3.5: firstly, the active catalytic species would be formed by the reaction of the Cp*Co(III)-based precatalyst with the additives added. Then, the Cp*Co(III) complex is thought to coordinate to the directing group of the (hetero)arene substrate and C-H activation, as well as metalation, occurs *ortho* to the auxiliary group, furnishing **I**. That species is proposed to coordinate to the olefin (**II**) and evolve through migratory insertion, forming **III**.



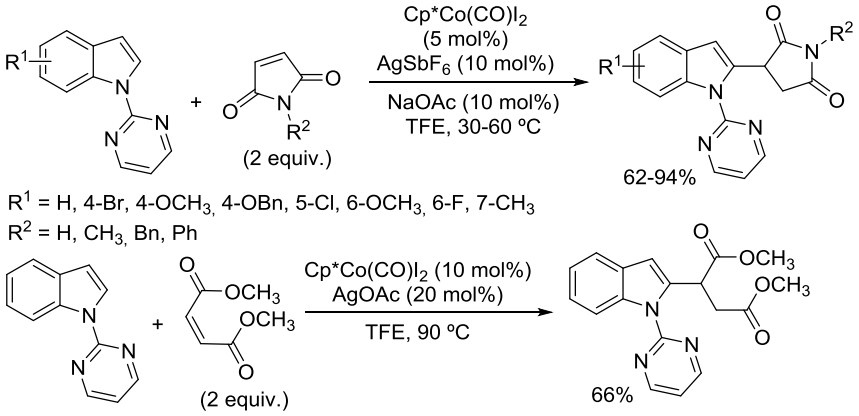
Scheme 3.5

This species can now follow three different pathways, being two of them capable of furnishing alkylated products, while the last one releases alkenylated arenes. On the one hand, proto-demetalation can happen (Pathway A), furnishing the product and recovering the catalytically active species. On the other hand, taking advantage of the coordination of the Co(III) to the directing group, reductive elimination can occur giving an annulated product and a Co(I) species (Pathway B). Due to the formation of that cobalt species, an oxidant (external or internal) is required to recover the catalyst. Last but not least,

alkenylation can also take place instead of the alkylation event. In order to achieve this process, the proto-demetalation and reductive elimination pathways should be precluded, allowing the β-hydride elimination to occur (Pathway C), releasing the olefinated product, as well as a Cp*Co(I) species after the subsequent reductive elimination event. Therefore, in order to recover the active Cp*Co(III) complex, this method also needs an oxidant.

1.1.1. Proto-demetalation pathway

Since Matsunaga and Kanai´s seminal work (Scheme 3.1),[7] several reports have been released regarding the hydroarylation of activated electron-deficient olefins.[21] For example, Ackermann and Li reported a protocol to carry out the alkylation of different indole derivatives with either maleimides or maleate esters as coupling partners (Scheme 3.6).[22] Deuterium-labeling experiments accomplished by the authors indicated that for this transformation the C-H metalation step was not rate-determining.

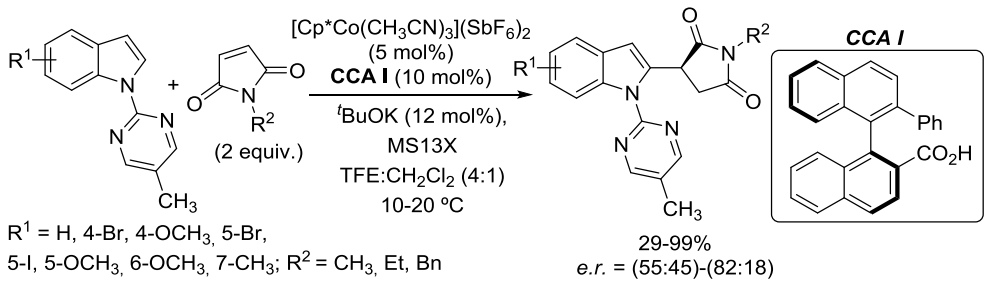


Scheme 3.6

Matsunaga showed that this coupling could also be carried out in an enantioselective fashion using a chiral carboxylic acid derived from BINOL (**CCA I**), obtaining, in general, from modest to good enantiomeric ratios (Scheme 3.7).[23] The enantioinduction would occur *via*

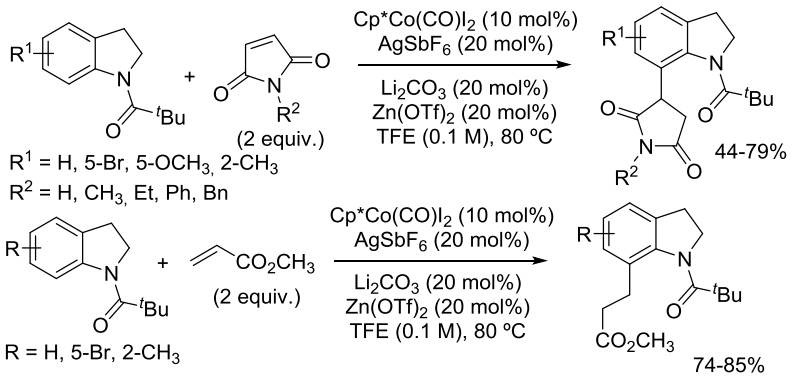
[21] a) Muniraj, N.; Prabhu, K.R. *J. Org. Chem.* **2017**, *82*, 6913; b) Muniraj, N.; Prabhu, K.R. *ACS Omega* **2017**, *2*, 4470; c) Li, J.; Zhang, Z.; Ma, W.; Tang, M.; Wang, D.; Zou, L.-H. *Adv. Synth. Catal.* **2017**, *359*, 1717; d) Barsu, N.; Emayavaramban, B.; Sundararaju, B. *Eur. J. Org. Chem.* **2017**, 4370; e) Kenny, A.; Pisarello, A.; Bird, A.; Chirila, P.G.; Hamilton, A.; Whiteoak, C.J. *Beilstein J. Org. Chem.* **2018**, *14*, 2366.
[22] Zhang, Z.; Han, S.; Tang, M.; Ackermann, L.; Li, J. *Org. Lett.* **2017**, *19*, 3315.
[23] Kurihara, T.; Kojima, M.; Yoshino, T.; Matsunaga, S. *Asian J. Org. Chem.* **2020**, *9*, 368.

selective proto-demetalation: after the C-H activation/metalation event, the reversible insertion of the alkene occurs, leading to the formation of two different enantiotopic intermediates, one of which would be selectively protonated by the chiral carboxylic acid, thus enantioselectively furnishing the alkylation product. Surprisingly, in this work, a dramatic increase of the yield was observed when changing the catalytic system from the more commonly used Cp*Co(CO)I_2/$AgSbF_6$ to [Cp*Co(CH_3CN)$_3$](SbF_6)$_2$/MS13X. In this case, the molecular sieves used as additives would remove the acetonitrile molecules bounded to the cobalt, generating the cationic active catalytic species.



Scheme 3.7

Following with the use of maleimides as coupling partners for the alkylation of heterocycles, Ravikumar has recently been able to promote the C-7 selective alkylation of indolines using a pivalate group tethered to the nitrogen atom as the director (Scheme 3.8).[24]

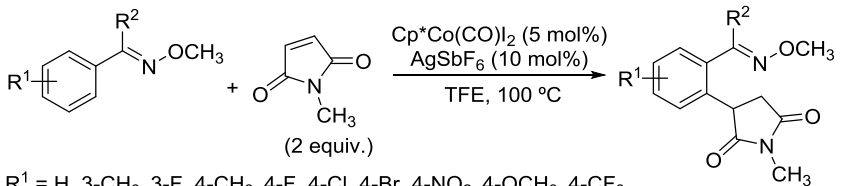


Scheme 3.8

[24] Banjare, S.K.; Chebolu, R.; Ravikumar, P.C. *Org. Lett.* **2019**, *21*, 4049.

That way, the 1,4-addition of this heterocyclic scaffold over different maleimides was efficiently accomplished. The reaction could be successfully extended to the use of acrylates as the Michael acceptors (Scheme 3.8). Mechanistic experiments suggested that the C-H activation step might be reversible.

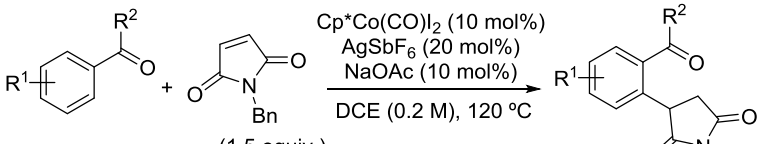
Although several works have been published describing the hydroarylation of activated olefins with heterocycles, these reactions are not only limited to those scaffolds. As an example, in 2018 Wu *et al.* developed a methodology for the alkylation of differently substituted benzene derivatives using oximes as directing groups and maleimides as coupling partners (Scheme 3.9).[25] Deuterium-labeling experiments gave some interesting insight about the reaction: the C-H activation step was reversible and non-rate-determining. Besides, TFE was responsible for the proto-demetalation step.



R^1 = H, 3-CH_3, 3-F, 4-CH_3, 4-F, 4-Cl, 4-Br, 4-NO_2, 4-OCH_3, 4-CF_3
R^2 = H, CH_3, Et, Ph

Scheme 3.9

That same year, Sundararaju and co-workers reported a very similar transformation that utilized weakly-coordinating directing groups for the hydroarylation of activated olefins (Scheme 3.10).[26] In this regard, several aromatic ketones could be alkylated using maleimides as the coupling partners.

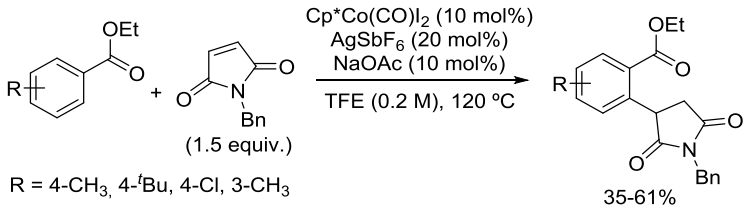


R^1 = H, 4-CH_3, 4-^{t}Bu, 4-OCH_3, 4-Cl, 4-Br, 3-CH_3
R^2 = CH_3, Et, ^{t}Bu, ^{i}Pr, Ph

Scheme 3.10

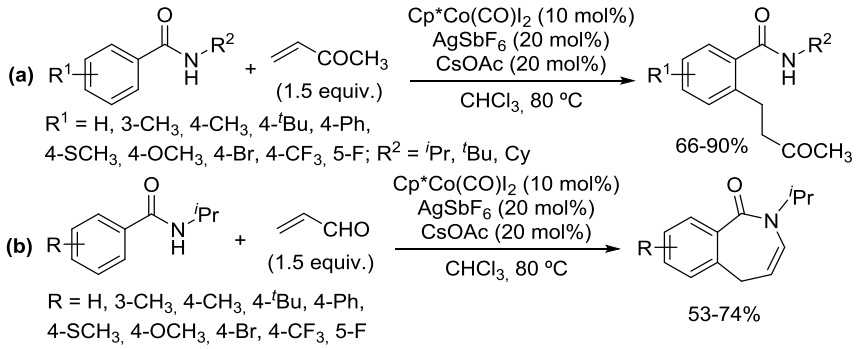
[25] Chen, X.; Ren, J.; Xie, H.; Sun, W.; Sun, M.; Wu, B. *Org. Chem. Front.* **2018**, *5*, 184.
[26] Mandal, R.; Emayavaramban, B.; Sundararaju, B. *Org. Lett.* **2018**, *20*, 2835.

The scope of the reaction could be extended to the use of esters as directing groups, although lower yields were obtained (Scheme 3.11). H/D exchange experiments accomplished by the authors suggested that the C-H activation event was reversible.



Scheme 3.11

Furthermore, also in 2018, Whiteoak's group could accomplish the hydroarylation of methyl vinyl ketone with benzamides (Scheme 3.12a).[27] Besides, they found that when acrolein was utilized instead of the previously mentioned ketone, the directing group underwent nucleophilic attack to the aldehyde after the hydroarylation event, leading to a Lewis-acid-catalyzed dehydrative cyclization that gave access to a variety azepinones (Scheme 3.12b).



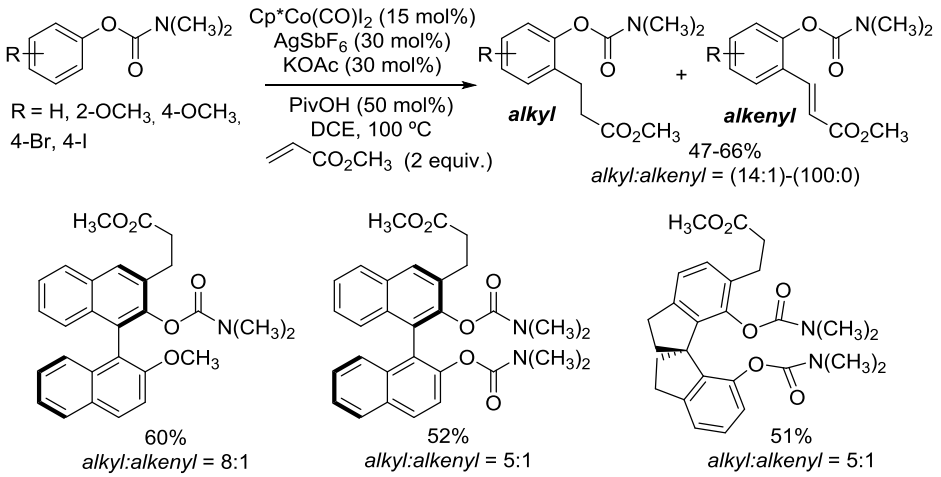
Scheme 3.12

DFT-based methods were used in order to explain why α,β-unsaturated ketones provided the corresponding alkylation products through proto-demetalation instead of their alkenylated counterparts through a β-elimination pathway. These computational studies suggested that a metallo-keto/enol tautomerization was the key step in the mechanism, leading to the hydroarylation products, while this isomerization was significantly

[27] Chirila, P.G.; Adams, J.; Dirjal, A.; Hamilton, A.; Whiteoak, C.J. *Chem. Eur. J.* **2018**, *24*, 3584.

destabilized when employing an α,β-unsaturated ester, driving the reaction towards olefinic products, as it will be commented later (Scheme 3.24).

In 2020, Maji *et. al* reported a method to achieve the alkylation of phenols employing a carbamate-based directing group and acrylates as the coupling partners (Scheme 3.13). Interestingly, this protocol could be efficiently used for the mono-alkylation of BINOL and SPINOL derivatives, obtaining in some cases small amounts of the corresponding mono-alkenylation and/or di-alkylation products.[28]

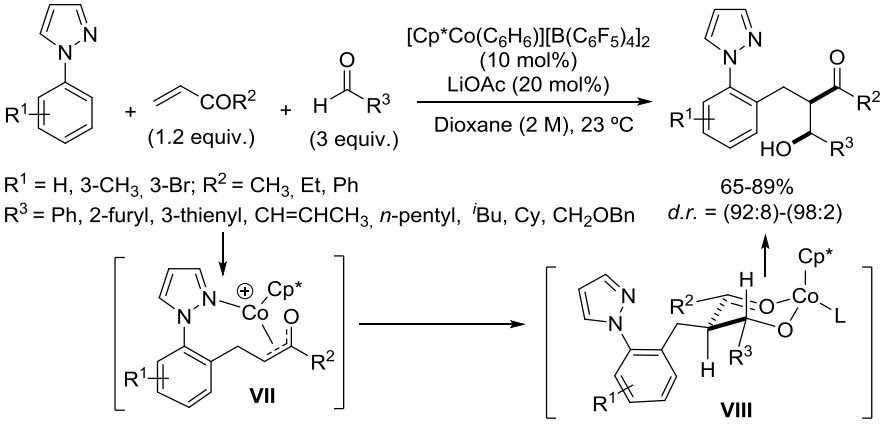


Scheme 3.13

The 1,4-addition reactions using α,β-unsaturated carbonyl compounds that have been disclosed in this section are proposed to take place *via* an oxa-π-allylcobalt species, which would be in equilibrium with the corresponding cobalt enolate. Taking advantage of the formation of this species, Ellman and co-workers developed an efficacious and highly stereoselective three-component C-H cascade addition of *N*-phenylpyrazoles to α,β-unsaturated ketones and aldehydes. To achieve such transformation, they used high-valent-cobalt complex $[Cp^*Co(C_6H_6)][(B(C_6F_5)_4]_2$, bearing a non-coordinating counter-anion, as catalyst. After accomplishing some mechanistic experiments, they proposed that this transformation starts with the 1,4-addition of the *N*-phenylpyrazole to the enone to give the racemic cobalt oxa-π/enolate species **VII**, whose nucleophilic addition to the aldehyde *via* the corresponding chair transition state **VIII** would afford the target alcohols

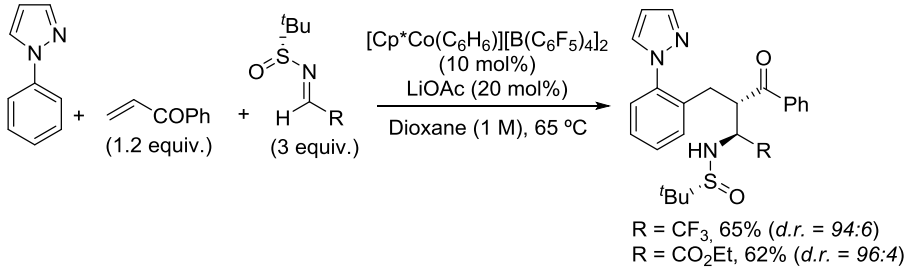
[28] Bera, S.S.; Maji, M.S. *Org. Lett.* **2020**, *22*, 2615.

diastereoselectively after protonolysis (Scheme 3.14).[29] However, a mechanism consisting of the reaction of the *Z*-enolate with the aldehyde *via* a boat transition state, that would involve coordination of the directing-group nitrogen, could not be discarded.



Scheme 3.14

The use of enantiomerically pure *N-tert*-butanesulfinylimines instead of aldehydes in this cascade reaction, led to the asymmetric synthesis of different sulfinyl amides (Scheme 3.15).

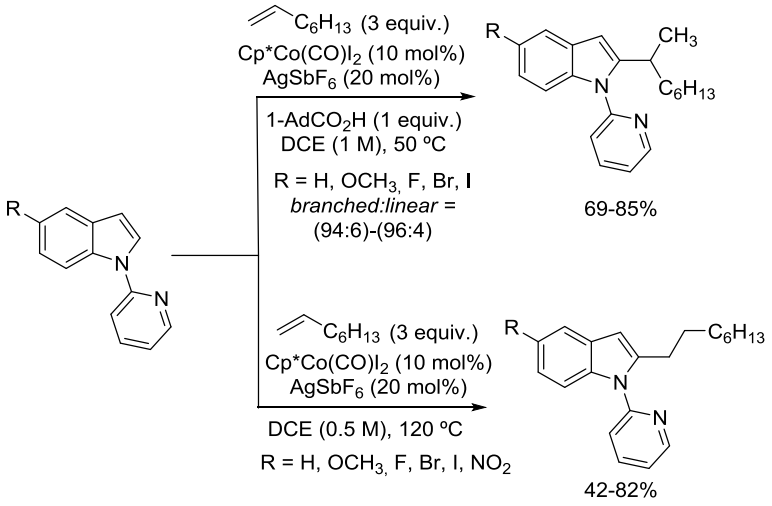


Scheme 3.15

Moving to the use of unactivated alkenes as coupling partners, in 2017, Ackermann´s group reported an interesting method for the C-2 alkylation of different indoles using unactivated monosubstituted olefins. The regioselectivity of the coupling could be switched from the

[29] Boerth, J.A.; Hummel, J.R.; Ellman, J.A. *Angew. Chem. Int. Ed.* **2016**, *55*, 12650.

linear to the branched product by using the bulky 1-adamantanecarboxylic acid (1-AdCO$_2$H) as additive (Scheme 3.16).[30]



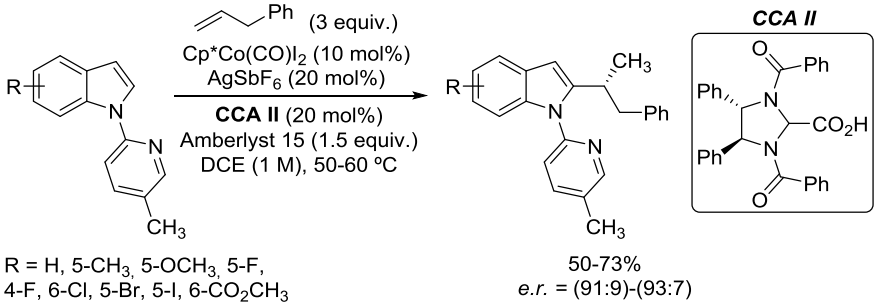
Scheme 3.16

After carrying out several experiments and DFT studies, they rationalized the change of the positional selectivity focusing on the C-H activation step. When no additive was added, it was proposed to proceed *via* a ligand-to-ligand hydrogen transfer (LLHT), affording the linear product upon proto-demetalation. On the other hand, in the presence of 1-AdCO$_2$H, the mechanism of the C-H activation event would proceed through a base-assisted intramolecular electrophilic substitution (BIES) to provide the branched scaffold after a proto-demetalation step facilitated by the carboxylic acid.

A year later, in 2018, that same group reported the enantioselective variant of the branched-selective alkylation, employing for that purpose a specially designed chiral carboxylic acid (**CCA II**) (Scheme 3.17).[31]

In this work, the enantioinduction was proposed to take place *via* insertion/selective proto-demetalation and, according to DFT studies, this event would afford enantiomer *R* preferentially. H/D scrambling experiments showed that the C-H activation was reversible.

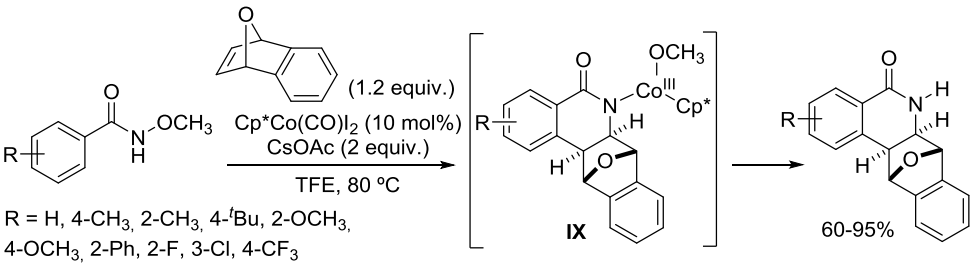
[30] Zell, D.; Bursch, M.; Müller, V.; Grimme, S.; Ackermann, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 10378.
[31] Pesciaioli, F.; Dhawa, U.; Oliveira, J.C.A.; Yin, R.; John, M.; Ackermann, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 15425.



Scheme 3.17

1.1.2. Reductive elimination pathway

As it has been previously stated, the final step of the catalytic cycle for the coupling of an aryl ring with an olefin may consist of the reductive elimination between the newly introduced moiety and the directing group. For example, in 2018, Volla and co-workers reported the redox-neutral [4+2] alkylative annulation reaction of *N*-methoxybenzamides with 7-oxa benzonorbornadienes to form diastereoselectively epoxybenzophenanthridinones. In this case, the Co(I) species released after reductive elimination is reoxidized to the initial active Cp*Co(III) species by the methoxy group attached to the nitrogen, which acts as an internal oxidant (Scheme 3.18).[32] This is thought to occur by the oxidative addition of Cp*Co(I) to the N-O bond of the cyclized product, providing **IX**. That way, the catalytically active species would be released upon proto-demetalation. After some KIE and deuterium exchange experiments, the authors concluded that the C-H activation step was irreversible and non-rate-determining.

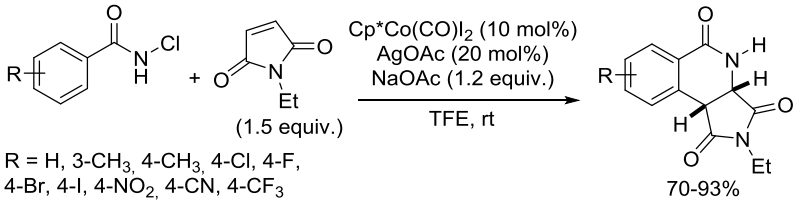


Scheme 3.18

[32] Dey, A.; Rathi, A.; Volla, C.M.R. *Asian J. Org. Chem.* **2018**, *7*, 1362.

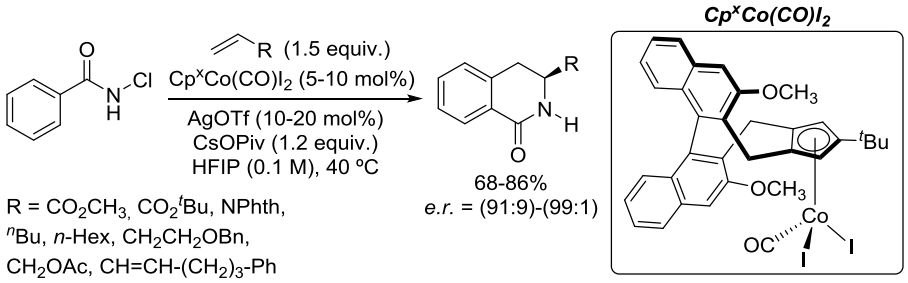
Following with the use of internal oxidants, very recently, Prabhu and co-workers described a protocol for the [4+2] annulation of *N*-chlorobenzamides with maleimides to give pryrroloisoquinolones (Scheme 3.19).[33] This is interesting, since as it has been shown earlier, when maleimides are utilized as coupling partners under Cp*Co(III) catalysis, the 1,4-addition products are usually obtained.

In this case, the N-Cl group acted as an internal oxidant to recover the catalytically active cobalt species. *N*-methoxy or *N*-hydroxybenzamides were not able to make the mentioned transformation proceed, which shows the higher oxidative activity of N-Cl bonds to promote this coupling. Besides, the C-H activation event was reversible and rate-determining.



Scheme 3.19

This annulative strategy has also been applied to the enantioselective synthesis of isoquinolones by reacting *N*-chlorobenzamide with different olefins using a Cp^{x}Co(III)-type catalyst bearing a chiral cyclopentadienyl ligand (Scheme 3.20).[34]

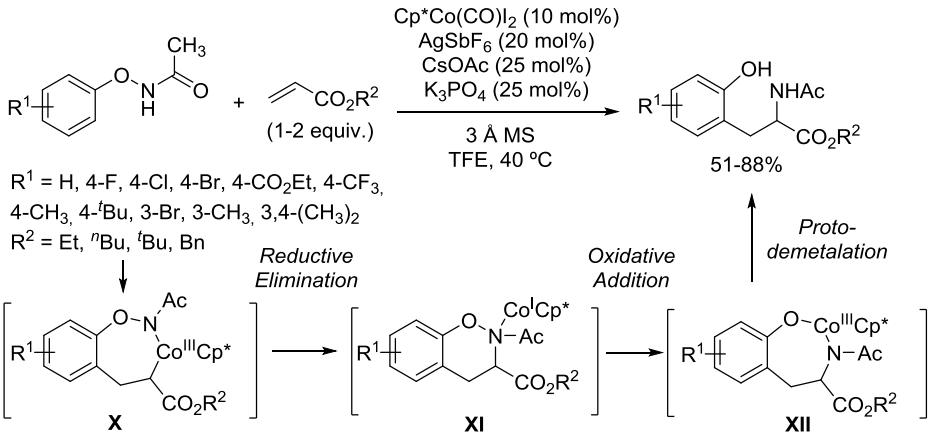


Scheme 3.20

[33] Muniraj, N.; Prabhu, K.R. *Org. Lett*. **2019**, *21*, 1068.
[34] Ozols, K.; Jang, Y.-S.; Cramer, N. *J. Am. Chem. Soc.* **2019**, *141*, 5675.

In this case, the enantioinduction would occur in the C-H activation/migratory insertion step. The optimal catalyst used in this work showed better enantio-[35] and regioselectivities[36] than its rhodium counterparts, being able to promote efficiently the reaction with troublesome olefins. For example, 1-hexene and 1-octene performed well under $Cp^xCo(III)$, while these olefins usually give low positional selectivity and enantioinduction with chiral Rh(III) catalysts.

In 2016, Glorius´ group developed the regioselective intermolecular carboamination of acrylates with *N*-phenoxyacetamides for the synthesis of unnatural amino acid derivatives (Scheme 3.21).[37]



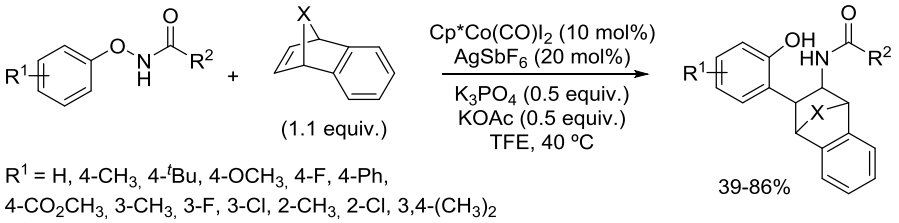
Scheme 3.21

According to their mechanistic proposal, after C-H activation and olefin insertion, intermediate **X** would be formed, which is thought to evolve to **XI** *via* reductive elimination. Then, the Cp*Co(I) complex released would perform oxidative addition towards the N-O bond, which would act as an internal oxidant, providing **XII**. After proto-demetalation of this last species, the corresponding amides would be obtained, along with the active Cp*Co(III) complex.

[35] a) Ye, B.; Cramer, N. *Science* **2012**, *338*, 504; b) Trifonova, E.A.; Ankudinov, N.M.; Mikhaylov, A.A.; Chusov, D.A.; Nelyubina, Y.V.; Perekalin, D.S. *Angew. Chem. Int. Ed.* **2018**, *57*, 7714.
[36] Hyster, T.K.; Dalton, D.M.; Rovis, T. *Chem. Sci.* **2015**, *6*, 254; *Correction:* Hyster, T.K.; Dalton, D.M.; Rovis, T. *Chem. Sci.* **2018**, *9*, 8024.
[37] Lerchen, A.; Knecht, T.; Daniliuc, C.G.; Glorius, F. *Angew. Chem. Int. Ed.* **2016**, *55*, 15166.

It is worth to mention the difference of reactivity between Cp*Co(III) and Cp*Rh(III). In fact, when Cp*Rh(III) catalysts were used instead of Cp*Co(III) complexes, the substrates preferred to undergo β-hydride elimination, forming the corresponding alkenylated phenols. In this context, Rovis[38a] and Liu[38b] had previously shown over similar substrates that under Cp*Rh(III) catalysis a crowded metal center is necessary to promote the carboamination process. However, in the case of Cp*Co(III), saturation of the metal center is not required and the carboamination pathway is favored over β-hydride elimination. This happens because, according to the hard and soft acids and bases (HSAB) concept, Cp*Co(III) is harder than Cp*Rh(III); therefore, the softer Rh(III) catalyst prefers to bind to the soft hydride, undergoing β-hydride elimination.[15]

Similarly, in 2019, Zhao and co-workers carried out the coupling between bicyclic alkenes and *N*-phenoxyamides, followed by the migration of the directing group, furnishing the corresponding carboamination products (Scheme 3.22).[39]



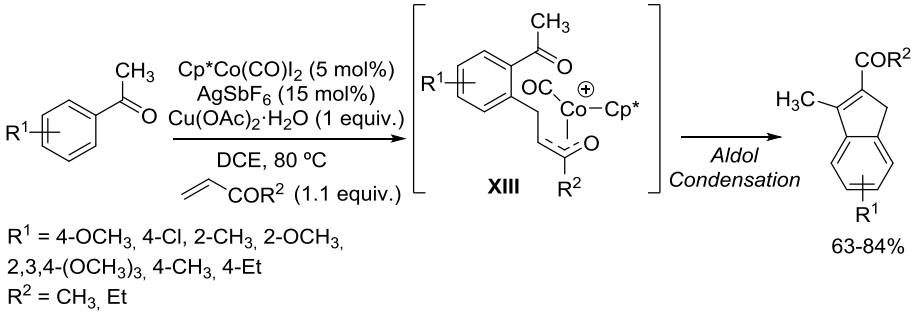
R^1 = H, 4-CH_3, 4-^{t}Bu, 4-OCH_3, 4-F, 4-Ph,
4-CO_2CH_3, 3-CH_3, 3-F, 3-Cl, 2-CH_3, 2-Cl, 3,4-$(CH_3)_2$
R^2 = CH_3, Et, ^{i}Pr; X = CH_2, NMs, NTs, NBoc, O

Scheme 3.22

Apart from the reductive elimination pathway herein disclosed, there is another possible route featuring the use of alkenes as coupling partners that may lead to cyclized products under Cp*Co(III) catalysis. This methodology consists of the nucleophilic addition of the organocobalt species **III** (Scheme 3.5, formed after C-H activation/migratory insertion) to the directing group, being this approach much more common when alkynes are utilized as the coupling partners.[40]

[38] a) Piou, T.; Rovis, T. *Nature* **2015**, *527*, 86; b) Hu, Z.; Tong, X.; Liu, G. *Org. Lett.* **2016**, *18*, 1702.
[39] Zhu, Y.; Chen, F.; Zhao, X.; Yan, D.; Yong, W.; Zhao, J. *Org. Lett.* **2019**, *21*, 5884.
[40] Fore selected examples on the use of alkynes as coupling partners, see: a) Ref. 20; b) Liu, H.; Li, J.; Xiong, M.; Jiang, J.; Wang, J. *J. Org. Chem.* **2016**, *81*, 6093; c) Liang, Y.; Jiao, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 4035; d) Kong, L.; Yang, X.; Zhou, X.; Yu, S.; Li, X. *Org. Chem. Front.* **2016**, *3*, 813; e) Yu, W.; Zhang, W.; Liu, Z.; Zhang, Y. *Chem. Commun.* **2016**, *52*, 6837; f) Lu, Q.; Vásquez-Céspedes, S.; Gensch, T.; Glorius, F. *ACS Catal.* **2016**, *6*, 2352; g) Ikemoto, H.; Tanaka, R.; Sakata, K.; Kanai, M.; Yoshino, T.;

In this context, Dethe´s group reported the use of weakly-coordinating ketones as directors for the alkylation of arenes with electron-deficient olefins, followed by subsequent intramolecular aldol condensation (Scheme 3.23).[41]



Scheme 3.23

Several benzophenones could be subjected to the reaction conditions, obtaining that way the corresponding indene derivatives in moderate to good yields. It was observed that when substrates with electron-rich *meta*-substituents were used, the reaction took place preferentially at the most hindered position. The transformation is proposed to proceed *via* oxa-π species **XIII**, which would undergo intramolecular nucleophilic addition to the ketone directing group, followed by dehydration, furnishing the indene products. According to the authors, H/D scrambling and deuterium labelling experiments indicated that the C-H activation step was reversible and rate-limiting.

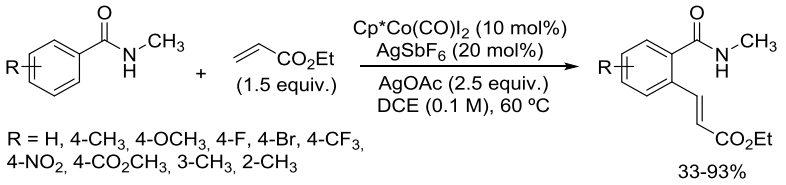
1.1.3. β-Hydride elimination pathway

Some oxidative Heck couplings have been efficiently achieved under Cp*Co(III) catalysis *via* a β-hydride elimination pathway. In 2015, Matsunaga and co-workers described a procedure for the alkenylation of *N*-methylbenzamides with ethyl acrylate, using $Cp^*Co(CO)I_2$ as catalyst, $AgSbF_6$ as the Lewis-acidic silver salt and AgOAc as the external oxidant to obtain the corresponding olefinated arenes (Scheme 3.24).[42]

Matsunaga, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 7156; h) Zhu, C.; Kuniyil, R.; Jei, B.B.; Ackermann, L. *ACS Catal.* **2020**, *10*, 4444.

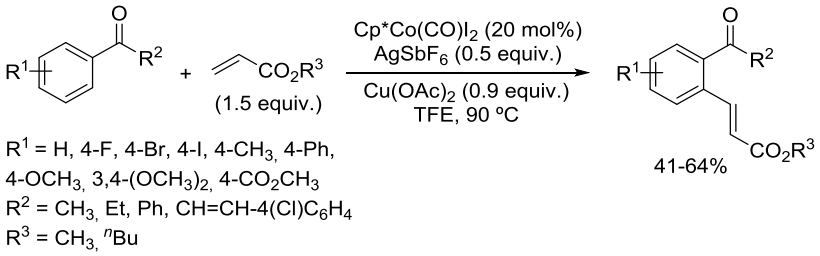
[41] Dethe, D.H.; Nagabhushana, C.B.; Bhat, A.A. *J. Org. Chem.* **2020**, *85*, 7565.

[42] Suzuki, Y.; Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Tetrahedron* **2015**, *71*, 4552.



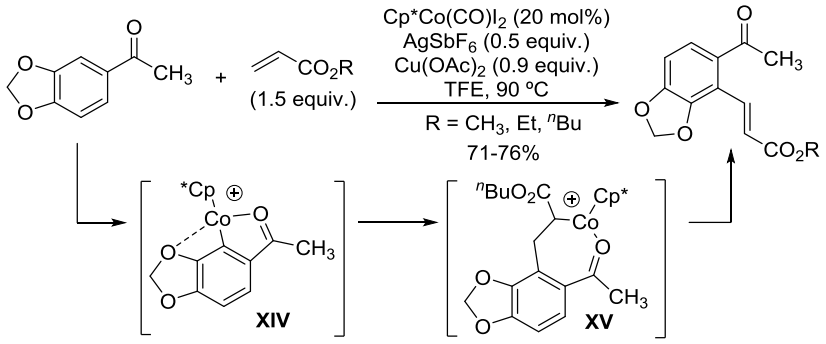
Scheme 3.24

In 2019, Maji expanded the scope of the Cp*Co(III)-catalyzed alkenylative coupling to the use of weakly-coordinating aromatic ketones as directing groups for the reaction of arenes with acrylates (Scheme 3.25).[43]



Scheme 3.25

After demonstrating that the C-H activation was reversible and non-rate-determining, the authors were able to detect species **XIV** and **XV** by LC-MS, unravelling the key factor of the mechanism (Scheme 3.26).

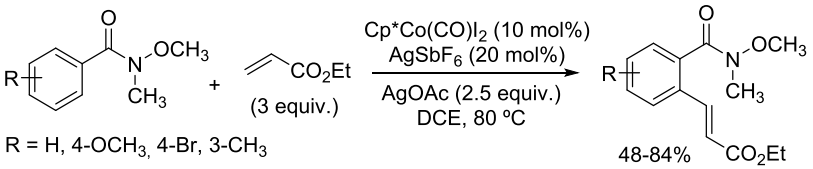


Scheme 3.26

[43] Sk, M.R.; Bera, S.S.; Maji, M.S *Adv. Synth. Catal.* **2019**, *361*, 585.

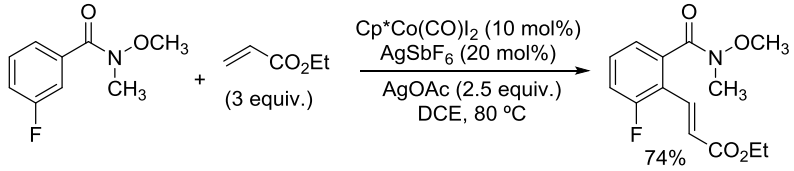
Besides, it must be mentioned that when the aromatic ketone bearing a 3,4-methylenedioxy group was subjected to the reaction conditions, the alkenylation took place at the most sterically hindered position, leading to the formation of 2-alkenylarenes.

In 2018, Matsunaga proved that it was possible to carry out several types of C-H functionalization reactions over Weinreb amides: allylation using allyl carbonates, amidation with dioxazolones, iodination utilizing *N*-iodosuccinimide, and oxidative alkenyaltion employing ethyl acrylate, being this last transformation depicted in Scheme 3.27.[44] The present oxidative coupling could take place under the reaction conditions developed for the alkenylation of *N*-methylbenzamides with ethyl acrylate (Scheme 3.24);[42] however, the temperature had to be increased.



Scheme 3.27

Interestingly, in contrast to usual results obtained under Cp*Co(III)-catalysis, when 3-fluoro-*N*-methoxy-*N*-methylbenzamide was utilized as the substrate, the C-H functionalization occurred at the most sterically hindered C-2 position (Scheme 3.28). Nevertheless, a more sterically demanding methyl group led to the alkenylation at the usual C-6 position. Kinetic isotopic experiments showed that the C-H activation step was rate-determining for this coupling.

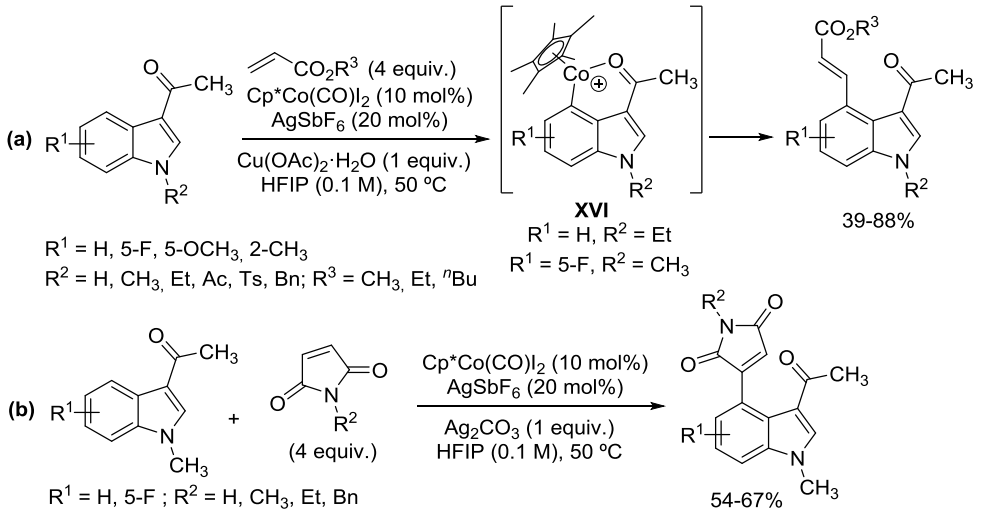


Scheme 3.28

In 2019, Ravikumar *et al*. carried out the selective C-4 alkenylation of indoles with different acrylates using an acetyl group attached to the C-3 position as a directing group. To achieve

[44] Kawai, K.; Bunno, Y.; Yoshino, T.; Matsunaga, S. *Chem. Eur. J.* **2018**, *24*, 10231.

this transformation, apart from the usual catalytic system [Cp*Co(CO)I_2 and $AgSbF_6$], $Cu(OAc)_2{\cdot}H_2O$ had to be used as the external oxidant (Scheme 3.29a).[45] They confirmed that the reaction proceeded through species **XVI** (that is proposed to be formed after a reversible C-H activation event), as they were able to detect it by HRMS when carrying out an experiment with stoichiometric amounts of the catalyst. Besides, the scope of the reaction could be extended to the use of maleimides as the electron-deficient olefins; however, in this case Ag_2CO_3 was used as the oxidant (Scheme 3.29b).

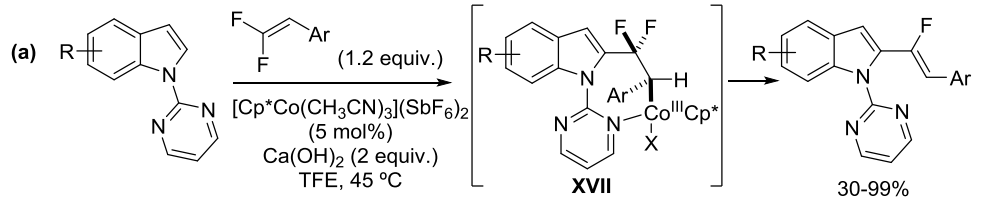


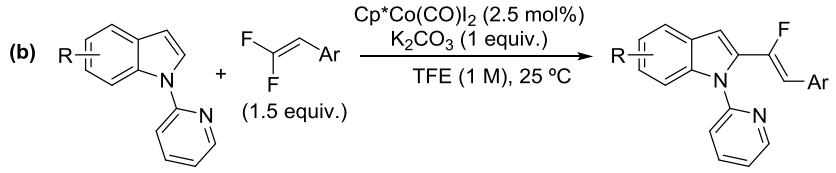
Scheme 3.29

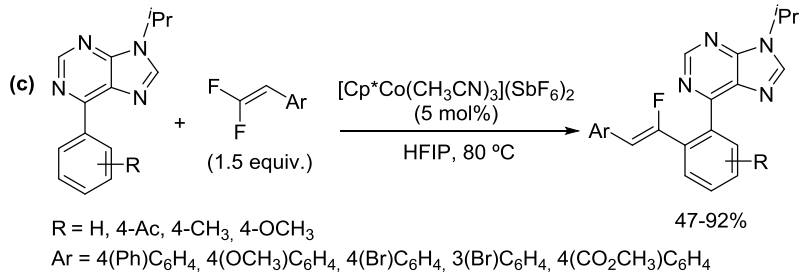
The alkenylation of arenes has also been successfully accomplished using *gem*-difluoroalkenes, as demonstrated by Li *et al.* in the reaction of *N*-pyrimidyl-protected indoles (Scheme 3.30a).[46] In this case, after a non-rate-determining C-H activation step followed by olefin insertion, intermediate **XVII** would be formed, which is proposed to undergo β-fluoride elimination, furnishing the corresponding product along with a Cp*Co(III)-F species. This is thought to undergo a defluorination event mediated by $HSbF_6$ (generated in the C-H activation step) to release the catalytically active Co(III) species and HF. Therefore, the reaction proceeds in a redox neutral manner, without the requirement for the addition of external oxidants.

[45] Banjare, S.K.; Nanda, T.; Ravikumar, P.C. *Org. Lett.* **2019**, *21*, 8138.
[46] Kong, L.; Zhou, X.; Li, X. *Org. Lett.* **2016**, *18*, 6320.

One year later, in 2017, Ackermann improved this methodology for the C-2 alkenylation of indoles with *gem*-difluoroalkenes, reducing the catalyst loading to 2.5 mol% and using K_2CO_3 at room temperature instead of $Ca(OH)_2$ at 45 ºC (Scheme 3.30b).[47] In this work, DFT studies were carried out. According to them, the recovery of the catalytically active species takes place *via* coordination of bicarbonate to the Cp*Co(III)-F species and elimination of HF, which is formed due to the transference of a proton from the bicarbonate ligand o the fluoride. Interestingly, in 2018 Matsunaga extended this procedure to the use of 6-arylpurines as substrates (Scheme 3.30c).[48]





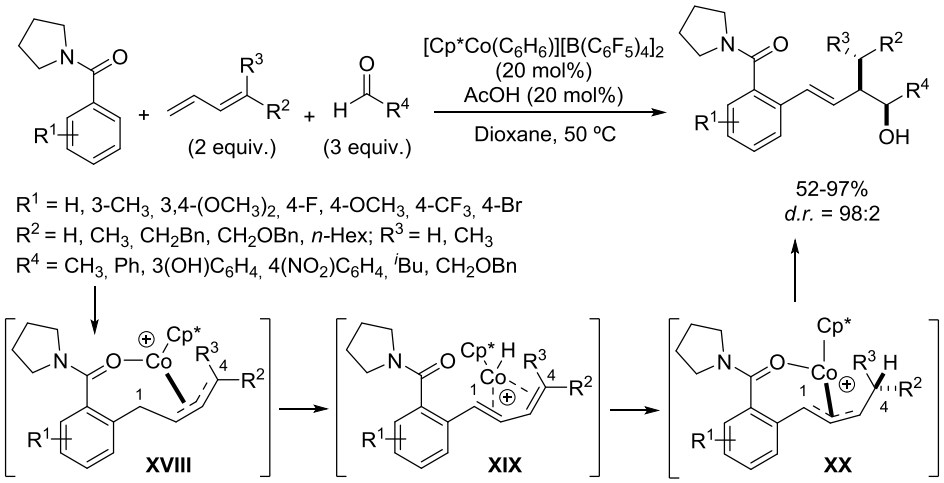


Scheme 3.30

[47] Zell, D.; Müller, V.; Dhawa, U.; Bursch, M.; Rubio Presa, R.; Grimme, S.; Ackermann, L. *Chem. Eur. J.* **2017**, *23*, 12145.

[48] Murakami, N.; Yoshida, M.; Yoshino, T.; Matsunaga, S. *Chem. Pharm. Bull.* **2018**, *66*, 51.

In 2018, Ellman´s group was able to expand the scope of their three-component Cp*Co(III)-catalyzed reaction (see Scheme 3.14)[29] to the use of dienes instead of α,β-unsaturated carbonyl compounds, allowing the alkenylation of arenes with olefins in a redox-neutral manner. The reaction proceeded in high yields and diatereoselectivities, using amide directing groups, to provide the corresponding homoallylic alcohols (Scheme 3.31).[49]



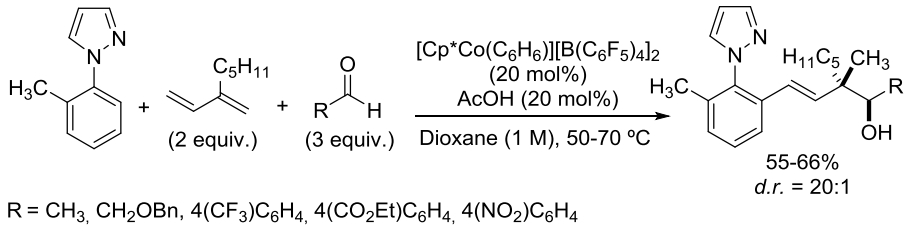
Scheme 3.31

According to some experiments conducted to elucidate the mechanism operating in the transformation, it is proposed to proceed through intermediate **XVIII** (that could be isolated) which would evolve to **XX** after formal hydrogen transfer from C-1 to C-4 through **XIX**. Reaction with the aldehyde would release the corresponding alcohol products after protonolysis. Besides, kinetic isotopic experiments showcased that the C-H metalation event was the rate-limiting step.

In 2019, that same group again moved beyond the limits of their three-component reaction. This time they managed to use internally substituted dienes, allowing the synthesis of a variety of homoallylic alcohols possessing acyclic quaternary centers (Scheme 3.32).[50] Furthermore, regarding the carbonyl coupling partners, in some cases, activated ketones could be used instead of aldehydes. It was proved that, in this transformation, the C-H cobaltation step was not the rate-limiting one.

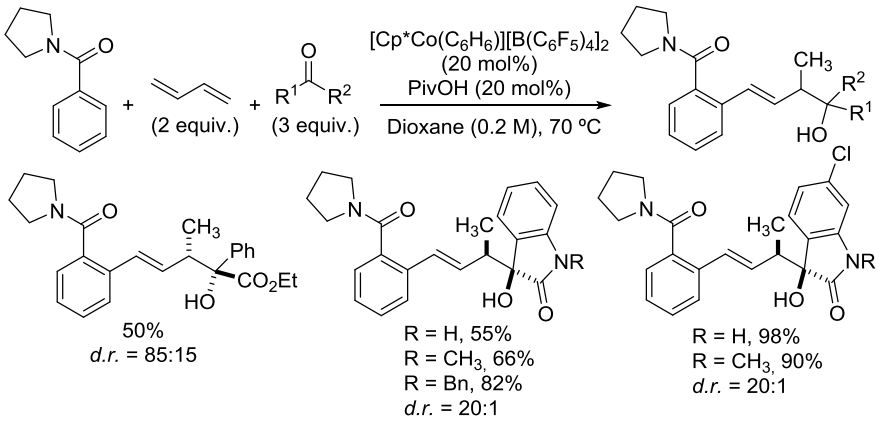
[49] Boerth, J.A.; Maity, S.; Williams, S.K.; Mercado, B.Q.; Ellman, J.A. *Nat. Catal.* **2018**, *1*, 673.
[50] Dongbang, S.; Shen, Z.; Ellman, J.A. *Angew. Chem. Int. Ed.* **2019**, *58*, 12590.

Before this work came to light, Zhao and co-workers had reported a three-component coupling using dienes under Cp*Rh(III) catalysis. In this article, two examples were given using internally substituted dienes; however, they were limited to the use of highly activated carbonyl coupling partners, such as ethyl glyoxylate, and the yields were modest.[51]



Scheme 3.32

Finally, Ellman´s group recently reported a highly diastereoselective three-component reaction between benzamides, 1,3-butadiene and activated ketones (Scheme 3.33).[52]

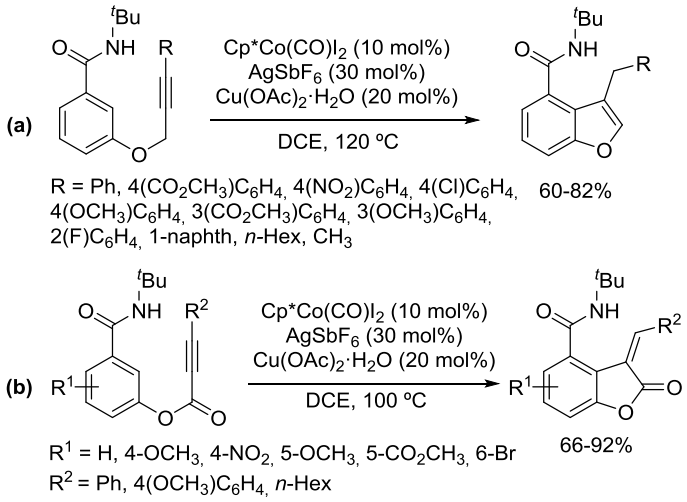


Scheme 3.33

[51] Li, R.; Ju, C.-W.; Zhao, D. *Chem. Commun.* **2019**, *55*, 695.
[52] Shen, Z.; Li, C.; Mercado, B.Q.; Ellman, J.A. *Synthesis* **2020**, *52*, 1239.

1.2. Cp*Co(III)-catalyzed intramolecular couplings involving C-H activation/C-C bond formation

Intermolecular C-H activation reactions involving the construction of C-C bonds under Cp*Co(III) catalysis have been extensively studied since the discovery of this kind of privileged complexes. On the contrary, the intramolecular version of the aforementioned transformations remains almost unexplored and limited to the use of alkynes as the coupling partners. In this sense, in 2018, Maji and co-workers reported the intramolecular Cp*Co(III)-catalyzed alkenylation of different phenyl propargyl ethers, as well as several phenyl propiolates, that led to the formation of the corresponding benzofurans (Scheme 3.34a) and benzofuranones (Scheme 3.34b), respectively. This transformation proceeded through a 5-*exo*-dig cyclization process and *N*-*tert*-butylamide was utilized as the directing group.[53] The mechanistic studies performed suggested that the C-H metalation was reversible.

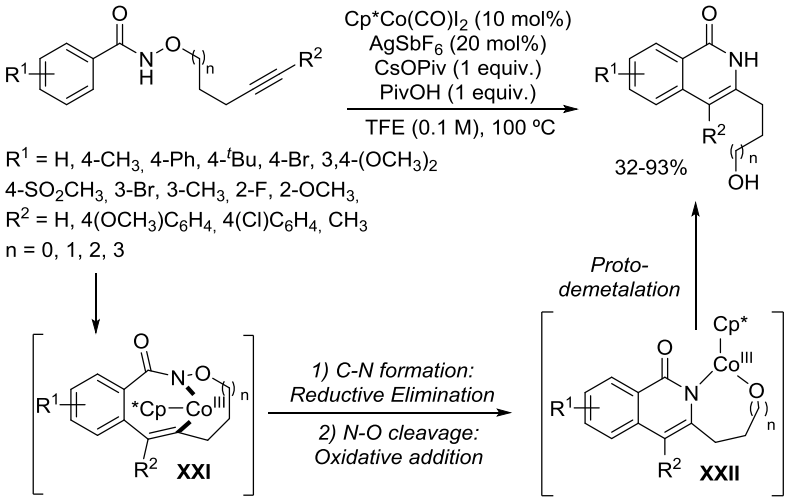


Scheme 3.34

Following a conceptually different approach, in 2017, Glorius and co-workers developed a Cp*Co(III)-catalyzed intramolecular alkenylation reaction to synthesize isoquinolones starting from different *N*-alkoxybenzamides bearing alkynes tethered to the *N*-alkoxy

[53] Bera, S.S.; Debbarma, S.; Jana, S.; Maji, M.S. *Adv. Synth. Catal.* **2018**, *360*, 2204.

moiety (Scheme 3.35).[54] This annulative coupling is proposed to proceed *via* cobaltacycle **XXI**, which would be furnished after C-H metalation of the aromatic ring and subsequent migratory insertion to the alkyne. Intermediate **XXI** is proposed to undergo reductive elimination, followed by oxidative addition of the Co(I) species to the N-O bond, that would act as internal oxidant. Thus, the catalytically active Cp*Co(III) species would be recovered after proto-demetalation of intermediate **XXII**, releasing the product upon that process. This transformation could be employed to perform the synthesis of aromathecin, protoberberine, and tylophora alkaloids. Interestingly, when this reaction was accomplished under Cp*Rh(III) catalysis, only internal alkynes could be used;[55] however, Cp*Co(III) catalysis allowed the reaction to take place even with terminal alkynes.



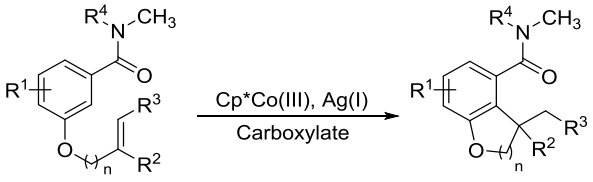
Scheme 3.35

[54] Lerchen, A.; Knecht, T.; Koy, M.; Daniliuc, C.G.; Glorius, F. *Chem. Eur. J.* **2017**, *23*, 12149.
[55] Xu, X.; Liu, Y.; Park, C.-M. *Angew. Chem. Int. Ed.* **2012**, *51*, 9372.

2. AIMS OF THE CHAPTER

On the basis of our recent findings on the Pd(II)-catalyzed intramolecular Fujiwara-Moritani coupling for the synthesis of nitrogen and oxygen heterocycles[56] (disclosed in the previous chapter), we explored the possibility of attaining a high-valent-cobalt-catalyzed C-H activation reaction, using an amide directing group, for the intramolecular formation of C-C bonds. Despite this kind of transformations featuring intramolecular C-H activation/hydroarylation reactions have been previously described with alkynes,[53,54] the use of olefins as the coupling partners is still unexplored.

Therefore, we became interested in performing the Cp*Co(III)-catalyzed intramolecular hydroarylation of unactivated olefins, envisioning that a variety of 2,3-dihydrobenzofurans could be obtained via 5-*exo*-trig cyclizations, starting from the corresponding allyl phenyl ethers. First of all, we will seek for the optimal reaction conditions and with them in hand, the scope of the present coupling will be studied, changing not only the substituents on the arene or the olefin, but also the length of the alkenyl chain (Scheme 3.36). Moreover, taking advantage of the formation of 2,3-dihydrobenzofurans possessing quaternary centers, an array of chiral carboxylic acids will be prepared and utilized in the reaction in order to try to induce enantioselectivity.



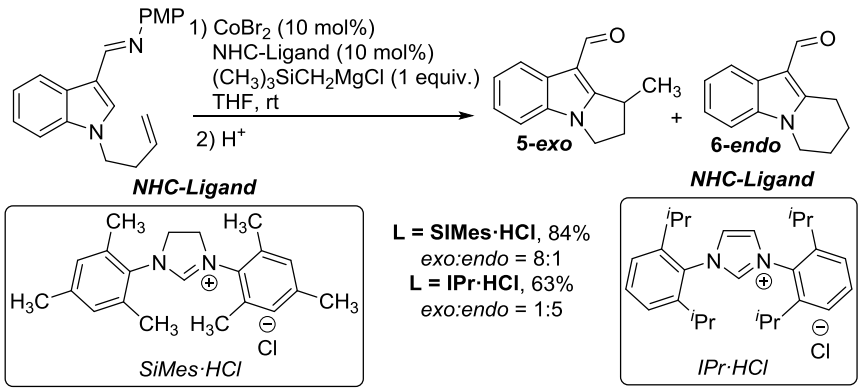
Scheme 3.36

[56] a) Carral-Menoyo, A.; Ortiz-de-Elguea, V.; Martinez-Nunes, M.; Sotomayor, N.; Lete, E. *Mar. Drugs* **2017**, *15*, 276; b) Carral-Menoyo, A.; Misol, A.; Gómez-Redondo, M.; Sotomayor, N.; Lete, E. *J. Org. Chem.* **2019**, *84*, 2048; c) Carral-Menoyo, A.; Sotorríos, L.; Ortiz-de-Elguea, V.; Díaz-Andrés, A.; Sotomayor, N.; Gómez-Bengoa, E.; Lete, E. *J. Org. Chem.* **2020**, *85*, 2486.

3. RESULTS AND DISCUSSION

3.1. Amide-directed intramolecular Co(III)-catalyzed C–H hydroarylation of alkenes for the synthesis of dihydrobenzofurans with a quaternary center[57]

As it has been shown in the introduction of this chapter, Cp*Co(III)-type catalysts allow to accomplish a wide variety of transformations comprising the assembly of C-C bonds starting from inert C-H bonds. Bearing this in mind, we decided to move from the palladium-based catalysts employed in the previous chapter to the more earth-abundant, cheaper and less toxic cobalt-based catalysts. Thereby, the utilization of high-valent-cobalt complexes, possessing pentamethylcyclopentadienyl (Cp*) ligands, allowed us to accomplish the first Cp*Co(III)-promoted intramolecular hydroarylation of unactivated olefins. As it has been previously stated, intramolecular hydroarylation reactions have been only achieved under Cp*Co(III) catalysis employing alkynes as the coupling partners. In contrast, cyclization reactions onto an alkene tethered to the (hetero)aromatic ring are underdeveloped, contrary to what can be observed in Pd(II)-catalyzed reactions. To the best of our knowledge, there are only examples of low-valent-cobalt-catalyzed intramolecular imine-directed C-2 alkylation of *N*-homoallylindoles. In this regard, Yoshikai and co-workers reported in 2013 a method to achieve the intramolecular alkylation of *N*-butenyl-substituted indoles bearing *para*-methoxyphenyl imine as the directing group in C-3 (Scheme 3.37).[58]

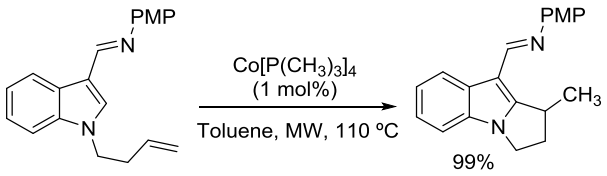


Scheme 3.37

[57] The work described in this section has been published in: Carral-Menoyo, A.; Sotomayor, N.; Lete, E. *J. Org. Chem.* **2020**, *85*, 10261.

[58] Ding, Z.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 8574.

This reaction proceeded at room temperature and $CoBr_2$ was used as catalyst, while Grignard reagent $(CH_3)_3SiCH_2MgCl$ was employed as reductant. The authors observed that they could control the site selectivity of the cyclization by changing the NHC ligand, leading to the regioselective formation of dihydropyrroloindoles (5-*exo*-trig) when SiMes·HCl was employed or tetrahydropyridoindoles (6-*endo*-trig) utilizing IPr·HCl. However, that control could not be effectively applied when substituted homoallylic scaffolds were used, being the site-selectivity of the cyclization mainly determined by the structure of the alkenyl chain. Later, in 2016, Petit reported a different strategy for the intramolecular 5-*exo*-trig C-2 alkylation of homoallylindoles under microwave irradiation, using an imine as directing group and employing the well-defined low-valent-cobalt complex $Co[P(CH_3)_3]_4$ as catalyst in the absence of reductants. However, high temperatures were required (Scheme 3.38).[59]



Scheme 3.38

Based on the precedents shown in the introduction and the lack of C-C bond-forming intramolecular transformations involving the use of olefins under Cp*Co(III) catalysis, we decided to employ those complexes to tackle the synthesis of 2,3-dihydrobenzofurans utilizing different 3-(allyloxy)benzamides as substrates. This transformation would proceed through an intramolecular 5-*exo*-trig hydroarylation reaction towards the unactivated olefins present in the substrates (Scheme 3.39). Despite related Rh(III)- (Scheme 3.39a),[60] Ir(I)- (Scheme 3.39b)[61] and Ru(II)-catalyzed (Scheme 3.39c)[62] protocols for the intramolecular hydroarylation of alkenes to access 2,3-dihydrobenzofurans have been described, the use of these 2nd- and 3rd-row-transition metals has some drawbacks, such as their low natural abundance, toxicity and high cost.

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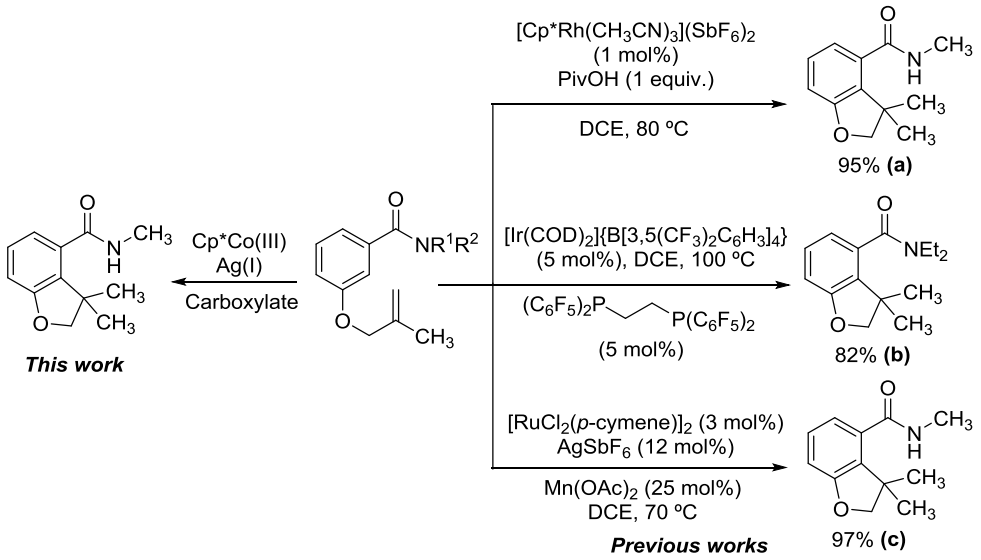
[59] Fallon, B.J.; Derat, E.; Amatore, M.; Aubert, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A.; Petit, M. *Org. Lett.* **2016**, *18*, 2292.

[60] a) Davis, T.A.; Hyster, T.K.; Rovis, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 14181; b) Ye, B.; Donets, P.A.; Cramer, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 507; c) Guan, Z.; Chen, S.; Huang, Y.; Yao, H. *Org. Lett.* **2019**, *21*, 3959.

[61] Fernandez, D.F.; Gulías, M.; Mascareñas, J.L.; López, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 9541.

[62] a) Ghosh, K.; Rit, R.K.; Ramesh, E.; Sahoo, A.K. *Angew. Chem. Int. Ed*. **2016**, *55*, 7821; b) Rit, R.K.; Ghosh, K.; Mandal, R.; Sahoo, A.K. *J. Org. Chem.* **2016**, *81*, 8552; c) Mukherjee, K.; Ramesh, E.; Ghosh, K.; Sahoo, A.K. *Asian J. Org. Chem.* **2018**, *7*, 1380.



Scheme 3.39

Concerning the biological interest of the 2,3-dihydrobenzofuran motif, it should be noted that it is present as a structural core in several biologically active natural products[63] and pharmaceuticals.[64] In particular, 3,3-disubstituted 2,3-dihydrobenzofurans are potent selective cannabinoid receptor 2 agonists[65] and synthetic retinoids (Figure 3.1).[66]

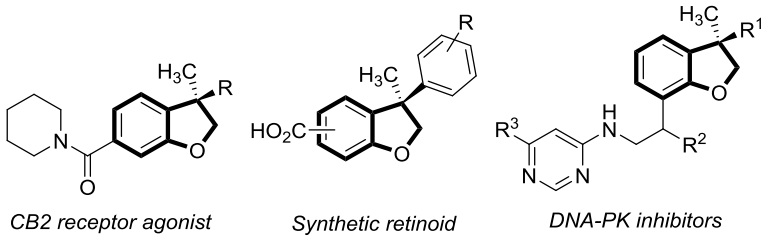


Figure 3.1

[63] a) Bertolini, F.; Pineschi, M. *Org. Prep. Proced. Int.* **2009**, *41*, 385; b) Sheppard, T.D. *J. Chem. Res.* **2011**, *35*, 377; c) Chen, Z.; Pitchakuntla, M.; Jia, Y. *Nat. Prod. Rep.* **2019**, *36*, 666.

[64] Dawood, K.M. *Expert Opin. Ther. Pat.* **2019**, *29*, 841.

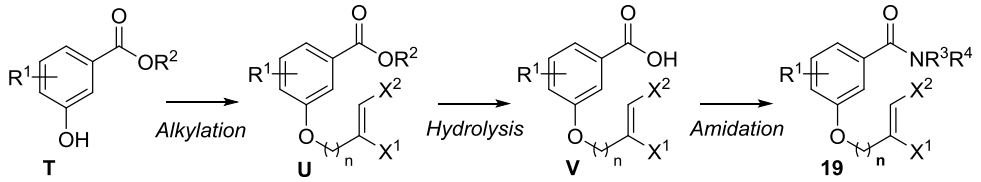
[65] Diaz, P.; Phatak, S.S.; Xu, J.; Fronczek, F.R.; Astruc-Diaz, F.; Thompson, C.M.; Cavasotto, C.N.; Naguib, M. *ChemMedChem* **2009**, *4*, 1615.

[66] Diaz, P.; Gendre, F.; Stella, L.; Charpentier, B. *Tetrahedron* **1998**, *54*, 4579.

They are also important building blocks in the synthesis of more complex molecules, such as DNA-dependent protein kinase (DNA-PK) inhibitors[67] or nonstructural protein 5B (NS5B) inhibitors used as antivirals in the treatment of chronic hepatitis C (HCVNS5B inhibitors) (Figure 3.1).[68]

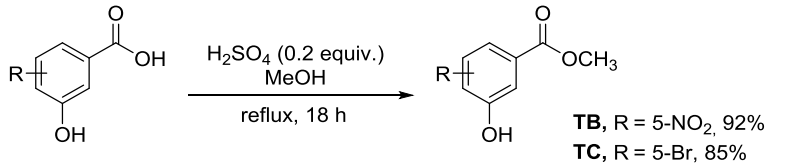
3.1.1. Synthesis of the substrates[69]

In this section, the preparation of benzamides **19aa-19fa** and **20aa** will be described, which were synthesized starting from different 3-hydroxybenzoic esters **TA-TO** and following the general synthetic route depicted in Scheme 3.40. In addition, the synthesis of indole-based amide **21** will also be commented.



Scheme 3.40

Some of the esters employed in the first step of the aforementioned pathway were commercially available; however, most of them had to be synthesized utilizing diverse methods. Among them, **TB-TO** were obtained *via* esterification of the corresponding 3-hydroxybenzoic acids (Scheme 3.41).

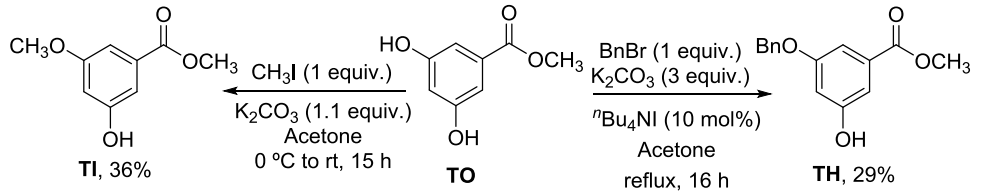


TB, R = 5-NO_2, 92%
TC, R = 5-Br, 85%
TE, R = 4-CH_3, 88%
TF, R = 4-OCH_3, 91%
TG, R = 4-F, 93%
TO, R = 5-OH, 91%

Scheme 3.41

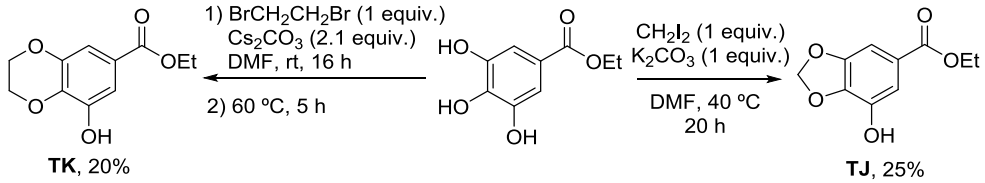
[67] Mohiuddin, I.S.; Kang, M.H. *Front. Oncol.* **2019**, *9*, 635.
[68] Patil, V.M.; Gupta, S.P.; Samanta, S.; Masand, N. *Curr. Med. Chem.* **2011**, *18*, 5564.
[69] References of compounds already reported in the literature are shown in the experimental part.

Besides, esters **TH** and **TI** were prepared by mono-*O*-alkylation of methyl 3,5-dihydroxybenzoate **TO**, using for that purpose benzyl bromide and methyl iodide, respectively (Scheme 3.42).



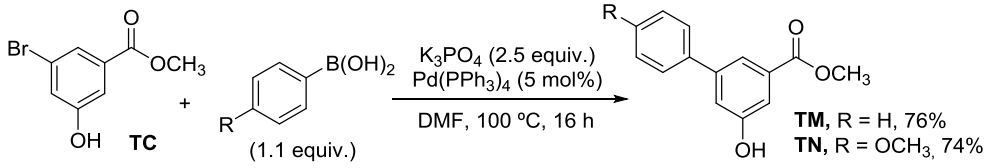
Scheme 3.42

Furthermore, ethyl gallate was reacted with diiodomethane to give **TJ** and with 1,2-dibromomethane to obtain **TK** (Scheme 3.43).



Scheme 3.43

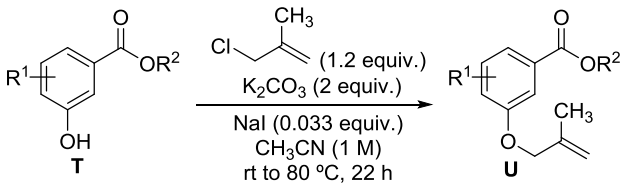
Finally, **TM** and **TN** were furnished by subjecting methyl 3-bromo-5-hydroxybenzoate **TC** to a Suzuki-Miyaura reaction utilizing phenylboronic acid and 4-methoxyphenylboronic acid as the cross-coupling partners, respectively (Scheme 3.44).



Scheme 3.44

According to the general route depicted in Scheme 3.40, 3-hydroxybenzoic esters **TA-TO** were then alkylated following different procedures depending on the chain introduced in the course of the reaction and the alkylating agent. In this context, the formation of esters **UAA-UAN** is shown in Table 3.1, using 3-chloro-2-methylprop-1-ene as the reaction partner.

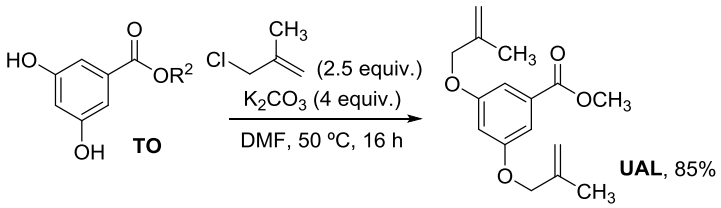
Table 3.1



Entry	Subst.	R^1	R^2	Prod.	Yield (%)[a]
1	**TA**	H	Et	**UAA**	82
2	**TB**	5-NO_2	CH_3	**UAB**	77
3	**TC**	5-Br	CH_3	**UAC**	94
4	**TD**	4,5-$(OCH_3)_2$	CH_3	**UAD**	92
5	**TE**	4-CH_3	CH_3	**UAE**	95
6	**TF**	4-OCH_3	CH_3	**UAF**	95
7	**TG**	4-F	CH_3	**UAG**	89
8	**TH**	5-OBn	CH_3	**UAH**	95
9	**TI**	5-OCH_3	CH_3	**UAI**	90
10	**TJ**	4,5-OCH_2O	Et	**UAJ**	quant.
11	**TK**	4,5-OCH_2CH_2O	Et	**UAK**	88
12	**TM**	5-Ph	CH_3	**UAM**	94
13	**TN**	5-[4(OCH_3)C_6H_4]	CH_3	**UAN**	93

[a] Yield of the isolated pure compounds.

A slightly different procedure was utilized for the synthesis of **UAL**, which was prepared through the di-*O*-allylation of methyl 3,5-dihydroxybenzoate **TO** (Scheme 3.45).

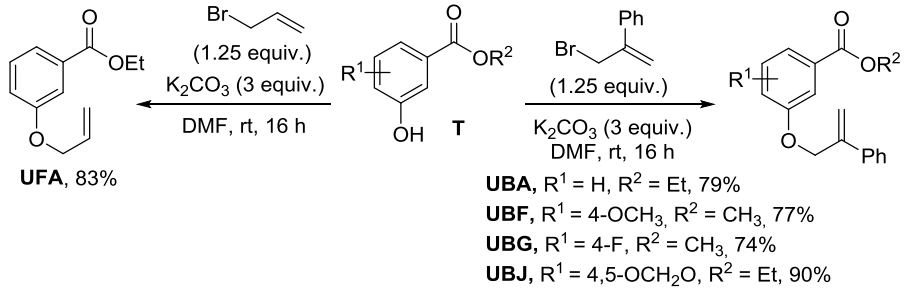


Scheme 3.45

Moreover, when using (3-bromoprop-1-en-2-yl)benzene (prepared following an already reported method)[70] as the allylating agent for the synthesis of **UBA-UBJ,** the procedure

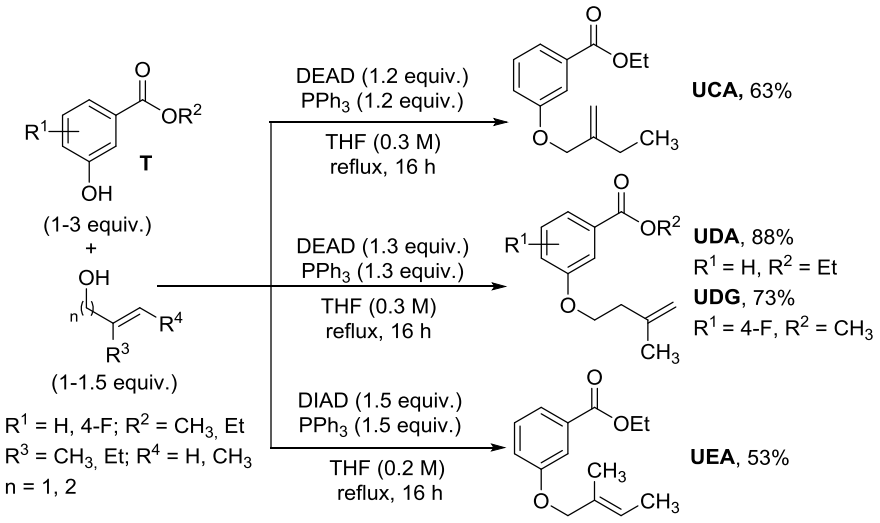
[70] Tripathi, C.B.; Mukherjee, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 8450.

displayed in Scheme 3.46 was followed, which could also be employed for the synthesis **UFA** starting from **TA** and allyl bromide.



Scheme 3.46

On the other hand, esters **UCA**-**UEA** could be obtained *via* the Mitsunobu reaction between the corresponding 3-hydroxybenzoate **T** and different alcohols (Scheme 3.47).[71]

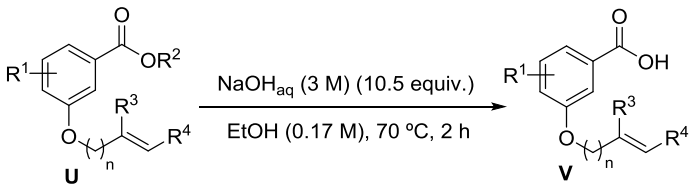


Scheme 3.47

[71] The preparations of 2-methylenebutan-1-ol (precursor of **UCA**) and *(E)*-2-methylbut-2-en-1-ol (precursor of **UEA**) are reported in: a) Liu, X.; Zhang, W.; Wang, Y.; Zhang, Z.-X.; Jiao, L.; Liu, Q. *J. Am. Chem. Soc.* **2018**, *140*, 6873 and b) Venning, A.R.O.; Kwiatkowski, M.R.; Roque Peña, J.E.; Lainhart, B.C.; Guruparan, A.A.; Alexanian, E.J. *J. Am. Chem. Soc.* **2017**, *139*, 11595; respectively.

Once the alkylated esters **UAA-UFA** were accessed, they were hydrolized in basic media to prepare benzoic acids **VAA-VFA** in high yields (Tables 3.2).

Table 3.2

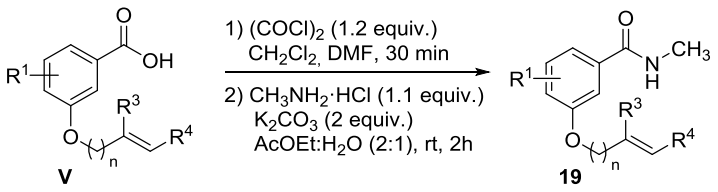


Entry	Subst.	R^1	R^2	R^3	R^4	n	Prod.	Yield (%)[a]
1	**UAA**	H	Et	CH_3	H	1	**VAA**	92
2	**UAB**	5-NO_2	CH_3	CH_3	H	1	**VAB**	85
3	**UAC**	5-Br	CH_3	CH_3	H	1	**VAC**	88
4	**UAD**	4,5-$(OCH_3)_2$	CH_3	CH_3	H	1	**VAD**	97
5	**UAE**	4-CH_3	CH_3	CH_3	H	1	**VAE**	97
6	**UAF**	4-OCH_3	CH_3	CH_3	H	1	**VAF**	91
7	**UAG**	4-F	CH_3	CH_3	H	1	**VAG**	91
8	**UAH**	5-OBn	CH_3	CH_3	H	1	**VAH**	86
9	**UAI**	5-OCH_3	CH_3	CH_3	H	1	**VAI**	93
10	**UAJ**	4,5-OCH_2O	Et	CH_3	H	1	**VAJ**	92
11	**UAK**	4,5-OCH_2CH_2O	Et	CH_3	H	1	**VAK**	94
12	**UAL**	5-$OCH_2C(CH_3)=CH_2$	CH_3	CH_3	H	1	**VAL**	89
13	**UAM**	5-Ph	CH_3	CH_3	H	1	**VAM**	93
14	**UAN**	5-[4$(OCH_3)C_6H_4$]	CH_3	CH_3	H	1	**VAN**	90
15	**UBA**	H	Et	Ph	H	1	**VBA**	92
16	**UBF**	4-OCH_3	CH_3	Ph	H	1	**VBF**	90
17	**UBG**	4-F	CH_3	Ph	H	1	**VBG**	93
18	**UBJ**	4,5-OCH_2O	Et	Ph	H	1	**VBJ**	95
19	**UCA**	H	Et	Et	H	1	**VCA**	96
20	**UDA**	H	Et	CH_3	H	2	**VDA**	92
21	**UDG**	4-F	CH_3	CH_3	H	2	**VDG**	75
22	**UEA**	H	Et	CH_3	CH_3	1	**VEA**	99
23	**UFA**	H	Et	H	H	1	**VFA**	99

[a] Yield of the isolated pure compounds.

Finally, all the acids **VAA-VFA** obtained in the previous step were amidated following one common methodology, being able to prepare *N*-methylbenzamides **19aa-19fa** (Table 3.3).

Table 3.3

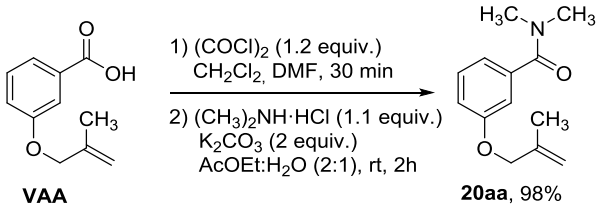


V **19**

Entry	Subst.	R^1	R^3	R^4	n	Prod.	Yield (%)[a]
1	**VAA**	H	CH_3	H	1	**19aa**	95
2	**VAB**	5-NO_2	CH_3	H	1	**19ab**	94
3	**VAC**	5-Br	CH_3	H	1	**19ac**	84
4	**VAD**	4,5-$(OCH_3)_2$	CH_3	H	1	**19ad**	95
5	**VAE**	4-CH_3	CH_3	H	1	**19ae**	90
6	**VAF**	4-OCH_3	CH_3	H	1	**19af**	89
7	**VAG**	4-F	CH_3	H	1	**19ag**	89
8	**VAH**	5-OBn	CH_3	H	1	**19ah**	96
9	**VAI**	5-OCH_3	CH_3	H	1	**19ai**	91
10	**VAJ**	4,5-OCH_2O	CH_3	H	1	**19aj**	90
11	**VAK**	4,5-OCH_2CH_2O	CH_3	H	1	**19ak**	92
12	**VAL**	5-$OCH_2C(CH_3)=CH_2$	CH_3	H	1	**19al**	91
13	**VAM**	5-Ph	CH_3	H	1	**19am**	94
14	**VAN**	5-[4$(OCH_3)C_6H_4$]	CH_3	H	1	**19an**	94
15	**VBA**	H	Ph	H	1	**19ba**	96
16	**VBF**	4-OCH_3	Ph	H	1	**19bf**	88
17	**VBG**	4-F	Ph	H	1	**19bg**	95
18	**VBJ**	4,5-OCH_2O	Ph	H	1	**19bj**	92
19	**VCA**	H	Et	H	1	**19ca**	90
20	**VDA**	H	CH_3	H	2	**19da**	94
21	**VDG**	4-F	CH_3	H	2	**19dg**	77
22	**VEA**	H	CH_3	CH_3	1	**19ea**	84
23	**VFA**	H	H	H	1	**19fa**	85

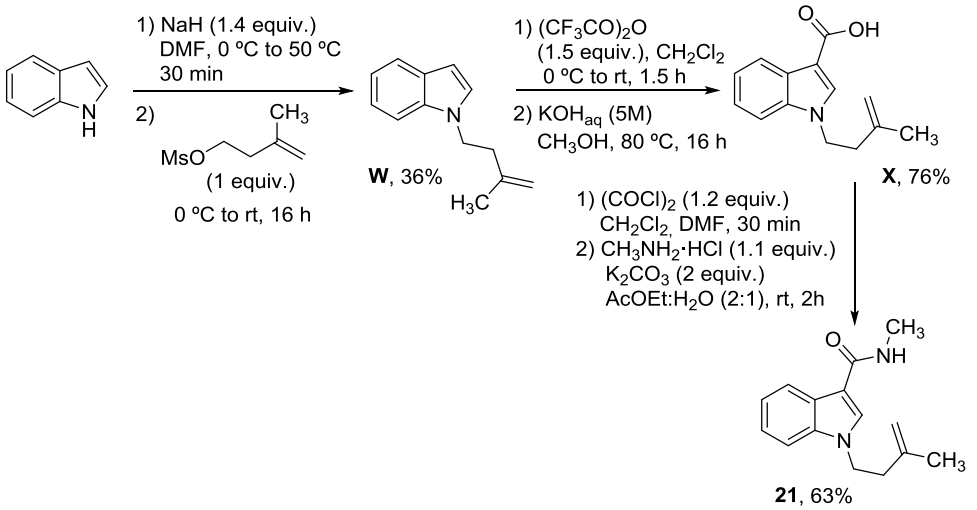
[a] Yield of the isolated pure compounds.

This same procedure was also followed for the formation of *N,N*-dimethylbenzamide **20aa** from **VAA**, using dimethylamine hydrochloride (Scheme 2.48).



Scheme 3.48

Indole **21,** possessing an amide moiety at C-3 and a butenyl chain tethered to the nitrogen, was prepared following the synthetic route depicted in Scheme 3.49: first of all, indole was alkylated on the nitrogen atom using 3-methylbut-3-en-1-yl methanesulfonate (synthesized according to a previously reported procedure),[72] to obtain **W**. Then, a carboxylate group was installed at the C-3 position of the indole moiety by reacting **W** with trifluoroacetic anhydride, followed by hydrolysis under basic media, to furnish **X.** Finally, amidation of the acid with methylamine hydrochloride afforded **21**.

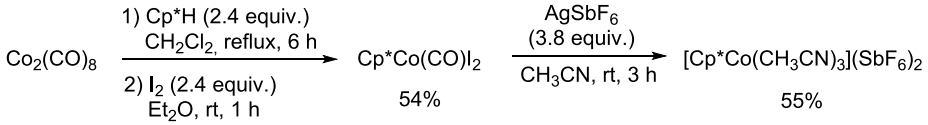


Scheme 3.49

In the present project two different Cp*Co(III) complexes were used: Cp*Co(CO)I_2[9,10a] and [Cp*Co(CH_3CN)$_3$](SbF_6)$_2$,[11] both of which had to be synthesized following already reported

[72] Brodney, M.A.; Cole, M.L.; Freemont, J.A.; Kyi, S.; Junk, P.C.; Padwa, A.; Riches, A.G.; Ryan, J.H. *Tetrahedron Lett.* **2007**, *48*, 1939.

procedures (Scheme 3.50). The first precatalyst could be synthesized reacting $Co_2(CO)_8$ with 1,2,3,4,5-pentamethylcyclopentadiene, followed by treatment with molecular iodine. Once with the product ($Cp^*Co(CO)I_2$) in hand, it was reacted with $AgSbF_6$ in CH_3CN to furnish the corresponding acetonitrile-complex $[Cp^*Co(CH_3CN)_3](SbF_6)_2$.



Scheme 3.50

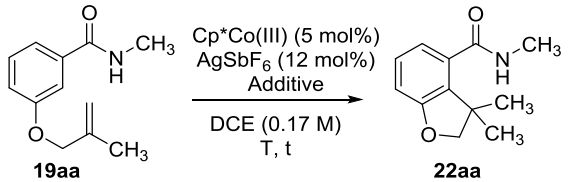
*3.1.2. Cp*Co(III)-catalyzed intramolecular alkylation of 3-(allyloxy)benzamides **19aa-19ca**, **19ea-19fa** and **20aa**, 3-(homoallyloxy)benzamides **19da-19dg**, as well as N-homoallylindole **21**. Synthesis of 2,3-dihydrobenzofurans **22aa-22ca**, chromanes **23da-23dg** and pyrroloindole **24***

Bearing in mind the precedents commented in previous sections concerning intramolecular C-H activation/C-C bond formation processes and with the aim of developing the first Cp*Co(III)-catalyzed intramolecular hydroarylation reaction over unactivated olefins, we attempted the synthesis of the 2,3-dihydrobenzofuran core, bearing a quaternary center. We started our study using amide **19aa** as the substrate and $Cp^*Co(CO)I_2$ (5 mol%) as precatalyst in the presence of $AgSbF_6$ (12 mol%), which has been applied to intermolecular amide-directed hydroarylations.[21e,27,53] We began the optimization of the reaction conditions utilizing KOAc as the carboxylate base (Table 3.4).

When employing DCE as the solvent at 80 ºC, dihydrobenzofuran **22aa** could be isolated as the only reaction product, but a low conversion of the starting material was observed after 24 h (30%, Table 3.4, entry 1). No improvement could be achieved using a 10 mol% precatalyst loading (with the subsequent increase in the amount of base and silver salt) (Table 3.4, entry 2). The use of a larger amount of base was detrimental (Table 3.4, entry 3), while a stoichiometric amount of acetate with respect to cobalt[26] did not have an impact on reactivity (Table 3.4, entry 4).

Different less hygroscopic acetate sources were also tested (Table 3.4, entries 5-11), but only NaOAc led to a comparable result (Table 3.4, entry 7), while the other ones furnished low conversions after 24 h (Table 3.4, entries 5, 6, 8-10), or even completely shut down the reactivity ($^nBu_4NOAc$, Table 3.4, entry 11). The use of acetic acid as the additive also provided poor results (Table 3.4, entry 12).

Table 3.4



19aa **22aa**

Entry	Additive (mol%)	Cp*Co(III)	T (ºC)	t (h)	Yield (%)[a]
1	KOAc (12)	$Cp^*Co(CO)I_2$	80	24	30
2[b]	KOAc (20)	$Cp^*Co(CO)I_2$	80	24	31
3	KOAc (25)	$Cp^*Co(CO)I_2$	80	24	10
4	KOAc (5)	$Cp^*Co(CO)I_2$	80	24	33
5	$Cu(OAc)_2$ (12)	$Cp^*Co(CO)I_2$	80	24	11
6	AgOAc (12)	$Cp^*Co(CO)I_2$	80	24	4
7	NaOAc (12)	$Cp^*Co(CO)I_2$	80	24	22
8	LiOAc (12)	$Cp^*Co(CO)I_2$	80	24	13
9	CsOAc (12)	$Cp^*Co(CO)I_2$	80	24	5
10	RbOAc (12)	$Cp^*Co(CO)I_2$	80	24	13
11	$^nBu_4NOAc$ (12)	$Cp^*Co(CO)I_2$	80	24	-[c]
12	AcOH (22)	$Cp^*Co(CO)I_2$	80	24	6
13	NaOPiv (12)	$Cp^*Co(CO)I_2$	80	24	6
14	$PhCO_2K$ (12)	$Cp^*Co(CO)I_2$	80	24	25
15[d]	KOAc (12)	$[Cp^*Co(CH_3CN)_3](SbF_6)_2$	80	24	30
16	KOAc (12)	$Cp^*Co(CO)I_2$	120	4	91
17	KOAc (12)	-	120	4	-[c]
18[d]	KOAc (12)	$Cp^*Co(CO)I_2$	120	4	-[c]
19	-	$Cp^*Co(CO)I_2$	120	4	30

[a] Yield of the isolated pure compound. Reactions were carried out in a 0.2 to 0.3 mmol scale. [b] $Cp^*Co(CO)I_2$ (10 mol%) and $AgSbF_6$ (20 mol%) were used. [c] No reaction. Starting material recovered. [d] No $AgSbF_6$ was used.

Based on the aforementioned results, we next tested different carboxylates (Table 3.4, entries 13-14), observing that while potassium benzoate gave a slightly lower yield of the desired product **22aa** (compared to the result obtained using KOAc) (Table 3.4, entry 14), sodium pivalate dramatically hampered the reaction (Table 3.4, entry 13). Besides, the reactivity was similar when a different cobalt precatalyst $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ was used (Table 3.4, entry 15).

Fortunately, an increase of the reaction temperature to 120 ºC resulted in a significant enhancement of the reactivity, leading to a complete conversion after just 4 h, and furnishing the expected dihydrobenzofuran **22aa** in an excellent isolated yield (91%, Table 3.4, entry 16).

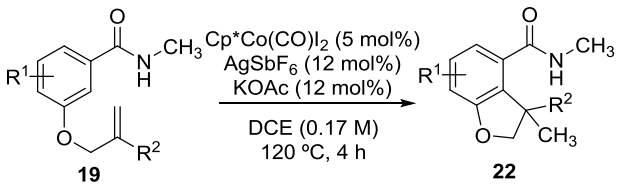
Control experiments were also carried out, confirming that the presence of both the cobalt precatalyst and the silver salt were indispensable for reactivity (Table 3.4, entries 17-18). On the other hand, in the absence of the carboxylate base (Table 3.4, entry 19), a notorious decrease of the yield was observed. This fact shows the importance of the carboxylate in assisting the C-H functionalization. It has been seen that the selectivity in the intermolecular hydroarylation of unbiased alkenes can be switched from the linear to the branched isomer by changing the additive used in the catalytic system, which results in a change of the C-H activation mechanism.[30] In our case, **22aa** was obtained with complete selectivity through a 5-*exo*-trig intramolecular hydroarylation process, regardless of the additive employed. However, although not on regioselectivity, the type of carboxylate (or its absence) had a high impact on reactivity in this transformation.

Once with the optimal reaction condition in hand, the scope of the coupling was extended to different substitution patterns in both the arene and the alkene (Table 3.5). The electronic nature of the substituents placed in the aromatic ring did not have a major impact on reactivity, as in general, high yields of the dihydrobenzofuran products **22** were obtained with electron-donating or electron-withdrawing functionalities.

However, **19ae** was almost unreactive (Table 3.5, entry 5), and lower yields were obtained in some of the examples bearing substituents *ortho* to the allyl ether moiety, such as **22af** (Table 3.5, entry 6), **22ak** (Table 3.5, entry 11) and **22bf** (Table 3.5, entry 16), which could be attributed to unfavorable steric effects for the hydroarylation. Nevertheless, when a small fluoro group was placed at that position, high yields were obtained (**22ag** and **22bg**, Table 3.5, entries 7 and 17, respectively). Curiously, when 4,5-methylenedioxy- and 4,5-dimethoxy-substituted substrates were utilized, the corresponding products were also furnished in good to excellent yields (Table 3.5, entries 4, 10 and 18).

In contrast to the use of ruthenium catalysts on related substrates,[62a] a two-fold hydroarylation of **19al** could also be hampered by steric effects, isolating **22al** (Table 3.5, entry 12) as the only product in a good yield. Different substituents on the alkene, such as phenyl (**22ba-22bj**, Table 3.5, entries 15-18) and ethyl groups (**22ca**, Table 3.5, entry 19) were also well tolerated.

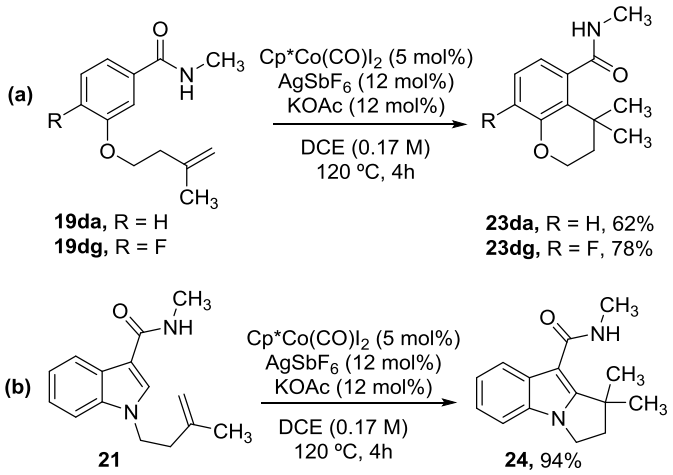
Table 3.5



Entry	Subst.	R^1	R^2	Prod	Yield (%)[a]
1	**19aa**	H	CH_3	**22aa**	91
2	**19ab**	5-NO_2	CH_3	**22ab**	91
3	**19ac**	5-Br	CH_3	**22ac**	84
4	**19ad**	4,5-$(OCH_3)_2$	CH_3	**22ad**	87
5	**19ae**	4-CH_3	CH_3	**22ae**	<5
6	**19af**	4-OCH_3	CH_3	**22af**	65
7	**19ag**	4-F	CH_3	**22ag**	93
8	**19ah**	5-OBn	CH_3	**22ah**	91
9	**19ai**	5-OCH_3	CH_3	**22ai**	81
10	**19aj**	4,5-OCH_2O	CH_3	**22aj**	94
11	**19ak**	4,5-OCH_2CH_2O	CH_3	**22ak**	58
12	**19al**	5-$OCH_2C(CH_3)=CH_2$	CH_3	**22al**	67
13	**19am**	5-Ph	CH_3	**22am**	96
14	**19an**	5-[4$(OCH_3)C_6H_4$]	CH_3	**22an**	88
15	**19ba**	H	Ph	**22ba**	76
16	**19bf**	4-OCH_3	Ph	**22bf**	44
17	**19bg**	4-F	Ph	**22bg**	86
18	**19bj**	4,5-OCH_2O	Ph	**22bj**	77
19	**19ca**	H	Et	**22ca**	80

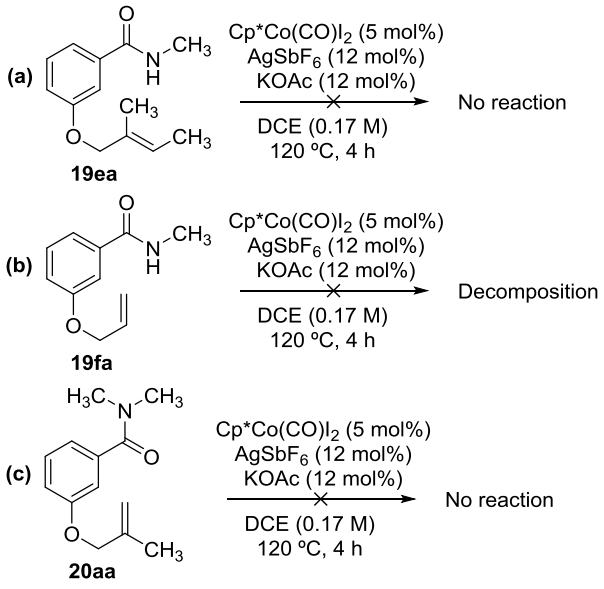
[a] Yield of the isolated pure compounds. Reactions were carried out in a 0.2 to 0.3 mmol scale in a 20-mL sealed reaction tube.

Under the same reaction conditions, the cyclization also proceeded efficiently through a 6-*exo* process for the formation of chromanes **23da** and **23dg** (Scheme 3.51a). Besides, the cobaltation of the indole ring on **21** was also possible, leading to the formation of pyrroloindole **24** in an excellent yield (Scheme 3.51b).



Scheme 3.51

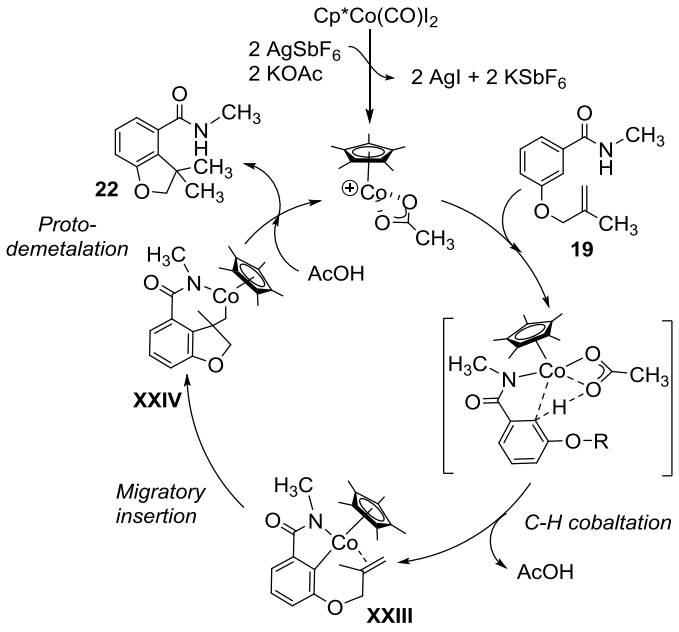
However, substitution on the terminal carbon of the alkene was not tolerated, probably due to steric reasons, as **19ea** was unreactive under the standard reaction conditions (Scheme 3.52a).



Scheme 3.52

On the other hand, **19fa**, bearing no substituent on the olefin, led to decomposition products (Scheme 3.52b). Finally, although dialkyl amides have been used as directing groups in related rhodium-[60a], iridium-[61] and ruthenium-mediated[62b] reactions, in this work, the presence of a N-H in the director was crucial for reactivity,[21e,27,28,53,54] as **20aa** was completely unreactive (Scheme 3.52c).

Regarding the mode of action of the amide directing group, the coordination of the Co(III)-center to the carbonyl oxygen has been proposed for the intermolecular alkenylation of benzamides with activated olefins.[42] Besides, it has also been reported that different substitution on the amide may result in different binding modes, as supported by DFT calculations.[21e,27] Nonetheless, based on our experimental results (Scheme 3.52) C-H activation of benzamides through a Co-N binding mode has been proposed. In this context, cobaltacycles supporting that mechanism have been characterized[73] and this pathway has been suggested for related hydroarylation reactions.[53,54,74] With all these considerations in mind, a schematic reaction mechanism proposal is depicted in Scheme 3.53.



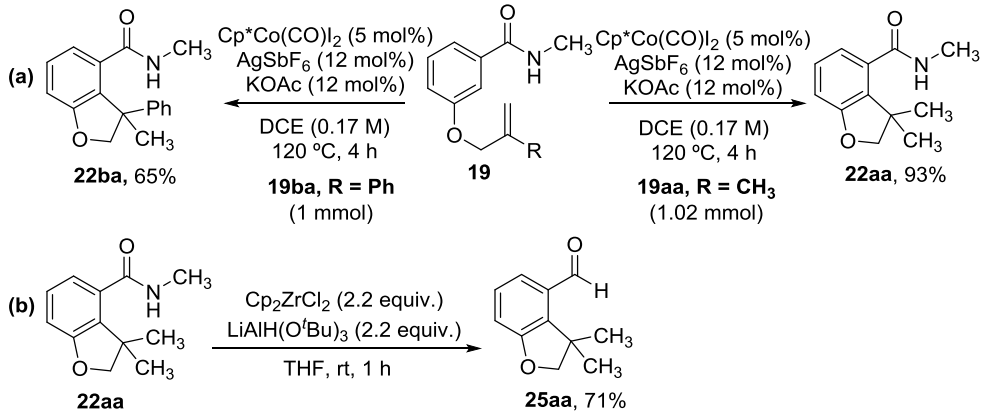
Scheme 3.53

[73] Yu, X.; Chen, K.; Guo, S.; Shi, P.; Song, C.; Zhu, J. *Org. Lett.* **2017**, *19*, 5348.
[74] Bera, S.S.; Debbarma, S.; Ghosh, A.K.; Chand, S.; Maji, M.S. *J. Org. Chem.* **2017**, *82*, 420.

The C-H cobaltation of substrates **19** with active species $[Cp^*Co(OAc)]^+$, generated *in situ* by the reaction of KOAc and $AgSbF_6$ with the $Cp^*Co(CO)I_2$ precatalyst, would take place to afford **XXIII**, with the assistance of the acetate through a CMD[13] or a BIES[14] mechanism, as it has been proposed for similar transformations.[22,26,27,30,41,43] KIE experiments carried out in related systems,[21c,21d,26,41] support that this C-H activation event is generally not the rate-determining step.

Subsequent selective migratory insertion would generate the seven-membered cobaltacycle **XXIV** that would selectively undergo proto-demetalation to afford **22**, regenerating the catalyst. An alternative pathway from **XXIV** leading to aminoarylation products, as reported for related rhodium-catalyzed systems,[60a] has not been observed, obtaining the corresponding dihydrobenzofurans with complete selectivity.

Finally, the reaction was carried out in a 1 mmol scale with **19aa** and **19ba**, obtaining comparable yields (**22aa**, 93% *vs* 91%, and **22ba**, 65% *vs* 76%) (Scheme 3.54a). Bearing in mind the possibility of transforming the amide director into another synthetically useful functional group that would allow further functionalization of the heterocyclic cores obtained, we managed to reduce the aforementioned group to an aldehyde using the Snieckus procedure for the *in situ* generation of the Schwartz reagent (Scheme 3.54b),[75] leading to aldehyde **25aa** in a good yield. This compound has already been reported to be able to undergo a variety of transformations, providing different derivatives.[60c]



Scheme 3.54

[75] Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 390.

In conclusion, the Cp*Co(III)-catalyzed intramolecular hydroarylation of unactivated alkenes takes place with complete selectivity for the generation of a quaternary center through an amide-directed cobaltation (*via* Co-N binding) followed by migratory insertion and proto-demetalation. The procedure allows the preparation of 3,3-disubstituted 2,3-dihydrobenzofurans in high yields avoiding the use of more toxic, more expensive and less earth-abundant metals, such as rhodium, ruthenium and iridium. Besides, this transformation can also be extended to the synthesis of chromanes through the formation of 6-membered rings. Pyrroloindoles can also be obtained *via* C-H activation at C-2 of the indole moiety. Additionally, the possibility of reducing the amide directing group to an aldehyde makes the derivatization of the heterocycles obtained easier, enhancing the synthetic utility of the present method.

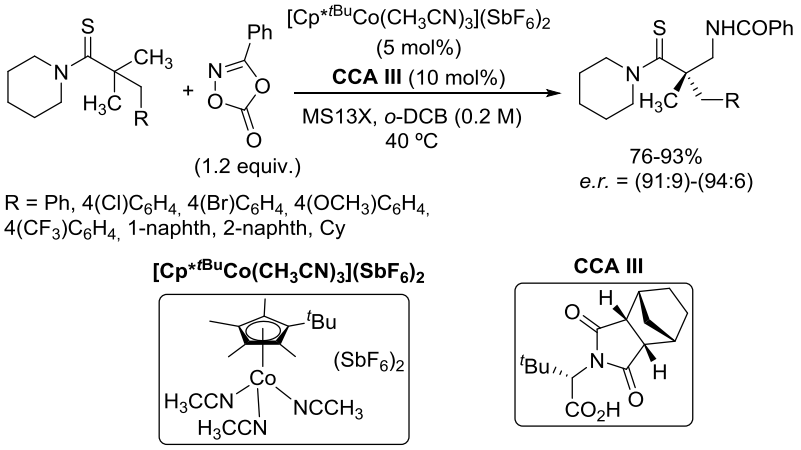
However, this intramolecular alkylative coupling also has its limitations. When a substituent is placed *ortho* to the tethered allyloxy chain, the reaction usually provides poorer results. This is possibly due to the steric effect related to the smaller ionic radius of cobalt, what brings the bulky Cp* ligand in close proximity to the substituents that are near the metalated C-H bond, as it has been explained in the introduction of this chapter (Scheme 3.2).[15,16] Moreover, possibly due to the higher steric bulkiness associated with placing an additional substituent on the alkene, the reaction does not proceed using internal olefins. Nevertheless, the removal of all the substituents from this moiety also proved to be detrimental for the reaction, leading to decomposition of the substrate.

*3.1.3. Cp*Co(III)-catalyzed intramolecular enantioselective hydroarylation of 3-(allyloxy)benzamide **19ba** using chiral carboxylic acids **CCA1-CCA7***

Bearing in mind that in the course of the reaction previously disclosed a quaternary stereocenter was formed, we envisioned the possibility of carrying out this transformation in an enantioselective manner. As it has been commented in the introduction of this chapter, intermolecular enantioselective alkylation reactions have been formerly accomplished between arenes and alkenes, employing two different strategies for achieving enantiocontrol. On the one hand, according to the work reported by Cramer in 2019, cobalt(III)-based catalysts can be used bearing chiral cyclopentadienyl-type ligands, being in this case the C-H activation/migratory insertion the step in which the enantioinduction takes places (Scheme 3.20).[34] On the other hand, asymmetric intermolecular hydroarylation reactions can be accomplished with the assistance of chiral carboxylic acids by enantioselective proto-demetalaltion (Schemes 3.7 and 3.17), as demonstrated by Matsunaga[23] and Ackermann.[31] In this case, the organocobalt species formed after C-H metalation undergoes a reversible insertion to the alkene, furnishing two different

enantiotopic intermediates, one of which is thought to be selectively protonated by the chiral carboxylic acid. Taking into account the complications associated to the preparation of chiral cyclopentadienyl ligands and to their precoordination to the metal, we decided to study the enantioselective version of our intramolecular hydroarylation reaction for the synthesis of dihydrobenzofurans using chiral carboxylic acids as additives together with an achiral Cp*Co(III) complex.

It has been already mentioned that under Cp*Co(III) catalysis the carboxylate-assisted CMD process is a common mechanism for the C-H activation event. On this basis, advantage can be taken of this fact to achieve enantiocontrol. For example, Matsunaga and Kanai recently reported the use of a chiral carboxylic acid in combination with an achiral Cp*Co(III) catalyst for the selective asymmetric activation of enantiotopic C(sp^3)-H bonds. Thus, they could carry out the enantioselective amidation of thioamides utilizing dioxazolones as coupling partners. In this case *(S)*-H_2-BHTL (**CCA III**), a chiral carboxylic acid derived from *tert*-leucine, was chosen as the optimal additive (Scheme 3.55).[76]

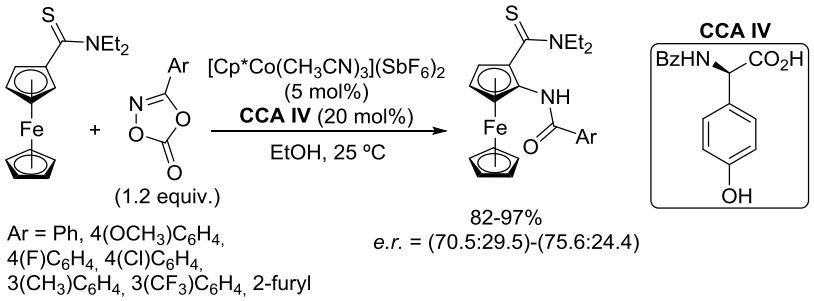


Scheme 3.55

This same strategy was also utilized by Shi and co-workers for the enantioselective amidation of ferrocenes with dioxazolones using a thioamide as directing group. After an extensive screening of different additives, the authors observed that mono-protected amino acid D-Bz-Hpg-OH (**CCA IV**) showed the best results, furnishing the corresponding

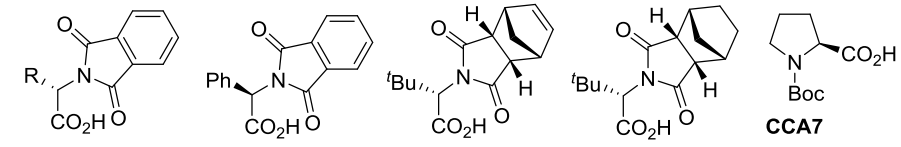
[76] Fukagawa, S.; Kato, Y.; Tanaka, R.; Kojima, M.; Yoshino, T.; Matsunaga, S. *Angew. Chem. Int. Ed.* **2019**, *58*, 1153.

amidated ferrocenes with moderate enantiomeric ratios *via* enantioselective C-H activation (Scheme 3.56).[77]



Scheme 3.56

Despite the enantioinduction in the aforementioned two examples is based on a conceptually different approach, we were encouraged by the possibility of applying cheap and readily available amino acid derivatives in our intramolecular coupling with the goal of achieving enantiocontrol *via* enantioselective proto-demetalation. Taking into consideration that phthaloyl-protected amino acids have been previously used together with chiral Cp*M(III) complexes (M = Rh, Ir) to attain a variety of asymmetric C-H functionalizations,[78] we decided to study their efficiency for the control of enantioselectivity in our intramolecular hydroarylation. Therefore, different cyclic imides **CCA1**-**CCA4** derived from amino acids were synthesized, as well as **CC5** (*(S)*-BHTL) and **CC6** (*(S)*-H_2-BHTL), investigated by Matsunaga[76] (Figure 3.2).



CCA1, R = *sec*-Bu
CCA2, R = ^{t}Bu
CCA3, R = Bn

CCA4 **CCA5** **CCA6** **CCA7**

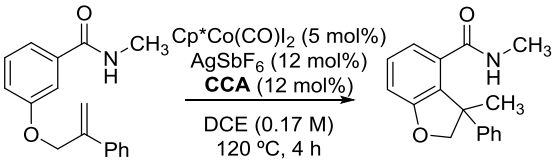
Figure 3.2

[77] Liu, Y.-H.; Li, P.-X.; Yao, Q.-J.; Zhang, Z.-Z.; Huang, D.-Y.; Le, M.D.; Song, H.; Liu, L.; Shi, B.-F. *Org. Lett.* **2019**, *21*, 1895.

[78] For selected examples, see: a) Jang, Y.-S.; Dieckmann, M.; Cramer, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 15088; b) Sun, Y.; Cramer, N. *Angew. Chem. Int. Ed.* **2018**, *57*, 15539; c) Jang, Y.-S.; Woźniak, Ł.; Pedroni, J.; Cramer, N. *Angew. Chem. Int. Ed.* **2018**, *57*, 12901.

In order to check the efficacy of mono-protected amino acids in the enantioinduction process, Boc-Pro-OH **CC7** was also prepared.[79] With the aim of investigating the feasibility of carrying out our Cp*Co(III)-promoted intramolecular hydroarylation in an asymmetric manner employing acids **CCA1**-**CCA7**, we selected amide **19ba**, whose product **22ba** would have a stereogenic center, as the model substrate. That compound was subjected to the optimal conditions developed for the racemic reaction, using in each case the corresponding CCA instead of KOAc (Table 3.6).

Table 3.6



Entry	CAA	Yield (%)[a]	e.r.[b]
1	**CAA1**	27	49:51
2	**CAA2**	21	53:47
3	**CAA3**	14	49:51
4	**CAA4**	11	50:50
5	**CAA5**	15	49:51
6	**CAA6**	16	48:52
7	**CAA7**	-[c]	-

[a] Yield of the isolated pure compound. Reactions were carried out in a 0.26 mmol scale in a 20-mL sealed vial. [b] Enantiomeric ratio determined by chiral stationary phase HPLC (Chiralpak IC-3, hexane/^{i}Pr, 9/1). [c] Traces of the product were observed.

Although with low yields, all the additives studied were able to make the reaction proceed except for Boc-Pro-OH **CCA7**, which only afforded traces of the product (Table 3.6, entry 7). However, none of them was able to provide **22ba** with promising enantioselectivities, obtaining in all the cases trace enantiomeric excesses.

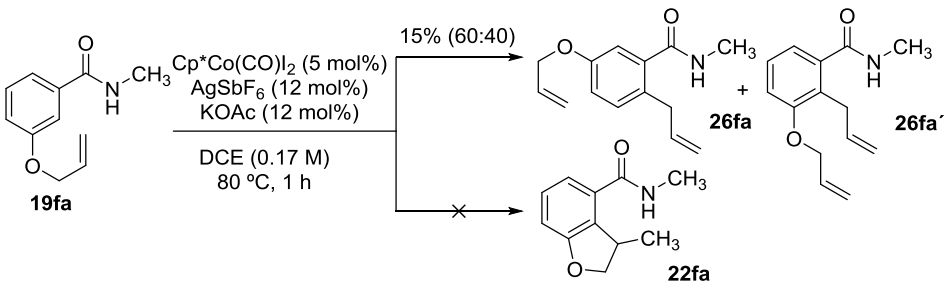
In conclusion, none of the acids tested was able to induce enantioselectivity in the intramolecular hydroarylation of **19ba** for the synthesis of 2,3-dihydrobenzofuran **22ba**. Thus, other CCAs derived from amino acids are ought to be tested, or even more sterically

[79] For the synthesis of the chiral carboxylic acids tested, see Experimental Section.

demanding carboxylic acids, such as the CCA derived from BINOL used by Matsunaga´s group for the asymmetric hydroarylation of maleimides with indoles (Scheme 3.7).[23] Additives of this kind have also been utilized under Cp*Rh(III) catalysis.[80] On the other hand, a new screening of the reaction conditions should be done, since the control experiments of the racemic version showed that without the acetate additive the coupling can take place, although with low yields (Table 3.4, entry 19). This means that irrespective of the chiral carboxylic acid added, a certain amount of the racemic product will be generated due to that background reaction. Finally, in case the migratory insertion process is not reversible, thus disabling the method based on the asymmetric proto-demetalation approach, another strategy to achieve enantioinduction would imply the synthesis and utilization of chiral Cp^{x}Co(III) complexes, as introduced by Cramer (Scheme 3.20).[34] Those type of asymmetric catalysts have been applied under rhodium and iridium catalysis.[81]

*3.1.4. Cp*Co(III)-catalyzed allylation of N-methylbenzamide **27** using methyl 4-(allyloxy)benzoate **28** as the coupling partner. Synthesis of 2-allyl-N-methylbenzamide **29***

As mentioned before in this chapter, when 3-(allyloxy)-*N*-methylbenzamide **19fa** was used as the substrate in the Cp*Co(III)-catalyzed intramolecular hydroarylation reaction under the optimal conditions, the substrate completely decomposed (Scheme 3.52b). In order to try to avoid this process and favor the alkylative cyclization, both the temperature and the reaction time were decreased (80 ºC, 1 h) (Scheme 3.57).



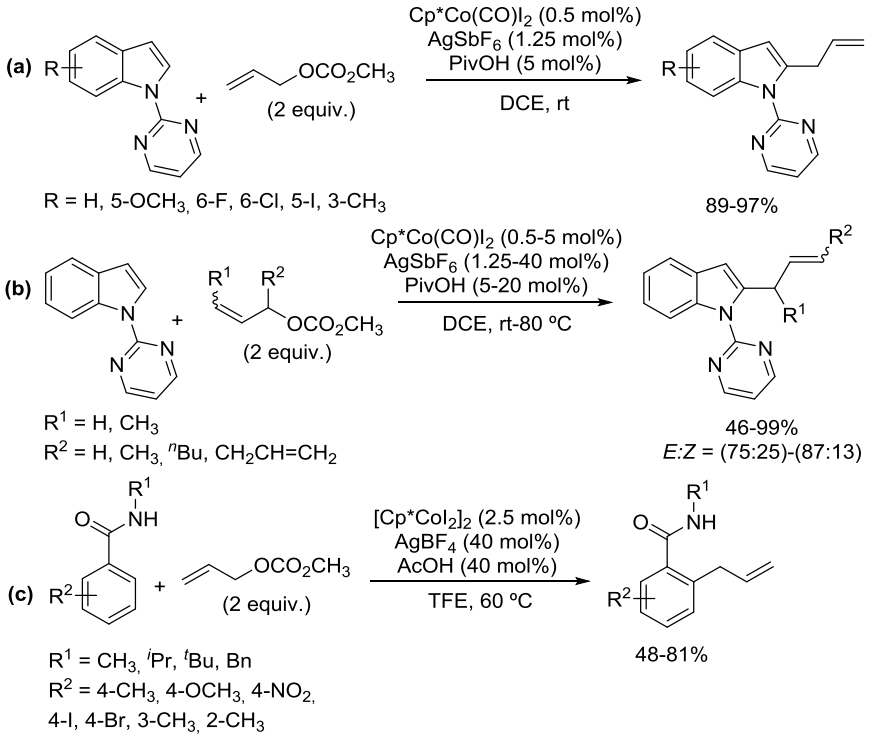
Scheme 3.57

[80] For recent reviews, see: a) Yoshino, T.; Matsunaga, S. *Synlett* **2019**, *30*, 1384; b) Yoshino, T.; Satake, S.; Matsunaga, S. *Chem. Eur. J.* **2020**, *26*, 7346; For recent examples, see: c) Lin, L.; Fukagawa, S.; Sekine, D.; Tomita, E.; Yoshino, T.; Matsunaga, S. *Angew. Chem. Int. Ed.* **2018**, *57*, 12048; d) Fukagawa, S.; Kojima, M.; Yoshino, T.; Matsunaga, S. *Angew. Chem. Int. Ed.* **2019**, *58*, 18154.

[81] For selected examples, see: a) Ref. 35; b) Ref. 60b; c) Ref. 78; For recent reviews: d) Newton, C.G.; Kossler, D.; Cramer, N. *J. Am. Chem. Soc.* **2016**, *138*, 3935; e) Ref. 80b; f) Cramer, N.; Mas-Roselló, J.; Herraiz, A.G.; Audic, B.; Laverny, A. *Angew. Chem. Int. Ed.* **2020**, *DOI:10.1002/anie.202008166.*

However, instead of the expected diydrobenzofuran **22fa**, the corresponding allylation product **26fa** was furnished as a mixture of regioisomers in 15% yield. The steric sensitivity of this transformation is clearly shown in the ratio of positional isomers (60:40), since the allylation at the less hindered position was favored. The formation of this product means that allyl phenyl ether **19fa** acted as an allylating agent.

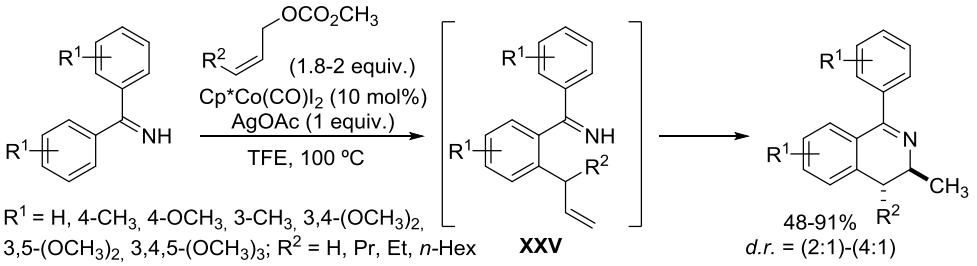
In this context, allyl alcohol derivatives have been reported to promote allylation of different (hetero)aromatic frameworks using high-valent-cobalt catalysts. In 2014, Glorius and co-workers studied the possibility of carrying out different formal S_N-type reactions under Cp*Co(III) catalysis (cyanation, halogenation and allylation), achieving the first high-valent-cobalt-catalyzed allylation reaction, using pyrimidyl indoles as the aromatic substrates and allyl methyl carbonate as the coupling partner (Scheme 3.58a).[11] Interestingly, this transformation could be achieved at room temperature.



Scheme 3.58

One year later, this same group was able to expand the scope of the transformation: they could introduce, *via* the corresponding carbonates, differently substituted allyl chains to the pyrimidyl indole framework with γ-selectivity and good *E/Z* ratios (Scheme 3.58b).[82] Different arenes bearing amide-based directing groups could also be employed as substrates in the reaction, undergoing Cp*Co(III)-catalyzed allylation in moderate to good yields (Scheme 3.58c).

Since those seminal works, allyl carbonates have been at many times the coupling partners of choice for the achievement of Cp*Co(III)-promoted C-H allylation of different aromatic scaffolds.[44,83] For instance, recently, Kim and co-workers reported an efficient methodology for the Cp*Co(III)-catalyzed synthesis of 3,4-dihydroisoquinolines starting from aromatic ketimines and unsubstituted or γ-alkyl-substituted *Z*-ally carbonates, which proved to be much more reactive than the *E*-counterparts. This transformation is proposed to proceed *via* selective C-H γ-allylation followed by Ag(I)-catalyzed intramolecular hydroamination (Scheme 3.59).[84]



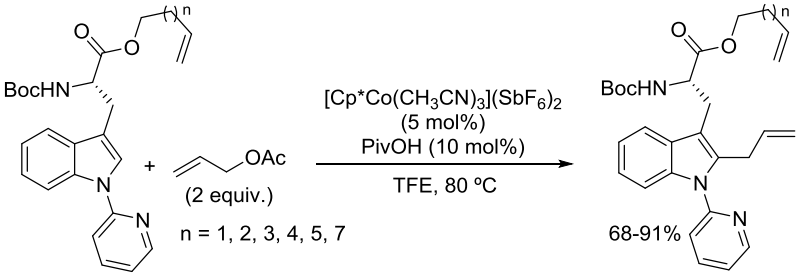
Scheme 3.59

Experimental evidences indicated that this coupling proceeded through intermediate **XXV**. After synthesizing this compound independently ($R^1 = R^2 = H$), it was subjected the optimal reaction conditions, yielding the corresponding product. When reacting **XXV** in the presence of stoichiometric and/or catalytic amounts of AgOAc in the absence of the Cp*Co(III) precatalyst, the product was obtained in high yields. The reaction did not proceed when the cobalt catalyst was used without the silver additive. All these results (along with other

[82] Gensch, T.; Vásquez-Céspedes, S.; Yu, D.-G.; Glorius, F. *Org. Lett.* **2015**, *17*, 3714.
[83] a) Kalsi, D.; Laskar, R.A.; Barsu, N.; Premkumar, J.R.; Sundararaju, B. *Org. Lett.* **2016**, *18*, 4198; b) Ramachandran, K.; Anbarasan, P. *Eur. J. Org. Chem.* **2017**, 3965; c) Wang, H.; Lorion, M.M.; Ackermann, L. *ACS Catal.* **2017**, *7*, 3430; d) Sk, M.R.; Bera, S.S.; Maji, M.S. *Org. Lett.* **2018**, *20*, 134; e) Tanaka, R.; Tanimoto, I.; Kojima, M.; Yoshino, T.; Matsunaga, S. *J. Org. Chem.* **2019**, *84*, 13203.
[84] Choi, S.Y.; Kim, H.D.; Park, J.-U.; Park.S.; Kim, J.H. *Org. Lett.* **2019**, *21*, 10038.

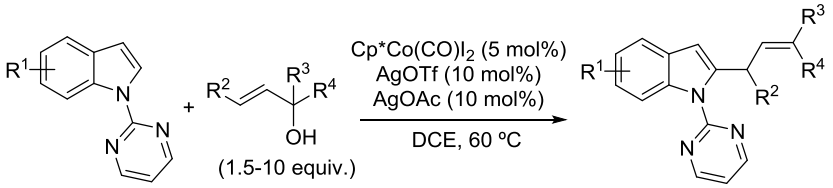
experiments run by the authors) not only showed that **XXV** was probably an intermediate in the transformation, but also suggested that the intramolecular hydroamination process was catalyzed by Ag(I).

Apart from carbonates, allyl esters have also been used as allylating agents in the presence of Cp*Co(III)-complexes.[85] As an example, in 2019, Ackermann reported a method for the C-2 allylation of the indole scaffold in a variety of tryptophan derivatives. For that purpose, a 2-pyridine moiety was used as the *N*-protecting/directing group (Scheme 3.60).[86] This reaction allowed the further formation of complex cyclic peptides through subsequent ring-closing metathesis/hydrogenation process, followed by removal of the directing group.



Scheme 3.60

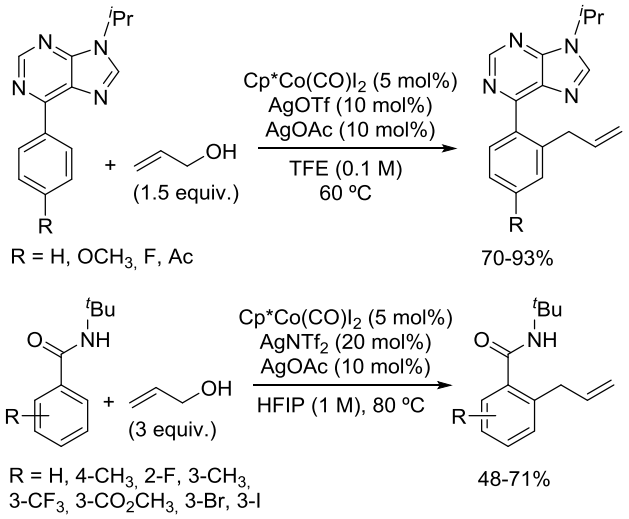
Allyl alcohol, bearing a free -OH group, has also been successfully employed in the allylation reaction of aromatic frameworks. In this context, in 2015, Matsunaga´s group developed a method for the C-2 allylation of pyrimidyl indoles with γ-selectivity using allylic alcohols as coupling partners (Scheme 3.61).[10b]



Scheme 3.61

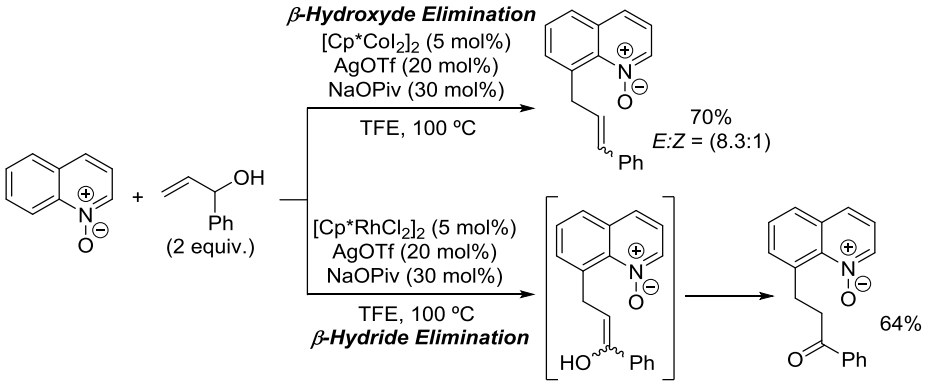
[85] Moselage, M.; Sauermann, N.; Koeller, J.; Liu, W.; Gelman, D.; Ackermann, L. *Synlett* **2015**, *26*, 1596.
[86] Lorion, M.M.; Kaplaneris, N.; Son, J.; Kuniyil, R.; Ackermann, L. *Angew. Chem. Int. Ed.* **2019,** *58*, 1684.

When the authors used $[Cp^*RhCl_2]_2$ instead of $Cp^*Co(CO)I_2$, lower yields were obtained. In 2016, this same group proved to be capable of broadening the scope of their allylation reaction to the use of 6-arylpurines and benzamides as substrates (Scheme 3.62).[10c]



Scheme 3.62

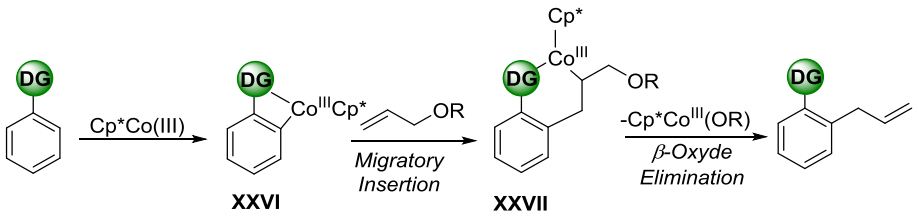
The difference in reactivity between Cp*Co(III) and Cp*Rh(III) catalysts was studied by Sundararaju in the C-8 allylation of quinoline *N*-oxides with allyl alcohols, obtaining different products depending on the precatalyst employed (Scheme 3.63).[83a]



Scheme 3.63

Whereas under cobalt catalysis the corresponding allylation products were obtained due to β-O elimination, Cp*Rh(III) precatalysts afforded the corresponding ketone products derived from β-hydride elimination followed by tautomerization of the enol formed. The difference of reactivity between both metals evidenced in this work is attributed to the harder nature of cobalt (HSAB theory), since due to that it is prompter to undergo β-oxygen elimination, while Rh prefers to abstract the soft hydride.[15]

In general, as supported by DFT studies,[10b,86] those types of allylation reactions are proposed to proceed *via* insertion of the organocobalt intermediate **XXVI** (formed after C-H metalation) to the C-C double bond of the allyl derivative in a γ-selective fashion (providing **XXVII**), followed by β-oxygen elimination to furnish the desired functionalized arenes. The Cp*Co(III)-OR species released in this process would evolve to the active catalytic complex through ligand exchange (Scheme 3.64).



Scheme 3.64

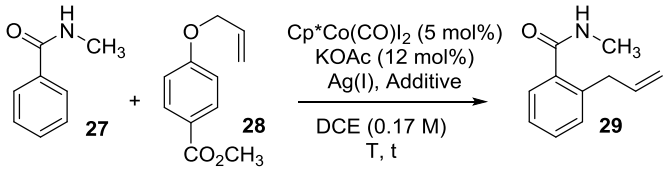
As it has been shown throughout the last pages, several types of allyl alcohol derivatives have been utilized as allylating agents under Cp*Co(III) catalysis. However, despite allyl phenyl ethers have been previously employed in the allylation of arenes with other transition metals,[87] they have not been yet reported to act as coupling partners in these kind of transformations using high-valent-cobalt complexes.

Taking all this into account and bearing in mind the result depicted in Scheme 3.57, we decided to check the possibility of accomplishing the Cp*Co(III)-catalyzed allylation of *N*-methylbenzamide **27** using methyl 4-(allyloxy)benzoate **28** as the allylating agent (Table 3.7). We commenced the study using 1.5 equivalents of **28** in DCE at 80 ºC for 15 h, utilizing

[87] For selected examples, see: a) Nishikata, T.; Lipshutz, B.H. *J. Am. Chem. Soc.* **2009**, *131*, 12103; b) Kiuchi, H.; Takahashi, D.; Funaki, K.; Sato, T.; Oi, S. *Org. Lett.* **2012**, *14*, 4502; c) Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 17755; d) Asako, S.; Norinder, J.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2014**, *356*, 1481; e) Qi, L.; Ma, E.; Jia, F.; Li, Z. *Tetrahedron Lett.* **2016**, *57*, 2211; f) Ma, E.; Jiang, Y.; Chen, Y.; Qi, L.; Yan, X.; Li, Z. *Asian J. Org. Chem.* **2018**, *7*, 914.

$Cp^*Co(CO)I_2$ (5 mol%) as the catalyst, $AgSbF_6$ (12 mol%) as additive and KOAc (12 mol%) as the base. Under these reaction conditions, the desired mono-allylated arene **29** was obtained selectively in 23% yield (Table 3.7, entry 1).

Table 3.7



Entry	28 (equiv.)	Ag(I) (equiv.)	Additive (equiv.)	t (h)	T (ºC)	Yield (%)[a]
1	1.5	$AgSbF_6$ (0.12)	-	15	80	23
2	1.5	$AgSbF_6$ (0.12)	$Cu(OAc)_2$ (0.5)	15	80	35
3	1.5	$AgSbF_6$ (0.12)	$Cu(OAc)_2$ (1)	15	80	31
4	1.5	$AgSbF_6$ (0.12)	$Cu(OAc)_2$ (2)	15	80	30
5	1.5	$AgSbF_6$ (0.12)	$Cu(OAc)_2$ (0.5)	15	100	30
6	1.5	$AgSbF_6$ (0.12)	AgOAc (0.5)	15	80	18
7	1.5	$AgSbF_6$ (0.12)	Ag_2CO_3 (0.5)	15	80	23
8	1.5	$AgSbF_6$ (0.12)	Ag_2O (0.5)	15	80	25
9	1.5	$AgSbF_6$ (0.5)	-	15	80	55
10	1.5	$AgSbF_6$ (1)	-	15	80	66
11	1.5	$AgSbF_6$ (1.5)	-	15	80	40
12	1.5	$AgSbF_6$ (1)	-	15	100	30
13	1.5	$AgSbF_6$ (1)	-	15	60	43
14	1.5	$AgSbF_6$ (1)	-	24	60	27
15	1.5	$AgBF_4$ (1)	-	15	80	32
16	1.5	AgOTf (1)	-	15	80	-[b]
17	1.5	$AgPF_6$ (1)	-	15	80	-[b]
18	1.5	$AgNTf_2$ (1)	-	15	80	55
19	1	$AgSbF_6$ (1)	-	15	80	60
20	2	$AgSbF_6$ (1)	-	15	80	66
21	2.5	$AgSbF_6$ (1)	-	15	80	60
22[c]	1.5	$AgSbF_6$ (1)	-	15	80	52

[a] Yield of the isolated pure compound. Reactions were carried out in a 0.26 mmol scale in a 16-mL sealed vial. [b] No reaction. Starting material recovered. [c] $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ was used as the precatalyst instead of $Cp^*Co(CO)I_2$.

Although according to the mechanism depicted in Scheme 3.64 they should not be required for the present transformation, the effect of the addition of oxidants was studied (in case the Co(III) catalyst suffered reductive decomposition). We first added 0.5 equivalents of $Cu(OAc)_2$, observing an improvement in the yield (Table 3.7, entry 2). Increase of the amount of $Cu(OAc)_2$ to 1 or 2 equivalents (Table 3.7, entries 3 and 4, respectively) or the reaction temperature to 100 ºC (Table 3.7, entry 5), led to slightly lower conversions. We then tested the utilization of silver-based oxidants, such as AgOAc, Ag_2CO_3 and Ag_2O (Table 3.7, entries 6, 7 and 8, respectively), which showed no improvement compared to the result obtained in their absence (Table 3.7, entry 1). The moderately better results obtained with $Cu(OAc)_2$ were attributed to its ability to act as an acetate source rather than to its oxidative ability.

We then decided to start testing the effect of increasing the amount of $AgSbF_6$, already used in the reaction. Interestingly, when 0.5 equivalents were added, a dramatic increase of the yield was observed, releasing **29** in 55% yield (Table 3.7, entry 9). The amount of the mentioned silver salt was further increased, obtaining the best result with 1 equivalent of $AgSbF_6$ (66%, Table 3.7, entry 10), while a larger quantity proved to be detrimental (Table 3.7, entry 11). Lower yields were also obtained when carrying out the transformation at both higher (100 ºC) and lower temperatures (60 ºC) (Table 3.7, entries 12 and 13, respectively). We thought that it would be possible to obtain better results at 60 ºC just by increasing the reaction time; however, this also hampered the reaction, furnishing even poorer results (Table 3.7, entry 14). We then moved to study the effect of the counter-anion in the efficiency of the silver salt. In this context, the addition of $AgBF_4$ led to lower yields (Table 3.7, entry 15), while AgOTf and $AgPF_6$ completely shut down the reactivity (Table 3.7, entries 16 and 17, respectively). On the contrary, $AgNTf_2$ gave only slightly lower results compared to $AgSbF_6$ (Table 3.7, entry 18).

Regarding the amount of the allylating agent **28**, it did not had a major impact on the outcome of the reaction. When 1 or 2.5 equivalents were used, lower, although almost comparable, results were observed (60%, Table 3.7, entries 19 and 21, respectively), while 2 equivalents of **28** led to the same result achieved with the amount initially used in this study (66%, Table 3.7, entry 20). Finally, when acetonitrile-complex $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ was added instead of the usual $Cp^*Co(CO)I_2$ precatalyst, a moderately poorer yield was obtained (Table 3.7, entry 22). This might have been due to the excessive amount of hexafluoroantimonate ion present in the reaction media, since the use of more than 1 equivalent of $AgSbF_6$ was detrimental for the transformation (Table 3.7, entry 11).

In conclusion, it has been demonstrated that the allylation of the benzene ring can be accomplished taking advantage of amide-based directing groups. To the best of our knowledge, the use of allyl phenyl ethers as allylating agents has not been previously reported under Cp*Co(III) catalysis. Although there is still work to do in order to improve the outcome and efficiency of the reaction, **29** has been obtained in a promising 66% yield employing similar conditions to the ones used for the high-valent-cobalt-catalyzed intramolecular hydroarylation of allyl phenyl ethers (Table 3.5), showcasing the broad applicability of the method.

On the other hand, different allyl phenyl ethers are ought to be tested in order to study the impact of the electronic nature of the aromatic ring on the reactivity. The effect of a variety of carboxylate sources should be checked, as well as different reaction times. For similar transformations Glorius employed dimer-complex $[Cp^*CoI_2]_2$,[82] thus, its efficacy as precatalyst should also be investigated.

The work described in this chapter has been carried out at the University of Manchester, under the supervision of Professor Igor Larrosa.

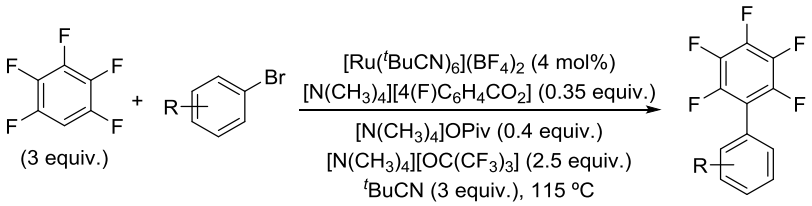
IV

Ru(II)-Catalyzed Methylation

1. INTRODUCTION OF THE CHAPTER

During the three-month stay carried out at the University of Manchester, in the research group of Professor Igor Larrosa, new methodologies involving Ru(II) catalysis were developed, taking advantage of their wide experience in this area.

In 2016, the group reported a method for the arylation of an array of fluoroarenes without the aid of directing groups and using aryl bromides as coupling partners. This protocol allowed the efficient preparation of biaryl compounds (Scheme 4.1).[1]



Scheme 4.1

Although during the investigation of this transformation $[Ru(^tBuCN)_6](BF_4)_2$ was found to be the optimal catalyst, they initially employed Ru(II)-complexes bearing a *p*-cymene moiety, such as $[Ru(OPiv)_2(p\text{-cymene})]$ and $[Ru(OBz)_2(p\text{-cymene})]$. However, in the study of the reaction conditions, a quantitative dissociation of that ligand was observed. Taking into account that *p*-cymene had previously been reported to be necessary for the cross-coupling of cycloruthenated phenylpyridine-complexes with aryl halides,[2] they decided to employ $\{Ru(OPiv)_2[C_6(CH_3)_6]\}$ complex, with a less labile arene ligand. Nonetheless, the use of this precatalyst led to poorer results.

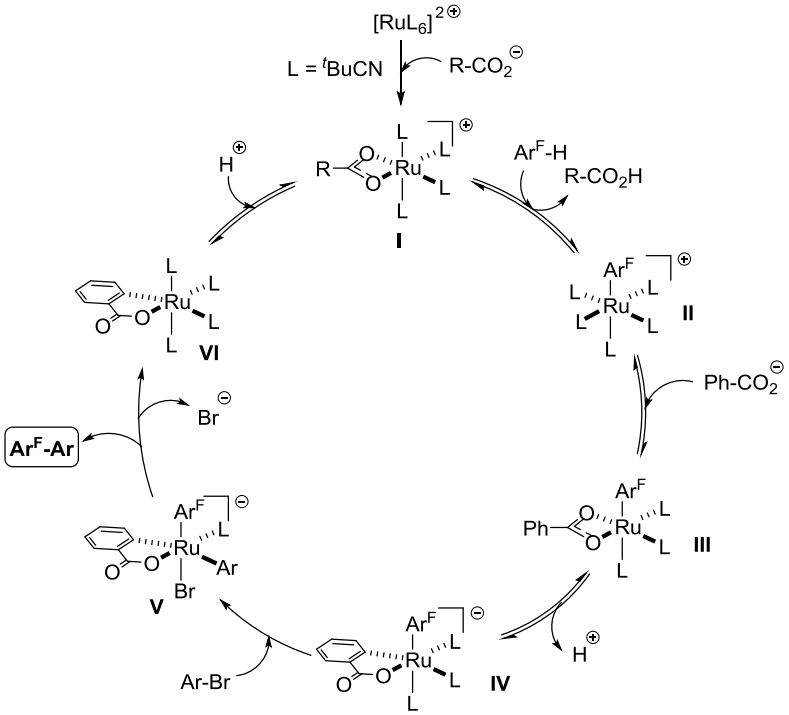
With those observations in mind, it was supposed that the dissociation of the arene-based ligand might be necessary to achieve the desired transformation; thus, several kinetic and NMR studies were run to try to elucidate the mechanism operating in the reaction. It was found that precatalyst $[Ru(OPiv)_2(p\text{-cymene})]$ was able to accomplish the C-H activation

[1] a) Simonetti, M.; Perry, G.J.P.; Cambeiro, X.C.; Juliá-Hernández, F.; Arokianathar, J.N.; Larrosa, I. *J. Am. Chem. Soc.* **2016**, *138*, 3596. For further mechanistic studies, see: b) Simonetti, M.; Kuniyil, R.; Macgregor, S.A.; Larrosa, I. *J. Am. Chem. Soc.* **2018,** *140*, 11836.

[2] Ferrer Flegeau, E.; Bruneau, C.; Dixneuf, P.H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161.

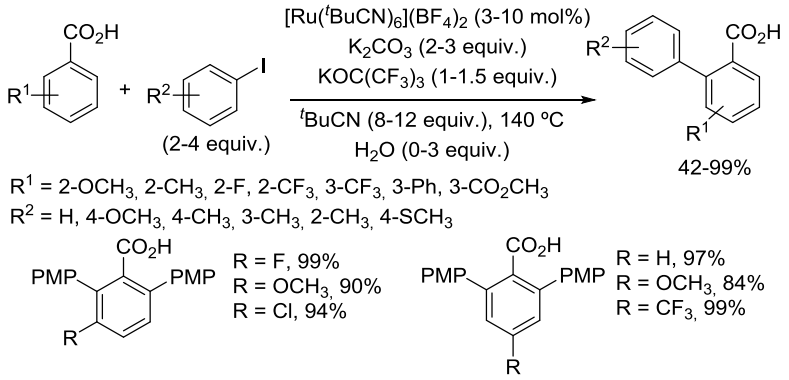
event; however, the subsequent reaction with the bromoarene required the loss of the *p*-cymene ligand to take place.

Therefore, they synthesized ruthenium(II)-complex $[Ru(^tBuCN)_6](BF_4)_2$, shown in Scheme 4.1 and lacking the η^6-arene ligand, which proved to be more efficient in promoting the desired coupling. The reaction conditions were further optimized and it was seen that the benzoate additive was essential for the transformation to take place, since although this compound was not required for the metalation step, it was crucial for the formal oxidative addition. Further mechanistic studies showcased the importance of such additive (Scheme 4.2).[1b] Intermediate **II** (formed after C-H metalation of the fluoroarene by active catalytic species **I**) was proposed to undergo a second C-H activation step towards the benzoate additive/ligand, generating anionic cyclometalated species **IV** (*via* species **III**), which has a higher lability and where the Ru(II) center is more electron rich. All these facts are thought to allow the oxidative addition of complex **IV** to the corresponding aryl bromide, to form **V**, which would release the biaryl product after reductive elimination.



Scheme 4.2

In 2017, this group reported a methodology for the Ru(II)-catalyzed C-H *ortho*-arylation of a variety of benzoic acids, taking advantage of the directing ability of the carboxylate group present in these motifs.[3] In this work, aryl halides were used as the coupling partners for the obtainment of the corresponding biaryl scaffolds, employing the previously mentioned η^6-arene-free precatalyst {[Ru(^{t}BuCN)$_6$](BF$_4$)$_2$}[1] (Scheme 4.3). During the study of the scope of the reaction, they observed a preference towards the mono-functionalization at the less hindered position when *meta*-substituted benzoic acids were used. However, the utilization of not-very-bulky substituents at that position (together with increasing the amounts of the reagents), allowed the selective formation of bis-arylated products. This could also be achieved with unsubstituted or *para*-substituted benzoic acids.



Scheme 4.3

Those two works, in which η^6-arene-free Ru(II) catalysts performed better, demonstrated that the mechanism of Ru(II)-catalyzed C-H arylations using aryl (pseudo)halides as coupling partners had to be deeply investigated.

In this regard, in 2018, Larrosa´s group published an extensive study[4] where they showed that the common catalytic cycle attributed to those reactions was oversimplified. It has been usually believed that the ruthenium(II)-catalyzed C-H direct arylation of aromatic scaffolds (bearing directing groups) with aryl (pseudo)halides proceeds *via* coordination of

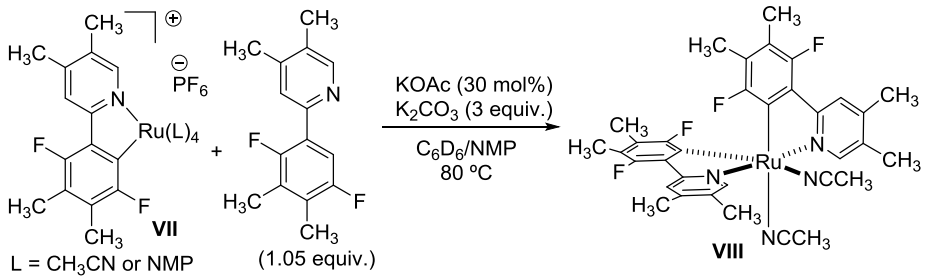
[3] a) Simonetti, M.; Cannas, D.M.; Panigrahi, A.; Kujawa, S.; Kryjewski, M.; Xie, P.; Larrosa, I. *Chem. Eur. J.* **2017**, *23*, 549 (the example shown in Scheme 4.3 corresponds to this publication); b) Just-Baringo, X.; Shin, Y.; Panigrahi, A.; Zarattini, M.; Nagyte, V.; Zhao, L.; Kostarelos, K.; Casiraghi, C.; Larrosa, I. *Chem. Sci.* **2020**, *11*, 2472.

[4] Simonetti, M.; Cannas, D.M.; Just-Baringo, X.; Vitorica-Yrezabal, I.J.; Larrosa, I. *Nat. Chem.* **2018**, *10*, 724.

Ru(II) to the directing group, followed by metalation of a specific C-H bond. Afterwards, oxidative addition would take place to the C-X bond of the coupling partner, forming a Ru(IV) species that is proposed to release the product upon reductive elimination.[5]

With the aim of checking this habitual proposal, they performed different experiments with complexes that were supposed to be intermediates in the Ru(II)-promoted C-H arylation. The results obtained indicated that the mechanism might not be as simple as the commonly accepted one and a possible catalytic cycle involving a bis-cyclometalated-type complex was envisoned.

With the aim of corroborating their hypothesis, the reaction depicted in Scheme 4.4, featuring the stoichiometric coupling of Ru(II) species **VII** with its non-metalated arylpyridine counterpart, was studied by ^{1}H- and ^{19}F-NMR.

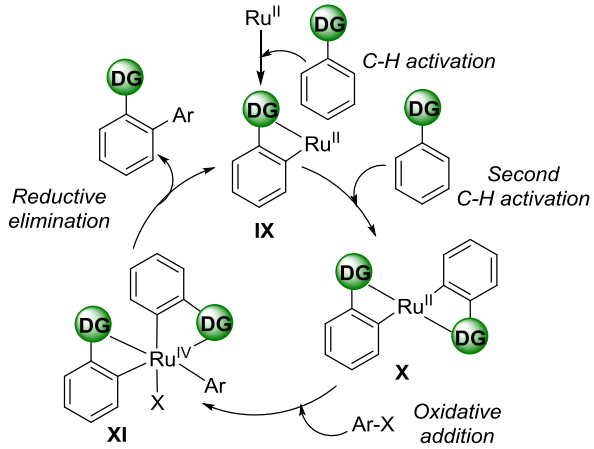


Scheme 4.4

The experiment mentioned above showed the formation of bis-cyclometalated species **VIII**, whose structure could be confirmed by X-ray analysis (Scheme 4.4). Interestingly, when 1-iodo-3,5-dimethylbenzene was added, **VIII** underwent the arylative coupling quantitatively to furnish the corresponding arylated phenylpyridine.

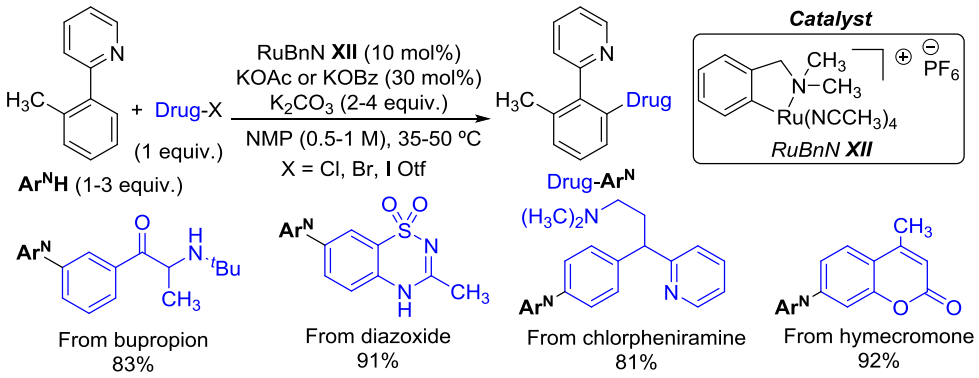
With all these considerations in mind, the mechanistic pathway depicted in Scheme 4.5 was proposed. Thereby, after coordination of Ru(II) to the directing group and C-H metalation, species **IX** would be generated, which undergoes a second C-H activation step, affording bis-cyclometalated intermediate **X**. After oxidative addition to the C-X bond of the aryl (pseudo)halide, **XI** is formed, which would render the product upon reductive elimination.

[5] a) Simonetti, M.; Cannas, D.M.; Larrosa, I. *Adv. Organomet. Chem.* **2017**, *67*, 299; b) Nareddy, P.; Jordan, F.; Szostak, M. *ACS Catal*. **2017**, *7*, 5721; c) Kuzman, P.; Požgan, F.; Meden, A.; Svete, J.; Štefane, B. *Chem.Cat.Chem*. **2017**, *9*, 3380.



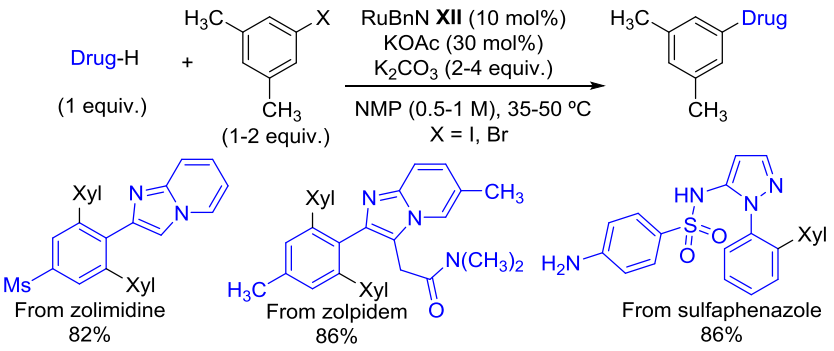
Scheme 4.5

After some investigation on different cycloruthenated complexes, it was found that Ru(II) complex **XII** (RuBnN), bearing a *N,N*-dimethylbenzilamine moiety, was optimal to promote the C-H direct arylation of 2-phenylpyridines with aryl halides. This catalyst could be used for the late-stage functionalization of a wide number of interesting drugs, being able to introduce the 2-(*o*-tolyl)pyridine moiety within their structures (Scheme 4.6).



Scheme 4.6

In this late-stage functionalization, drugs could not only be used as the (pseudo)halide coupling partners, but also as the aromatic scaffolds (bearing directing groups) that undergo the C-H direct arylation process (Scheme 4.7).



Scheme 4.7

Two years later, Larrosa and co-workers published a new work broadening the applicability of their cycloruthenated catalyst **XII**, employing it to achieve the *ortho*-alkylation of 2-phenylpyridine derivatives with secondary alkyl bromides.[6]

Interestingly, when unactivated secondary alkyl halides are employed as coupling partners under Ru(II)-catalysis, the corresponding *meta*-alkylated aryl rings have been usually reported to be obtained selectively.[7] This selectivity is thought to be driven by a single electron transfer (SET) mechanism, involving the formation of a secondary alkyl radical, which is added *para* to the C-Ru bond formed after C-H metalation, instead of undergoing oxidative addition to the metal center (Scheme 4.8a). On the other hand, the utilization of primary alkyl and benzyl halides leads to the *ortho*-functionalized arenes.[8]

As it has been told, Larrosa´s previous studies on the field of Ru(II)-catalyzed C-H direct arylation[1,4] showcased the necessity of a bis-cyclometalated Ru(II)-complex to undergo the oxidative addition to the (pseudo)halide coupling partner (Scheme 4.5). Based on this, the

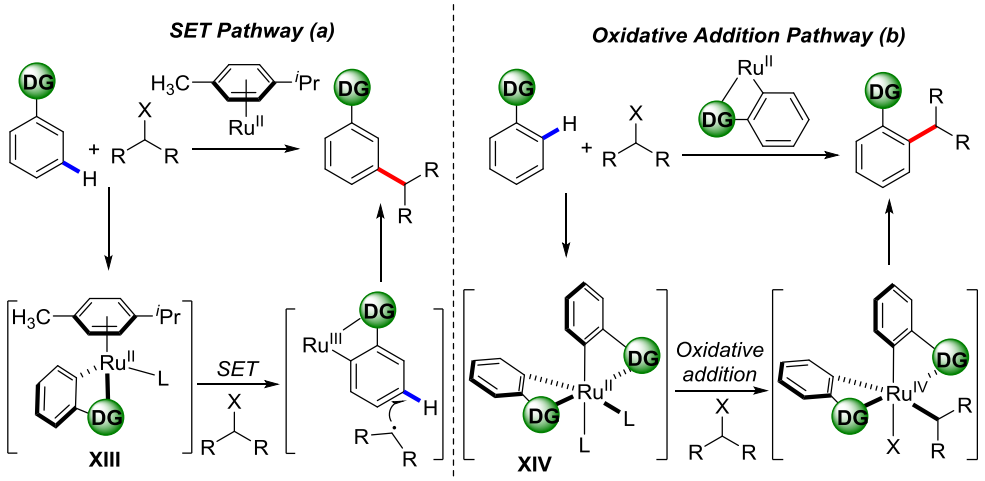
[6] Wang, G.-W.; Wheatley, M.; Simonetti, M.; Cannas, D.M.; Larrosa, I. *Chem* **2020**, *6*, 1459.

[7] a) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877; b) Li, J.; Warratz, S.; Zell, D.; De Sakar, S.; Ishikawa, E.E.; Ackermann, L. *J. Am. Chem. Soc.* **2015**, *137*, 13894; c) Li, J.; Korvorapun, K.; De Sarkar, S.; Rogge, T.; Burns, D.J.; Warratz, S.; Ackermann, L. *Nat. Commun.* **2017**, *8*, 15430; d) Fumagalli, F.; Warratz, S.; Zhang, S.-K.; Rogge, T.; Zhu, C.; Stückl, A.C.; Ackermann, L. *Chem. Eur. J.* **2018**, *24*, 3984; e) Gandeepan, P.; Koeller, J.; Korvorapun, K.; Mohr, J.; Ackermann, L. *Angew. Chem. Int. Ed.* **2019**, *58*, 9820; f) Choi, I.; Müller, V.; Wang, Y.; Xue, K.; Kuniyil, R.; Andreas, L.B.; Karius, V.; Alauzun, J.G.; Ackermann, L. *Chem. Eur. J.* **2020**, *26*, 15290.

[8] a) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6045; b) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966; c) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875.

group envisioned that the use of cycloruthenated catalysts would lead to the formation of that kind of complexes (**XIV**) in the reaction between secondary alkyl halides and arenes, precluding the usual SET mechanism. Thus, *ortho*-alkylation products would be selectively rendered (Scheme 4.8b).

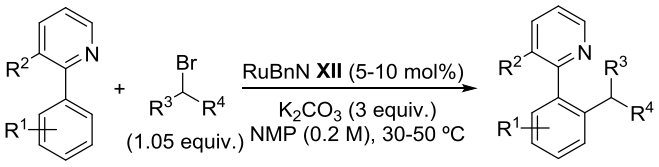
They proposed that the coordinative saturation of the metal center in **XIII** was responsible for the SET mechanism and subsequent *meta*-selective alkylation. Therefore, it was envisaged that **XIV**-like electron-rich bis-cyclometalated Ru(II) intermediates, bearing labile ligands, would promote the oxidative addition pathway, leading to the formation of *ortho*-alkylated arenes.



Scheme 4.8

After the optimization of the reaction conditions, and taking advantage of cyclometalated Ru(II) complex **XII** (RuBnN), they were capable of carrying out the *ortho*-mono-functionalization of 2-arylpyridines using secondary alkyl bromides as coupling partners. This methodology showed a wide scope regarding not only the 2-phenylpyridine moiety, but also the alkyl bromide reagent.

When *meta*-substituted 2-phenylpyridine substrates were used, the alkylation took place selectively at the less sterically hindered position (Scheme 4.9). Late-stage functionalization of some drugs and natural products could even be achieved. Further experiments were also accomplished, indicating that the coupling proceeded *via* a S_N2-type oxidative addition, with inversion of the configuration.

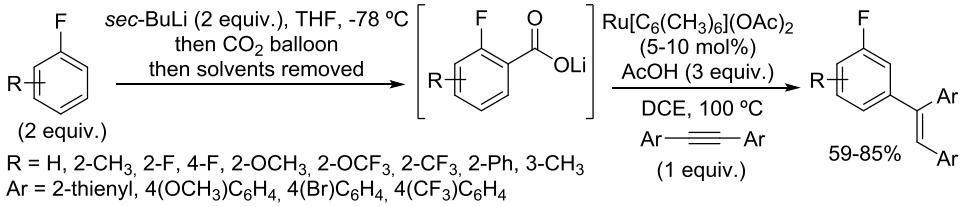


R^1 = H, 2-CH_3, 2-F, 2-OCH_3, 3-CF_3, 3-CO_2CH_3, 4-CF_3, 4-CO_2CH_3, 4-OCH_3
R^2 = H, CH_3; R^3 = CH_3, *n*-Hex
R^4 = CH_3, CH_2OTBS, CH_2CH_2NPhth
R^3, R^4 = -CH_2CH_2-O-CH_2CH_2-, -$CH_2(CH_2)_3CH_2$-, -$CH_2(CH_2)_2CH_2$-

Scheme 4.9

The Larrosa group has previously reported that the carboxylate functionality can be utilized as a transient directing group to attain the palladium(II)-catalyzed formal *meta*-arylation of phenols, fluorobenzenes and anisoles.[9] This approach consists of the installation of a carboxylate group on the aromatic moiety, being this newly inserted scaffold able to direct the desired arylation reaction. This director would then be cleaved in a cascade process, leading to the selective *meta*-functionalization.

Based on the precedents of the group, they decided to carry out the *meta*-olefination of fluorobenzenes under Ru(II) catalysis using alkynes as coupling partners. This coupling involved two steps. Firstly, fluorobenzenes were treated with *sec*-BuLi at -78 ºC to generate an organolithium intermediate that could be quenched with CO_2, forming the corresponding 2-fluorobenzoates. After this process, AcOH, the alkyne coupling partner and the Ru(II) catalyst were added to the same reaction flask in DCE (Scheme 4.10).[10]



(2 equiv.)
R = H, 2-CH_3, 2-F, 4-F, 2-OCH_3, 2-OCF_3, 2-CF_3, 2-Ph, 3-CH_3
Ar = 2-thienyl, 4(OCH_3)C_6H_4, 4(Br)C_6H_4, 4(CF_3)C_6H_4

Scheme 4.10

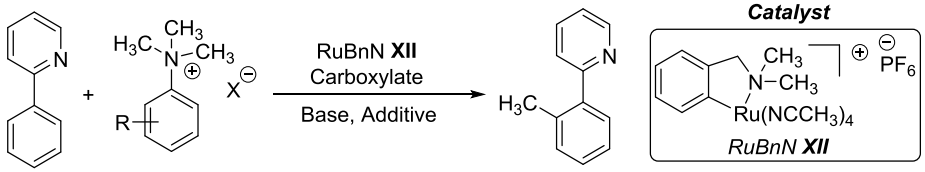
[9] a) Luo, J.; Preciado, S.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136*, 4109; b) Luo, J.; Preciado, S.; Araromi, S.O.; Larrosa, I. *Chem. Asian. J.* **2016**, *11*, 347; c) Font, M.; Spencer, A.R.A.; Larrosa, I. *Chem. Sci*. **2018**, *9*, 7133.
[10] Spencer, A.R.A.; Korde, R.; Font, M.; Larrosa, I. *Chem. Sci*. **2020**, *11*, 4204.

That way, the newly introduced carboxylate acted as the director allowing olefination to take place *ortho* to itself, leading to the corresponding *meta*-alkenylated fluorobenzenes after decarboxylation.

Interestingly, during the optimization of the reaction conditions, they observed that the ruthenium catalyst required a η^6-arene ligand for the transformation to proceed, in contrast with the cases that have been presented throughout this section.

2. AIMS OF THE CHAPTER

Taking into account the inherent potential of Ru(II) to promote interesting and attractive C-H bond functionalizations and based on the outstanding efficiency of the cyclometalated RuBnN **XII** complex, we decided to study the possibility of achieving the Ru(II)-catalyzed methylation of the 2-phenylpyridine framework, with the bigger scenario in mind of carrying out the late-stage methylation of a variety of drugs. Moreover, we focused on employing bench-stable and readily available methylating agents, such as aryltrimethylammonium salts. The aim of the work performed during this Ph.D. stay was to optimize the reaction conditions for the *ortho*-mono-methylation of 2-phenylpyridine, taking advantage of different aryltrimethylammonium salts (Scheme 4.11).

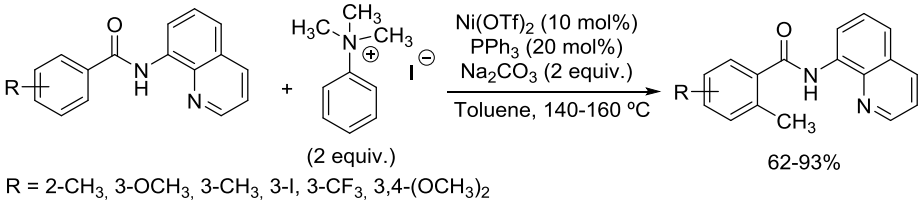


Scheme 4.11

3. RESULTS AND DISCUSSION

3.1. Ru(II) catalysis for the *ortho*-mono-methylation of 2-phenylpyridine utilizing bench-stable ammonium salts

As it has been mentioned in the aims of the chapter, the goal of this work was to develop an effective approach to carry out the *ortho*-mono-methylation of 2-phenylpyridine, utilizing aryltrimethylammonium salts as the coupling partners (Scheme 4.11). Interestingly, despite those ammonium salts have been employed as arylation agents in palladium-,[11] nickel-[12] and iron-catalyzed[13] reactions *via* cleavage of the N-aryl bond, their utilization as methyl sources is underdeveloped. In this context, those compounds were employed by Chatani´s group in the Ni(II)-catalyzed C-H mono-methylation of benzamides using the 8-aminoquinoline moiety as the directing group (Scheme 4.12).[14]



Scheme 4.12

Regarding methylating couplings under Ru(II)-catalysis, in 2016, Ackermann and co-workers reported a methodology for the C-2 methylation of *N*-(2-pyridyl)indole derivatives using potassium methyl trifluoroborate as the methylation reagent and $[RuCl_2(p\text{-cymene})]_2$ as the catalyst (Scheme 4.13).[15]

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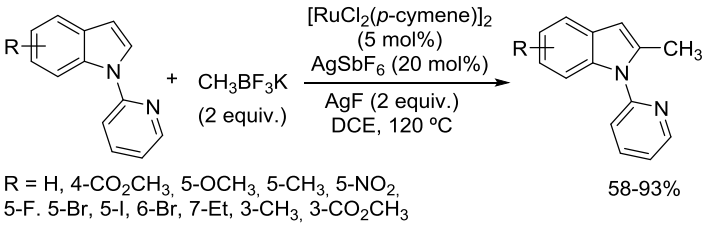
[11] a) Reeves, J.T.; Fandrick, D.R.; Tan, Z.; Song, J.J.; Lee, H.; Yee, N.K.; Senanayake, C.H. *Org. Lett.* **2010**, *12*, 4388; b) Zhu, F.; Tao, J.-L.; Wang, Z.-X. *Org. Lett.* **2015**, *17*, 4926; c) Chen, Q.; Gao, F.; Tang, H.; Yao, M.; Zhao, Q.; Shi, Y.; Dang, Y.; Cao, C. *ACS Catal.* **2019**, *9*, 3730; d) Liu, L.; Yu, W.-Q.; Huang, T.; Chen, T. *Tetrahedron Lett.* **2020**, *61*, 151647.

[12] a) Wenkert, E.; Han, A.-L.; Jenny, C.-J. *J. Chem. Soc., Chem. Commun.* **1988**, 975; b) Blakey, S.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2003**, *125*, 6046; c) Xie, L.-G.; Wang, Z.-X. *Angew. Chem. Int. Ed.* **2011**, *50*, 4901; d) Zhang, X.-Q.; Wang, Z.-X. *J. Org. Chem.* **2012**, *77*, 3658; e) Wu, D.; Tao, J.-L.; Wang, Z.-X. *Org. Chem. Front.* **2015**, *2*, 265; f) Wang, D.-Y.; Kawahata, M.; Yang, Z.-K.; Miyamoto, K.; Komagawa, S.; Yamaguchi, K.; Wang, C.; Uchiyama, M. *Nat. Commun.* **2016**, *7*, 12937; g) Li, J.; Wang, Z.-X. *Org. Biomol. Chem.* **2016**, *14*, 7579; h) He, F.; Wang, Z.-X. *Tetrahedron* **2017**, *73*, 4450.

[13] Guo, W.-J.; Wang, Z.-X. *Tetrahedron* **2013**, *69*, 9580.

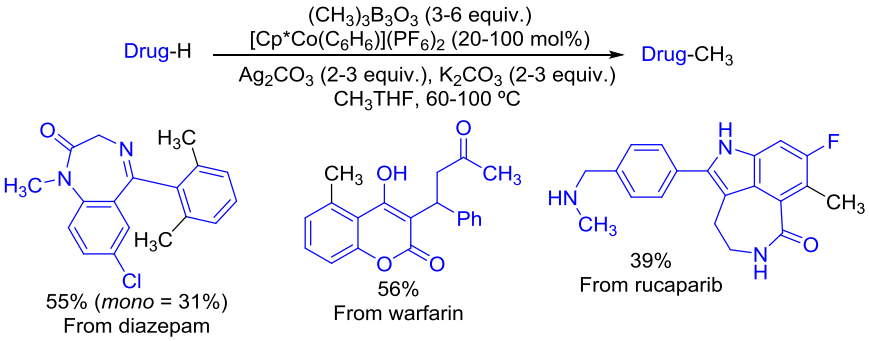
[14] Uemura, T.; Yamaguchi, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 3162.

[15] Tonin, M.D.L.; Zell, D.; Müller, V.; Ackermann, L. *Synthesis* **2017**, *49*, 127.



Scheme 4.13

Recently, in 2020, that same group reported the use of Cp*Co(III)-based catalyst $[Cp^*Co(C_6H_6)](SbF_6)_2$ for the late-stage methylation of a wide array of drugs employing trimethylboroxine $[(CH_3)_3B_3O_3]$ as the coupling partner.[16] This methodology not only showed a broad functional group compatibility but it also tolerated the use of several directing groups. Although efficient, in some of the cases mono-methylation of the substrates could not be selectively achieved, also obtaining the corresponding di-methylated products (Scheme 4.14).



Scheme 4.14

*3.1.1. Three-month stay. Ruthenium(II)-catalyzed methylation of 2-phenylpyridine utilizing aryltrimethylammonium salts **30**, **33** and **34** as the coupling partners. Synthesis of 2-(o-tolyl)pyridine **31***

With the aforementioned precedents in mind, we began our study checking the feasibility of the Ru(II)-catalyzed *ortho*-methylation of 2-phenylpyridine with phenyltrimethylammonium salts by subjecting the reagents to conditions previously

[16] Friis, S.D.; Johansson, M.J.; Ackermann, L. *Nat. Chem.* **2020**, *12*, 511.

explored by the group in similar transformations (Table 4.1).[4,6] When mixing 2-phenylpyridine with phenyltrimethylammonium iodide **30-I** (1 equiv.),[17] together with RuBnN **XII** (10 mol%), KOAc (30 mol%) and K_2CO_3 (3 equiv.) in NMP at 50 ºC, the transformation proceeded to furnish the corresponding *ortho*-mono-methylated product **31** in a low yield after 24 h (14%, Table 4.1, entry 1), while traces of the di-methylated counterpart **32** were obtained.

With this promising results in hand, we decided to increase the amount of the methylating agent, observing an improvement in the outcome of the reaction (Table 4.1, entries 2-5). However, 5 equivalents of the ammonium salt **30-I** only yielded a moderate 41% yield of **31**, keeping **32** in trace amounts (Table 4.1, entry 5).

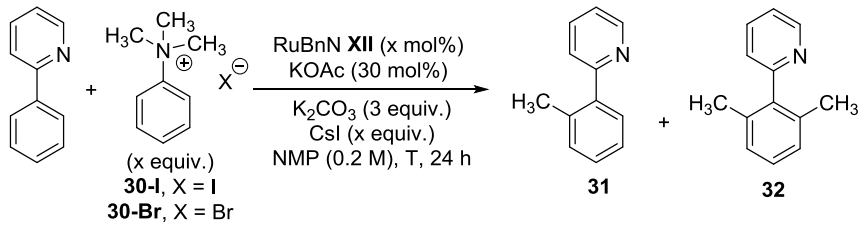
Then, we decided to increase the temperature to 70 ºC, obtaining the desired mono-product **31** in a very good yield (80%) with 1 equivalent of the ammonium salt **30-I** (Table 4.1, entry 6). Regarding the di-methylated by-product **32**, a low yield of 4% was observed. Increasing the amount of the methylating agent to 2 equivalents led to a non-selective reaction to give a mixture of **31** and **32** in 36% and 53% yield, respectively (Table 4.1, entry 7). Nevertheless, when the equivalents of **30-I** were further augmented to 3, **32** was selectively furnished in 61% yield, together with **31** in 2% yield (Table 4.1, entry 8), although the overall conversion was poorer than in previous cases.

Before carrying out any further screening investigation, we run some control experiments to study the impact of each reagent on the present transformation. When the Ru(II) catalyst **XII** was removed, the reaction did not proceed at all (Table 4.1, entry 9), while in the absence of K_2CO_3, the yield experimented a dramatic decrease, leading to 25% of the mono-methylated product **31** (Table 4.1, entry 10). Regarding KOAc, no negative effect was observed in the overall yield when it was not added; however, the reaction showed slightly less selectivity, furnishing a moderately higher amount of **32**, in detriment of **31** (Table 4.1, entry 11).

Although easy to prepare, phenyltrimethylammonium iodide **30-I** is not commercially available, so, with the aim of using more readily accessible reagents, we studied the possibility of employing phenyltrimethylammonium bromide **30-Br**, which is cheap and commercial. However, when **30-Br** was utilized as the methylating agent, it showed a poorer performance than its iodide counterpart (71%, Table 4.1, entry 12).

[17] For the preparation of the not-commercially-available aryltrimethylammonium salts utilized in this chapter, see Experimental Section.

Table 4.1



Entry	X	30 (equiv.)	RuBnN (mol%)	CsI (equiv.)	T (ºC)	Yield 31 (%)[a]	Yield 32 (%)[a]
1	I	1	10	-	50	14	-[b]
2	I	1.5	10	-	50	19	-[b]
3	I	2	10	-	50	25	-[b]
4	I	3	10	-	50	38	-[b]
5	I	5	10	-	50	41	-[b]
6	I	1	10	-	70	80	4
7	I	2	10	-	70	36	53
8	I	3	10	-	70	2	61
9	I	1	-	-	70	-	-[c]
10[d]	I	1	10	-	70	25	-[b]
11[e]	I	1	10	-	70	76	7
12	Br	1	10	-	70	71	4
13	Br	1	10	0.3	70	75	3
14	Br	1	10	1	70	83	4
15	Br	1	5	1	70	79	3
16	Br	1	5	1.5	70	83	4
17	Br	1	5	2	70	82	4
18	Br	1	5	3	70	83	4

[a] Yields were determined by GC-FID, using hexadecane as internal standard. [b] Traces of the product were detected by GC-FID. [c] No reaction, starting material recovered. [d] No K_2CO_3 was added. [e] No KOAc was added.

This problem could be overcome by the addition of an iodide salt. We checked the effect of catalytic and stoichiometric amounts of CsI (Table 4.1, entries 13 and 14, respectively), furnishing the mono-methylated product **31** in 83% yield when 1 equivalent of the iodide was added. We then lowered the catalyst loading to 5 mol%, obtaining a comparable yield of 79% (Table 4.1, entry 15), which could be increased to 83%, by utilizing 1.5 equivalents

of CsI (Table 4.1, entry 16), while higher amounts of that salt provided almost the same result (Table 4.1, entries 17 and 18).

With the reaction conditions shown in Table 4.1 (entry 16) in hand, we studied the effect of a variety of carboxylate sources, bases and iodide salts in the present coupling (Table 4.2). We commenced our investigation by screening several available carboxylates. Firstly, different acetates were tested; however, KOAc proved to be the most efficient one for the synthesis of **31** (Table 4.1, entry 16), obtaining almost comparable (although lower) results with LiOAc and NaOAc (Table 4.2, entries 1 and 2, respectively), while their cesium counterpart provided poorer results (Table 4.2, entry 3). $Cu(OAc)_2$ only furnished traces of **31** (Table 4.2, entry 4) and AgOAc gave nearly equimolecular amounts of both products **31** and **32** in an overall low yield (Table 4.2, entry 5). The last two acetates were almost incapable of promoting the desired process, surely due to their oxidative ability, which led to catalyst decomposition.

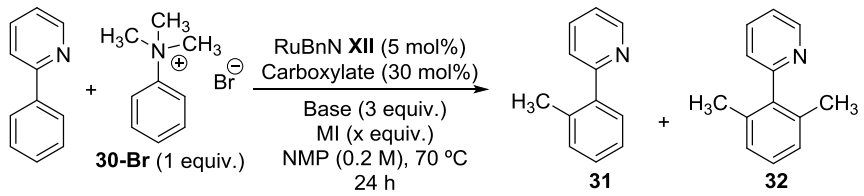
We then moved to test the use of different sodium and potassium carboxylates, which are usually very common and readily accessible. While potassium benzoate (Table 4.2, entry 6) led to the same yield obtained with KOAc (Table 4.1, entry 16) and sodium pivalate was not efficient for the coupling (Table 4.2, entry 7), potassium formate afforded 85% of product **31** (Table 4.2, entry 8), showing a better performance than the carboxylates screened so far.

Less basic trifluoroacetates were also investigated (Table 4.2, entries 9 and 10) and NaTFA gave the best results of mono-methylated product **31** (86%), while maintaining the yield of **32** very low (5%, Table 4.2, entry 9). Afterwards, different bases other than potassium carbonate, such as Li_2CO_3, Na_2CO_3, Cs_2CO_3 and K_3PO_4 (Table 4.2, entries 11, 12, 13 and 14, respectively), were utilized in the reaction, obtaining the best result with Na_2CO_3, which afforded the mono-methylated product **31** in 84% yield (Table 4.2, entry 12).

Finally, different iodide sources were investigated. LiI and NaI (Table 4.2, entries 15 and 16, respectively) showed better reactivity than CsI (Table 4.1, entry 16), furnishing both of them **31** in 86% yield. KI (Table 4.2, entry 17) was also more efficient than CsI, but not as effective as LiI and NaI. On the other hand, TBAI only afforded 66% of the desired **31** product (Table 4.2, entry 18). With these results in hand, we decided to continue the screening of the reaction conditions using NaI as the optimal iodide salt. Afterwards, once the best additives were selected, the optimal amount of NaI was investigated, finding that the best results were achieved with 2 equivalents of that salt (89%, Table 4.2, entry 21). Under-stoichiometric amounts of NaI (30 mol%) gave lower yields of **31** (Table 4.2, entry 19), while

the addition of 1 or 3 equivalents furnished the product with 86% yield (Table 4.2, entries 20 and 22, respectively).

Table 4.2



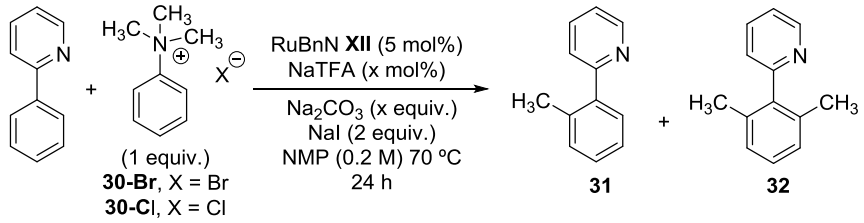
Entry	Carboxylate	Base	MI (equiv.)	Yield 31 (%)[a]	Yield 32 (%)[a]
1	LiOAc	K_2CO_3	CsI (1.5)	81	4
2	NaOAc	K_2CO_3	CsI (1.5)	79	3
3	CsOAc	K_2CO_3	CsI (1.5)	72	3
4	$Cu(OAc)_2$	K_2CO_3	CsI (1.5)	-[b]	0
5	AgOAc	K_2CO_3	CsI (1.5)	12	9
6	$PhCO_2K$	K_2CO_3	CsI (1.5)	83	4
7	NaOPiv	K_2CO_3	CsI (1.5)	64	2
8	HCO_2K	K_2CO_3	CsI (1.5)	85	4
9	NaTFA	K_2CO_3	CsI (1.5)	86	5
10	KTFA	K_2CO_3	CsI (1.5)	83	7
11	KOAc	Li_2CO_3	CsI (1.5)	83	2
12	KOAc	Na_2CO_3	CsI (1.5)	84	3
13	KOAc	Cs_2CO_3	CsI (1.5)	49	3
14	KOAc	K_3PO_4	CsI (1.5)	78	3
15	KOAc	K_2CO_3	LiI (1.5)	86	4
16	KOAc	K_2CO_3	NaI (1.5)	86	4
17	KOAc	K_2CO_3	KI (1.5)	84	4
18	KOAc	K_2CO_3	TBAI (1.5)	66	4
19	KOAc	K_2CO_3	NaI (0.3)	70	3
20	KOAc	K_2CO_3	NaI (1)	86	4
21	KOAc	K_2CO_3	NaI (2)	89	4
22	KOAc	K_2CO_3	NaI (3)	86	4

[a] Yields were determined by GC-FID, using hexadecane as internal standard. [b] Traces of the product were detected by GC-FID.

Once the optimal number of equivalents of NaI was found, the effect of different amounts of the other additives was studied (Table 4.3). We began setting an array of experiments varying only the equivalents of Na_2CO_3 (Table 4.3, entries 1-4) and curiously, in all of them **31** was provided with the same yield, being able to reduce the amount of the carbonate to 2 equivalents (Table 4.3, entry 1).

Regarding NaTFA, a similar trend was seen, since the addition of 30 mol% (Table 4.3, entries 1-4), 50 mol% (Table 4.3, entries 5 and 8) or even 70 mol% (Table 4.3, entry 6) led to almost the same yields of **31**. Nevertheless, when 1 equivalent was added, the yield decreased to 78% (Table 4.3, entry 7).

Table 4.3



Entry	X	NaTFA (mol%)	Na_2CO_3 (equiv.)	Yield 31 (%)[a]	Yield 32 (%)[a]
1	Br	30	2	84	6
2	Br	30	3	84	5
3	Br	30	4	84	5
4	Br	30	5	84	6
5	Br	50	3	85	6
6	Br	70	3	84	5
7	Br	100	3	78	6
8	Br	50	2	86	3
9	Br	20	2	88	4
10	Br	-	2	86	5
11	Cl	-	2	91	5
12	Cl	-	1	90	5

[a] Yields were determined by GC-FID, using hexadecane as internal standard.

In view of this fact, we decided to reduce its amount to 20 mol% (Table 4.3, entry 9), which, far from being detrimental, allowed us to slightly increase the yield. The complete removal of NaTFA led to no significant decrease of neither the yield of **31** nor the selectivity of the

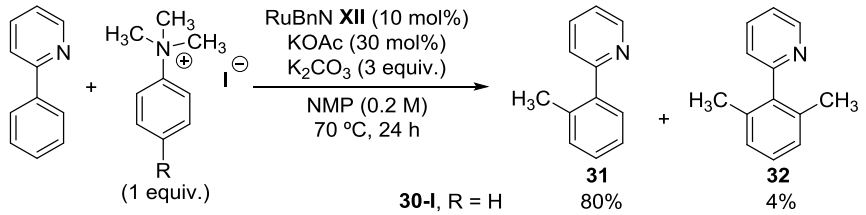
process (Table 4.3, entry 10). With that conditions in hand and after realizing that phenyltrimethylammonium chloride **30-Cl** was cheaper than its bromide counterpart **30-Br**, we decided to investigate its performance as methylating agent in our reaction, showing a higher efficiency (91%, Table 4.3, entry 11). We were even capable of reducing the loading of the carbonate additive to 1 equivalent, being the reaction conditions shown in this entry the optimal ones (90%, Table 4.3, entry 12).

Parallel to the screening of the reaction conditions for the Ru(II)-catalyzed methylation of 2-phenylpyridine at 70 ºC, we decided to study the feasibility of lowering the temperature of the transformation. In his Ni(II)-catalyzed methylation reaction of benzamides (Scheme 4.12),[14] Chatani proposed that these anilinium salts may work as methylating agents due to a S_N2-type oxidative addition of the metal center to the N-CH_3 bond; however, he did not rule out the possibility of methyl iodide (released from thermal decomposition of phenyltrimethylammonium iodide) being involved in the process.

Based on this, we proposed that the efficiency of aryltrimethylammonium salts as methylating agents in our transformation might lie on their slow thermal decomposition, gradually releasing halomethane (probably iodomethane, due to the improvement of the yield observed after adding an iodide salt), which would be responsible for the methylation process. Nevertheless, a S_N2-type reaction onto the highly electrophilic ammonium salt cannot be discarded. In both cases, the presence of electron-withdrawing groups in the aromatic ring of those salts would be beneficial for the methylation reaction, since they would not only have a destabilizing effect on the cation (probably reducing the thermal stability of the ammonium salts), but they would also increase the electrophilicity of the compound (thus, making it prompter to undergo nucleophilic attack).

Encouraged by the possibility of carrying out the reaction at lower temperatures based on the aforementioned proposal, we synthesized two different trimethylanilinium iodides, **33** and **34**, bearing electron-withdrawing groups at the *para*-position of the arene moiety.

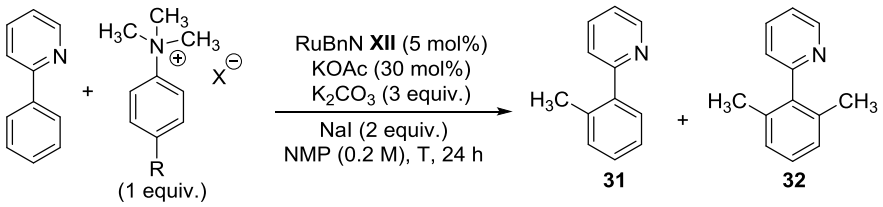
To compare their reactivity with that of their unsubstituted counterpart **30-I**, we subjected them to the reaction conditions shown in Table 4.1 (entry 6) (Scheme 4.15). According to this experiment, **33** and **34** provided mono-methylated product **31** in almost the same yield obtained with **30-I**, furnishing larger amounts of the di-methylated product **32** due to their higher reactivity.



Scheme 4.15

Far from being discouraged, we then set up three different reactions with **30-Br**, **33** and **34** at 50 ºC using the conditions indicated in Table 4.2 (Entry 21) (Table 4.4, entries 1-3).

Table 4.4



Entry	Ammonium Salt	R	X	T (ºC)	Yield 31 (%)[a]	Yield 32 (%)[a]
1	**30-Br**	H	Br	50	19	-[b]
2	**33**	CF_3	I	50	85	5
3	**34**	CO_2Et	I	50	83	3
4	**33**	CF_3	I	35	23	-[b]
5	**34**	CO_2Et	I	35	17	-[b]

[a] Yields were determined by GC-FID, using hexadecane as internal standard. [b] Traces of the product were detected by GC-FID.

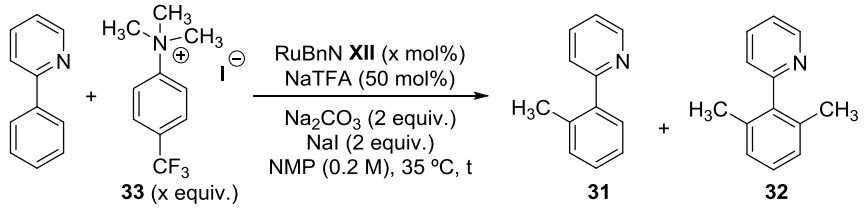
While the yield of **31** was dramatically decreased using **30-Br** (19% *vs* 89%, Table 4.4, entry 1 *vs* Table 4.2, entry 21), ammonium salt **33** afforded **31** in 85% yield (Table 4.4, entry 2) and **34** gave that same product in 83% yield (Table 4.4, entry 3). Unfortunately, those results were substantially reduced when running the reaction at 35 ºC, obtaining 23% yield of the product with **33** and 17% with salt **34** (Table 4.4, entries 4 and 5, respectively).

With the aim of enhancing these results, the effect of the reaction time, the catalyst loading and the amount of ammonium salt **33**, which was observed to be more reactive than **34**,

were investigated (Table 4.5). Under the conditions of Table 4.3 (entry 8), the mono-methylated product **31** was obtained in 23% yield after 24 h (Table 4.5, entry 1), while the outcome was improved to 41% upon 48 h (Table 4.5, entry 2).

The increase of the catalyst loading to 10 mol% led to no significant improvement of the yield neither after 24 h (Table 4.5, entry 3), nor after 48 h (Table 4.5, entry 4). Contrastingly, higher amounts of aryltrimethylammonium iodide **33** led to higher yields of **31** (Table 4.5, entries 5-7), reaching the limit of this increase with 4 equivalents of the ammonium salt. This reaction conditions provided the mono-methylated product **31** in a moderate, though promising, 61% yield, while the formation of **32** was still negligible (Table 4.5, entry 7).

Table 4.5



Entry	33 (equiv.)	RuBnN (mol%)	t (h)	Yield 31 (%)[a]	Yield 32 (%)[a]
1	1	5	24	23	-[b]
2	1	5	48	41	-[b]
3	1	10	24	24	-[b]
4	1	10	48	43	-[b]
5	2	5	24	42	-[b]
6	3	5	24	58	2
7	4	5	24	61	2

[a] Yields were determined by GC-FID, using hexadecane as internal standard. [b] Traces of the product were detected by GC-FID.

In conclusion, we have developed a methodology for the Ru(II)-catalyzed selective *ortho*-mono-methylation of 2-phenylpyridine using readily available aryltrimethylammonium salts as the coupling partners. Despite we have been capable of making the reaction take place at 70 ºC and at 50 ºC with very good yields and selectivities, the obtainment of a comparable result at 35 ºC remains elusive. Nevertheless, the outcome of the reaction may be enhanced by a careful screening of the reaction conditions and the choice of the appropriate aryltrimethylammonium salt.

Although the scope and applicability of the reaction still has to be investigated, it may serve as a powerful tool for the late-stage methylation of drugs, which might be of the utmost interest taking into account the so-called *magic methyl effect*. This phenomenon consists of the fact that the addition of a methyl group to one drug can increase several times the binding affinity of that molecule towards its biological target.[18] The reason why this improvement occurs is because the introduction of a methyl group changes the shape of the functionalized drug in such a way that it can easily fit into the active site of the target protein.

[18] a) Schönherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256; b) Corcoran, E.B.; Schultz, D.M. *Nature* **2020**, *580*, 592.

V

General Conclusions

1. GENERAL CONCLUSIONS

1. GENERAL CONCLUSIONS

- The intramolecular Fujiwara-Moritani reaction has proved to be an efficient tool for the synthesis of a variety of chromanes (with exocyclic double bonds) starting from the corresponding butenyl phenyl ethers bearing electron-withdrawing functionalities on the alkene terminus. Besides, the removal of those groups from the alkene moiety led to the formation of different chromenes, due to isomerization of the exocyclic double bond to the endocyclic position in the course of the reaction. Furthermore, the procedure could be extended to the synthesis of the coumarin core starting from the corresponding aryl butenoate.

- The procedure for the alkenylative cyclization of butenyl phenyl ethers and aryl butenoates is very versatile, as it allows the synthesis of alkylidenechromanes and 2*H*-chromenes with different types of substituents (alkyl, electron-rich and electron-deficient aryl and heteroaryl) at C-2 or C-3 of the chromene moiety, therefore accessing relevant flavenes, isoflavenes and even coumarins.

- The intramolecular oxidative Heck reaction has also been successfully utilized for the obtainment of the quinoline framework. When *N*-protected butenylanilines bearing electron-withdrawing groups on the alkene were subjected to relatively harsh reaction conditions, 6-*exo*-trig cyclization took place, followed by isomerization of the exocyclic olefin to the *endo* position and aromatization. This process allowed us to synthesize an array of 4-substituted quinolines in good yields.

- As hypothesized, this last aromatization event could be avoided by using milder reaction conditions. That way, different 1,2-dihydroquinolines were effectively obtained, preserving the *N*-protecting groups present in the substrates. Nevertheless, electron-withdrawing substituents on the alkene terminus were not tolerated.

- The intramolecular dehydrogenative Heck coupling has allowed us to access a wide range of 1,2- and 1,4-dihydroquinolines, starting from the corresponding *N*-protected allylanilines (generally in very good yields), by means of 6-*endo*-trig cyclization events. A variety of substituents were well tolerated on the terminal position of the alkene; nonetheless, when a methyl group was placed in the internal position, the reaction did not proceed to furnish the corresponding product.

- It could be seen that the efficiency of the reaction was highly dependent on the coordinating ability of the *N*-protecting/directing group (*N*-protecting groups with higher coordinating abilities, afforded higher yields under milder reaction conditions), being methyl carbamate the optimal one.

- In that 6-*endo*-trig cyclization of allylanilines, the positional selectivity was controlled by the nature of the *N*-protecting group and DFT studies provided understanding of the factors that govern this unusual 6-*endo* process, which were in agreement with the experimentally observed outcome. The reaction proceeds *via* prior activation of the alkene, being the coordination of the remote *N*-protecting group to the palladium center crucial for the formation of the six-membered ring. The coordination of the palladium center to the *N*-protecting group could be experimentally confirmed by using a chiral enantiopure group, since that way, a moderate level of diastereoselectivity was induced in the corresponding 1,4-dihydroquinoline products.

- The placement of electron-withdrawing functionalities on the terminal position of the olefin present in the substrate, led to a change in the regioselectivity of the cyclization: the reaction took place *via* a 5-*exo*-trig process instead of a 6-*endo* one. Therefore, different 3-substituted indoles could be selectively obtained.

- For all the Fujiwara-Moritani reactions accomplished during this Ph.D., it is worth to point out the importance of the presence of the 3,5-dimethoxyphenyl ring in the substrates. In some of the cases, such as in the 6-*exo*-trig cyclizations for the formation of chromanes and 1,2-dihydroquinolines, the aromatic ring of the substrates could be changed. However, this was highly limited to the use of other electron-rich arenes and in all the cases the results were poorer than when using the 3,5-dimethoxyphenyl ring.

- Cp*Co(III) complexes can be good, cheap, environmentally-friendly and earth-abundant alternatives to palladium catalysts, since they have allowed us to accomplish the first high-valent-cobalt-catalyzed intramolecular hydroarylation of unactivated alkenes effectively. We were capable of using them for the cyclization of several (homo)allyl phenyl ethers, leading to the synthesis of 2,3-dihydrobenzofurans and chromanes in high yields. This reaction took place with complete selectivity towards the generation of a quaternary center by means of an amide-directed cobaltation of the arene (*via* Co-N binding) followed by intramolecular migratory insertion to the alkene (in a 5- or 6-*exo* manner) and proto-demetalation.

- It has been proved that allyl phenyl ethers can be utilized as allylating agents for the Cp*Co(III)-promoted *ortho*-mono-allylation of *N*-methylbenzamide. Although the reaction conditions still have to be optimized, to the best of our knowledge, this is the first example of the use of those ethers as allylating agents under high-valent-cobalt catalysis.

- During the three-month stay carried out in the Larrosa Group (University of Manchester), the optimization of the reaction conditions for the Ru(II)-promoted methylation of 2-phenylpyridine was performed, using readily available aryltrimethylammonium salts as the coupling partners. Although the scope of this transformation is still to be investigated, it may be a useful methodology to achieve the late-stage methylation of a variety of drugs. Besides, the use of aryltrimethylammonium salts possessing electron-deficient aromatic rings allowed us to reduce the reaction temperature.

VI

Experimental Section

5.1. Preparation of $Cp^*Co(CO)I_2$ catalyst

5.2. Preparation of $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ catalyst

5.3. General procedure for the esterification of 3-hydroxybenzoic acids. Synthesis of methyl 3-hydroxybenzoates TB-TO

5.4. Synthesis of methyl 3-(benzyloxy)-5-hydroxybenzoate (TH)

5.5. Synthesis of methyl 3-hydroxy-5-methoxybenzoate (TI)

5.6. Synthesis of ethyl 7-hydroxybenzo[d][1,3]dioxole-5-carboxylate (TJ)

5.7. Synthesis of ethyl 8-hydroxy-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate (TK)

5.8. General procedure for the Suzuki-Miyaura coupling of methyl 3-bromo-5-hydroxybenzoate (TC). Synthesis of methyl 3-hydroxybenzoates TM and TN

5.9. General procedure for the alkylation of 3-hydroxybenzoates TA-TN. Synthesis of 3-((2-methylallyl)oxy)benzoates UAA-UAN

5.10. Dialkylation of methyl 3,5-dihydroxybenzoate (TO). Synthesis of methyl 3,5-bis((2-methylallyl)oxy)benzoate (UAL)

5.11. Synthesis of (3-bromoprop-1-en-2-yl)benzene

5.12. General procedure for the alkylation of 3-hydroxybenzoates TA, TF, TG and TJ. Synthesis of 3-((2-phenylallyl)oxy)benzoates UBA-UBJ

5.13. Synthesis of 2-methylenebutan-1-ol

5.14. Mitsunobu reaction for the alkylation of ethyl 3-hydroxybenzoate (TA). Synthesis of ethyl 3-(2-methylenebutoxy)benzoate (UCA)

5.15. General procedure for the Mitsunobu reaction of 3-hydroxybenzoates TA and TG. Synthesis of 3-((3-methylbut-3-en-1-yl)oxy)benzoates UDA-UDG

5.16. Synthesis of (E)-2-methybut-2-en-1-ol

5.17. Mitsunobu reaction for the alkylation of ethyl 3-hydroxybenzoate (TA). Synthesis of ethyl (E)-3-((2-methylbut-2-en-1-yl)oxy)benzoate (UEA)

5.18. Alkylation of ethyl 3-hydroxybenzoate (TA). Synthesis of ethyl 3-(allyloxy)benzoate (UFA)

5.19. General procedure for the hydrolysis of esters UAA-UFA. Synthesis of carboxylic acids VAA-VFA

5.20. General procedure for the amidation of carboxylic acids VAA-VFA. Synthesis of amides 19aa-19fa

5.21. Synthesis of N,N-dimethyl-3-((2-methylallyl)oxy)benzamide (20aa)

5.22. Synthesis of 3-methylbut-3-en-1-yl methanesulfonate

5.23. N-Alkylation of indole. Synthesis of 1-(3-methylbut-3-en-1-yl)-1H-indole (W)

5.24. Synthesis of 1-(3-methylbut-3-en-1-yl)-1H-indole-3-carboxylic acid (X)

5.25. Synthesis of N-methyl-1-(3-methylbut-3-en-1-yl)-1H-indole-3-carboxamide (21)

5.26. General procedure for the Co(III)-catalyzed intramolecular C-H alkylation of amides 19aa-19dg and 21. Synthesis of dihydrobenzofurans 22aa-22ca, chromanes 23da-23dg and pyrroloindole 24

*5.27. Cp*Co(III)-catalyzed synthesis of 22aa and 22ba in a 1 mmol scale*

6.4. General procedure for the optimization of the reaction conditions for the ortho-mono-methylation of 2-phenylpyridine using 30, 33 and 34 as the methylating agents

7. CRYSTAL DATA FOR 3-(4-FLUOROPHENYL)-5,7-DIMETHOXY-4-METHYL-2H-CHROMENE (4am)

1. GENERAL METHODS AND MATERIALS

Nuclear Magnetic Resonance

Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H NMR and ^{13}C NMR) were acquired at 20-25 ºC on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) and on a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C).

Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR; CD_3OD, 3.31 ppm for ^{1}H NMR, CD_3OD, 49.0 ppm for ^{13}C NMR; $(CD_3)_2CO$, 2.09 ppm for ^{1}H NMR, $(CD_3)_2CO$, 30.6 ppm and 205.9 ppm for ^{13}C NMR; DMSO-*d*6, 2.50 ppm for ^{1}H NMR, DMSO-*d*6, 39.5 ppm for ^{13}C NMR; CD_3CN, 1.94 ppm for ^{1}H NMR, CD_3CN, 1.3 ppm and 118.3 ppm for ^{13}C NMR; D_2O, 4.80 ppm for ^{1}H NMR) and coupling constants (*J*) are expressed in hertz (Hz).

The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quadruplet; h, hexaplet and combinations thereof; m, multiplet and br s, broad signal. Assignments of individual ^{13}C and ^{1}H resonances are supported by DEPT experiments and 2D correlations experiments (COSY, HSQCed or HMBC), when necessary.[1]

Infrared Spectroscopy

IR spectra were obtained using Attenuated Total Reflection (ATR) in a JASCO FT/IR 4100 in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case.

Mass Spectrometry

GC-MS analyses were performed on an Agilent 7890A, using a column HP-1 (100% methylpolysiloxane, 30 m × 0.25 mm × 0.25 µm). Mass spectra were recorded using electron impact conditions (EI) at 70 eV on an agilent MSD 5975C spectrometer.

[1] Kinss, M.; Sanders, J.K.M. *J. Mag. Res.* **1984**, *56*, 518.

High resolution mass spectra (HRMS) were performed by the Mass Spectrometry General Service at the University of the Basque Country using a Micromass GCT, equipped with a TOF detector under chemical ionization (CI) to 230 eV (methane as the reagent gas, positive mode), or using an ultra performance liquid chromatograph (Acquity UPLC, Waters Cromatografía S.A.), in tandem with a QTOF mass spectrometer (SYNAPT G2 HDMS, Waters Cromatografía S.A.), with an electrospray ionization source in a positive mode. However, as it will be stated for each of those cases, some of the compounds required an electrospray ionization source in a negative mode to be detected.

Melting Points

Melting points were measured in a Büchi B-540 apparatus in open capillary tubes and are uncorrected.

X-Ray Diffraction

Intensity data were collected on an Agilent Technologies Super-Nova diffractometer, wich was equipped with monochromated Cu kα radiation (λ = 1.54184 Å) and Atlas CCD detector. Measurement was carried out at 149.99(10) K with the help of an Oxford Cryostream 700 PLUS temperature device.

Data frames were processed (united cell determination, analytical absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) using the Crysalis software package.[2] The structure was solved using SHELXT[3] and refined by full-matrix least-squares with SHELXL-97(version2018/3).[4] Final geometrical calculations were carried out with Mercury[5] and PLATON[6] as integrated in WinGX.[7]

[2] CrysAlisPro, Agilent Technologies, Version 1.171.37.31 (release 14-01-2014 CrysAlis171.NET) (compiled Jan 14 2014,18:38:05).
[3] Sheldrick, G.M. *Acta Cryst*. **2015,** *A71*, 3.
[4] Sheldrick, G.M. *Acta Cryst*. **2008,** *A64*, 112.
[5] Macrae, C.F.; Bruno, I.J.; Chisholm, J.A.; Edgington, P.R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J.; Wood, P.A. *J. Appl. Cryst*. **2008**, *41*, 466.
[6] a) Spek, A.L. *PLATON, A Multipurpose Crystallographic Tool*, Utrecht University: Utrecht, 2010; b) Spek A.L. *J. Appl. Cryst.* **2003**, *36*, 7.
[7] Farrugia L.J. *J. Appl. Cryst.* **1999**, *32*, 837.

Reagents and Solvents

Anhydrous solvents were purified according to standard procedures, and dried with activated molecular sieves prior to their use.[8] When *n*-hexane was used as solvent for flash column chromatography, it was distilled prior to use.

Commercially available starting materials and reagents (Sigma-Aldrich, Fluka, Alfa Aesar and Acros Organics) were used without further purification. Except for pyridine, which was distilled prior to use and stored under argon atmosphere.

Palladium catalysts $Pd(OAc)_2$ (98% purity), $Pd(CH_3CN)_4(BF_4)_2$ (99.9% purity), $PdCl_2(CH_3CN)_2$ (99% purity) and $PdCl_2(PhCN)_2$ (95% purity), as well as 2nd Generation Grubbs Catalyst (98% purity) were purchased from Sigma-Aldrich and were used without further purification.

Cp*Co(III) catalysts $Cp^*Co(CO)I_2$[9] and $[Cp^*Co(CH_3CN)_3](SbF_6)_2$[10] were not commercially available and had to be prepared following reported methods, as it will be disclosed later. Ru(II) catalyst RuBnN, used during the stay at the University of Manchester, was already available in the laboratories of Professor Igor Larrosa.[11]

Miscellaneous

The reactions were monitored by thin layer chromatography (TLC) in pre-coated aluminum-backed 0.2 mm-thick silica-gel Merck F_{254} plates. Visualization was accomplished with UV light (λ = 254 nm and 360 nm) or by immersion in phosphomolybdic acid solution (10% in ethanol) and/or vanillin solution (0.07 M in ethanol).[12] For column chromatographic separations Silica Flash P60 (Silicycle), 230-400 mesh ASTM was used when performed under pressure.[13]

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[8] a) Armarego, W.L.F., Chai, C.L.L. *Purification of Laboratory Chemicals*, 6th Ed.; Elsevier Science: Burlington, 2009; b) Williams, d.B.G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351.
[9] Sun, B.; Yoshino, T.; Matsuaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 1491.
[10] Yu, D.-G.; Gensch, T.; de Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722.
[11] Simonetti, M.; Cannas, D.M.; Just-Baringo, X.; Vitorica-Yrezabal, I.J.; Larrosa, I. *Nat. Chem.* **2018**, *10*, 724.
[12] Stahl, E. *Thin Layer Chromatography*, Springer-Verlag: Berlin, 1969.
[13] Still, W.C.; Kann, H.; Miltra, A.J. *J. Org. Chem.* **1978**, *43*, 2923.

All air- and moisture-sensitive reactions were performed under argon. All the glassware was previously dried for 12 h prior to utilization in an oven at 130 ºC and allowed to cool under a dehumidified atmosphere, and purged with argon. The addition of solutions and liquids was carried out by oven-dried syringe or cannula.[14]

The solvents were removed at reduced pressure on Rotavapors Büchi R210, R200 and R114. Weighs were made in analytical balances Mettler AE-260 or Sartorius Practum 224-1S. Low temperature reactions were performed using baths or immersion coolers TERMO HAAKE EK90. Preheated heating blocks or oil baths (both of them with temperature control) were employed for reactions that required heating.

Computational Methods

All structures were optimized using density functional theory (DFT) as implemented in Gaussian[15] with B3LYP[16] as functional, 6-31G** as basis set for nonmetallic atoms, and LANL2DZ[17] as basis set for palladium. Final energies were obtained performing single-point calculations on the previously optimized structures using the M06[18] functional, 6-311 + G** as basis set for nonmetallic atoms and SDD[19] for palladium. Solvation factors were

[14] Cranwell, P.B.; Harwood, L.M.; Moody, C.J. *Experimental Organic Chemistry,* 3rd Ed.; Wiley-VCH: Chichester, 2017.

[15] Gaussian 16, Revision B.01, Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Petersson, G.A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.V.; Bloino, J.; Janesko, B.G.; Gomperts, R.; Mennucci, B.; Hratchian, H.B.; Ortiz, J.V.; Izmaylov, A.F.; Sonnenberg, J.L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V.G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J.A.; Peralta, J.E.; Ogliaro, F.; Bearpark, M.J.; Heyd, J.J.; Brothers, E.N.; Kudin, K.N.; Staroverov, V.N.; Keith, T.A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.P.; Burant, J.C.; Iyengar, S.S.; Tomasi, J.; Cossi, M.; Millam, J.M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J.W.; Martin, R.L.; Morokuma, K.; Farkas, O.; Foresman, J.B. and Fox, D.J.; Gaussian, Inc., Wallingford CT, **2016**.

[16] a) Lee, C.; Yang, W.; Parr; R.G. *Phys. Rev. B* **1988**, *37*, 785; b) Becke, A.D. *J. Chem. Phys.* **1993**, *98*, 5648; c) Kohn, W.; Becke, A.D.; Parr, R.G. *J. Phys. Chem.* **1996**, *100*, 12974.

[17] a) Hay, P.J.; Wadt, W.R. *J. Chem. Phys.* **1985**, *82*, 270; b) Wadt, W.R.; Hay, P.J. *J. Chem. Phys.* **1985**, *82*, 284; c) Hay, P.J.; Wadt, W.R. *J. Chem. Phys.* **1985**, *82*, 299.

[18] Zhao, Y.; Truhlar, D.G. *Theor. Chem. Acc.* **2008**, *120*, 215.

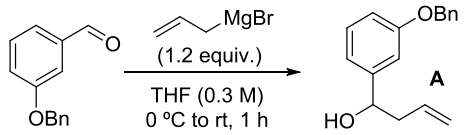
[19] a) Dolg, M.; Wedig, U.; Stoll, H.; Preuss, H. *J. Chem. Phys.* **1987**, *86*, 866; b) Andrae, D.; Haussermann, U.; Dolg, M.; Stoll H.; Preuss, H. *Theor. Chim. Acta* **1990**, *77*, 123.

introduced with the IEF-PCM[20] method, using 1,4-dioxane as solvent. The stationary points were characterized by frequency calculations to verify that they have the right number of imaginary frequencies

[20] a) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032; b) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253; c) Tomasi, J.; Mennucci, B.; Cancès, E. *J. Mol. Struct: THEOCHEM* **1999**, *464*, 211.

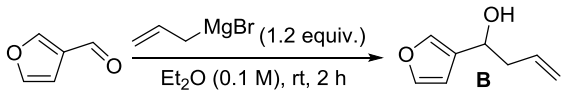
2. PALLADIUM(II)-CATALYZED INTRAMOLECULAR C-H ALKENYLATION FOR THE SYNTHESIS OF CHROMANES

2.1. Synthesis of 1-(3-(benzyloxy)phenyl)but-3-en-1-ol (A)[21]



Over a solution of 3-benzyloxybenzaldehyde (0.85 g, 4.0 mmol) in dry THF (13.4 mL), allylmagnesium bromide (1 M solution in Et_2O) (4.8 mL, 4.8 mmol) was added dropwise at 0 ºC and under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 1 h. Then, it was quenched by addition of a saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and after flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) homoallylic alcohol **A** was obtained as an oil (0.81 g, 80%): ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.24 (bs, 1H, OH), 2.43-2.61 (m, 2H, C$\underline{H_2}$CH=CH$_2$), 4.72 (t, *J* = 6.3 Hz, 1H, OCH), 5.09 (s, 2H, OC$\underline{H_2}$Ph), 5.12-5.22 (m, 2H, CH=C$\underline{H_2}$), 5.82 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H, C$\underline{H}$=CH$_2$), 6.84-7.11 (m, 3H, H_2, H_4, H_6), 7.23-7.51 (m, 6H, H_5, Ph); ^{13}C NMR ($CDCl_3$): δ (ppm) = 43.8 ($\underline{C}H_2CH=CH_2$), 70.0 (O$\underline{C}H_2$Ph), 73.2 (OCH), 112.4 (C_2), 113.9 (C_4), 118.4 (CH=$\underline{C}H_2$), 118.5 (C_6), 127.6 ($C_{2'}$, $C_{6'}$), 128.0 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 129.5 (C_5), 134.5 ($\underline{C}H$=CH$_2$), 137.0 ($C_{1'}$), 145.7 (C_1), 159.0 (C_3).

2.2. Synthesis of 1-(furan-3-yl)but-3-en-1-ol (B)[22]



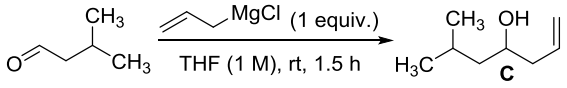
Over a solution of 3-furancarboxaldehyde (0.74 g, 7.7 mmol) in dry Et_2O (77.0 mL), allylmagnesium bromide (1 M solution in Et_2O) (9.3 mL, 9.3 mmol) was added dropwise at

[21] Kim, Y.-J.; Brown, S.P.; Cao, Q.; Dransfield, P.J.; Du, X.; Houze, J.; Jiao, X.Y.; Khon, T.J.; Lai, S.; Li, A.-R.; Lin, D.; Luo, J.; Medina, J.C.; Reagan, J.D.; Pattaropong, V.; Schwarz, M.; Shen, W.; Su, Y.; Swaminath, G.; Vimolratana, M.; Wang, X.; Xiong, Y.; Yang, L.; Yu, M.; Zhang, J.; Zhu, L. Substituted biphenyl GPR40 modulators and their preparation, pharmaceutical compositions and use in the treatment of metabolic disorders. WO 2009048527 A1, April 16, 2009.

[22] Yoo, J.; Oh, K.E.; Keum, G.; Kang, S.B.; Kim, Y. *Polyhedron* **2000**, *19*, 549.

room temperature and under argon atmosphere. The reaction mixture was stirred for 2 h and then, it was poured over a saturated aqueous solution of NH_4Cl (20 mL). The mixture was extracted with Et_2O (3 × 20 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. After flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) homoallylic alcohol **B** was obtained as an oil (0.83 g, 78%): ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.36-2.57 (m, 3H, OH, C<u>H$_2$</u>CH=CH$_2$), 4.66 (t, *J* = 6.4 Hz, 1H, OCH), 5.04-5.25 (m, 2H, CH=C<u>H$_2$</u>), 5.78 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H, C<u>H</u>=CH$_2$), 6.38 (s, 1H, H_4), 7.35 (s, 2H, H_2, H_5); ^{13}C NMR ($CDCl_3$): δ (ppm) = 42.4 (<u>C</u>H$_2$CH=CH$_2$), 66.1 (OCH), 108.6 (C_4), 118.3 (CH=<u>C</u>H$_2$), 128.5 (C_3), 134.2 (<u>C</u>H=CH$_2$), 139.0 (C_2), 143.2 (C_5).

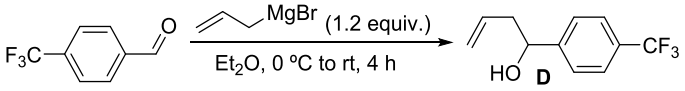
2.3. Synthesis of 6-methylhept-1-en-4-ol (C)[23]



Over a solution of isovaleraldehyde (1.0 g, 12.0 mmol) in dry THF (12.0 mL), allylmagnesium chloride (2 M solution in THF) (6.0 mL, 12.0 mmol) was added dropwise at room temperature and under argon atmosphere. The reaction mixture was stirred for 1.5 h and then, it was quenched by addition of a saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (30 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. After flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) homoallylic alcohol **C** was obtained as an oil (0.82 g, 53%): ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.87 (d, *J* = 4.1 Hz, 3H, CH_3), 0.89 (d, *J* = 4.1 Hz, 3H, CH_3), 1.10-1.45 (m, 2H, C<u>H$_2$</u>CH(CH$_3$)$_2$), 1.61-2.33 (m, 4H, C<u>H$_2$</u>CH=CH$_2$, C<u>H</u>(CH$_3$)$_2$, OH), 3.59-3.76 (m, 1H, OCH), 5.00-5.18 (m, 2H, CH=C<u>H$_2$</u>), 5.69-5.90 (m, 1H, C<u>H</u>=CH$_2$); ^{13}C NMR ($CDCl_3$): δ (ppm) = 22.0 (CH_3), 23.4 (CH_3), 24.4 (<u>C</u>H(CH$_3$)$_2$) 42.5 (<u>C</u>H$_2$CH=CH$_2$), 46.0 (<u>C</u>H$_2$CH(CH$_3$)$_2$), 68.9 (OCH), 117.8 (CH=<u>C</u>H$_2$), 134.9 (<u>C</u>H=CH$_2$).

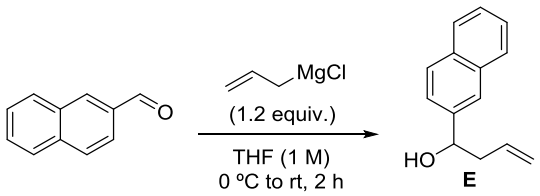
[23] Reetz, M.T.; Steinbach, R.; Westermann, J.; Peter, R. *Angew. Chem*. **1980**, *92*, 1044.

2.4. Synthesis of 1-(4-(trifluoromethyl)phenyl)but-3-en-1-ol (D)[24]



Over a solution of 4-(trifluoromethyl)benzaldehyde (1.1 g, 6.3 mmol) in dry Et_2O (6.6 mL), allylmagnesium bromide (1 M solution in Et_2O) (7.5 mL, 7.5 mmol) was added dropwise at 0 ºC and under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 4 h. Then, it was quenched by addition of a saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried (Na_2SO_4). The solvent was evaporated *in vacuo* and after flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) homoallylic alcohol **D** was obtained as an oil (1.1 g, 80%): ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.33-2.61 (m, 2H, C$\underline{H_2}$CH=CH$_2$), 2.68-2.83 (m, 1H, OH), 4.75 (br s, 1H, 1 × CH$_2$CH=C$\underline{H_2}$), 5.08-5.14 (m, 1H, OCH), 5.16 (br s, 1H, 1 × CH$_2$CH=C$\underline{H_2}$), 5.67-5.84 (m, 1H, C$\underline{H}$=CH$_2$), 7.43 (d, *J* = 8.0 Hz, H_2, H_6), 7.59 (d, *J* = 8.0 Hz, H_3, H_5); ^{13}C NMR ($CDCl_3$): δ (ppm) = 43.7 (C$\underline{H_2}$CH=CH$_2$), 72.6 (OCH), 118.9 (CH=C$\underline{H_2}$), 124.2 (q, *J* = 273.0 Hz, CF_3), 125.3 (q, *J* = 3.8 Hz, C_3, C_5), 126.1 (C_2, C_6), 129.6 (q, *J* = 32.5 Hz, C_4), 133.7 (C$\underline{H}$=CH$_2$), 147.8 (C_1).

2.5. Synthesis of 1-(naphthalen-2-yl)but-3-en-1-ol (E)[25]

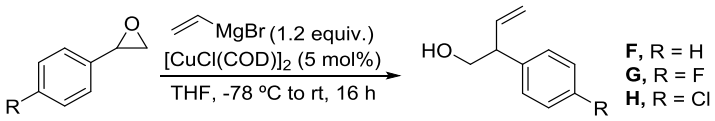


Over a solution of 2-naphthaldehyde (2.0 g, 13.0 mmol) in dry THF (13.0 mL) was added dropwise allylmagnesium chloride (2 M solution in THF) (7.8 mL, 15.6 mmol) at 0 ºC and under argon atmosphere. The reaction mixture was allowed to warm up to room temperature for 2 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (15 mL). The mixture was extracted with Et_2O (3 × 20 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. After flash

[24] Li, L.-H.; Chan, T.H. *Tetrahedron Lett.* **2000**, *41*, 5009.
[25] Grigg, R.; Putnikovic, B.; Urch, C.J. *Tetrahedron Lett.* **1997**, *38*, 6307.

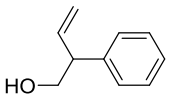
column chromatography (silica gel, petroleum ether/AcOEt 8/2) homoallylic alcohol **E** was obtained as an oil (2.3 g, 88%): ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.57 (d, *J* = 8.0 Hz, 1H, OH), 2.58-2.66 (m, 2H, C$\underline{H}_2$CH=CH_2), 4.84-4.92 (m, 1H, OCH), 5.12-5.28 (m, 2H, CH=C$\underline{H}_2$), 5.85 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H, C$\underline{H}$=CH_2), 7.42-7.58 (m, 3H, H_3, H_6, H_7), 7.73-7.92 (m, 4H, H_1, H_4, H_5, H_8); ^{13}C NMR ($CDCl_3$): δ (ppm) = 43.7 (C$\underline{H}_2$CH=CH_2), 73.6 (OCH), 118.3 (CH=C$\underline{H}_2$), 124.2 (C_6), 124.7 (C_1), 125.9 (C_7), 126.2 (C_8), 127.8 (C_5), 128.1 (C_3, C_4), 128.3 (C_2), 133.1 (C_{8a}), 133.4 (C$\underline{H}$=CH_2), 141.5 (C_{4a}).

2.6. General procedure for the synthesis of homoallylic alcohols F-H



Over a suspension of the corresponding oxirane (1 mmol) and $[CuCl(COD)]_2$ (0.05 mmol) in dry THF (1.4 mL), vinylmagnesium bromide (1 M in THF) (1.2 mmol) was added at -78 ºC and under argon atmosphere. The reaction mixture was allowed to warm up to room temperature for 16 h and quenched by addition of a saturated aqueous solution of NH_4Cl (30 mL). The aqueous phase was extracted with AcOEt (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded the corresponding homoallylic alcohols **F-H**.

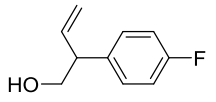
*2-Phenylbut-3-en-1-ol (**F**)*[26]



Prepared from phenyloxirane (2.0 mL, 17.5 mmol), $[CuCl(COD)]_2$ (0.36 g, 0.88 mmol) and vinylmagnesium bromide (1 M in THF) (21.1 mL, 21.1 mmol) in dry THF (25 mL). After work-up and purification by flash column chromatography, homoallylic alcohol **F** was obtained as an oil (1.4 g, 56%): ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.29 (bs, 1H, OH), 3.55 (q, *J* = 7.2 Hz, 1H, C$\underline{H}$CH=CH_2), 3.74-3.87 (m, 2H, OCH_2), 5.11-5.32 (m, 2H, CH=C$\underline{H}_2$), 6.05 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H, C$\underline{H}$=CH_2), 7.23-7.42 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ (ppm) = 52.5 (C$\underline{H}$CH=CH_2), 66.0 (OCH_2), 116.9 (CH=C$\underline{H}_2$), 126.9 (C_4), 128.1 (C_2, C_6), 128.7 (C_3, C_5), 138.5 (C$\underline{H}$=CH_2), 140.9 (C_1).

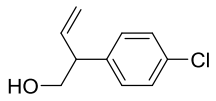
[26] Lu, J.-T.; Shi, Z.-F.; Cao, X.-P. *J. Org. Chem.* **2017**, *82*, 7774.

*2-(4-Fluorophenyl)but-3-en-1-ol (**G**)*[27]



Prepared from 2-(4-fluorophenyl)oxirane (1.0 mL, 8.3 mmol), $[CuCl(COD)]_2$ (0.18 g, 0.42 mmol) and vinylmagnesium bromide (1 M in THF) (10.1 mL, 10.1 mmol) in dry THF (11.8 mL). After work-up and purification by flash column chromatography, homoallylic alcohol **G** was obtained as an oil (0.65 g, 46%): ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.62 (t, *J* = 6.3 Hz, 1H, OH), 3.51 (q, *J* = 7.3 Hz, 1H, C<u>H</u>CH=CH_2), 3.79 (t, *J* = 6.3 Hz, 2H, OCH_2), 5.07-5.30 (m, 2H, CH=C<u>H_2</u>), 5.97 (ddd, *J* = 17.2, 10.4, 7.5 Hz, 1H, C<u>H</u>=CH_2), 6.97-7.07 (m, 2H, C_3, C_5), 7.14-7.24 (m, 2H, C_2, C_6); ^{13}C NMR ($CDCl_3$): δ (ppm) = 51.6 (<u>C</u>HCH=CH_2), 66.0 (OCH_2), 115.5 (d, *J* = 21.1 Hz, C_3, C_5), 117.2 (CH=<u>C</u>H_2), 129.4 (d, *J* = 7.9 Hz, C_2, C_6), 136.4 (d, *J* = 3.2 Hz, C_1), 138.1 (<u>C</u>H=CH_2), 161.8 (d, *J* = 245.1 Hz, C_4).

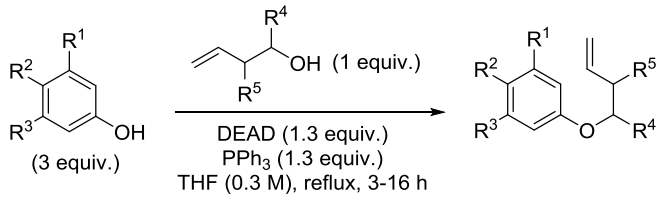
*2-(4-Chlorophenyl)but-3-en-1-ol (**H**)*[28]



Prepared from 2-(4-Chlorophenyl)oxirane (1.0 mL, 8.4 mmol), $[CuCl(COD)]_2$ (0.17 g, 0.41 mmol) and vinylmagnesium bromide (1 M in THF) (9.9 mL, 9.9 mmol) in dry THF (11.8 mL). After work-up and purification by flash column chromatography, homoallylic alcohol **H** was obtained as an oil (0.91 g, 60%): ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.24 (bs, 1H, OH), 3.47 (q, *J* = 7.1 Hz, 1H, C<u>H</u>CH=CH_2), 3.74 (d, *J* = 6.7 Hz, 2H, OCH_2), 5.02-5.28 (m, 2H, CH=C<u>H_2</u>), 5.95 (ddd, *J* = 17.5, 10.4, 7.5 Hz, 1H, C<u>H</u>=CH_2), 7.15 (d, *J* = 8.3 Hz, 2H, C_3, C_5), 7.29 (d, *J* = 8.3 Hz, 2H, C_2, C_6); ^{13}C NMR ($CDCl_3$): δ (ppm) = 51.7 (<u>C</u>HCH=CH_2), 65.8 (OCH_2), 117.3 (CH=<u>C</u>H_2), 128.8 (C_3, C_5), 129.4 (C_2, C_6), 132.6 (C_4), 137.9 (<u>C</u>H=CH_2), 139.4 (C_1).

[27] Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 595.
[28] Ent, H.; De Koning, H.; Speckamp, W.N. *J. Org. Chem.* **1986**, *51*, 1687.

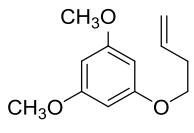
2.7. General procedure for the Mitsunobu reaction for the synthesis of aryl homoallyl ethers 1aa-1db.



1aa, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = H$, $R^5 = H$
1ab, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = CH_3$, $R^5 = H$
1ac, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = Pr$, $R^5 = H$
1ad, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = Ph$, $R^5 = H$
1ae, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = 3(OBn)C_6H_4$, $R^5 = H$
1af, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = 3$-furyl, $R^5 = H$
1ba, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = H$, $R^5 = H$
1bb, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = CH_3$, $R^5 = H$
1bc, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = Pr$, $R^5 = H$
1bd, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = Ph$, $R^5 = H$
1be, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = 3(OBn)C_6H_4$, $R^5 = H$
1bf, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = 3$-furyl, $R^5 = H$
1bg, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = {}^i Bu$, $R^5 = H$
1bh, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = 4(CH_3)C_6H_4$, $R^5 = H$
1bi, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = 4(CF_3)C_6H_4$, $R^5 = H$
1bj, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = 2$-naphthyl, $R^5 = H$
1cb, $R^1 = H$, $R^2 = R^3 = OCH_3$, $R^4 = CH_3$, $R^5 = H$
1cd, $R^1 = H$, $R^2 = R^3 = OCH_3$, $R^4 = Ph$, $R^5 = H$
1db, $R^1 = H$, $R^2 = R^3 = OCH_2O$, $R^4 = CH_3$, $R^5 = H$
1ak, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = H$, $R^5 = CH_3$
1al, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = H$, $R^5 = Ph$
1am, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = H$, $R^5 = 4(F)C_6H_4$
1an, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = H$, $R^5 = 4(Cl)C_6H_4$

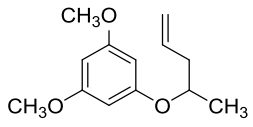
Over a solution of the corresponding homoallylic alcohol (1 mmol) in dry THF (3.3 mL) the corresponding phenol (3 mmol), PPh_3 (1.3 mmol) and DEAD (40 % wt solution in toluene) (1.3 mmol) were added under argon atmosphere. The resulting solution was heated at reflux for 3-16 h. The reaction mixture was allowed to cool down to room temperature and it was concentrated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum ether/AcOEt) afforded the corresponding aryl alkenyl ethers **1aa-1db.**

*1-(But-3-en-1-yloxy)-3,5-dimethoxybenzene (**1aa**)*[29]



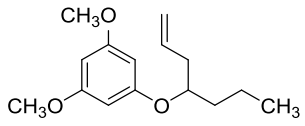
Prepared from 3-buten-1-ol (0.17 mL, 2.0 mmol), 3,5-dimethoxyphenol (0.92 g, 6.0 mmol), PPh_3 (0.68 g, 2.6 mmol) and DEAD (1.1 g, 2.6 mmol) in dry THF (6.6 mL). The reaction mixture was heated at reflux for 4 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **1aa** was obtained as an oil (0.35 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.53 (q, *J* = 6.7 Hz, 2H, $C\underline{H_2}CH=CH_2$), 3.77 (s, 6H, 2 x OCH_3), 3.98 (t, *J* = 6.7 Hz, 2H, OCH_2), 5.07-5.22 (m, 2H, $CH=C\underline{H_2}$), 5.90 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, $C\underline{H}=CH_2$), 6.09 (s, 3H, H_2, H_4, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 33.6 ($\underline{C}H_2CH=CH_2$), 55.3 (2 x OCH_3), 67.2 (OCH_2), 93.0 (C_4), 93.4 (C_2, C_6), 117.0 ($CH=\underline{C}H_2$), 134.4 ($\underline{C}H=CH_2$), 160.8 (C_1), 161.5 (C_3, C_5).

*1,3-Dimethoxy-5-(pent-4-en-2-yloxy)benzene (**1ab**)*[30]



Prepared from 4-penten-2-ol (0.14 mL, 1.4 mmol), 3,5-dimethoxyphenol (0.64 g, 4.1 mmol), PPh_3 (0.47 g, 1.8 mmol) and DEAD (0.78 g, 1.8 mmol) in dry THF (4.6 mL). The reaction mixture was heated at reflux for 3 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **1ab** was obtained as an oil (0.22 g, 73%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.32 (d, *J* = 6.1 Hz, 3H, CH_3), 2.26-2.59 (m, 2H, $C\underline{H_2}CH=CH_2$), 3.77 (s, 6H, 2 × OCH_3), 4.16-4.34 (m, 1H, OCH), 5.02-5.21 (m, 2H, $CH=C\underline{H_2}$), 5.86 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, $C\underline{H}=CH_2$), 6.06-6.14 (m, 3H, H_2, H_4, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (CH_3), 40.5 ($\underline{C}H_2CH=CH_2$), 55.3 (2 × OCH_3), 73.2 (OCH), 92.9 (C_4), 94.7 (C_2, C_6), 117.5 ($CH=\underline{C}H_2$), 134.2 ($\underline{C}H=CH_2$), 159.8 (C_1), 161.5 (C_3, C_5).

*1-(Hept-1-en-4-yloxy)-3,5-dimethoxybenzene (**1ac**)*

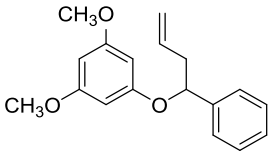


Prepared from 1-hepten-4-ol (0.10 g, 0.90 mmol), 3,5-dimethoxyphenol (0.42 g, 2.7 mmol), PPh_3 (0.30 g, 1.2 mmol) and DEAD (0.51 g, 1.2 mmol) in dry THF (3.0 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **1ac** was obtained as an oil (0.14 g, 63%): IR (ATR): ν (cm^{-1}) = 2841, 2934, 2959 3006, 3081 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.95 (t, *J* = 7.3 Hz, 3H, CH_3), 1.30-1.76 (m, 4H, CH_2CH_2), 2.35-2.52 (m, 2H, $C\underline{H_2}CH=CH_2$), 3.77 (s, 6H, 2 × OCH_3), 4.18-4.33 (m, 1H, OCH), 5.04-5.19 (m, 2H, $CH=C\underline{H_2}$),

[29] Youn, S.W.; Eom, J.I. *Org. Lett*. **2005**, *7*, 3355.
[30] Li, S.; Li, F.; Gong, J.; Yang, Z. *Org. Lett.* **2015**, *17*, 1240.

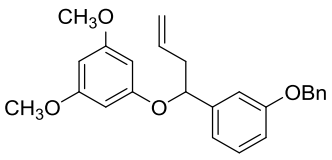
5.87 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, C<u>H</u>=CH$_2$), 6.07-6.12 (m, 3H, H$_2$, H$_4$, H$_6$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 14.1 (CH$_3$), 18.7 (<u>C</u>H$_2$CH$_3$), 35.9 (<u>C</u>H$_2$CH$_2$CH$_3$), 38.2 (<u>C</u>H$_2$CH=CH$_2$), 55.3 (2 × OCH$_3$), 77.0 (OCH), 92.8 (C$_4$), 94.7 (C$_2$, C$_6$), 117.4 (CH=<u>C</u>H$_2$), 134.2 (<u>C</u>H=CH$_2$), 160.3 (C$_1$), 161.5 (C$_3$, C$_5$); MS (ESI): *m/z* (%): 251.2 (MH$^+$, 100), 155.1 (30); HRMS (ESI): *m/z* calcd. for C$_{15}$H$_{23}$O$_3$: 251.1647 [MH$^+$]; found: 251.1650.

*1,3-Dimethoxy-5-((1-phenylbut-3-en-1-yl)oxy)benzene (**1ad**)*[30]



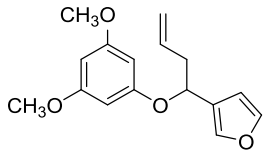
Prepared from 4-phenyl-1-buten-4-ol (0.25 mL, 1.7 mmol), 3,5-dimethoxyphenol (0.79 g, 5.1 mmol), PPh$_3$ (0.58 g, 2.2 mmol) and DEAD (0.96 g, 2.2 mmol) in dry THF (5.7 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **1ad** was obtained as an oil (0.23 g, 47%): ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 2.52-2.87 (m, 2H, C<u>H$_2$</u>CH=CH$_2$), 3.71 (s, 6H, 2 × OCH$_3$), 5.04-5.21 (m, 3H, OCH, CH=C<u>H$_2$</u>), 5.88 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, C<u>H</u>=CH$_2$), 6.05 (t, *J* = 2.0, 1H, H$_4$), 6.08 (d, *J* = 2.0 Hz, 2H, H$_2$, H$_6$), 7.23-7.42 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 42.8 (<u>C</u>H$_2$CH=CH$_2$), 55.2 (2 × OCH$_3$), 79.9 (OCH), 93.1 (C$_4$), 94.9 (C$_2$, C$_6$), 117.6 (CH=<u>C</u>H$_2$), 126.0 (C$_{2'}$, C$_{6'}$), 127.6 (C$_{4'}$), 128.6 (C$_{3'}$, C$_{5'}$), 134.1 (<u>C</u>H=CH$_2$), 141.4 (C$_{1'}$), 160.0 (C$_1$), 161.3 (C$_3$, C$_5$).

*5-((1-(3-(Benzyloxy)phenyl)but-3-en-1-yl)oxy)-1,3-dimethoxybenzene (**1ae**)*



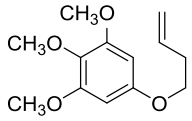
Prepared from 1-(3-(benzyloxy)phenyl)but-3-en-1-ol **A** (0.17 g, 0.68 mmol), 3,5-dimethoxyphenol (0.31 g, 2.0 mmol), PPh$_3$ (0.23 g, 0.88 mmol) and DEAD (0.39 g, 0.88 mmol) in dry THF (2.3 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1ae** was obtained as an oil (0.13 g, 50%): IR (ATR): ν (cm^{-1}) = 2841, 2901, 2934, 3009, 3031, 3074 (C-H); ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 2.55-2.85 (m, 2H, C<u>H$_2$</u>CH=CH$_2$), 3.73 (s, 6H, 2 × OCH$_3$), 5.02-5.25 (m, 5H, OC<u>H$_2$</u>Ph, CH=C<u>H$_2$</u>, OCH), 5.90 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H, C<u>H</u>=CH$_2$), 6.07-6.10 (m, 1H, H$_4$), 6.12 (d, *J* = 2.1 Hz, 2H, H$_2$, H$_6$), 6.82-7.08 (m, 3H, H$_{2'}$, H$_{4'}$, H$_{6'}$), 7.20-7.51 (m, 6H, H$_{5'}$, Ph); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 42.8 (<u>C</u>H$_2$CH=CH$_2$), 55.3 (2 × OCH$_3$), 70.0 (O<u>C</u>H$_2$Ph), 79.8 (OCH), 93.2 (C$_4$), 94.9 (C$_2$, C$_6$), 112.6 (C$_{2'}$), 113.9 (C$_{4'}$), 117.6 (CH=<u>C</u>H$_2$), 118.7 (C$_{6'}$), 127.6 (C$_{2''}$, C$_{6''}$), 128.0 (C$_{4''}$), 128.6 (C$_{3''}$, C$_{5''}$), 129.7 (C$_{5'}$), 134.1 (<u>C</u>H=CH$_2$), 137.0 (C$_{1''}$), 143.2 (C$_{1'}$), 159.1 (C$_{3'}$), 160.0 (C$_1$), 161.4 (C$_3$, C$_5$); MS (ESI): *m/z* (%): 391.2 (MH$^+$, 76), 156.1 (5), 155.1 (100); HRMS (ESI): *m/z* calcd. for C$_{25}$H$_{27}$O$_4$: 391.1909 [MH$^+$]; found: 391.1907.

*3-(1-(3,5-Dimethoxyphenoxy)but-3-en-1-yl)furan (**1af**)*



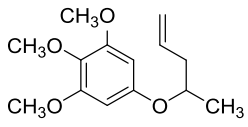
Prepared from 1-(furan-3-yl)but-3-en-1-ol **B** (0.21 g, 1.5 mmol), 3,5-dimethoxyphenol (0.70 g, 4.5 mmol), PPh_3 (0.51 g, 2.0 mmol) and DEAD (0.85 g, 2.0 mmol) in dry THF (5.0 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1af** was obtained as an oil (0.12 g, 29%): IR (ATR): ν (cm^{-1}) = 2841, 2901, 2941, 2999, 3074 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.52-2.83 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.77 (s, 6H, 2 × OCH_3), 5.04-5.23 (m, 3H, CH=C$\underline{H_2}$, OCH), 5.85 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, C$\underline{H}$=CH_2), 6.06-6.10 (m, 1H, H_4), 6.12 (d, *J* = 1.9 Hz, 2H, H_2, H_6), 6.41 (s, 1H, $H_{4'}$), 7.38 (s, 1H, $H_{2'}$), 7.40 (s, 1H, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 40.9 (C$\underline{H_2}$CH=CH_2), 55.3 (2 × OCH_3), 72.9 (OCH), 93.3 (C_4), 94.9 (C_2, C_6), 108.9 ($C_{4'}$), 117.8 (CH=C$\underline{H_2}$), 125.6 ($C_{3'}$), 133.7 (C$\underline{H}$=CH_2), 139.7 ($C_{2'}$), 143.3 ($C_{5'}$), 159.9 (C_1), 161.4 (C_3, C_5); MS (ESI): *m/z* (%): 275.1 (MH^+, 100), 233.1 (9), 155.1 (31); HRMS (ESI): *m/z* calcd. for $C_{16}H_{19}O_4$: 275.1283 [MH^+]; found: 275.1289.

*5-(But-3-en-1-yloxy)-1,2,3-trimethoxybenzene (**1ba**)*[30]



Prepared from 3-buten-1-ol (0.22 mL, 2.5 mmol), 3,4,5-trimethoxyphenol (1.4 g, 7.6 mmol), PPh_3 (0.86 g, 3.3 mmol) and DEAD (1.4 g, 3.3 mmol) in dry THF (8.4 mL). The reaction mixture was heated at reflux for 5.5 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1ba** was obtained as an oil (0.47 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.49 (q, *J* = 6.7 Hz, 2H, C$\underline{H_2}$CH=CH_2), 3.75 (s, 3H, OCH_3), 3.79 (s, 6H, 2 × OCH_3), 3.94 (t, *J* = 6.7 Hz, 2H, OCH_2), 5.02-5.21 (m, 2H, CH=C$\underline{H_2}$), 5.87 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, C$\underline{H}$=CH_2), 6.12 (s, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 33.7 (C$\underline{H_2}$CH=CH_2), 56.0 (2 × OCH_3), 60.9 (OCH_3), 67.5 (OCH_2), 92.3 (C_2, C_6), 117.0 (CH=C$\underline{H_2}$), 132.3 (C_4), 134.4 (C$\underline{H}$=CH_2), 153.7 (C_3, C_5), 155.5 (C_1).

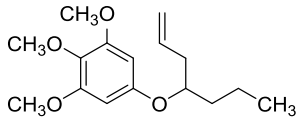
*1,2,3-Trimethoxy-5-(pent-4-en-2-yloxy)benzene (**1bb**)*



Prepared from 4-penten-2-ol (0.12 mL, 1.2 mmol), 3,4,5-trimethoxyphenol (0.66 g, 3.6 mmol), PPh_3 (0.41 g, 1.6 mmol) and DEAD (0.68 g, 1.6 mmol) in dry THF (4.0 mL). The reaction mixture was heated at reflux for 6 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1bb** was obtained as an oil (0.24 g, 78%): IR (ATR): ν (cm^{-1}) = 2844, 2977, 3077 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.29 (d, *J* = 6.1 Hz, 3H, CH_3), 2.26-2.55 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.77 (s, 3H, OCH_3), 3.81 (s, 6H, 2

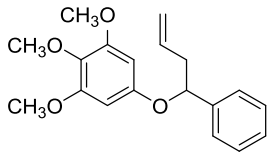
× OCH_3), 4.27-4.39 (m, 1H, OCH), 5.05-5.18 (m, 2H, CH=C$\underline{H_2}$), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, C$\underline{H}$=CH_2), 6.14 (s, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.5 (CH_3), 40.6 (C$\underline{H_2}$CH=CH_2), 56.0 (2 × OCH_3), 61.0 (OCH_3), 73.9 (OCH), 93.9 (C_2, C_6), 117.5 (CH=C$\underline{H_2}$), 132.4 (C_4), 134.2 (C$\underline{H}$=CH_2), 153.7 (C_3, C_5), 154.4 (C_1); MS (EI): *m/z* (%): 252.1 (M^+, 36), 184.1 (43), 169.0 (100), 141.0 (27); HRMS (ESI): *m/z* calcd. for $C_{14}H_{21}O_4$: 253.1440 [MH^+]; found: 253.1449.

*5-(Hept-1-en-4-yloxy)-1,2,3-trimethoxybenzene (**1bc**)*



Prepared from 1-hepten-4-ol (0.10 g, 0.90 mmol), 3,4,5-trimethoxyphenol (0.49 g, 2.7 mmol), PPh_3 (0.30 g, 1.2 mmol) and DEAD (0.51 g, 1.2 mmol) in dry THF (3.0 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1bc** was obtained as an oil (0.16 g, 63%): IR (ATR): ν (cm^{-1}) = 2841, 2872, 2937, 2962, 3074 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.93 (t, *J* = 7.2 Hz, 3H, CH_3), 1.30-1.76 (m, 4H, CH_2CH_2), 2.28-2.50 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.77 (s, 3H, OCH_3), 3.81 (s, 6H, 2 × OCH_3), 4.13-4.28 (m, 1H, OCH), 5.02-5.19 (m, 2H, CH=C$\underline{H_2}$), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, C$\underline{H}$=CH_2), 6.14 (s, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.1 (CH_3), 18.7 (C$\underline{H_2}$$CH_3$), 36.0 (C$\underline{H_2}$$CH_2CH_3$), 38.3 (C$\underline{H_2}$CH=$CH_2$), 56.0 (2 × OCH_3), 61.0 (OCH_3), 77.7 (OCH), 93.9 (C_2, C_6), 117.4 (CH=C$\underline{H_2}$), 132.3 (C_4), 134.2 (C$\underline{H}$=CH_2), 153.7 (C_3, C_5), 154.9 (C_1); MS (EI): *m/z* (%): 280.2 (M^+, 28), 184.0 (62), 169.0 (100), 141.0 (18), 69.0 (15); HRMS (ESI): *m/z* calcd. for $C_{16}H_{25}O_4$: 281.1753 [MH^+]; found: 281.1753.

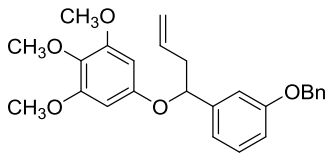
*1,2,3-Trimethoxy-5-((1-phenylbut-3-en-1-yl)oxy)benzene (**1bd**)*



Prepared from 4-phenyl-1-buten-4-ol (0.39 mL, 2.6 mmol), 3,4,5-trimethoxyphenol (1.4 g, 7.9 mmol), PPh_3 (0.89 g, 3.4 mmol) and DEAD (1.5 g, 3.4 mmol) in dry THF (8.7 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1bd** was obtained as an oil (0.37 g, 41%): IR (ATR): ν (cm^{-1}) = 2841, 2901, 2937, 2959, 2987, 3070 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.50-2.88 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.72 (s, 6H, 2 × OCH_3), 3.74 (s, 3H, OCH_3), 5.02-5.21 (m, 3H, OCH, CH=C$\underline{H_2}$), 5.76-5.96 (m, 1H, C$\underline{H}$=CH_2), 6.11 (s, 2H, H_2, H_6), 7.20-7.44 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 42.8 (C$\underline{H_2}$CH=CH_2), 55.9 (2 × OCH_3), 60.9 (OCH_3), 80.5 (OCH), 93.9 (C_2, C_6), 117.6 (CH=C$\underline{H_2}$), 126.0 ($C_{2'}$, $C_{6'}$), 127.7 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 132.3 (C_4), 134.1 (C$\underline{H}$=CH_2), 141.5 ($C_{1'}$), 153.5 (C_3, C_5), 154.7 (C_1); MS (EI): *m/z* (%): 314.1 (M^+, 13), 184.1 (100), 169.0 (85), 131.1

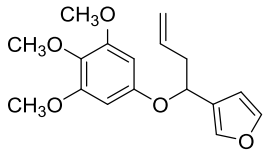
(33), 129.1 (35), 115.0 (27), 91.1 (38); HRMS (ESI): *m/z* calcd. for $C_{19}H_{23}O_4$: 315.1596 [MH^+]; found: 315.1602.

*5-((1-(3-(Benzyloxy)phenyl)but-3-en-1-yl)oxy)-1,2,3-trimethoxybenzene (**1be**)*



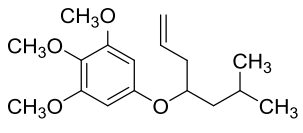
Prepared from 1-(3-(benzyloxy)phenyl)but-3-en-1-ol **A** (0.21 g, 0.83 mmol), 3,4,5-trimethoxyphenol (0.46 g, 2.5 mmol), PPh_3 (0.28 g, 1.1 mmol) and DEAD (0.47 g, 1.1 mmol) in dry THF (2.8 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1be** was obtained as an oil (0.16 g, 45%): IR (ATR): ν (cm^{-1}) = 2841, 2934, 2970, 3002, 3077 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.50-2.85 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.73 (s, 6H, 2 × OCH_3), 3.77 (s, 3H, OCH_3), 5.00-5.23 (m, 5H, OC$\underline{H_2}$Ph, CH=C$\underline{H_2}$, OCH), 5.88 (ddt, *J* = 17.2, 10.3, 6.9 Hz, 1H, C$\underline{H}$=CH_2), 6.12 (s, 2H, H_2, H_6), 6.82-7.08 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$), 7.20-7.51 (m, 6H, $H_{5'}$, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 42.7 (C$\underline{H_2}$CH=CH_2), 55.9 (2 × OCH_3), 61.0 (OCH_3), 70.0 (OC$\underline{H_2}$Ph), 80.4 (OCH), 93.8 (C_2, C_6), 112.6 ($C_{2'}$), 114.0 ($C_{4'}$), 117.6 (CH=C$\underline{H_2}$), 118.7 ($C_{6'}$), 127.6 ($C_{2''}$, $C_{6''}$), 128.0 ($C_{4''}$), 128.6 ($C_{3''}$,$C_{5''}$), 129.7 ($C_{5'}$), 132.3 (C_4), 134.1 (C$\underline{H}$=CH_2), 136.9 ($C_{1''}$), 143.3 ($C_{1'}$), 153.5 (C_3, C_5), 154.7 (C_1), 159.1 ($C_{3'}$); MS (EI): *m/z* (%): 420.2 (M^+, 2), 184.1 (49), 169.0 (26), 91.1 (100); HRMS (ESI): *m/z* calcd. for $C_{26}H_{29}O_5$: 421.2015 [MH^+]; found: 421.2014.

*3-(1-(3,4,5-Trimethoxyphenoxy)but-3-en-1-yl)furan (**1bf**)*



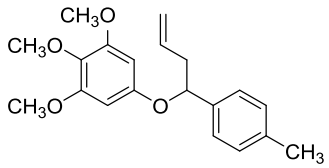
Prepared from 1-(furan-3-yl)but-3-en-1-ol **B** (0.38 g, 2.7 mmol), 3,4,5-trimethoxyphenol (1.5 g, 8.2 mmol), PPh_3 (0.93 g, 3.6 mmol) and DEAD (1.5 g, 3.6 mmol) in dry THF (9.1 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1bf** was obtained as an oil (0.22 g, 27%): IR (ATR): ν (cm^{-1}) = 2841, 2934, 2987, 3009, 3074 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.50-2.83 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.76 (s, 3H, OCH_3), 3.77 (s, 6H, 2 × OCH_3), 5.04-5.21 (m, 3H, CH=C$\underline{H_2}$, OCH), 5.73-5.95 (m, 1H, C$\underline{H}$=CH_2), 6.15 (s, 2H, H_2, H_6), 6.41 (s, 1H, $H_{4'}$), 7.38 (s, 2H, $H_{2'}$, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 41.0 (C$\underline{H_2}$CH=CH_2), 56.0 (2 × OCH_3), 60.9 (OCH_3), 73.5 (OCH), 94.1 (C_2, C_6), 108.7 ($C_{4'}$), 117.9 (CH=C$\underline{H_2}$), 125.8 ($C_{3'}$), 132.6 (C_4), 133.7 (C$\underline{H}$=CH_2), 139.7 ($C_{2'}$), 143.4 ($C_{5'}$), 153.5 (C_3, C_5), 154.5 (C_1); MS (EI): *m/z* (%): 304.1 (M^+, 7), 263.1 (17), 184.1 (100), 169.0 (85), 91.1 (56); HRMS (ESI): *m/z* calcd. for $C_{17}H_{21}O_5$: 305.1389 [MH^+]; found: 305.1398.

*1,2,3-Trimethoxy-5-((6-methylhept-1-en-4-yl)oxy)benzene (**1bg**)*



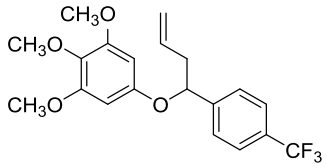
Prepared from 6-methylhept-1-en-4-ol **C** (0.12 g, 0.95 mmol), 3,4,5-trimethoxyphenol (0.52 g, 2.9 mmol), PPh_3 (0.32 g, 1.2 mmol) and DEAD (0.54 g, 1.2 mmol) in dry THF (3.2 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1bg** was obtained as an oil (0.10 g, 36%): IR (ATR): ν (cm^{-1}) = 2833, 2872, 2934, 2959, 3070 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.91 (d, *J* = 6.6 Hz, 3H, CH_3), 0.95 (d, *J* = 6.6 Hz, 3H, CH_3), 1.30-1.49 (m, 1H, C<u>H</u>$(CH_3)_2$), 1.55-1.90 (m, 2H, C<u>H$_2$</u>CH$(CH_3)_2$), 2.39 (t, *J* = 6.1 Hz, 2H, C<u>H$_2$</u>CH=CH_2), 3.78 (s, 3H, OCH_3), 3.82 (s, 6H, 2 × OCH_3), 4.15-4.32 (m, 1H, OCH), 5.04-5.18 (m, 2H, CH=C<u>H$_2$</u>), 5.85 (ddt, *J* = 17.4, 10.4, 7.1 Hz, 1H, C<u>H</u>=CH_2), 6.14 (s, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.5 (CH_3), 23.1 (CH_3), 24.6 (<u>C</u>H$(CH_3)_2$), 38.6 (<u>C</u>H_2CH=CH_2), 43.1 (<u>C</u>H_2CH$(CH_3)_2$), 56.0 (2 × OCH_3), 61.0 (OCH_3), 76.0 (OCH), 93.7 (C_2, C_6), 117.5 (CH=<u>C</u>H_2), 132.2 (C_4), 134.1 (<u>C</u>H=CH_2), 153.7 (C_3, C_5), 154.8 (C_1); MS (EI): *m/z* (%): 294.2 (M^+, 23), 184.1 (64), 169.0 (100); HRMS (ESI): *m/z* calcd. for $C_{17}H_{27}O_4$: 295.1909 [MH^+]; found: 295.1910.

*1,2,3-Trimethoxy-5-((1-(p-tolyl)but-3-en-1-yl)oxy)benzene (**1bh**)*



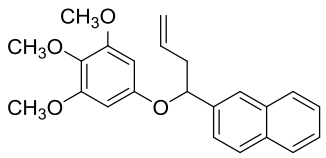
Prepared from 1-(4-methylphenyl)-3-buten-1-ol (0.30 mL, 1.8 mmol), 3,4,5-trimethoxyphenol (1.0 g, 5.4 mmol), PPh_3 (0.62 g, 2.3 mmol) and DEAD (1.0 g, 2.3 mmol) in dry THF (6.0 mL). The reaction mixture was stirred at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1bh** was obtained as an oil (0.23 g, 42%): IR (ATR): ν (cm^{-1}) = 2837, 2937, 3002, 3077 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.33 (s, 3H, CH_3), 2.51-2.83 (m, 2H, C<u>H$_2$</u>CH=CH_2), 3.73 (s, 9H, 3 × OCH_3), 5.01-5.17 (m, 3H, OCH, CH=C<u>H$_2$</u>), 5.86 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, C<u>H</u>=CH_2), 6.11 (s, 2H, H_2, H_6), 7.15 (d, *J* = 7.9 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.25 (d, *J* = 7.9 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.1 (CH_3), 42.8 (<u>C</u>H_2CH=CH_2), 55.9 (2 × OCH_3), 60.9 (OCH_3), 80.3 (OCH), 93.8 (C_2, C_6), 117.5 (CH=<u>C</u>H_2), 126.0 ($C_{2'}$, $C_{6'}$), 129.3 ($C_{3'}$, $C_{5'}$), 132.2 (C_4), 134.2 (<u>C</u>H=CH_2), 137.4 ($C_{4'}$), 138.5 ($C_{1'}$), 153.4 (C_3, C_5), 154.7 (C_1); MS (ESI): *m/z* (%): 329.2 (MH^+, 18), 186.1 (7), 185.1 (100). HRMS (ESI): *m/z* calcd. for $C_{20}H_{25}O_4$: 329.1753 [MH^+]; found: 329.1759.

*1,2,3-Trimethoxy-5-((1-(4-(trifluoromethyl)phenyl)but-3-en-1-yl)oxy)benzene (**1bi**)*



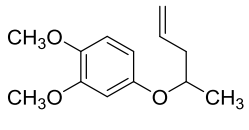
Prepared from 1-(4-(trifluoromethyl)phenyl)but-3-en-1-ol **D** (0.40 g, 1.9 mmol), 3,4,5-trimethoxyphenol (1.0 g, 5.6 mmol), PPh_3 (0.64 g, 2.4 mmol) and DEAD (1.1 g, 2.4 mmol) in dry THF (6.2 mL). The reaction mixture was stirred at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1bi** was obtained as an oil (0.49 g, 68%): IR (ATR): ν (cm^{-1}) = 2833, 2941, 3002, 3077 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.50-2.85 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.73 (s, 6H, 2 × OCH_3), 3.74 (s, 3H, OCH_3), 5.04-5.18 (m, 3H, OCH, CH=C$\underline{H_2}$), 5.83 (ddt, *J* = 16.7, 9.7, 7.0 Hz, 1H, C$\underline{H}$=CH_2), 6.07 (s, 2H, H_2, H_6), 7.48 (d, *J* = 8.1 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.61 (d, *J* = 8.1 Hz, 2H, $H_{3'}$, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 42.5 (C$\underline{H_2}$CH=CH_2), 56.0 (2 × OCH_3), 60.9 (OCH_3), 79.7 (OCH), 93.8 (C_2, C_6), 118.2 (CH=C$\underline{H_2}$), 124.3 (q, *J* = 271.3 Hz, CF_3), 125.6 (q, *J* = 3.7 Hz, $C_{3'}$, $C_{5'}$), 126.4 ($C_{2'}$, $C_{6'}$), 130.4 (q, *J* = 32.5 Hz, $C_{4'}$), 132.6 (C_4), 133.3 (C$\underline{H}$=CH_2), 145.5 ($C_{1'}$), 153.6 (C_3, C_5), 154.2 (C_1); MS (ESI): *m/z* (%): 383.1 (MH^+, 100), 185.1 (21). HRMS (ESI): *m/z* calcd. for $C_{20}H_{22}F_3O_4$: 383.1470 [MH^+]; found: 383.1479.

*2-(1-(3,4,5-Trimethoxyphenoxy)but-3-en-1-yl)naphthalene (**1bj**)*



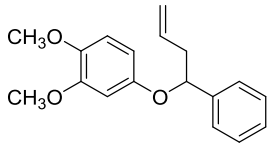
Prepared from 1-(naphthalen-2-yl)but-3-en-1-ol **E** (0.21 g, 1.1 mmol), 3,4,5-trimethoxyphenol (0.60 g, 3.2 mmol), PPh_3 (0.37 g, 1.4 mmol) and DEAD (0.61 g, 1.4 mmol) in dry THF (3.6 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1bj** was obtained as an oil (0.12 g, 31%): IR (ATR): ν (cm^{-1}) = 2851, 2930, 2959, 2999, 3060, 3077 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.62-2.95 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.73 (s, 6H, 2 × OCH_3), 3.75 (s, 3H, OCH_3), 5.04-5.37 (m, 3H, OCH, CH=C$\underline{H_2}$), 5.92 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, C$\underline{H}$=CH_2), 6.19 (s, 2H, H_2, H_6), 7.43-7.60 (m, 3H, $H_{3'}$, $H_{6'}$, $H_{7'}$), 7.79-7.90 (m, 4H, $H_{1'}$, $H_{4'}$, $H_{5'}$, $H_{8'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 42.7 (C$\underline{H_2}$CH=CH_2), 56.0 (2 × OCH_3), 60.9 (OCH_3), 80.7 (OCH), 94.0 (C_2, C_6), 117.8 (CH=C$\underline{H_2}$), 123.9 ($C_{6'}$), 125.1 ($C_{1'}$), 126.0 ($C_{7'}$), 126.3 ($C_{8'}$), 127.8 ($C_{5'}$), 127.9 ($C_{3'}$), 128.6 ($C_{4'}$), 132.4 ($C_{2'}$), 133.1, 133.3 (C_4, $C_{8a'}$), 134.0 (C$\underline{H}$=CH_2), 139.0 ($C_{4a'}$), 153.5 (C_3, C_5), 154.7 (C_1); MS (ESI): *m/z* (%): 365.2 (MH^+, 15), 185.1 (100). HRMS (ESI): *m/z* calcd. for $C_{23}H_{25}O_4$: 365.1753 [MH^+]; found: 365.1754.

*1,2-Dimethoxy-4-(pent-4-en-2-yloxy)benzene (**1cb**)*



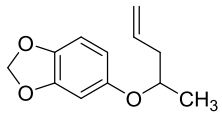
Prepared from 4-penten-2-ol (0.28 mL, 3.3 mmol), 3,4-dimethoxyphenol (1.5 g, 9.8 mmol), PPh_3 (1.1 g, 4.2 mmol) and DEAD (1.8 g, 4.2 mmol) in dry THF (10.9 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1cb** was obtained as an oil (0.49 g, 67%): IR (ATR): ν (cm^{-1}) = 2833, 2908, 2930, 2977, 3002, 3070 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.26 (d, *J* = 6.1 Hz, 3H, CH_3), 2.21-2.55 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.29 (h, *J* = 6.1 Hz, 1H, OCH), 5.00-5.18 (m, 2H, CH=C$\underline{H_2}$), 5.84 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H, C$\underline{H}$=CH_2), 6.39 (dd, *J* = 8.7, 2.5 Hz, 1H, H_6), 6.49 (d, *J* = 2.5 Hz, 1H, H_2), 6.74 (d, *J* = 8.7, 1H, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.5 (CH_3), 40.6 ($\underline{C}H_2CH=CH_2$), 55.8 (OCH_3), 56.4 (OCH_3), 74.1 (OCH), 102.5 (C_2), 106.0 (C_6), 111.9 (C_5), 117.4 (CH=$\underline{C}H_2$), 134.3 ($\underline{C}H=CH_2$), 143.5 (C_4), 149.9 (C_3), 152.3 (C_1); MS (EI): *m/z* (%): 222.1 (M^+, 41), 154.1 (100), 139.0 (88), 111.0 (23); HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}O_3$: 223.1334 [MH^+]; found: 223.1334.

*1,2-Dimethoxy-4-((1-phenylbut-3-en-1-yl)oxy)benzene (**1cd**)*



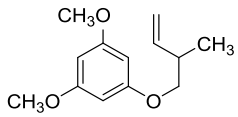
Prepared from 4-phenyl-1-buten-4-ol (0.64 mL, 4.3 mmol), 3,4-dimethoxyphenol (2.0 g, 13.0 mmol), PPh_3 (1.5 g, 5.6 mmol) and DEAD (2.6 g, 5.6 mmol) in dry THF (14.4 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **1cd** was obtained as an oil (0.38 g, 31%): IR (ATR): ν (cm^{-1}) = 2830, 2937, 3006, 3031, 3077 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.52-2.90 (m, 2H, C$\underline{H_2}$CH=CH_2), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.00-5.23 (m, 3H, CH=C$\underline{H_2}$, OCH), 5.88 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, C$\underline{H}$=CH_2), 6.30 (dd, *J* = 8.8, 2.8 Hz, 1H, H_6), 6.54 (d, *J* = 2.8 Hz, 1H, H_2), 6.65 (d, *J* = 8.8, 1H, H_5), 7.20-7.42 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 42.8 ($\underline{C}H_2CH=CH_2$), 55.7 (OCH_3), 56.3 (OCH_3), 80.6 (OCH), 102.1 (C_2), 106.1 (C_6), 111.7 (C_5), 117.9 (CH=$\underline{C}H_2$), 126.1 ($C_{2'}$,$C_{6'}$), 127.6 ($C_{4'}$), 128.5 ($C_{3'}$,$C_{5'}$), 134.3 ($\underline{C}H=CH_2$), 141.6 ($C_{1'}$), 143.5 (C_4), 149.7 (C_3), 152.6 (C_1); MS (EI): *m/z* (%): 284.1 (M^+, 6), 154.1 (100), 139.0 (36), 131.1 (24), 129.1 (23), 91.1 (29); HRMS (ESI): *m/z* calcd. for $C_{18}H_{20}O_3Na$: 307.1310 [MNa^+]; found: 307.1315.

*5-(Pent-4-en-2-yloxy)benzo[d][1,3]dioxole (**1db**)*



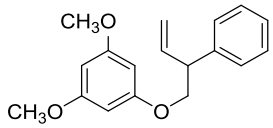
Prepared from 4-penten-2-ol (0.17 mL, 2.0 mmol), sesamol (0.83 g, 6.0 mmol), PPh_3 (0.69 g, 2.6 mmol) and DEAD (1.1 g, 2.6 mmol) in dry THF (6.7 mL). The reaction mixture was heated at reflux for 8 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **1db** was obtained as an oil (0.36 g, 86%): IR (ATR): ν (cm^{-1}) = 2833, 2908, 2930, 2977, 3002, 3070 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.28 (d, *J* = 6.1 Hz, 3H, CH_3), 2.24-2.55 (m, 2H, C$\underline{H_2}$CH=CH_2), 4.26 (h, *J* = 6.1 Hz, 1H, OCH), 5.05-5.21 (m, 2H, CH=C$\underline{H_2}$), 5.91 (s, 2H, OCH_2O), 5.75-5.99 (m, 1H, C$\underline{H}$=CH_2), 6.35 (dd, *J* = 8.4, 2.5 Hz, 1H, H_6), 6.51 (d, *J* = 2.5 Hz, 1H, H_2), 6.70 (d, *J* = 8.4, 1H, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (CH_3), 40.6 ($\underline{C}H_2CH=CH_2$), 74.9 (OCH), 99.8 (C_2), 101.1 (OCH_2O), 108.0 (C_6), 108.3 (C_5), 117.4 (CH=$\underline{C}H_2$), 134.3 ($\underline{C}H=CH_2$), 141.8 (C_4), 148.2 (C_3), 153.3 (C_1); MS (EI): *m/z* (%): 206.1 (M^+, 24), 138.0 (100), 137.0 (54); HRMS (ESI): *m/z* calcd. for $C_{12}H_{15}O_3$: 207.1021 [MH^+]; found: 207.1022.

*1,3-Dimethoxy-5-((2-methylbut-3-en-1-yl)oxy)benzene (**1ak**)*



Prepared from 2-methyl-3-buten-1-ol (0.23 mL, 2.6 mmol), 3,5-dimethoxyphenol (1.2 g, 7.9 mmol), PPh_3 (0.90 g, 3.4 mmol) and DEAD (1.5 g, 3.4 mmol) in dry THF (8.8 mL). The reaction mixture was heated at reflux for 3.5 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **1ak** was obtained as an oil (0.47 g, 79%): IR (ATR): ν (cm^{-1}) = 2841, 2872, 2912, 2926, 2959, 2987, 3005 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.15 (d, *J* = 6.8 Hz, 3H, CH_3), 2.59-2.80 (m, 1H, C$\underline{H}$CH=CH_2), 3.77 (s, 6H, 2 × OCH_3), 3.69-3.94 (m, 2H, OCH_2), 5.04-5.25 (m, 2H, CH=C$\underline{H_2}$), 5.88 (ddd, *J* = 17.3, 10.4, 6.8 Hz, 1H, C$\underline{H}$=CH_2), 6.10 (s, 3H, H_2, H_4, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.5 (CH_3), 37.3 ($\underline{C}$HCH=CH_2), 55.3 (2 × OCH_3), 72.4 (OCH_2), 93.0 (C_4), 93.5 (C_2, C_6), 114.7 (CH=$\underline{C}H_2$), 140.4 ($\underline{C}H=CH_2$), 161.0 (C_1), 161.5 (C_3, C_5); MS (EI): *m/z* (%): 222.1 (M^+, 10), 154.0 (100), 126.1 (37), 125.1 (43); HRMS (ESI): *m/z* calcd. for $C_{13}H_{19}O_3$: 223.1334 [MH^+]; found: 223.1328.

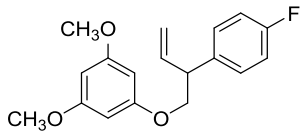
*1,3-Dimethoxy-5-((2-phenylbut-3-en-1-yl)oxy)benzene (**1al**)[30]*



Prepared from 2-phenylbut-3-en-1-ol **F** (0.35 g, 2.4 mmol), 3,5-dimethoxyphenol (1.1 g, 7.1 mmol), PPh_3 (0.81 g, 3.1 mmol) and DEAD (1.3 g, 3.1 mmol) in dry THF (7.9 mL). The reaction mixture was heated at reflux for 16 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **1al** was obtained as an oil (0.20 g,

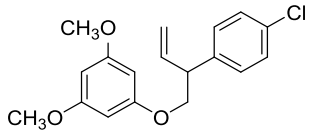
30%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.76 (s, 6H, 2 × OCH_3), 3.84 (q, *J* = 7.0 Hz, 1H, C<u>H</u>CH=CH_2), 4.11-4.23 (m, 2H, OCH_2), 5.11-5.28 (m, 2H, CH=C<u>H_2</u>), 6.01-6.21 (m, 4H, H_2, H_4, H_6, C<u>H</u>=CH_2), 7.20-7.42 (m. 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 49.0 (<u>C</u>HCH=CH_2), 55.3 (2 × OCH_3), 71.1 (OCH_2), 93.3 (C_4), 93.6 (C_2, C_6), 116.5 (CH=<u>C</u>H_2), 126.9 ($C_{4'}$), 128.1 ($C_{2'}$, $C_{6'}$), 128.6 ($C_{3'}$, $C_{5'}$), 138.3 (<u>C</u>H=CH_2), 140.8 ($C_{1'}$), 160.7 (C_1), 161.5 (C_3, C_5).

*1-((2-(4-Fluorophenyl)but-3-en-1-yl)oxy)-3,5-dimethoxybenzene (**1am**)*



Prepared from 2-(4-fluorophenyl)but-3-en-1-ol **G** (0.34, 2.0 mmol), 3,5-dimethoxyphenol (0.95 g, 6.1 mmol), PPh_3 (0.70 g, 2.7 mmol) and DEAD (1.2 g, 2.7 mmol) in dry THF (6.8 mL). The reaction mixture was heated at reflux for 5 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **1am** was obtained as an oil (0.18 g, 30%): IR (ATR): ν (cm^{-1}) = 2841, 2926, 2959, 3006, 3081 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.77 (s, 6H, 2 × OCH_3), 3.84 (q, *J* = 6.9 Hz, 1H, C<u>H</u>CH=CH_2), 4.11-4.23 (m, 2H, OCH_2), 5.09-5.32 (m, 2H, CH=C<u>H_2</u>), 6.01-6.21 (m, 4H, H_2, H_4, H_6, C<u>H</u>=CH_2), 7.05 (t, *J* = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.27 (dd, *J* = 8.7, 5.4 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 48.2 (<u>C</u>HCH=CH_2), 55.3 (2 × OCH_3), 71.0 (OCH_2), 93.3 (C_4), 93.6 (C_2, C_6), 115.4 (d, *J* = 21.2 Hz, $C_{3'}$, $C_{5'}$), 116.7 (CH=<u>C</u>H_2), 129.6 (d, *J* = 7.9 Hz, $C_{2'}$, $C_{6'}$), 136.4 (d, *J* = 3.2 Hz, $C_{1'}$), 138.0 (<u>C</u>H=CH_2), 160.6 (C_1), 161.5 (C_3, C_5), 161.8 (d, *J* = 247.4 Hz, $C_{4'}$); MS (ESI): *m/z* (%): 303.1 (MH^+, 100), 155.1 (7). HRMS (ESI): *m/z* calcd. for $C_{18}H_{20}O_3F$: 303.1396 [MH^+]; found: 303.1395.

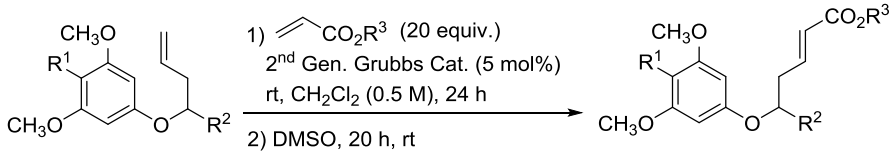
*1-((2-(4-Chlorophenyl)but-3-en-1-yl)oxy)-3,5-dimethoxybenzene (**1an**)*



Prepared from 2-(4-chlorophenyl)but-3-en-1-ol **H** (0.32, 1.8 mmol), 3,5-dimethoxyphenol (0.81 g, 5.3 mmol), PPh_3 (0.60 g, 2.3 mmol) and DEAD (0.99 g, 2.3 mmol) in dry THF (5.8 mL). The reaction mixture was heated at reflux for 5 h. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **1an** was obtained as an oil (0.13 g, 23%): IR (ATR): ν (cm^{-1}) = 2841, 2876, 2934, 2955, 3006, 3085 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.76 (s, 6H, 2 × OCH_3), 3.77-3.85 (m, 1H, C<u>H</u>CH=CH_2), 4.04-4.23 (m, 2H, OCH_2), 5.09-5.26 (m, 2H, CH=C<u>H_2</u>), 5.95-6.15 (m, 4H, H_2, H_4, H_6, C<u>H</u>=CH_2), 7.22 (d, *J* = 8.4 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.31 (d, *J* = 8.4 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 48.3 (<u>C</u>HCH=CH_2), 55.3 (2 × OCH_3), 70.8 (OCH_2), 93.3 (C_4), 93.6 (C_2, C_6), 116.9 (CH=<u>C</u>H_2), 128.7 ($C_{3'}$, $C_{5'}$), 129.5 ($C_{2'}$, $C_{6'}$), 132.6 ($C_{4'}$), 137.7 (<u>C</u>H=CH_2), 139.3 ($C_{1'}$), 160.5 (C_1), 161.5 (C_3, C_5); MS (ESI): *m/z* (%): 321.1 (MH^+ +

2, 28), 319.1 (MH^+, 100), 155.1 (4). HRMS (ESI): *m/z* calcd. for $C_{18}H_{20}O_3Cl$: 319.1101 [MH^+]; found: 319.1099.

2.8. General procedure for the metathesis reaction of ethers 1aa-1bb. Synthesis of esters 2aaa-2bba

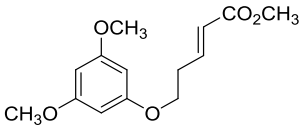


1aa, R^1 = H, R^2 = H
1ab, R^1 = H, R^2 = CH_3
1ad, R^1 = H, R^2 = Ph
1bb, R^1 = OCH_3, R^2 = CH_3

2aaa, R^1 = H, R^2 = H, R^3 = CH_3
2aba, R^1 = H, R^2 = CH_3, R^3 = CH_3
2ada, R^1 = H, R^2 = Ph, R^3 = CH_3
2aab, R^1 = H, R^2 = H, R^3 = Et
2aac, R^1 = H, R^2 = H, R^3 = ^{n}Bu
2aad, R^1 = H, R^2 = H, R^3 = ^{t}Bu
2abd, R^1 = H, R^2 = CH_3, R^3 = ^{t}Bu
2bba, R^1 = OCH_3, R^2 = CH_3, R^3 = CH_3

Over a solution of the corresponding aryl alkenyl ether **1aa-1bb** (1 mmol) and acrylate (20 mmol) in dry CH_2Cl_2 (2 mL), 2nd generation Grubbs catalyst (0.05 mmol) was added under argon atmosphere. The reaction mixture was stirred at room temperature for 24 h, after which DMSO (2.5 mmol) was added. The resulting mixture was further stirred for 20 h. The volatile compounds were evaporated *in vacuo* and the residue obtained was purified by flash column chromatography (silica gel, petroleum ether/AcOEt) to obtain the corresponding esters **2aaa-2bba**.

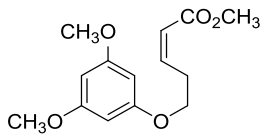
*Methyl (E)-5-(3,5-dimethoxyphenoxy)pent-2-enoate (**2aaa**)*



Prepared from 1-(but-3-en-1-yloxy)-3,5-dimethoxybenzene **1aa** (0.27 g, 1.3 mmol), methyl acrylate (2.3 mL, 25.4 mmol) and 2nd generation Grubbs catalyst (54.0 mg, 0.06 mmol) in dry CH_2Cl_2 (2.6 mL). The reaction mixture was stirred for 24 h, and afterwards, DMSO (0.23 mL, 3.2 mmol) was added. The resulting solution was further stirred for 20 h. After evaporation of the volatile compounds *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **2aaa** was obtained as a solid (0.29 g, 87%): mp (CH_2Cl_2) 47-49 ºC; IR (ATR): ν (cm^{-1}) = 1724 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.64-2.70 (m, 2H, $C\underline{H_2}CH$=CH),

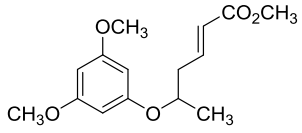
3.74 (s, 3H, CO_2CH_3), 3.76 (s, 6H, 2 × OCH_3), 4.03 (t, *J* = 5.8 Hz , 2H, OCH_2), 5.95 (d, *J* = 15.7 Hz, 1H, CH=C<u>H</u>CO_2CH_3), 6.07 (s, 3H, H_2, H_4, H_6), 7.03 (dt, *J* = 15.7, 6.9 Hz, 1H, C<u>H</u>=CHCO_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 32.0 (<u>C</u>H_2CH=CH), 51.5 (CO_2<u>C</u>H_3), 55.3 (2 × OCH_3), 65.9 (O<u>C</u>H_2), 93.2 (C_4), 93.4 (C_2, C_6), 123.0 (CH=<u>C</u>HCO_2CH_3), 144.5 (<u>C</u>H=CHCO_2CH_3), 160.4 (C_1), 161.5 (C_3, C_5), 166.7 (<u>C</u>O_2CH_3); MS (EI): *m/z* (%): 266.1 (M^+, 38), 154.1 (96), 126.1 (50), 113.1 (100); HRMS (ESI): *m/z* calcd. for $C_{14}H_{19}O_5$: 267.1233 [MH^+]; found: 267.1232.

*Methyl (Z)-5-(3,5-dimethoxyphenoxy)pent-2-enoate [**(Z)-2aaa**]*



Obtained as a side-product in the reaction of 1-(but-3-en-1-yloxy)-3,5-dimethoxybenzene **1aa** (0.27 g, 1.3 mmol), methyl acrylate (2.3 mL, 25.4 mmol) and 2nd generation Grubbs catalyst (54.0 mg, 0.06 mmol) in dry CH_2Cl_2 (2.6 mL). After evaporation of the volatile compounds *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), ***(Z)*-2aaa** was obtained as a solid (19 mg, 6%): mp (CH_2Cl_2) 62-64 ºC; IR (ATR): ν (cm^{-1}) = 1720; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.07-3.19 (m, 2H, C<u>H</u>$_2$CH=CH), 3.72 (s, 3H, CO_2CH_3), 3.76 (s, 6H, 2 × OCH_3), 4.04 (t, *J* = 5.8 Hz , 2H, OCH_2), 5.91 (d, *J* = 11.5 Hz, 1H, CH=C<u>H</u>CO_2CH_3), 6.09 (s, 3H, H_2, H_4, H_6), 6.40 (dt, *J* = 11.5, 7.3 Hz, 1H, C<u>H</u>=CHCO_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 29.1 (<u>C</u>H_2CH=CH), 51.1 (CO_2<u>C</u>H_3), 55.3 (2 × OCH_3), 66.8 (OCH_2), 93.2 (C_4), 93.4 (C_2, C_6), 121.2 (CH=<u>C</u>HCO_2CH_3), 146.1 (<u>C</u>H=CHCO_2CH_3), 160.7 (C_1), 161.5 (C_3, C_5), 166.6 (<u>C</u>O_2CH_3); MS (EI): *m/z* (%): 266.2 (M^+, 24), 154.1 (84), 113.1 (100), 81.1 (34); HRMS (ESI): *m/z* calcd. for $C_{14}H_{19}O_5$: 267.1233 [MH^+]; found: 267.1232.

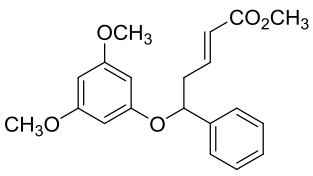
*Methyl (E)-5-(3,5-dimethoxyphenoxy)hex-2-enoate (**2aba**)*



Prepared from 1,3-dimethoxy-5-(pent-4-en-2-yloxy)benzene **1ab** (1.9 g, 8.4 mmol), methyl acrylate (15.1 mL, 0.17 mol) and 2nd generation Grubbs catalyst (0.36 g, 0.42 mmol) in dry CH_2Cl_2 (16.7 mL). The reaction mixture was stirred for 24 h, and afterwards, DMSO (1.5 mL, 20.9 mmol) was added. The resulting solution was further stirred for 20 h. After evaporation of the volatile compounds *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **2aba** was obtained as an oil (1.3 g, 55%): IR (ATR): ν (cm^{-1}) = 1720 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.32 (d, *J* = 6.1 Hz, 3H, CH_3), 2.42-2.69 (m, 2H, C<u>H</u>$_2$CH=CH), 3.72 (s, 3H, CO_2C<u>H</u>$_3$), 3.75 (s, 6H, 2 × OCH_3), 4.45 (h, *J* = 6.0 Hz , 1H, OCH), 5.91 (dt, *J* = 15.7, 1.4 Hz, 1H, CH=C<u>H</u>CO_2CH_3), 6.05-6.09 (m, 3H, H_2, H_4, H_6), 6.99 (dt, *J* = 15.7, 7.3 Hz, 1H, C<u>H</u>=CHCO_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.6 (CH_3), 38.8 (<u>C</u>H_2CH=CH),

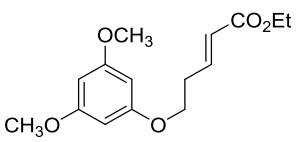
51.5 ($CO_2\underline{C}H_3$), 55.3 (2 × OCH_3), 72.2 ($O\underline{C}H$), 93.2 (C_4), 93.7 (C_2, C_6), 123.5 ($CH=\underline{C}HCO_2CH_3$), 144.5 ($\underline{C}H=CHCO_2CH_3$), 159.3 ($C_1$), 161.6 ($C_3$, C_5), 166.7 ($\underline{C}O_2CH_3$); MS (EI): *m/z* (%): 280.1 (M^+, 20), 207.1 (28), 181.1 (29), 154.0 (100), 127.1 (72), 125.1 (74), 95.1 (32); HRMS (ESI): *m/z* calcd. for $C_{15}H_{21}O_5$: 281.1389 [MH^+]; found: 281.1399.

*Methyl (E)-5-(3,5-dimethoxyphenoxy)-5-phenylpent-2-enoate (**2ada**)*



Prepared from 1,3-dimethoxy-5-((1-phenylbut-3-en-1-yl)oxy)benzene **1ad** (0.30 g, 1.1 mmol), methyl acrylate (1.9 mL, 21.2 mol) and 2nd generation Grubbs catalyst (45.0 mg, 0.053 mmol) in dry CH_2Cl_2 (2.1 mL). The reaction mixture was stirred for 24 h, and afterwards, DMSO (0.19 mL, 2.6 mmol) was added. The resulting solution was further stirred for 20 h. After evaporation of the volatile compounds *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **2ada** was obtained as a solid (0.27 g, 75%): mp (CH_2Cl_2) 67-69 ºC; IR (ATR): ν (cm^{-1}) = 1713 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.62-2.95 (m, 2H, $C\underline{H}_2CH=CH$), 3.69 (s, 6H, 2 × OCH_3), 3.72 (s, 3H, CO_2CH_3), 5.20 (dd, *J* = 7.6, 5.0 Hz , 1H, OCH), 5.90 (d, *J* = 15.7 Hz, 1H, $CH=C\underline{H}CO_2CH_3$), 6.03 (s, 3H, H_2, H_4, H_6), 7.01 (dt, *J* = 15.7, 7.6 Hz, 1H, $C\underline{H}=CHCO_2CH_3$), 7.20-7.39 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 41.1 ($\underline{C}H_2CH=CH$), 51.5 ($CO_2\underline{C}H_3$), 55.5 (2 × OCH_3), 78.6 ($O\underline{C}H$), 93.3 (C_4), 94.9 (C_2, C_6), 123.6 ($CH=\underline{C}HCO_2CH_3$), 125.8 ($C_{2'}$, $C_{6'}$), 127.9 ($C_{4'}$), 128.8 ($C_{3'}$, $C_{5'}$), 140.6 ($C_{1'}$), 144.3 ($\underline{C}H=CHCO_2CH_3$), 159.6 ($C_1$), 161.3 ($C_3$, C_5), 166.6 ($\underline{C}O_2CH_3$); MS (ESI): *m/z* (%): 343.2 (MH^+, 60), 155.1 (100); HRMS (ESI): *m/z* calcd. for $C_{20}H_{23}O_5$: 343.1546 [MH^+]; found: 343.1557.

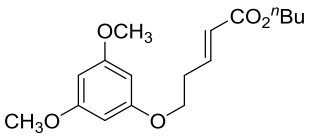
*Ethyl (E)-5-(3,5-dimethoxyphenoxy)pent-2-enoate (**2aab**)*



Prepared from 1-(but-3-en-1-yloxy)-3,5-dimethoxybenzene **1aa** (0.30 g, 1.5 mmol), ethyl acrylate (3.2 mL, 29.1 mmol) and 2nd generation Grubbs catalyst (61.7 mg, 0.07 mmol) in dry CH_2Cl_2 (2.9 mL). The reaction mixture was stirred for 24 h, and afterwards, DMSO (0.26 mL, 3.6 mmol) was added. The resulting solution was further stirred for 20 h. After evaporation of the volatile compounds *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **2aab** was obtained as an oil (0.23 g, 57%): IR (ATR): ν (cm^{-1}) = 1716 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.29 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.64-2.70 (m, 2H, $C\underline{H}_2CH=CH$), 3.76 (s, 6H, 2 × OCH_3), 4.03 (t, *J* = 5.8 Hz , 2H, $OC\underline{H}_2CH_2$), 4.20 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.95 (dq, *J* = 15.7, 1.5 Hz, 1H, $CH=C\underline{H}CO_2Et$), 6.05-6.10 (m, 3H, H_2, H_4, H_6), 7.02

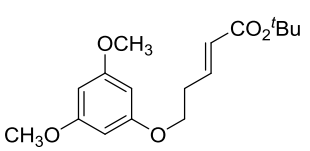
(dt, *J* = 15.7, 6.9 Hz, 1H, C<u>H</u>=CHCO$_2$Et); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 14.3 (CH$_3$), 31.9 (<u>C</u>H$_2$CH=CH), 55.3 (2 × OCH$_3$), 60.3 (O<u>C</u>H$_2$CH$_3$), 65.9 (O<u>C</u>H$_2$CH$_2$), 93.2 (C$_4$), 93.4 (C$_2$, C$_6$), 123.5 (CH=<u>C</u>HCO$_2$Et), 144.5 (<u>C</u>H=CHCO$_2$Et), 160.5 (C$_1$), 161.5 (C$_3$, C$_5$), 166.3 (<u>C</u>O$_2$Et); MS (ESI): *m/z* (%): 281.1 (MH$^+$, 100), 127.1 (35); HRMS (ESI): *m/z* calcd. for C$_{15}$H$_{21}$O$_5$: 281.1389 [MH$^+$]; found: 281.1390.

*n-Butyl (E)-5-(3,5-dimethoxyphenoxy)pent-2-enoate (**2aac**)*



Prepared from 1-(but-3-en-1-yloxy)-3,5-dimethoxybenzene **1aa** (0.49 g, 2.4 mmol), *n*-butyl acrylate (6.8 mL, 47.1 mmol) and 2nd generation Grubbs catalyst (99.9 mg, 0.12 mmol) in dry CH$_2$Cl$_2$ (4.7 mL). The reaction mixture was stirred for 24 h, and afterwards, DMSO (0.42 mL, 5.9 mmol) was added. The resulting solution was further stirred for 20 h. After evaporation of the volatile compounds *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **2aac** was obtained as an oil (0.59 g, 82%): IR (ATR): ν (cm^{-1}) = 1716 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 0.93 (t, *J* = 7.3 Hz, 3H, CH$_3$), 1.28-1.47 (m, 2H, C<u>H$_2$</u>CH$_3$), 1.54-1.70 (m, 2H, CO$_2$CH$_2$C<u>H$_2$</u>), 2.59-2.71 (m, 2H, C<u>H$_2$</u>CH=CH), 3.75 (s, 6H, 2 × OCH$_3$), 4.02 (t, *J* = 6.4 Hz, 2H, CO$_2$CH$_2$), 4.13 (t, *J* = 6.7 Hz , 2H, OCH$_2$), 5.94 (dt, *J* = 15.7, 1.5 Hz, 1H, CH=C<u>H</u>CO$_2^n$Bu), 6.04-6.10 (m, 3H, H$_2$, H$_4$, H$_6$), 7.01 (dt, *J* = 15.7, 6.8 Hz, 1H, C<u>H</u>=CHCO$_2^n$Bu); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 13.7 (CH$_3$), 19.2 (<u>C</u>H$_2$CH$_3$), 30.7 (CO$_2$CH$_2$<u>C</u>H$_2$), 31.9 (<u>C</u>H$_2$CH=CH), 55.3 (2 × OCH$_3$), 64.2 (CO$_2$<u>C</u>H$_2$), 65.9 (O<u>C</u>H$_2$CH$_2$), 93.2 (C$_4$), 93.4 (C$_2$, C$_6$), 123.4 (CH=<u>C</u>HCO$_2^n$Bu), 144.5 (<u>C</u>H=CHCO$_2^n$Bu), 160.5 (C$_1$), 161.5 (C$_3$, C$_5$), 166.4 (<u>C</u>O$_2^n$Bu); MS (ESI): *m/z* (%): 309.2 (MH$^+$, 100), 155.1 (23); HRMS (ESI): *m/z* calcd. for C$_{17}$H$_{25}$O$_5$: 309.1702 [MH$^+$]; found: 309.1703.

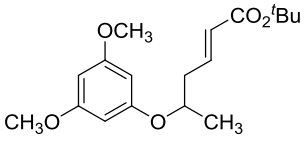
*tert-Butyl (E)-5-(3,5-dimethoxyphenoxy)pent-2-enoate (**2aad**)*



Prepared from 1-(but-3-en-1-yloxy)-3,5-dimethoxybenzene **1aa** (0.41 g, 2.0 mmol), *tert*-butyl acrylate (5.8 mL, 39.3 mmol) and 2nd generation Grubbs catalyst (83.4 mg, 0.098 mmol) in dry CH$_2$Cl$_2$ (4.0 mL). The reaction mixture was stirred for 24 h, and afterwards, DMSO (0.35 mL, 4.9 mmol) was added. The resulting solution was further stirred for 20 h. After evaporation of the volatile compounds *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **2aad** was obtained as an oil (0.44 g, 73%): IR (ATR): ν (cm^{-1}) = 1710 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 1.47 (s, 9H, 3 × CH$_3$), 2.52-2.68 (m, 2H, C<u>H$_2$</u>CH=CH), 3.74 (s, 6H, 2 × OCH$_3$), 4.00 (t, *J* = 6.4 Hz , 2H, OCH$_2$), 5.86 (dt, *J* = 15.7, 1.4 Hz,

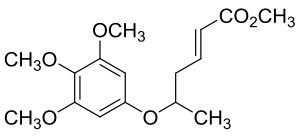
1H, CH=C<u>H</u>$CO_2{}^t$Bu), 6.04-6.09 (m, 3H, H_2, H_4, H_6), 6.90 (dt, *J* = 15.7, 6.8 Hz, 1H, C<u>H</u>=CH$CO_2{}^t$Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.1 (3 × CH_3), 31.8 (<u>C</u>H_2CH=CH), 55.3 (2 × OCH_3), 66.0 (O<u>C</u>H_2), 80.2 (<u>C</u>$(CH_3)_3$), 93.2 (C_4), 93.4 (C_2, C_6), 125.1 (CH=<u>C</u>H$CO_2{}^t$Bu), 143.2 (<u>C</u>H=CH$CO_2{}^t$Bu), 160.5 (C_1), 161.5 (C_3, C_5), 165.6 (<u>C</u>$O_2{}^t$Bu); MS (ESI): *m/z* (%): 309.2 (MH^+, 15), 253.1 (100); HRMS (ESI): *m/z* calcd. for $C_{17}H_{25}O_5$: 309.1702 [MH^+]; found: 309.1697.

*tert-Butyl (E)-5-(3,5-dimethoxyphenoxy)hex-2-enoate (**2abd**)*



Prepared from 1,3-dimethoxy-5-(pent-4-en-2-yloxy)benzene **1ab** (0.27 g, 1.2 mmol), *tert*-butyl acrylate (3.5 mL, 23.8 mmol) and 2nd generation Grubbs catalyst (50.6 mg, 0.060 mmol) in dry CH_2Cl_2 (2.4 mL). The reaction mixture was stirred for 24 h, and afterwards, DMSO (0.21 mL, 2.9 mmol) was added. The resulting solution was further stirred for 20 h. After evaporation of the volatile compounds *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **2abd** was obtained as an oil (0.33 g, 87%): IR (ATR): ν (cm^{-1}) = 1713 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.34 (d, *J* = 6.1 Hz, 3H, CH_3), 1.50 (s, 9H, 3 × CH_3), 2.40-2.67 (m, 2H, C<u>H</u>$_2$CH=CH), 3.78 (s, 6H, 2 × OCH_3), 4.37-4.53 (m, 1H, OCH), 5.74-5.92 (m, 1H, CH=C<u>H</u>$CO_2{}^t$Bu), 6.09 (s, 3H, H_2, H_4, H_6), 6.79-6.98 (m, 1H, C<u>H</u>=CH$CO_2{}^t$Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.6 (CH_3), 28.1 (3 × CH_3), 38.7 (<u>C</u>H_2CH=CH), 55.3 (2 × OCH_3), 72.3 (O<u>C</u>H), 80.3 (<u>C</u>$(CH_3)_3$), 93.2 (C_4), 94.7 (C_2, C_6), 125.7 (CH=<u>C</u>H$CO_2{}^t$Bu), 142.8 (<u>C</u>H=CH$CO_2{}^t$Bu), 159.4 (C_1), 161.5 (C_3, C_5), 165.6 (<u>C</u>$O_2{}^t$Bu); MS (ESI): *m/z* (%): 323.2 (MH^+, 19), 268.1 (13), 267.1 (100), 155.1 (10); HRMS (ESI): *m/z* calcd. for $C_{18}H_{27}O_5$: 323.1858 [MH^+]; found, 323.1859.

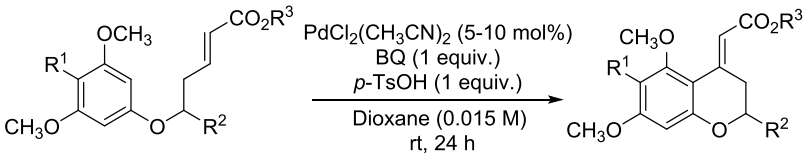
*Methyl (E)-5-(3,4,5-trimethoxyphenoxy)hex-2-enoate (**2bba**)*



Prepared from 1,2,3-trimethoxy-5-(pent-4-en-2-yloxy)benzene **1bb** (0.29 g, 1.1 mmol), methyl acrylate (2.1 mL, 23.0 mmol) and 2nd generation Grubbs catalyst (48.8 mg, 0.057 mmol) in dry CH_2Cl_2 (2.3 mL). The reaction mixture was stirred for 24 h, and afterwards, DMSO (0.20 mL, 2.9 mmol) was added. The resulting solution was further stirred for 20 h. After evaporation of the volatile compounds *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **2bba** was obtained as an oil (0.29 g, 83%): IR (ATR): ν (cm^{-1}) = 1720 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.22 (d, *J* = 6.0 Hz, 3H, CH_3), 2.33-2.59 (m, 2H, C<u>H</u>$_2$CH=CH), 3.62 (s, 3H, CO_2C<u>H</u>$_3$), 3.68 (s, 3H, OCH_3), 3.72 (s, 6H, 2 × OCH_3), 4.26-4.44 (m , 1H, OCH), 5.86 (dt, *J* = 15.7, 1.5 Hz, 1H, CH=C<u>H</u>CO_2CH_3), 6.06 (s, 2H, H_2, H_6), 6.91 (dt, *J* =

15.7, 7.3 Hz, 1H, C<u>H</u>=CHCO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 19.6 (CH$_3$), 38.8 (<u>C</u>H$_2$CH=CH), 51.3 (CO$_2$<u>C</u>H$_3$), 55.9 (2 × OCH$_3$), 60.8 (OCH$_3$), 72.8 (O<u>C</u>H), 94.0 (C$_2$, C$_6$), 123.4 (CH=<u>C</u>HCO$_2$CH$_3$), 132.5 (C$_4$), 144.5 (<u>C</u>H=CHCO$_2$CH$_3$), 153.6 (C$_3$, C$_5$), 153.9 (C$_1$), 166.5 (<u>C</u>O$_2$CH$_3$); MS (EI): *m/z* (%): 310.1 (M$^+$, 23), 184.0 (34), 169.0 (100), 127.1 (57), 69.0 (22); HRMS (ESI): *m/z* calcd. for C$_{16}$H$_{23}$O$_6$: 311.1495 [MH$^+$]; found: 311.1499.

2.9. General procedure for the Pd(II)-catalyzed cyclization of esters 2aaa-2bba. Synthesis of chromanes 3aaa-3bba

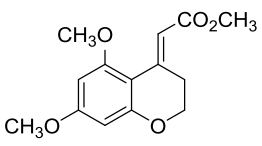


2aaa-2bba

3aaa, R^1 = H, R^2 = H, R^3 = CH$_3$
3aba, R^1 = H, R^2 = CH$_3$, R^3 = CH$_3$
3ada, R^1 = H, R^2 = Ph, R^3 = CH$_3$
3aab, R^1 = H, R^2 = H, R^3 = Et
3aac, R^1 = H, R^2 = H, R^3 = ^{n}Bu
3aad, R^1 = H, R^2 = H, R^3 = ^{t}Bu
3abd, R^1 = H, R^2 = CH$_3$, R^3 = ^{t}Bu
3bba, R^1 = OCH$_3$, R^2 = CH$_3$, R^3 = CH$_3$

A solution of the corresponding esters **2aaa-2bba** (1 mmol), *p*-TsOH (1 mmol), benzoquinone (1 mmol) and PdCl$_2$(CH$_3$CN)$_2$ (0.05 or 0.1 mmol) in dioxane (66.7 mL) was stirred at room temperature for 24 h. Then, the reaction was quenched by addition of water and the mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt) the corresponding chromanes **3aaa-3bba** were obtained.

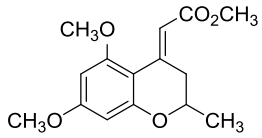
*Methyl (E)-2-(5,7-dimethoxychroman-4-ylidene)acetate (**3aaa**)*



Prepared from methyl (*E*)-5-(3,5-dimethoxyphenoxy)pent-2-enoate **2aaa** (43.8 mg, 0.16 mmol), *p*-TsOH (31.8 mg, 0.16 mmol), benzoquinone (18.2 mg, 0.16 mmol) and PdCl$_2$(CH$_3$CN)$_2$ (2.1 mg, 0.008 mmol) in dioxane (11.0 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **3aaa** was obtained as a solid (31.5 mg, 73%): mp (CH$_2$Cl$_2$) 96-98 ºC; IR

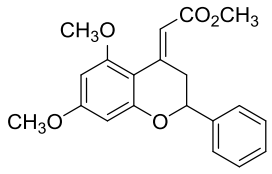
(ATR): ν (cm^{-1}) = 1706; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.36 (t , *J* = 6.0 Hz, 2H, 2 × H_3), 3.71 (s, 3H, CO_2CH_3), 3.77 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.16 (t, *J* = 6.0 Hz, 2H, 2 × H_2), 6.04 (d, *J* = 2.5 Hz, 1H, H_8), 6.07 (d, *J* = 2.5 Hz, 1H, H_6), 6.92 (s, 1H, C=C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 27.3 (C_3), 50.9 ($CO_2\underline{C}H_3$), 55.3 (OCH_3), 55.6 (OCH_3), 65.8 (C_2), 92.7 (C_6), 93.9 (C_8), 104.8 (C_{4a}), 112.4 (C=<u>C</u>H), 145.6 (<u>C</u>=CH), 159.4 (C_{8a}), 160.7 (C_7), 162.0 (C_5), 168.5 (CO); MS (EI): *m/z* (%): 264.2 (M^+, 75), 233.1 (100), 191.1 (80), 175.1 (20); HRMS (ESI): *m/z* calcd. for $C_{14}H_{17}O_5$: 265.1076 [MH^+]; found: 265.1073.

*Methyl (E)-2-(5,7-dimethoxy-2-methylchroman-4-ylidene)acetate (**3aba**)*



Prepared from methyl (*E*)-5-(3,5-dimethoxyphenoxy)hex-2-enoate **2aba** (89.6 mg, 0.32 mmol), *p*-TsOH (60.8 mg, 0.32 mmol), benzoquinone (34.6 mg, 0.32 mmol) and $PdCl_2(CH_3CN)_2$ (4.2 mg, 0.016 mmol) in dioxane (21.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **3aba** was obtained as a solid (71.1 mg, 80%): mp (CH_2Cl_2) 76-78 ºC; IR (ATR): ν (cm^{-1}) = 1695; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.40 (d, *J* = 6.2 Hz, 3H, CH_3), 2.52-2.69 (m, 1H, 1 × H_3), 3.71 (s, 3H, CO_2CH_3), 3.77 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.82-3.92 (m, 1H, 1 × H_3), 4.06-4.24 (m, 1H, H_2), 6.98-6.10 (m, 2H, H_6, H_8), 6.93 (s, 1H, C=C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 20.8 (CH_3), 33.9 (C_3), 50.9 ($CO_2\underline{C}H_3$), 55.3 (OCH_3), 55.6 (OCH_3), 72.1 (C_2), 92.6 (C_6), 93.9 (C_8), 104.4 (C_{4a}), 112.5 (C=<u>C</u>H), 145.9 (<u>C</u>=CH), 159.4 (C_{8a}), 160.6 (C_7), 162.1 (C_5), 168.4 (CO); MS (ESI): *m/z* (%): 279.1 (MH^+, 100), 247.1 (23); HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}O_5$: 279.1233 [MH^+]; found: 279.1236.

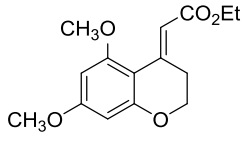
*Methyl (E)-2-(5,7-dimethoxy-2-phenylchroman-4-ylidene)acetate (**3ada**)*



Prepared from methyl (*E*)-5-(3,5-dimethoxyphenoxy)-5-phenylpent-2-enoate **2ada** (65.2 mg, 0.19 mmol), *p*-TsOH (36.2 mg, 0.19 mmol), benzoquinone (20.6 mg, 0.19 mmol) and $PdCl_2(CH_3CN)_2$ (2.5 mg, 0.01 mmol) in dioxane (12.7 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **3ada** was obtained as a solid (38.3 mg, 59%): mp (CH_2Cl_2) 142-144 ºC; IR (ATR): ν (cm^{-1}) = 1695; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.86-3.03 (m, 1H, 1 × H_3), 3.71 (s, 3H, CO_2CH_3), 3.79 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.10-4.25 (m, 1H, 1 × H_3), 5.00-5.14 (m, 1H, H_2), 6.13 (d, *J* = 2.1 Hz, 1H, H_8), 6.18 (d, *J* = 2.1 Hz, 1H, H_6), 6.99 (s, 1H, C=C<u>H</u>), 7.27-7.51 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 34.1 (C_3), 50.9 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.6 (OCH_3), 77.6 (C_2), 93.0 (C_6), 94.1 (C_8), 104.5 (C_{4a}), 112.9 (C=<u>C</u>H), 126.2 ($C_{2'}$, $C_{6'}$), 128.2 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 140.1 ($C_{1'}$), 145.5

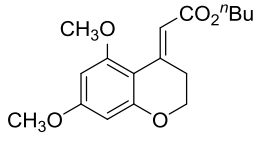
(C=CH), 159.5 (C_{8a}), 160.7 (C_7), 162.2 (C_5), 168.4 (CO); MS (ESI): *m/z* (%): 341.1 (MH^+, 100), 309.1 (13); HRMS (ESI): *m/z* calcd. for $C_{20}H_{21}O_5$: 341.1389 [MH^+]; found: 341.1388.

*Ethyl (E)-2-(5,7-dimethoxychroman-4-ylidene)acetate (**3aab**)*



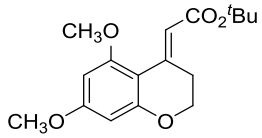
Prepared from ethyl (*E*)-5-(3,5-dimethoxyphenoxy)pent-2-enoate **2aab** (68.3, 0.24 mmol), *p*-TsOH (46.3 mg, 0.24 mmol), benzoquinone (26.3 mg, 0.24 mmol) and $PdCl_2(CH_3CN)_2$ (6.3 mg, 0.024 mmol) in dioxane (24.6 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **3aab** was obtained as a solid (51.7 mg, 77%): mp (CH_2Cl_2) 107-108 ºC; IR (ATR): ν (cm^{-1}) = 1739; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.30 (t, *J* = 7.1 Hz, 3H, CH_3), 3.37 (t, *J* = 5.8 Hz, 2H, 2 × H_3), 3.78 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.08-4.25 (m, 4H, CO_2CH_2, 2 × H_2), 6.05 (d, *J* = 2.3 Hz, 1H, H_8), 6.08 (d, *J* = 2.3 Hz, 1H, H_6), 6.91 (s, 1H, C=C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.4 (CH_3), 27.3 (C_3), 55.3 (OCH_3), 55.6 (OCH_3), 59.5 ($CO_2\underline{C}H_2$), 65.8 (C_2), 92.7 (C_6), 93.9 (C_8), 104.8 (C_{4a}), 112.9 (C=<u>C</u>H), 145.2 (<u>C</u>=CH), 159.3 (C_{8a}), 160.7 (C_7), 161.9 (C_5), 168.1 (CO); MS (ESI): *m/z* (%): 279.1 (MH^+, 100), 233.1 (3); HRMS (ESI) Calcd. for $C_{15}H_{19}O_5$: 279.1233 [MH^+]; found: 279.1240.

*n-Butyl (E)-2-(5,7-dimethoxychroman-4-ylidene)acetate (**3aac**)*



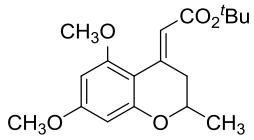
Prepared from *n*-butyl (*E*)-5-(3,5-dimethoxyphenoxy)pent-2-enoate **2aac** (0.11, 0.37 mmol), *p*-TsOH (70.1 mg, 0.37 mmol), benzoquinone (39.8 mg, 0.37 mmol) and $PdCl_2(CH_3CN)_2$ (9.6 mg, 0.037 mmol) in dioxane (24.6 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **3aac** was obtained as a solid (79.2 mg, 70%): mp (CH_2Cl_2) 81-82 ºC; IR (ATR): ν (cm^{-1}) = 1691; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.95 (t, *J* = 7.3 Hz, 3H, CH_3), 1.32-1.49 (m, 2H, $C\underline{H}_2CH_3$), 1.56-1.73 (m, 2H, $CO_2CH_2C\underline{H}_2$), 3.27-3.41 (m, 2H, 2 × H_3), 3.77 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.11 (t, *J* = 6.8 Hz, 2H, CO_2CH_2), 4.17 (t, *J* = 6.0 Hz, 2H, 2 × H_2), 6.04 (d, *J* = 2.4 Hz, 1H, H_8), 6.07 (d, *J* = 2.4 Hz, 1H, H_6), 6.90 (s, 1H, C=C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 13.8 (CH_3), 19.3 ($\underline{C}H_2CH_3$), 27.3 (C_3), 30.9 ($CO_2CH_2\underline{C}H_2$), 55.3 (OCH_3), 55.6 (OCH_3), 63.5 ($CO_2\underline{C}H_2$), 65.2 (C_2), 92.7 (C_6), 93.9 (C_8), 104.8 (C_{4a}), 113.0 (C=<u>C</u>H), 145.1 (<u>C</u>=CH), 159.3 (C_{8a}), 160.7 (C_7), 161.9 (C_5), 168.2 (CO); MS (ESI): *m/z* (%): 307.2 (MH^+, 100), 305.1 (3); HRMS (ESI): *m/z* calcd. for $C_{17}H_{23}O_5$: 307.1546 [MH^+]; found: 307.1546.

*tert-Butyl (E)-2-(5,7-dimethoxychroman-4-ylidene)acetate (**3aad**)*



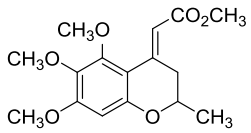
Prepared from *tert*-butyl (*E*)-5-(3,5-dimethoxyphenoxy)pent-2-enoate **2aad** (0.13 g, 0.42 mmol), *p*-TsOH (79.5 mg, 0.42 mmol), benzoquinone (45.2 mg, 0.42 mmol) and $PdCl_2(CH_3CN)_2$ (10.8 mg, 0.042 mmol) in dioxane (28.0 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **3aad** was obtained as an oil (75.8 mg, 59%): IR (ATR): ν (cm^{-1}) = 1695; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.52 (s, 9H, 3 × CH_3), 3.28-3.42 (m, 2H, 2 × H_3), 3.79 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.18 (t, *J* = 6.0 Hz, 2H, 2 × H_2), 6.05 (d, *J* = 2.3 Hz, 1H, H_8), 6.09 (d, *J* = 2.3 Hz, 1H, H_6), 6.84 (s, 1H, C=C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 27.2 (C_3), 28.4 (3 × CH_3), 55.3 (OCH_3), 55.6 (OCH_3), 65.2 (C_2), 79.5 (<u>C</u>(CH_3)$_3$), 92.6 (C_6), 93.9 (C_8), 104.9 (C_{4a}), 115.0 (C=<u>C</u>H), 143.8 (<u>C</u>=CH), 159.1 (C_{8a}), 160.6 (C_7), 161.7 (C_5), 167.7 (CO); MS (ESI): *m/z* (%): 307.2 (MH^+, 100), 251.1 (76); HRMS (ESI): *m/z* calcd. for $C_{17}H_{23}O_5$: 307.1546 [MH^+]; found: 307.1563.

*tert-Butyl (E)-2-(5,7-dimethoxy-2-methylchroman-4-ylidene)acetate (**3abd**)*



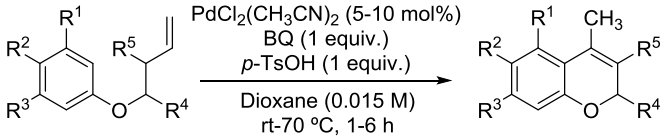
Prepared from *tert*-butyl (*E*)-5-(3,5-dimethoxyphenoxy)hex-2-enoate **2abd** (0.11 g, 0.33 mmol), *p*-TsOH (63.0 mg, 0.33 mmol), benzoquinone (35.8 mg, 0.33 mmol) and $PdCl_2(CH_3CN)_2$ (8.6 mg, 0.033 mmol) in dioxane (22.1 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **3abd** was obtained as a solid (74.1 mg, 69 %): mp (CH_2Cl_2) 83-84 ºC; IR (ATR): ν (cm^{-1}) = 1685; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.40 (d, *J* = 6.2 Hz, 3H, CH_3), 1.50 (s, 9H, 3 × CH_3), 2.55 (ddd, *J* = 15.8, 11.3, 1.8 Hz, 1H, 1 × H_3), 3.76 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.81-3.89 (m, 1H, 1 × H_3), 4.08-4.23 (m, 1H, H_2), 6.04 (d, *J* = 2.3 Hz, 1H, H_8), 6.06 (d, *J* = 2.3 Hz, 1H, H_6), 6.83 (s, 1H, C=C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 20.9 (CH_3), 28.4 (3 × CH_3), 33.8 (C_3), 55.3 (OCH_3), 55.6 (OCH_3), 72.1 (C_2), 79.4 (<u>C</u>(CH_3)$_3$), 92.6 (C_6), 93.8 (C_8), 104.5 (C_{4a}), 115.0 (C=<u>C</u>H), 144.2 (<u>C</u>=CH), 159.3 (C_{8a}), 160.5 (C_7), 161.7 (C_5), 167.8 (CO); MS (ESI): *m/z* (%): 321.2 (MH^+, 100), 284.1 (6); 265.1 (62). HRMS (ESI): *m/z* calcd. for $C_{18}H_{25}O_5$: 321.1702 [MH^+]; found: 321.1708.

*Methyl (E)-2-(5,6,7-trimethoxy-2-methylchroman-4-ylidene)acetate (**3bba**)*



Prepared from methyl (*E*)-5-(3,4,5-trimethoxyphenoxy)hex-2-enoate **2bba** (0.11 g, 0.38 mmol), *p*-TsOH (73.0 mg, 0.38 mmol), benzoquinone (41.5 mg, 0.38 mmol) and $PdCl_2(CH_3CN)_2$ (10.0 mg, 0.038 mmol) in dioxane (25.6 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **3bba** was obtained as a solid (67.4 mg, 60 %): mp (CH_2Cl_2) 90-92 ºC; IR (ATR): ν (cm^{-1}) = 1706; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.38 (d, *J* = 6.2 Hz, 3H, CH_3), 2.48-2.64 (m, 1H, 1 × H_3), 3.70 (s, 3H, CO_2CH_3), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.48-3.96 (m, 1H, 1 × H_3), 4.04-4.23 (m, 1H, H_2), 6.19 (s, 1H, H_8), 6.97 (s, 1H, C=C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.8 (CH_3), 33.7 (C_3), 50.9 ($CO_2\underline{C}H_3$), 55.8 (OCH_3), 60.2 (OCH_3), 61.0 (OCH_3), 72.2 (C_2), 96.6 (C_8), 107.7 (C_{4a}), 112.7 (C=<u>C</u>H), 136.9 (C_6), 145.8 (<u>C</u>=CH), 153.4 (C_{8a}), 154.1 (C_5), 155.5 (C_7), 168.4 (CO); MS (ESI): *m/z* (%): 309.1 (MH^+, 100), 277.1 (27); HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}O_6$: 309.1338 [MH^+]; found: 309.1347.

2.10. General procedure for the Pd(II)-catalyzed cyclization of ethers 1aa-1db. Synthesis of 2*H*-chromenes 4aa-4db

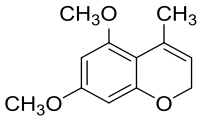


1aa-1db

4aa, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = H$, $R^5 = H$
4ab, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = CH_3$, $R^5 = H$
4ac, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = Pr$, $R^5 = H$
4ad, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = Ph$, $R^5 = H$
4ae, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = 3(OBn)C_6H_4$, $R^5 = H$
4af, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = 3$-furyl, $R^5 = H$
4ba, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = H$, $R^5 = H$
4bb, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = CH_3$, $R^5 = H$
4bc, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = Pr$, $R^5 = H$
4bd, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = Ph$, $R^5 = H$
4be, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = 3(OBn)C_6H_4$, $R^5 = H$
4bf, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = 3$-furyl, $R^5 = H$
4bg, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = {}^i$Bu, $R^5 = H$
4bh, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = 4(CH_3)C_6H_4$, $R^5 = H$
4bi, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = 4(CF_3)C_6H_4$, $R^5 = H$
4bj, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = 2$-naphthyl, $R^5 = H$
4cb, $R^1 = H$, $R^2 = R^3 = OCH_3$, $R^4 = CH_3$, $R^5 = H$
4cd, $R^1 = H$, $R^2 = R^3 = OCH_3$, $R^4 = Ph$, $R^5 = H$
4db, $R^1 = H$, $R^2 = R^3 = OCH_2O$, $R^4 = CH_3$, $R^5 = H$
4ak, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = H$, $R^5 = CH_3$
4al, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = H$, $R^5 = Ph$
4am, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = H$, $R^5 = 4(F)C_6H_4$
4an, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = H$, $R^5 = 4(Cl)C_6H_4$

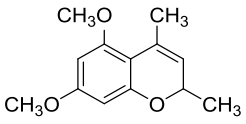
A solution of the corresponding ethers **1aa-1db** (1 mmol), *p*-TsOH (1 mmol), benzoquinone (1 mmol) and $PdCl_2(CH_3CN)_2$ (0.05 or 0.1 mmol) in dioxane (66.7 mL) was stirred at room temperature (or 70 ºC) for 1-6 h. Then, the reaction was quenched by addition of water and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), the corresponding 2*H*-chromenes **4aa-4db** were obtained.

*5,7-Dimethoxy-4-methyl-2H-chromene (**4aa**)*[29]



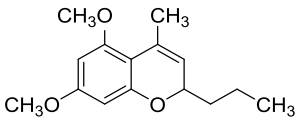
Prepared from 1-(but-3-en-1-yloxy)-3,5-dimethoxybenzene **1aa** (0.14 g, 0.66 mmol), *p*-TsOH (0.12 g, 0.66 mmol), benzoquinone (71.6 mg, 0.66 mmol) and $PdCl_2(CH_3CN)_2$ (8.7 mg, 0.033 mmol) in dioxane (44.6 mL) for 2 h at rt. After work-up and purification by flash column chromatography, **4aa** was obtained and as an oil (0.10 g, 74%) (mixture of regioisomers 93:7): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.15 (s, 3H, CH_3), 3.78 (s, 6H, 2 × OCH_3), 4.42-4.54 (m, 2H, 2 × H_2), 5.35-5.47 (m, 1H, H_3), 6.09 (d, *J* = 2.3 Hz, 1H, H_6), 6.12 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.8 (CH_3), 55.3 (OCH_3), 55.4 (OCH_3), 65.0 (C_2), 92.9 (C_6), 93.8 (C_8), 108.0 (C_{4a}), 115.2 (C_3), 131.7 (C_4), 157.2 (C_{8a}), 158.2 (C_7), 160.6 (C_5).

*5,7-Dimethoxy-2,4-dimethyl-2H-chromene (**4ab**)*



Prepared from 1,3-dimethoxy-5-(pent-4-en-2-yloxy)benzene **1ab** (0.15 g, 0.67 mmol), *p*-TsOH (0.13 g, 0.67 mmol), benzoquinone (72.3 mg, 0.67 mmol) and $PdCl_2(CH_3CN)_2$ (8.7 mg, 0.034 mmol) in dioxane (44.6 mL) for 2 h at rt. After work-up and purification by flash column chromatography, **4ab** was obtained as an oil (0.13 g, 86%) (mixture of regioisomers 83:17): IR (ATR): ν (cm^{-1}) = 2837, 2934, 2966, 2999, 3034 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.41 (d, *J* = 6.6 Hz, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.77 (s, 6H, 2 × OCH_3), 4.61-4.74 (m, 1H, H_2), 5.22-5.26 (m, 1H, H_3), 6.08 (d, *J* = 2.4 Hz, 1H, H_6), 6.12 (d, *J* = 2.4 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 20.4 (CH_3), 21.8 (CH_3), 55.2 (OCH_3), 55.3 (OCH_3), 71.1 (C_2), 92.8 (C_6), 94.0 (C_8), 107.5 (C_{4a}), 121.0 (C_3), 130.9 (C_4), 156.8 (C_{8a}), 158.2 (C_7), 161.5 (C_5); MS (ESI): *m/z* (%): 221.1 (MH^+, 100), 219.1 (10). HRMS (ESI): *m/z* calcd. for $C_{13}H_{17}O_3$: 221.1178 [MH^+]; found: 221.1178.

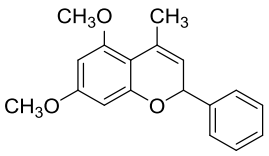
*5,7-Dimethoxy-4-methyl-2-propyl-2H-chromene (**4ac**)*



Prepared from 1-(hept-1-en-4-yloxy)-3,5-dimethoxybenzene **1ac** (73.8 mg, 0.29 mmol), *p*-TsOH (56.1 mg, 0.29 mmol), benzoquinone (31.9 mg, 0.29 mmol) and $PdCl_2(CH_3CN)_2$ (3.8 mg, 0.015 mmol) in dioxane (19.7 mL) for 2 h at rt. After work-up and purification by flash column chromatography, **4ac** was obtained as an oil (62.0 mg, 85%) (mixture of regioisomers 93:7): IR (ATR): ν (cm^{-1}) = 2841, 2872, 2937, 2959, 3006 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.98 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H_3}$), 1.40-1.90 (m, 4H, CH_2CH_2), 2.17 (s, 3H, CH_3), 3.79 (s, 6H, 2 × OCH_3), 4.51-4.60 (m, 1H, H_2), 5.30 (d, *J* = 1.6 Hz, 1H, H_3), 6.09 (d, *J* = 2.1 Hz, 1H, H_6), 6.14 (d, *J* = 2.1 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ

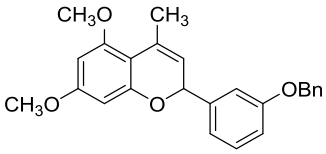
(ppm) = 14.0 ($CH_2\underline{C}H_3$), 18.3 ($\underline{C}H_2CH_3$), 21.9 (CH_3), 36.5 ($\underline{C}H_2CH_2CH_3$), 55.3 (OCH_3), 55.4 (OCH_3), 74.6 (C_2), 92.7 (C_6), 94.0 (C_8), 107.6 (C_{4a}), 120.0 (C_3), 130.8 (C_4), 156.7 (C_{8a}), 158.1 (C_7), 160.5 (C_5); MS (ESI): *m/z* (%): 249.1 (MH^+, 100), 247.1 (3); HRMS (ESI): *m/z* calcd. for $C_{15}H_{21}O_3$: 249.1491 [MH^+]; found: 249.1489.

*5,7-Dimethoxy-4-methyl-2-phenyl-2H-chromene (**4ad**)*



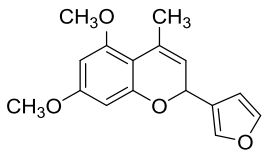
Prepared from 1,3-dimethoxy-5-((1-phenylbut-3-en-1-yl)oxy)benzene **1ad** (77.2 mg, 0.27 mmol), *p*-TsOH (51.6 mg, 0.27 mmol), benzoquinone (29.4 mg, 0.27 mmol) and $PdCl_2(CH_3CN)_2$ (3.5 mg, 0.014 mmol) in dioxane (18.0 mL) for 2h at rt. After work-up and purification by flash column chromatography, **4ad** was obtained as an oil (63.4 mg, 83%) (mixture of regioisomers 90:10): IR (ATR): ν (cm^{-1}) = 2837, 2930, 2973, 3009 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.25 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.41-5.46 (m, 1H, H_2), 5.60-5.64 (m, 1H, H_3), 6.11 (d, *J* = 2.4 Hz, 1H, H_6), 6.18 (d, *J* = 2.4 Hz, 1H, H_8), 7.24-7.54 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.0 (CH_3), 55.3 (OCH_3), 55.4 (OCH_3), 76.8 (C_2), 93.0 (C_6), 94.1 (C_8), 107.2 (C_{4a}), 119.1 (C_3), 127.1 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 131.4 (C_4), 140.9 ($C_{1'}$), 156.2 (C_{8a}), 158.3 (C_7), 160.8 (C_5); MS (ESI): *m/z* (%): 283.1 (MH^+, 100), 155.1 (3); HRMS (ESI): *m/z* calcd. for $C_{18}H_{19}O_3$: 283.1334 [MH^+]; found: 283.1337.

*2-(3-(Benzyloxy)phenyl)-5,7-dimethoxy-4-methyl-2H-chromene (**4ae**)*



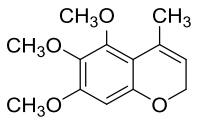
Prepared from 5-((1-(3-(benzyloxy)phenyl)but-3-en-1-yl)oxy)-1,3-dimethoxybenzene **1ae** (0.10 g, 0.26 mmol), *p*-TsOH (50.0 mg, 0.26 mmol), benzoquinone (28.4 mg, 0.26 mmol) and $PdCl_2(CH_3CN)_2$ (3.4 mg, 0.013 mmol) in dioxane (17.5 mL) for 2h at rt. After work-up and purification by flash column chromatography, **4ae** was obtained as an oil (88.3 mg, 87%) (mixture of regioisomers 90:10): IR (ATR): ν (cm^{-1}) = 2837, 2930, 2959, 2999, 3031, 3066 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.22 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.07 (s, 2H, $OC\underline{H_2}Ph$), 5.38-5.41 (m, 1H, H_2), 5.56-5.59 (m, 1H, H_3), 6.09 (d, *J* = 2.4 Hz, 1H, H_6), 6.16 (d, *J* = 2.4 Hz, 1H, H_8), 6.86-7.17 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$), 7.22-7.51 (m, 6H, $H_{5'}$, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.0 (CH_3), 55.3 (OCH_3), 55.4 (OCH_3), 70.0 ($O\underline{C}H_2Ph$), 76.6 (C_2), 93.0 (C_6), 94.1 (C_8), 107.2 (C_{4a}), 113.6 ($C_{2'}$), 114.5 ($C_{4'}$), 119.0 (C_3), 119.7 ($C_{6'}$), 127.6 ($C_{2''}$, $C_{6''}$), 128.0 ($C_{4''}$), 128.6 ($C_{3''}$, $C_{5''}$), 129.6 ($C_{5'}$), 131.4 (C_4), 137.0 ($C_{1''}$), 142.6 ($C_{1'}$), 156.2 (C_{8a}), 158.3 (C_7), 159.0 ($C_{3'}$), 160.8 (C_5); MS (ESI): *m/z* (%): 389.2 (MH^+, 100), 363.2 (2); HRMS (ESI): *m/z* calcd. for $C_{25}H_{25}O_4$: 389.1753 [MH^+]; found: 389.1749.

*2-(Furan-3-yl)-5,7-dimethoxy-4-methyl-2H-chromene (**4af**)*



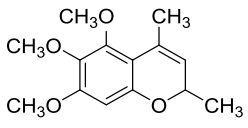
Prepared from 3-(1-(3,5-dimethoxyphenoxy)but-3-en-1-yl)furan **1af** (77.2 mg, 0.27 mmol), *p*-TsOH (51.6 mg, 0.27 mmol), benzoquinone (29.4 mg, 0.27 mmol) and $PdCl_2(CH_3CN)_2$ (3.5 mg, 0.014 mmol) in dioxane (18.0 mL) for 2h at rt. After work-up and purification by flash column chromatography, **4af** was obtained as an oil (63.4 mg, 86%) (mixture of regioisomers 85:15): IR (ATR): ν (cm^{-1}) = 2841, 2926, 2962, 2991, 3006 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.21 (t, *J* = 1.5 Hz, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.38-5.47 (m, 1H, H_2), 5.50-5.59 (m, 1H, H_3), 6.09 (d, *J* = 2.4 Hz, 1H, H_6), 6.13 (d, *J* = 2.4 Hz, 1H, H_8), 6.47-6.49 (m, 1H, $H_{4'}$), 7.38 (t, *J* = 1.7 Hz, 1H, $H_{2'}$), 7.44-7.46 (m, 1H, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.9 (CH_3), 55.3 (OCH_3), 55.4 (OCH_3), 69.2 (C_2), 93.0 (C_6), 94.2 (C_8), 107.4 (C_{4a}), 109.6 ($C_{4'}$), 117.9 (C_3), 125.2 ($C_{3'}$), 131.8 (C_4), 140.8 ($C_{2'}$), 143.3 ($C_{5'}$), 156.0 (C_{8a}), 158.3 (C_7), 160.8 (C_5); MS (ESI): *m/z* (%): 273.1 (MH^+, 100), 171.1 (2). HRMS (ESI): *m/z* calcd. for $C_{16}H_{17}O_4$: 273.1127 [MH^+]; found: 273.1123.

*5,6,7-Trimethoxy-4-methyl-2H-chromene (**4ba**)*



Prepared from 5-(but-3-en-1-yloxy)-1,2,3-trimethoxybenzene **1ba** (0.13 g, 0.53 mmol), *p*-TsOH (0.10 g, 0.53 mmol), benzoquinone (57.4 mg, 0.53 mmol) and $PdCl_2(CH_3CN)_2$ (13.8 mg, 0.053 mmol) in dioxane (35.4 mL) for 6 h at rt. After work-up and purification by flash column chromatography, **4ba** was obtained as an oil (76.5 mg, 61%) (mixture of regioisomers 94:6): IR (ATR): ν (cm^{-1}) = 2833, 2934, 2966, 3006 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.17 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.48 (d, *J* = 2.2 Hz, 2H, 2 × H_2), 5.46 (br s, 1H, H_3), 6.28 (s, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.1 (CH_3), 55.9 (OCH_3), 60.9 (OCH_3), 61.2 (OCH_3), 64.9 (C_2), 96.3 (C_8), 111.7 (C_{4a}), 117.0 (C_3), 131.1 (C_4), 137.1 (C_6), 151.4 (C_5), 151.7 (C_{8a}), 153.4 (C_7); MS (ESI): *m/z* (%): 237.1 (MH^+, 100), 236.1 (3). HRMS (ESI): *m/z* calcd. for $C_{13}H_{17}O_4$: 237.1127 [MH^+]; found: 237.1126.

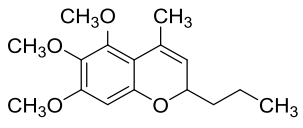
*5,6,7-Trimethoxy-2,4-dimethyl-2H-chromene (**4bb**)*



Prepared from 1,2,3-trimethoxy-5-(pent-4-en-2-yloxy)benzene **1bb** (0.11 g, 0.43 mmol), *p*-TsOH (81.0 mg, 0.43 mmol), benzoquinone (46.0 mg, 0.43 mmol) and $PdCl_2(CH_3CN)_2$ (11.0 mg, 0.043 mmol) in dioxane (28.4 mL) for 2 h at rt. After work-up and purification by flash column chromatography, **4bb** was obtained as an oil (94.2 mg, 88%)

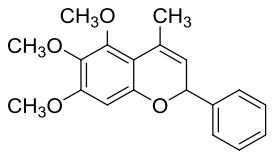
(mixture of regioisomers 92:8): IR (ATR): ν (cm^{-1}) = 2833, 2930, 2970, 3034 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.39 (d, *J* = 6.6 Hz, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.58-4.71 (m, 1H, H_2), 5.25-5.33 (m, 1H, H_3), 6.27 (s, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 20.4 (CH_3), 21.1 (CH_3), 55.8 (OCH_3), 60.9 (OCH_3), 61.2 (OCH_3), 70.9 (C_2), 96.4 (C_8), 111.2 (C_{4a}), 122.6 (C_3), 130.3 (C_4), 136.9 (C_6), 151.2 (C_5), 151.3 (C_{8a}), 153.4 (C_7); MS (ESI): *m/z* (%): 251.1 (MH^+, 100). HRMS (ESI): *m/z* calcd. for $C_{14}H_{19}O_4$: 251.1283 [MH^+]; found 251.1293.

*5,6,7-Trimethoxy-4-methyl-2-propyl-2H-chromene (**4bc**)*



Prepared from 5-(hept-1-en-4-yloxy)-1,2,3-trimethoxy-benzene **1bc** (50.0 mg, 0.18 mmol), *p*-TsOH (34.0 mg, 0.18 mmol), benzoquinone (19.3 mg, 0.18 mmol) and $PdCl_2(CH_3CN)_2$ (4.6 mg, 0.018 mmol) in dioxane (12.0 mL) for 2.5 h at rt. After work-up and purification by flash column chromatography, **4bc** was obtained as an oil (42.9 mg, 86%) (mixture of regioisomers 96:4): IR (ATR): ν (cm^{-1}) = 2869, 2934, 2959 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.97 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.40-1.88 (m, 4H, CH_2CH_2), 2.17 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.53-4.59 (m, 1H, H_2), 5.35 (d, *J* = 1.6 Hz, 1H, H_3), 6.29 (s, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.0 ($CH_2\underline{C}H_3$), 18.3 ($\underline{C}H_2CH_3$), 21.2 (CH_3), 36.5 ($\underline{C}H_2CH_2CH_3$), 55.8 (OCH_3), 60.9 (OCH_3), 61.2 (OCH_3), 74.4 (C_2), 96.5 (C_8), 111.2 (C_{4a}), 121.7 (C_3), 130.2 (C_4), 136.8 (C_6), 151.2 (C_5), 151.3 (C_{8a}), 153.3 (C_7); MS (ESI): *m/z* (%): 279.2 (MH^+, 100), 278.2 (1), 235.1 (1); HRMS (ESI): *m/z* calcd. for $C_{16}H_{23}O_4$: 279.1596 [MH^+]; found: 279.1601.

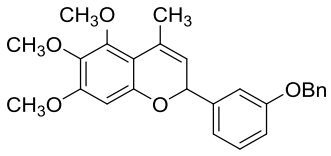
*5,6,7-Trimethoxy-4-methyl-2-phenyl-2H-chromene (**4bd**)*



Prepared from 1,2,3-trimethoxy-5-((1-phenylbut-3-en-1-yl)oxy)benzene **1bd** (0.12 g, 0.40 mmol), *p*-TsOH (75.2 mg, 0.40 mmol), benzoquinone (42.7 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (10.3 mg, 0.040 mmol) in dioxane (26.4 mL) for 2 h at rt. After work-up and purification by flash column chromatography, **4bd** was obtained as an oil (98.4 mg, 79%) (mixture of regioisomers 94:6): IR (ATR): ν (cm^{-1}) = 2841, 2934, 2966, 3034, 3063 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.25 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.42-5.52 (m, 1H, H_2), 5.57-5.66 (m, 1H, H_3), 6.32 (s, 1H, H_8), 7.25-7.51 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.3 (CH_3), 55.9 (OCH_3), 60.9 (OCH_3), 61.3 (OCH_3), 76.8 (C_2), 96.6 (C_8), 110.8 (C_{4a}), 120.9 (C_3), 127.1 ($C_{2'}$, $C_{6'}$), 128.2 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 130.9 (C_4), 137.1 (C_6), 140.7 ($C_{1'}$), 150.7 (C_5), 151.4

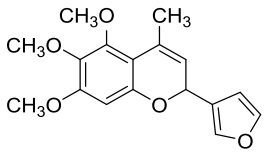
(C_{8a}), 153.7 (C_7); MS (ESI): *m/z* (%): 313.1 (MH^+, 100); HRMS (ESI): *m/z* calcd. for $C_{19}H_{21}O_4$: 313.1440 [MH^+]; found: 313.1451.

*2-(3-(Benzyloxy)phenyl)-5,6,7-trimethoxy-4-methyl-2H-chromene (**4be**)*



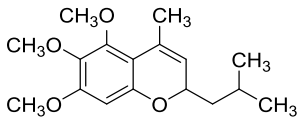
Prepared from 5-((1-(3-(benzyloxy)phenyl)but-3-en-1-yl)oxy)-1,2,3-trimethoxybenzene **1be** (0.14 g, 0.34 mmol), *p*-TsOH (64.1 mg, 0.34 mmol), benzoquinone (36.4 mg, 0.34 mmol) and $PdCl_2(CH_3CN)_2$ (8.7 mg, 0.034 mmol) in dioxane (22.5 mL) for 2.5 h at rt. After work-up and purification by flash column chromatography, **4be** was obtained as an oil (0.12, 84%) (mixture of regioisomers 93:7): IR (ATR): ν (cm^{-1}) = 2851, 2934, 2962, 2991, 3009 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.24 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.07 (s, 2H, $OC\underline{H_2}Ph$), 5.46 (d, *J* = 1.6 Hz, 1H, H_2), 5.58 (br s, 1H, H_3), 6.33 (s, 1H, H_8), 6.89-7.17 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$), 7.20-7.49 (m, 6H, $H_{5'}$, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.3 (CH_3), 55.9 (OCH_3), 60.9 (OCH_3), 61.3 (OCH_3), 70.0 ($O\underline{C}H_2Ph$), 76.6 (C_2), 96.6 (C_8), 110.8 (C_{4a}), 113.6 ($C_{2'}$), 114.6 ($C_{4'}$), 119.7 ($C_{6'}$), 120.8 (C_3), 127.6 ($C_{2''}$, $C_{6''}$), 128.0 ($C_{4''}$), 128.6 ($C_{3''}$, $C_{5''}$), 129.6 ($C_{5'}$), 130.9 (C_4), 136.9 (C_6), 137.1 ($C_{1''}$), 142.4 ($C_{1'}$), 150.7 (C_5), 151.5 (C_{8a}), 153.7 (C_7), 159.0 ($C_{3'}$); MS (ESI): *m/z* (%): 419.2 (MH^+, 100), 235.1 (1). HRMS (ESI): *m/z* calcd. for $C_{26}H_{27}O_5$: 419.1859 [MH^+]; found: 419.1862.

*2-(Furan-3-yl)-5,6,7-trimethoxy-4-methyl-2H-chromene (**4bf**)*



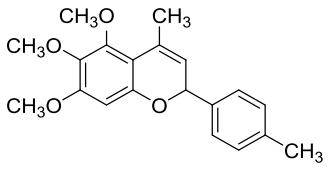
Prepared from 3-(1-(3,4,5-trimethoxyphenoxy)but-3-en-1-yl)furan **1bf** (0.11 g, 0.37 mmol), *p*-TsOH (69.5 mg, 0.37 mmol), benzoquinone (39.5 mg, 0.37 mmol) and $PdCl_2(CH_3CN)_2$ (9.5 mg, 0.037 mmol) in dioxane (24.4 mL) for 3 h at rt. After work-up and purification by flash column chromatography, **4bf** was obtained as an oil (80.2 mg, 72%) (mixture of regioisomers 92:8): IR (ATR): ν (cm^{-1}) = 2851, 2934, 2962, 2991, 3009 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.22 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.47-5.51 (m, 1H, H_2), 5.52-5.56 (m, 1H, H_3), 6.29 (s, 1H, H_8), 6.46 (s, 1H, $H_{4'}$), 7.39 (s, 1H, $H_{2'}$), 7.43 (s, 1H, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.2 (CH_3), 55.8 (OCH_3), 60.9 (OCH_3), 61.2 (OCH_3), 69.0 (C_2), 96.7 (C_8), 109.5 ($C_{4'}$), 111.0 (C_{4a}), 119.7 (C_3), 125.1 ($C_{3'}$), 131.3 (C_4), 137.1 (C_6), 140.8 ($C_{2'}$), 143.4 ($C_{5'}$), 150.4 (C_5), 151.4 (C_{8a}), 153.6 (C_7); MS (ESI): *m/z* (%): 303.1 (MH^+, 100), 302.1 (2). HRMS (ESI): *m/z* calcd. for $C_{17}H_{19}O_5$: 303.1233 [MH^+]; found, 303.1240.

*2-Isobutyl-5,6,7-trimethoxy-4-methyl-2H-chromene (**4bg**)*



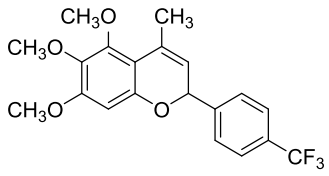
Prepared from 1,2,3-trimethoxy-5-((6-methylhept-1-en-4-yl)oxy)benzene **1bg** (99.2 mg, 0.34 mmol), *p*-TsOH (64.2 mg, 0.34 mmol), benzoquinone (36.5 mg, 0.34 mmol) and $PdCl_2(CH_3CN)_2$ (8.8 mg, 0.034 mmol) in dioxane (22.5 mL) for 2.5 h at rt. After work-up and purification by flash column chromatography, **4bg** was obtained as an oil (78.1 mg, 79%) (mixture of regioisomers 94:6): IR (ATR): ν (cm^{-1}) = 2833, 2872, 2934, 2955, 2987, 3009 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.93 (d, *J* = 3.4 Hz, 3H, CH_3), 0.95 (d, *J* = 3.4 Hz, 3H, CH_3), 1.28-1.48 (m, 1H, CH), 1.66-1.98 (m, 2H, $C\underline{H_2}CH$), 2.15 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.50-4.64 (m, 1H, H_2), 5.26-5.39 (m, 1H, H_3), 6.26 (s, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.2 (CH_3), 22.3 (CH_3), 23.1 (CH_3), 24.4 (CH), 43.3 ($\underline{C}H_2CH$), 55.8 (OCH_3), 60.9 (OCH_3), 61.2 (OCH_3), 73.0 (C_2), 96.5 (C_8), 111.4 (C_{4a}), 121.9 (C_3), 130.1 (C_4), 136.8 (C_6), 151.1 (C_5), 151.3 (C_{8a}), 153.3 (C_7); MS (ESI): *m/z* (%): 293.2 (MH^+, 100), 292.2 (1). HRMS (ESI): *m/z* calcd. for $C_{17}H_{25}O_4$: 293.1753 [MH^+]; found: 293.1762.

*5,6,7-Trimethoxy-4-methyl-2-(p-tolyl)-2H-chromene (**4bh**)*



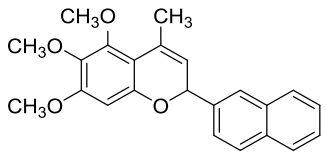
Prepared from 1,2,3-trimethoxy-5-((1-(*p*-tolyl)but-3-en-1-yl)oxy)benzene **1bh** (0.12 g, 0.37 mmol), *p*-TsOH (70.6 mg, 0.37 mmol), benzoquinone (40.1 mg, 0.37 mmol) and $PdCl_2(CH_3CN)_2$ (9.6 mg, 0.037 mmol) in dioxane (24.7 mL) for 3 h at rt. After work-up and purification by flash column chromatography, **4bh** was obtained as an oil (0.11, 87%) (mixture of regioisomers 92:8): IR (ATR): ν (cm^{-1}) = 2841, 2934, 2959, 2987, 3009 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.25 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.42-5.52 (m, 1H, H_2), 5.52-5.62 (m, 1H, H_3), 6.31 (s, 1H, H_8), 7.19 (d, *J* = 7.9 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.35 (d, *J* = 7.9 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.2 (CH_3), 21.3 (CH_3), 55.8 (OCH_3), 60.9 (OCH_3), 61.3 (OCH_3), 76.3 (C_2), 96.7 (C_8), 110.8 (C_{4a}), 120.9 (C_3), 127.2 ($C_{2'}$, $C_{6'}$), 129.2 ($C_{3'}$, $C_{5'}$), 130.8 (C_4), 137.0 (C_6), 137.7 ($C_{4'}$), 138.0 ($C_{1'}$), 150.7 (C_5), 151.4 (C_{8a}), 153.6 (C_7); MS (ESI): *m/z* (%): 327.2 (MH^+, 100), 326.2 (2); HRMS (ESI): *m/z* calcd. for $C_{20}H_{23}O_4$: 327.1596 [MH^+]; found: 327.1600.

*5,6,7-Trimethoxy-4-methyl-2-(4-(trifluoromethyl)phenyl)-2H-chromene (**4bi**)*



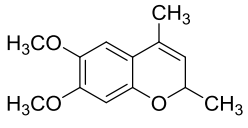
Prepared from 1,2,3-trimethoxy-5-((1-(4-(trifluoromethyl)-phenyl)but-3-en-1-yl)oxy)benzene **1bi** (0.12 g, 0.32 mmol), *p*-TsOH (61.2 mg, 0.32 mmol), benzoquinone (34.8 mg, 0.32 mmol) and $PdCl_2(CH_3CN)_2$ (8.3 mg, 0.032 mmol) in dioxane (21.4 mL) for 5.5 h at rt. After work-up and purification by flash column chromatography, **4bi** was obtained as an oil (0.11 g, 91%) (mixture of regioisomers 92:8): IR (ATR): ν (cm^{-1}) = 2841, 2937, 2987, 3006 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.24 (s, 3H, CH_3), 3.81 (s, 6H, 2 × OCH_3), 3.89 (s, 3H, OCH_3), 5.45 (d, *J* = 1.6 Hz, 1H, H_2), 5.65 (d, *J* = 1.6 Hz, 1H, H_3), 6.32 (s, 1H, H_8), 7.56 (d, *J* = 8.4 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.63 (d, *J* = 8.4 Hz, 2H, $H_{3'}$, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.3 (CH_3), 55.9 (OCH_3), 60.9 (OCH_3), 61.3 (OCH_3), 75.8 (C_2), 96.6 (C_8), 110.7 (C_{4a}), 119.8 (C_3), 124.3 (q, *J* = 272.5 Hz, CF_3), 125.5 (q, *J* = 3.8 Hz, $C_{3'}$, $C_{5'}$), 127.2 ($C_{2'}$, $C_{6'}$), 130.2 (q, *J* = 32.7 Hz, $C_{4'}$), 131.5 (C_4), 137.3 (C_6), 144.7 ($C_{1'}$), 150.3 (C_5), 151.5 (C_{8a}), 153.9 (C_7); MS (ESI): *m/z* (%): 381.1 (MH^+, 100), 380.1 (2); HRMS (ESI): *m/z* calcd. for $C_{20}H_{20}F_3O_4$: 381.1314 [MH^+]; found: 381.1311.

*5,6,7-Trimethoxy-4-methyl-2-(naphthalene-2-yl)-2H-chromene (**4bj**)*



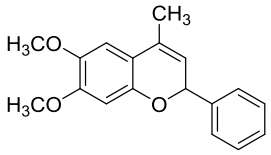
Prepared from 2-(1-(3,4,5-trimethoxyphenoxy)but-3-en-1-yl)naphthalene **1bj** (0.12 g, 0.34 mmol), *p*-TsOH (64.6 mg, 0.34 mmol), benzoquinone (36.7 mg, 0.34 mmol) and $PdCl_2(CH_3CN)_2$ (8.8 mg, 0.034 mmol) in dioxane (22.7 mL) for 2.5 h at rt. After work-up and purification by flash column chromatography, **4bj** was obtained as an oil (0.10 g, 81 %) (mixture of regioisomers 89:11): IR (ATR): ν (cm^{-1}) = 2837, 2934, 2962, 3056 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.31 (t, *J* = 1.5 Hz, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.56-5.67 (m, 1H, H_2), 5.72-5.83 (m, 1H, H_3), 6.36 (s, 1H, H_8), 7.41-7.53 (m, 2H, $H_{6'}$, $H_{7'}$), 7.62 (dd, *J* = 8.5, 1.6 Hz, 1H, $H_{3'}$), 7.81-7.94 (m, 4H, $H_{1'}$, $H_{4'}$, $H_{5'}$, $H_{8'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.4 (CH_3), 55.9 (OCH_3), 60.9 (OCH_3), 61.3 (OCH_3), 76.8 (C_2), 96.7 (C_8), 110.9 (C_{4a}), 120.7 (C_3), 125.1 ($C_{1'}$, $C_{6'}$), 126.1 ($C_{7'}$), 126.2 ($C_{8'}$), 127.7 ($C_{5'}$), 128.2 ($C_{3'}$), 128.4 ($C_{4'}$), 131.1 (C_4), 133.2 ($C_{2'}$), 133.3 ($C_{8a'}$), 137.1 (C_6), 138.0 ($C_{4a'}$), 150.7 (C_5), 151.5 (C_{8a}), 153.8 (C_7); MS (ESI): *m/z* (%): 363.2 (MH^+, 100); HRMS (ESI): *m/z* calcd. for $C_{23}H_{23}O_4$: 363.1596 [MH^+]; found: 363.1592.

*6,7-Dimethoxy-2,4-dimethyl-2H-chromene (**4cb**)*



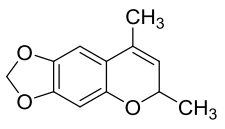
Prepared from 1,2-dimethoxy-4-(pent-4-en-2-yloxy)benzene **1cb** (0.12 g, 0.53 mmol), *p*-TsOH (0.10 g, 0.53 mmol), benzoquinone (56.9 mg, 0.53 mmol) and $PdCl_2(CH_3CN)_2$ (13.7 mg, 0.053 mmol) in dioxane (35.1 mL) for 1 h at 70 ºC. After work-up and purification by flash column chromatography, **4cb** was obtained as an oil (71.0 mg, 61%): IR (ATR): ν (cm^{-1}) = 2837, 2858, 2934, 2970, 3088 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.40 (d, *J* = 6.5 Hz, 3H, CH_3), 1.99 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.78-4.94 (m, 1H, H_2), 5.28-5.38 (m, 1H, H_3), 6.45 (s, 1H, H_8), 6.69 (s, 1H, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 18.0 (CH_3), 21.1 (CH_3), 55.9 (OCH_3), 56.8 (OCH_3), 71.4 (C_2), 100.7 (C_8), 107.6 (C_5), 115.8 (C_{4a}), 121.1 (C_3), 129.4 (C_4), 143.2 (C_6), 148.3 (C_{8a}), 149.6 (C_7); MS (ESI): *m/z* (%): 221.1 (MH^+, 100), 220.1 (5), 219.1 (32); HRMS (ESI): *m/z* calcd. for $C_{13}H_{17}O_3$: 221.1178 [MH^+]; found: 221.1182.

*6,7-Dimethoxy-4-methyl-2-phenyl-2H-chromene (**4cd**)*



Prepared from 1,2-dimethoxy-4-((1-phenylbut-3-en-1-yl)oxy)-benzene **1cd** (0.11 g, 0.39 mmol), *p*-TsOH (74.6 mg, 0.39 mmol), benzoquinone (42.4 mg, 0.39 mmol) and $PdCl_2(CH_3CN)_2$ (10.2 mg, 0.039 mmol) in dioxane (26.1 mL) for 3 h at 70 ºC. After work-up and purification by flash column chromatography, **4cd** was obtained as an oil (60.5 mg, 55%): IR (ATR): ν (cm^{-1}) = 2833, 2855, 2920, 2955, 3002, 3031, 3060 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.10 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.50-5.55 (m, 1H, H_2), 5.79-5.83 (m, 1H, H_3), 6.49 (s, 1H, H_8), 6.76 (s, 1H, H_5), 7.20-7.54 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 18.1 (CH_3), 55.9 (OCH_3), 56.8 (OCH_3), 77.3 (C_2), 100.7 (C_8), 107.6 (C_5), 115.3 (C_{4a}), 119.2 (C_3), 127.0 ($C_{2'}$, $C_{6'}$), 128.2 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 129.8 (C_4), 141.3 ($C_{1'}$), 143.3 (C_6), 147.9 (C_{8a}), 149.9 (C_7); MS (ESI): *m/z* (%): 281.1 ([M-H]$^+$, 100), 267.1 (1). HRMS (ESI): *m/z* calcd. for $C_{18}H_{17}O_3$: 281.1178 [M-H] $^+$; found: 281.1172.

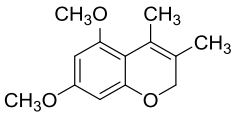
*6,8-Dimethyl-6H-[1,3]dioxolo[4,5-g]chromene (**4db**)*



Prepared from 5-(pent-4-en-2-yloxy)benzo[*d*][1,3]dioxole **1db** (81.5 mg, 0.40 mmol), *p*-TsOH (75.2 mg, 0.40 mmol), benzoquinone (42.7 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (10.3 mg, 0.040 mmol) in dioxane (26.3 mL) for 2.5 h at 70 ºC. After work-up and purification by flash column chromatography, **4db** was obtained as an oil (48.3 mg, 60%): IR (ATR): ν (cm^{-1}) =

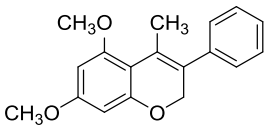
2895, 2923, 2973, 3006 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.41 (d, *J* = 6.5 Hz, 3H, CH_3), 1.98 (s, 3H, CH_3), 4.77-4.92 (m, 1H, H_2), 5.30-5.40 (m, 1H, H_3), 5.92 (s, 2H, OCH_2O), 6.43 (s, 1H, H_8), 6.68 (s, 1H, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 18.3 (CH_3), 20.8 (CH_3), 71.4 (C_2), 98.6 (C_8), 101.0 (C_5), 103.2 (OCH_2O), 117.0 (C_{4a}), 121.1 (C_3), 129.7 (C_4), 141.7 (C_6), 147.3 (C_{8a}), 149.1 (C_7); MS (ESI): *m/z* (%): 203.1 ([M - H]$^+$, 100), 189.1 (1). HRMS (ESI): *m/z* calcd. for $C_{12}H_{11}O_3$: 203.0708 [M - H]$^+$; found: 203.0717.

*5,7-Dimethoxy-3,4-dimethyl-2H-chromene (**4ak**)*[31]



Prepared from 1,3-dimethoxy-5-((2-methylbut-3-en-1-yl)oxy)-benzene **1ak** (0.11 g, 0.51 mmol), *p*-TsOH (97.4 mg, 0.51 mmol), benzoquinone (55.3 mg, 0.51 mmol) and $PdCl_2(CH_3CN)_2$ (6.6 mg, 0.026 mmol) in dioxane (34.1 mL) for 1.5 h at rt. After work-up and purification by flash column chromatography, **4ak** was obtained as a solid (93.2 mg, 83%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.83 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.38 (s, 2H, 2 × H_2), 6.09-6.20 (m, 2H, H_6, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 15.9 (CH_3), 16.0 (CH_3), 55.3 (OCH_3), 55.4 (OCH_3), 69.8 (C_2), 93.2 (C_6), 93.6 (C_8), 109.3 (C_{4a}), 122.9 (C_3), 123.6 (C_4), 156.7 (C_{8a}), 158.0 (C_7), 159.7 (C_5).

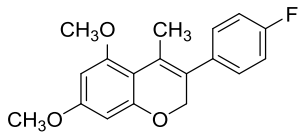
*5,7-Dimethoxy-4-methyl-3-phenyl-2H-chromene (**4al**)*



Prepared from 1,3-dimethoxy-5-((2-phenylbut-3-en-1-yl)oxy)-benzene **1al** (96.3 mg, 0.34 mmol), *p*-TsOH (64.4 mg, 0.34 mmol), benzoquinone (36.6 mg, 0.34 mmol) and $PdCl_2(CH_3CN)_2$ (4.4 mg, 0.017 mmol) in dioxane (22.6 mL) for 2.5 h at rt. After work-up and purification by flash column chromatography, **4al** was obtained as an oil (83.3 mg, 87%): IR (ATR): ν (cm^{-1}) = 2837, 2934, 2966, 3002, 3060, 3077 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.12 (t, *J* = 1.4 Hz, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.69 (q, *J* = 1.4 Hz, 2H, 2 × H_2), 6.17 (d, *J* = 2.4 Hz, 1H, H_6), 6.20 (d, *J* = 2.4 Hz, 1H, H_8), 7.22-7.46 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 18.0 (CH_3), 55.4 (OCH_3), 55.5 (OCH_3), 69.8 (C_2), 93.3 (C_8), 93.5 (C_6), 109.5 (C_{4a}), 126.4 (C_4), 126.8 ($C_{4'}$), 128.3 ($C_{3'}$, $C_{5'}$), 128.4 (C_3), 129.4 ($C_{2'}$, $C_{6'}$), 139.1 ($C_{1'}$), 157.3 (C_{8a}), 158.5 (C_7), 160.6 (C_5); MS (ESI): *m/z* (%): 283.1 (MH^+, 100), 282.1 (7), 281.1 (37). HRMS (ESI): *m/z* calcd. for $C_{18}H_{19}O_3$: 283.1334 [MH^+]; found: 283.1334.

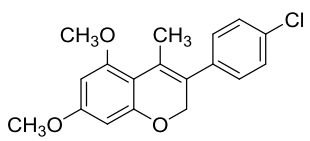
[31] Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett*. **2007**, *9*, 4821.

*3-(4-Fluorophenyl)-5,7-dimethoxy-4-methyl-2H-chromene (**4am**)*



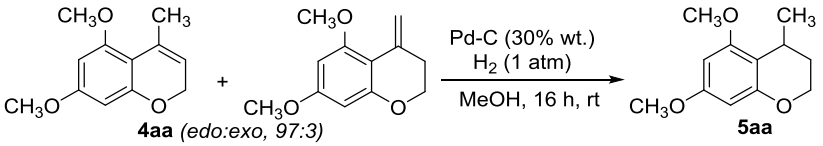
Prepared from 1-((2-(4-fluorophenyl)but-3-en-1-yl)oxy)-3,5-dimethoxybenzene **1am** (0.11 g, 0.35 mmol), *p*-TsOH (67.3 mg, 0.35 mmol), benzoquinone (38.2 mg, 0.35 mmol) and $PdCl_2(CH_3CN)_2$ (4.6 mg, 0.018 mmol) in dioxane (23.6 mL) for 4 h at rt. After work-up and purification by flash column chromatography, **4am** was obtained as a solid (83.7 mg, 79%): mp (CH_2Cl_2) 94-95 ºC; IR (ATR): ν (cm^{-1}) = 2851, 2923, 2952, 2970, 2995, 3049 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.09 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.65 (s, 2H, 2 × H_2), 6.17 (d, *J* = 2.3 Hz, 1H, H_6), 6.19 (d, *J* = 2.3 Hz, 1H, H_8), 7.07 (t, *J* = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.25-7.33 (m, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 18.0 (CH_3), 55.3 (OCH_3), 55.4 (OCH_3), 69.7 (C_2), 93.3 (C_6), 93.5 (C_8), 109.3 (C_{4a}), 115.2 (d, *J* = 21.3 Hz, $C_{3'}$, $C_{5'}$), 126.7 (C_4), 127.3 (C_3), 131.0 (d, *J* = 7.9 Hz, $C_{2'}$, $C_{6'}$), 134.9 (d, *J* = 3.4 Hz, $C_{1'}$), 157.3 (C_{8a}), 158.5 (C_7), 160.7 (C_5), 161.7 (d, *J* = 248.1 Hz, $C_{4'}$); MS (ESI): *m/z* (%): 301.1 (MH^+, 100), 299.1 (20), 287.1 (4); HRMS (ESI): *m/z* calcd. for $C_{18}H_{18}FO_3$: 301.1240 [MH^+]; found: 301.1235.

*3-(4-Chlorophenyl)-5,7-dimethoxy-4-methyl-2H-chromene (**4an**)*



Prepared from 1-((2-(4-chlorophenyl)but-3-en-1-yl)oxy)-3,5-dimethoxybenzene **1an** (94.0 mg, 0.29 mmol), *p*-TsOH (56.1 mg, 0.29 mmol), benzoquinone (31.9 mg, 0.29 mmol) and $PdCl_2(CH_3CN)_2$ (3.8 mg, 0.015 mmol) in dioxane (19.7 mL) for 5.5 h at rt. After work-up and purification by flash column chromatography, **4an** was obtained as a solid (68.6 mg, 73%): mp (CH_2Cl_2) 101-102 ºC; IR (ATR): ν (cm^{-1}) = 2837, 2855, 2901, 2934, 2952, 2977, 2995, 3006, 3056 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.10 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.64 (s, 2H, 2 × H_2), 6.16 (d, *J* = 2.2 Hz, 1H, H_6), 6.19 (d, *J* = 2.2 Hz, 1H, H_8), 7.26 (d, *J* = 8.4 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.35 (d, *J* = 8.4 Hz, 2H, $H_{3'}$, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 18.0 (CH_3), 55.3 (OCH_3), 55.4 (OCH_3), 69.6 (C_2), 93.4 (C_6), 93.5 (C_8), 109.3 (C_{4a}), 127.1 (C_4), 127.2 (C_3), 128.5 ($C_{3'}$, $C_{5'}$), 130.8 ($C_{2'}$, $C_{6'}$), 132.6 ($C_{4'}$), 137.5 ($C_{1'}$), 157.3 (C_{8a}), 158.5 (C_7), 160.7 (C_5); MS (ESI): *m/z* (%): 319.1 (MH^+ + 2, 24), 317.1 (MH^+, 100), 316.1 (11), 315.1 (25); HRMS (ESI): *m/z* calcd. for $C_{18}H_{18}ClO_3$: 317.0944 [MH^+]; found: 317.0930.

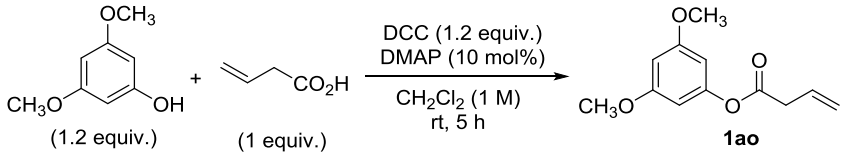
2.11. Hydrogenation of regioisomeric mixture 4aa. Synthesis of 5,7-dimethoxy-4-methylchromane (5aa)[31]



4aa *(edo:exo, 97:3)* **5aa**

Over a solution of regioisomeric misxture **4aa** (*endo:exo* 93:7) (24.5 mg, 0.12 mmol) in dry MeOH (3 mL), Pd-C (7.4 mg) (5% in 50% water) was added under argon atmosphere. The reaction flask was evacuated and refilled with H_2 twice and the reaction mixture was stirred vigorously under H_2 atmosphere for 16 h. The resulting mixture was filtered through Celite® and washed with MeOH. The solvent was evaporated *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 19/1) afforded the corresponding chromane **5aa** as an oil (21.7 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.23 (d, *J* = 6.9 Hz, 3H, CH_3), 1.54-1.60 (m, 1H, 1 × H_3), 1.94-2.12 (m, 1H, 1 × H_3), 2.96-3.08 (m, 1H, H_4), 3.75 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.05-4.16 (m, 1H, 1 × H_2), 4.17-4.25 (m, 1H, 1 × H_2), 6.02 (d, *J* = 2.3 Hz, 1H, H_6), 6.05 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.2 (CH_3), 22.9 (C_4), 29.1 (C_3), 55.2 (OCH_3), 55.3 (OCH_3), 60.0 (C_2), 91.3 (C_6), 93.2 (C_8), 108.9 (C_{4a}), 155.3 (C_{8a}), 158.9 (C_5), 159.2 (C_7).

2.12. Synthesis of 3,5-dimethoxyphenyl but-3-enoate (1ao)

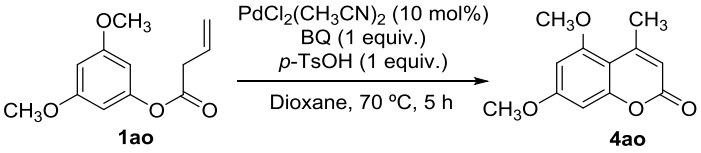


1ao

Over a solution of 3-butenoic acid (0.40 mL, 4.7 mmol) in CH_2Cl_2 (4.7 mL), were added subsequently 3,5-dimethoxyphenol (0.87 g, 5.6 mmol), *N,N´*-dicyclohexylcarbodiimide (DCC) (1.2 g, 6.5 mmol) and 4-dimethylaminopyrine (DMAP) (69.0 mg, 0.47 mmol). The reaction mixture was stirred at room temperature for 5 h. After that time, the reaction mixture was filtered and the filtrate was washed with a 1 M aqueous solution of NaOH (2 × 20 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. Purification by flash column chromatography (petroleum ether/AcOEt 8/2), afforded **1ao** as an oil (0.95 g, 91%): IR (ATR): ν (cm^{-1}) = 1739 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.32 (d, *J* = 6.8 Hz, 2H,

COC<u>H</u>$_2$CH=CH$_2$), 3.75 (s, 6H, 2 × OCH$_3$), 5.19-5.35 (m, 2H, CH=C<u>H</u>$_2$), 5.92-6.12 (m, 1H, C<u>H</u>=CH$_2$), 6.28-6.31 (m, 2H, H$_2$, H$_6$), 6.34-6.38 (m, 1H, H$_4$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 39.1 (CO<u>C</u>H$_2$CH=CH$_2$), 55.4 (2 × OCH$_3$), 98.3 (C$_4$), 100.1 (C$_2$, C$_6$), 119.2 (CH=<u>C</u>H$_2$), 129.6 (<u>C</u>H=CH$_2$), 152.2 (C$_1$), 161.2 (C$_3$, C$_5$), 169.8 (CO); MS (ESI): *m/z* (%): 245.1 (MNa$^+$, 33), 242.1 (12), 155.1 (100); HRMS (ESI): *m/z* calcd. for C$_{12}$H$_{14}$O$_4$Na: 245.0790 [MNa$^+$]; found: 245.0783.

2.13. Pd(II)-catalyzed cyclization of aryl butenoate 1ao. Synthesis of 5,7-dimethoxy-4-methyl-2*H*-chromen-2-one (4ao)[32]

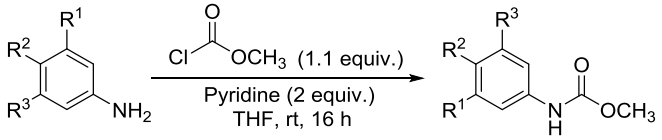


A solution of aryl butenoate **1ao** (0.10, 0.46 mmol), *p*-TsOH (86.6 mg, 0.46 mmol), benzoquinone (49.2 mg, 0.46 mmol) and PdCl$_2$(CH$_3$CN)$_2$ (11.8 mg, 0.046 mmol) in dioxane (30.4 mL) was stirred at 70 ºC for 5 h. Then, the reaction was quenched by addition of water and the mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic extracts were washed with an aqueous 1M solution of NaOH (3 × 15 mL) and with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) coumarin **4ao** was obtained as a solid (70.1 mg, 70%): ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 2.50 (d, *J* = 1.2 Hz, 3H, CH$_3$), 3.82 (s, 3H, OCH$_3$), 3.83 (s, 3H, OCH$_3$), 5.91 (s, 1H, H$_3$), 6.26 (d, *J* = 2.4 Hz, 1H, H$_6$), 6.39 (d, *J* = 2.4 Hz, 1H, H$_8$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 24.2 (CH$_3$), 55.6 (OCH$_3$), 55.7 (OCH$_3$), 93.4 (C$_8$), 95.4 (C$_6$), 104.8 (C$_{4a}$), 111.3 (C$_3$), 154.5 (C$_{8a}$), 156.9 (C$_4$), 159.1 (C$_7$), 161.0 (CO), 162.8 (C$_5$).

[32] Trost, B.M.; Toste, F.D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518.

3. PALLADIUM-CATALYZED DEHYDROGENATIVE COUPLING. AN EFFICIENT SYNTHETIC STRATEGY FOR THE CONSTRUCTION OF THE QUINOLINE CORE

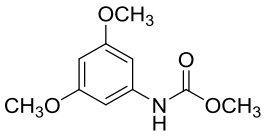
3.1. General procedure for the synthesis of carbamates I-M



I, $R^1 = R^3 = OCH_3$, $R^2 = H$
J, $R^1 = R^2 = R^3 = OCH_3$
K, $R^1 = H$, $R^2 = R^3 = OCH_3$,
L, $R^1 = H$, $R^2 = R^3 = OCH_2O$
M, $R^1 = R^3 = CH_3$, $R^2 = H$

Over a solution of commercially available aniline (1 mmol) and pyridine (2 mmol) in dry THF (4 mL) under argon atmosphere, methyl chloroformate (1.6 mmol) was added dropwise. The reaction was stirred for 16 h at room temperature and afterwards the solvent was removed under reduced pressure. The crude reaction was dissolved in CH_2Cl_2 (30 mL) and washed with a 10% aqueous solution of HCl (2 x 15 mL) and with water (15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* affording carbamates **I-M.**

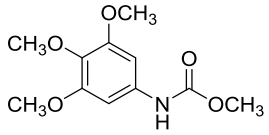
*Methyl (3,5-dimethoxyphenyl)carbamate (**I**)*[33]



Prepared from 3,5-dimethoxyaniline (2.3 g, 15.0 mmol), pyridine (2.4 mL, 30.0 mmol) and methyl chloroformate (1.3 mL, 16.5 mmol) in dry THF (35 mL). After work-up, **I** was obtained as a solid without further purification (2.5 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.70- 3.78 (m, 9H, 2 × OCH_3, CO_2CH_3), 6.17 (t, *J* = 1.9 Hz, 1H, H_4), 6.62 (d, *J* = 1.9 Hz, 2H, H_2, H_6), 6.94 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.3 ($CO_2\underline{C}H_3$), 55.3 (2 × OCH_3), 95.7 (C_2, C_6), 97.0 (C_4), 139.8 (C_1), 154.1 (CO), 161.1 (C_3, C_5).

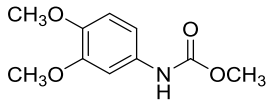
[33] Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012***, 134,* 15331.

*Methyl (3,4,5-trimethoxyphenyl)carbamate (**J**)*[33]



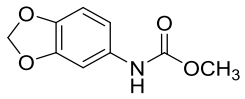
Prepared from 3,4,5-trimethoxyaniline (1.0 g, 5.3 mmol), pyridine (0.85 mL, 10.6 mmol) and methyl chloroformate (0.45 mL, 5.8 mmol) in dry THF (20 mL). After work-up, **J** was obtained as a solid without further purification (1.1 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.71 (s, 3H, OCH_3), 3.73 (s, 6H, 2 × OCH_3), 3.75 (s, 3H, OCH_3), 6.66 (s, 2H, H_2, H_6), 7.04 (s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.2 ($CO_2\underline{C}H_3$), 55.9 (2 × OCH_3), 60.9 (OCH_3), 96.4 (C_2, C_6), 133.8 (C_1), 134.3 (C_4), 153.3 (C_3, C_5), 154.3 (CO).

*Methyl (3,4-dimethoxyphenyl)carbamate (**K**)*[34]



Prepared from 3,4-dimethoxyaniline (0.80 g, 5.1 mmol), pyridine (0.83 mL, 10.2 mmol) and methyl chloroformate (0.44 mL, 5.6 mmol) in dry THF (15 mL). After work-up, **K** was obtained as a solid without further purification (0.90 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.68 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.70 (d, *J* = 8.6 Hz, 1H, H_5), 6.75 (dd, *J* = 8.6, 2.1 Hz, 1H, H_6) 7.06-7.09 (m, 2H, H_2, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.2 ($CO_2\underline{C}H_3$), 55.7 (OCH_3), 56.1 (OCH_3), 104.0 (C_2), 110.9 (C_5), 111.5 (C_6), 131.6 (C_1), 145.2 (C_4), 149.1 (C_3), 154.6 (CO).

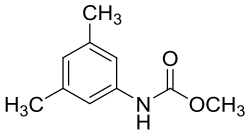
*Methyl benzo[d][1,3]dioxol-5-ylcarbamate (**L**)*[35]



Prepared from 3,4-(methylenedioxy)aniline (0.80 g, 5.7 mmol), pyridine (0.92 mL, 11.3 mmol) and methyl chloroformate (0.49 mL, 6.2 mmol) in dry THF (15 mL). After work-up, **L** was obtained as a solid without further purification (1.1 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.75 (s, 3H, OCH_3), 5.93 (s, 2H, OCH_2O), 6.48-6.58 (m, 1H, H_2), 6.66 (dd, *J* = 8.3, 1.9, 1H, H_6), 6.72 (d, *J* = 8.3, 1H, H_5), 7.07 (s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.3 ($CO_2\underline{C}H_3$), 101.2 (OCH_2O), 102.1 (C_2), 108.1 (C_5), 112.0 (C_6), 132.1 (C_1), 143.9 (C_4), 147.9 (C_3), 154.3 (CO).

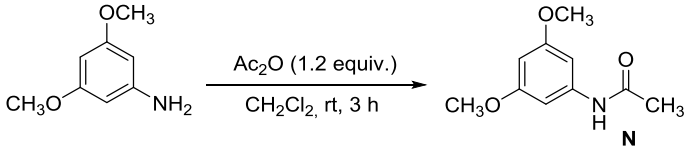
[34] Huang, X.; Seid, M.; Keillor, J.W. *J. Org. Chem.* **1997**, *62*, 7495.
[35] Yang, Q.; Robertson, A.; Alper, H. *Org. Lett.* **2008**, *10*, 5079.

*Methyl (3,5-dimethylphenyl)carbamate (**M**)*[36]



Prepared from 3,5-dimethylaniline (0.80 g, 6.5 mmol), pyridine (1.1 mL, 12.9 mmol) and methyl chloroformate (0.56 mL, 7.1 mmol) in dry THF (15 mL). After work-up, **M** was obtained as an oil without further purification (1.0 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.29 (s, 6H, CH_3), 3.79 (s, 3H, OCH_3), 6.72 (s, 1H, H_4), 7.09 (s, 2H, H_2, H_6), 7.27 (s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.3 (2 × CH_3), 52.1 (OCH_3), 116.7 (C_2, C_6), 125.1 (C_4), 138.0 (C_1), 138.6 (C_3, C_5), 154.6 (CO).

3.2. Synthesis of *N*-(3,5-dimethoxyphenyl)acetamide (N)[37]

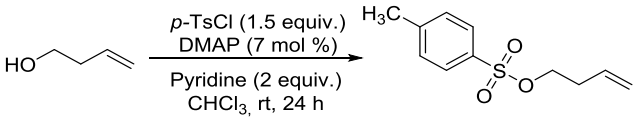


Over a solution of commercial 3,5-dimethoxyaniline (2.0 g, 13.2 mmol) in dry CH_2Cl_2 (35 mL), acetic anhydride (1.5 mL, 15.8 mmol) was added, and the reaction was stirred for 3h at room temperature. Afterwards, the reaction mixture was washed with a saturated aqueous solution of Na_2CO_3 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*, yielding acetamide **N** as a solid without further purification (1.4 g, 54%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.16 (s, 3H, $COCH_3$), 3.77 (s, 6H, 2 × OCH_3), 6.23 (s, 1H, H_4), 6.75 (s, 2H, H_2, H_6), 7.28 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 24.7 ($CO\underline{C}H_3$), 55.4 (2 × OCH_3), 96.6 (C_4), 98.1 (C_2, C_6), 139.7 (C_1), 161.0 (C_3, C_5), 168.5 (CO).

[36] a) Hartstock, F.W.; Herrington, D.G.; McMahon, L.B. *Tetrahedron Lett.* **1994**, *35*, 8761; b) Han, M.; Jin, X.; Yang, H.; Liu, X.; Liu, Y.; Ji, S. *Carbohydr. Polym.* **2017**, *172*, 223.

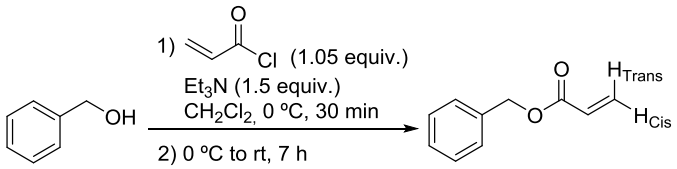
[37] Duan, H.; Zheng, J.; Lai, Q.; Liu, Z.; Tian, G.; Wang, Z.; Li, J.; Shen, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2777.

3.3. Synthesis of but-3-en-1-yl 4-methylbenzenesulfonate[38]



Over a solution of commercial 3-buten-1-ol (3.5 mL, 40.3 mmol) in $CHCl_3$ (30 mL), pyridine (6.5 mL, 80.5 mmol), *p*-TsCl (11.5 g, 60.4 mmol) and DMAP (0.34 g, 2.8 mmol) were added. The reaction mixture was stirred for 24 h at room temperature and afterwards, the mixture was poured into Et_2O (30 mL) and water (10 mL). The organic layer was separated and washed with a 2 M aqueous solution of HCl (2 x 15 mL), a saturated aqueous solution of $NaHCO_3$ (15 mL) and water (15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/AcOEt 85/15) afforded but-3-en-1-yl 4-methylbenzenesulfonate as an oil (9.1 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.28-2.41 (m, 5H, $OCH_2C\underline{H}_2$, CH_3), 4.01 (t, *J* = 6.7 Hz, 2H, SO_3CH_2), 4.96-5.07 (m, 2H, $CH=C\underline{H}_2$), 5.62 (ddt, *J* = 17.0 Hz, 10.3 Hz, 6.7 Hz, 1H, $C\underline{H}=CH_2$), 7.30 (d, *J* = 8.3 Hz, 2H, H_3, H_5), 7.73 (d, *J* = 8.3 Hz, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.3 (CH_3), 33.0 ($OCH_2\underline{C}H_2$), 69.4 ($O\underline{C}H_2CH_2$), 117.9 ($CH=\underline{C}H_2$), 127.7 (C_2, C_6), 129.8 (C_3, C_5), 132.6 (C_4), 133.0 ($\underline{C}H=CH_2$), 144.8 (C_4).

3.4. Synthesis of benzyl acrylate[39]

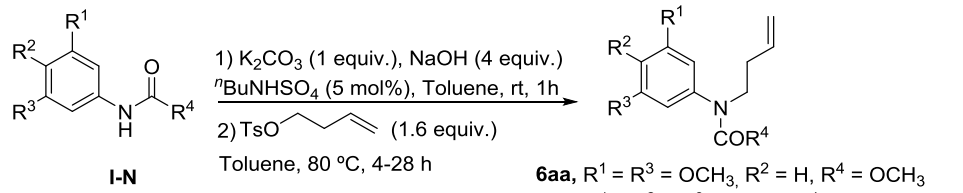


Over a solution of benzyl alcohol (3.4 mL, 32.9 mmol) and triethylamine (6.9 mL, 49.3 mmol) in dry CH_2Cl_2 (35 mL), acryloyl chloride (2.8 mL, 34.5 mmol) was added dropwise at 0 ºC under argon atmosphere. The mixture was stirred at 0 ºC for 30 min and then it was further stirred for 7 h at room temperature. Afterwards, the reaction was quenched by addition of water, the organic layer was separated and washed with water (2 × 30 mL) and an aqueous solution of NH_4Cl (2 × 30 mL). The organic extract was dried (Na_2SO_4) and concentrated *in*

[38] Falb, E.; Nudelman, A.; Gottlieb, H.E.; Hassner, A. *Eur. J. Org. Chem.* **2000**, 645.
[39] Chanthamath, S.; Takaki, S.; Shibatomi, K.; Iwasa, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 5818.

vacuo. Flash column chromatography (silica gel, hexane/AcOEt 9/1) afforded benzyl acrylate as an oil (4.4 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) 5.16 (s, 2H, C$\underline{H_2}$Ph), 5.70 (dd, *J* = 10.4, 1.5 Hz, 1H, H_{cis}), 6.13 (dd, *J* = 17.3, 10.4 Hz, 1H, C$\underline{H}$=CH_2), 6.41 (dd, *J* = 17.3, 1.5 Hz, 1H, H_{trans}), 7.07-7.73 Hz (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$) 66.3 (OCH_2), 128.3 (C_2, C_6), 128.4 (C_4), 128.6 (C_3, C_5), 131.1 ($\underline{C}$H=$\underline{C}H_2$) , 136.0 (C_1), 165.9 (CO).

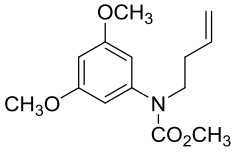
3.5. General procedure for the alkylation of protected anilines I-N. Synthesis of *N*-protected butenylanilines 6aa-6ba



6aa, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = OCH_3$
6ab, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = OCH_3$
6ac, $R^1 = H$, $R^2 = R^3 = OCH_3$, $R^4 = OCH_3$
6ad, $R^1 = H$, $R^2 = R^3 = -OCH_2O-$, $R^4 = OCH_3$
6ae, $R^1 = R^3 = CH_3$, $R^2 = H$, $R^4 = OCH_3$
6ba, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = CH_3$

Over a solution of the corresponding protected aniline **I-N** (1 mmol) in toluene (12 mL), anhydrous K_2CO_3 (1 mmol), powdered NaOH (4 mmol) and ^{n}Bu$_4$NHSO$_4$ (0.05 mmol) were added. The mixture was stirred for 1 h at room temperature and then, it was heated at 80 ºC for 15 min. Afterwards, a solution of but-3-en-1-yl 4-methylbenzenesulfonate (1.6 mmol) in toluene (1.5 mL) was added, and the reaction was heated at 80 ºC for 4-28 h. The mixture was allowed to cool down to room temperature, and a 1 M aqueous solution of HCl (25 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/AcOEt) afforded the corresponding *N*-substituted but-3-en-1-ylanilines **6aa-6ba.**

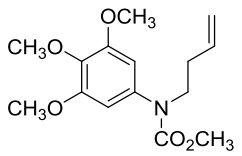
*Methyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate (**6aa**)*



Prepared from methyl (3,5-dimethoxyphenyl)carbamate **I** (2.1 g, 9.7 mmol), anhydrous K_2CO_3 (1.3 g, 9.7 mmol), powdered NaOH (1.6 g, 38.9 mmol) and ^{n}Bu$_4$NHSO$_4$ (0.16 g, 0.49 mmol) in toluene (29.2 mL). The mixture was stirred for 1 h at room temperature and then, it was heated at 80 ºC for 15 min. Afterwards, a solution of but-3-en-1-yl 4-

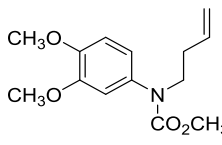
methylbenzenesulfonate (3.5 g, 15.6 mmol) in toluene (11 mL) was added, and the reaction was heated at 80 ºC for 28 h. After work-up, the crude reaction product was purified by flash column chromatography (silica gel, hexane/AcOEt 8/2), affording **6aa** as an oil (2.4 g, 93%): IR (ATR): ν (cm^{-1}) = 1706 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.17-2.31 (m, 2H, $NCH_2\underline{C}H_2$), 3.51-3.78 (m, 11H, CO_2CH_3, $NC\underline{H}_2CH_2$, 2 × OCH_3), 4.82-5.11 (m, 2H, $CH=C\underline{H}_2$), 5.69 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H, $C\underline{H}=CH_2$), 6.30 (s, 3H, H_2, H_4, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 32.7 ($NCH_2\underline{C}H_2$), 49.6 ($N\underline{C}H_2CH_2$), 52.6 ($CO_2\underline{C}H_3$), 55.2 (2 × $O\underline{C}H_3$), 98.7 (C_4), 105.9 (C_2, C_6), 116.6 ($CH=\underline{C}H_2$), 135.2 ($\underline{C}H=CH_2$), 143.3 (C_1), 155.8 (CO), 160.8 (C_3, C_5); MS (EI): *m/z* (%): 265.1 (M^+, 25), 225.1 (13), 224.1 (100), 211.1 (12), 180.1 (23), 165.1 (22), 152.1 (39), 137.1 (10); HRMS (CI): *m/z* calcd. for $C_{14}H_{20}NO_4$: 266.1396 [MH^+]; found: 266.1392.

*Methyl but-3-en-1-yl(3,4,5-trimethoxyphenyl)carbamate (**6ab**)*



Prepared from methyl (3,4,5-trimethoxyphenyl)carbamate **J** (0.40 g, 1.7 mmol), anhydrous K_2CO_3 (0.24 g, 1.7 mmol), powder NaOH (0.27 g, 6.7 mmol) and ^{n}Bu_4NHSO_4 (29.0 mg, 0.083 mmol) in toluene (20 mL). The mixture was stirred for 1 h at room temperature and then heated at 80 ºC for 15 min. Afterwards a solution of but-3-en-1-yl 4-methylbenzenesulfonate (0.60 g, 2.7 mmol) in toluene (3 mL) was added and the reaction mixture was heated at 80 ºC for 28 h. After work-up, the crude reaction product was purified by flash column chromatography (silica gel, hexane/AcOEt 6/4) affording **6ab** as an oil (0.29 g, 59%): IR (ATR): ν (cm^{-1}) = 1700 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.26-2.37 (m, 2H, $NCH_2\underline{C}H_2$), 3.64-3.76 (m, 5H, CO_2CH_3, NCH_2), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.04-5.11 (m, 2H, $CH=C\underline{H}_2$), 5.78 (ddt, *J* = 17.1 Hz, 10.3 Hz, 6.8 Hz, 1 H, $C\underline{H}=CH_2$), 6.41 (s, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 32.7 ($NCH_2\underline{C}H_2$), 49.9 ($CO_2\underline{C}H_3$), 52.8 (NCH_2), 56.1 (2 × OCH_3), 60.7 (OCH_3), 105.1 (C_2, C_6), 116.7 ($CH=\underline{C}H_2$), 135.2 (C_1), 136.8 (C_4), 137.3 ($\underline{C}H=CH_2$), 153.2 (C_3, C_5), 156.0 (CO); MS (EI): *m/z* (%): 295 (M^+, 71), 280.2 (19), 254.2 (100), 226.2 (23), 195.2 (46), 182.2 (24), 180.2 (51), 167.2 (13); HRMS (ESI): *m/z* calcd. for $C_{15}H_{22}NO_5$: 296.1498 [MH^+]; found: 296.1509.

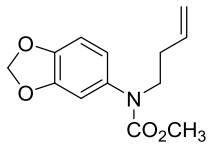
*Methyl but-3-en-1-yl(3,4-dimethoxyphenyl)carbamate (**6ac**)*



Prepared from methyl (3,4-dimethoxyphenyl)carbamate **K** (0.63 g, 3.0 mmol), anhydrous K_2CO_3 (0.42 g, 3.0 mmol), powder NaOH (0.48 g, 11.9 mmol) and ^{n}Bu_4NHSO_4 (51.0 mg, 0.15 mmol) in toluene (35 mL). The mixture was stirred for 1 h at room temperature and then, it was heated at 80 ºC for 15 min. Afterwards, a solution of but-3-en-1-yl 4-methylbenzenesulfonate (1.1 g, 4.7 mmol) in toluene (4.5 mL) was added, and the reaction

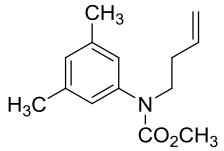
mixture was heated at 80 °C for 28 h. After work-up, the crude reaction product was purified by flash column chromatography (silica gel, hexane/AcOEt 7/3) affording **6ac** as an oil (0.71 g, 91%): IR (ATR): ν (cm^{-1}) = 1700 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.23-2.30 (m, 2H, $NCH_2C\underline{H}_2$), 3.62-3.71 (m, 5H, CO_2CH_3, NCH_2), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.97-5.07 (m, 2H, $CH=C\underline{H}_2$), 5.73 (ddt, *J* = 17.0 Hz, 10.2 Hz, 6.8 Hz, 1H, $C\underline{H}=CH_2$), 6.62-6.75 (m, 2H, H_2, H_5), 6.80 (d, *J* = 8.4 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 32.6 ($NCH_2\underline{C}H_2$), 49.9 ($CO_2\underline{C}H_3$), 52.7 (NCH_2), 55.8 (OCH_3), 111.0 (C_2), 111.4 (C_5), 116.6 (C_6), 119.6 ($CH=\underline{C}H_2$), 134.5 (C_1), 135.2 ($\underline{C}H=CH_2$), 147.8 (C_4), 149.0 (C_3), 156.1 (CO); MS (EI): *m/z* (%): 265.1 (M^+, 47), 225.1 (13), 224.1 (100), 192.1 (15), 180.1 (11), 165.1 (50), 152.1 (39), 150.1 (31); HRMS (ESI): *m/z* calcd. for $C_{14}H_{20}NO_4$: 266.1396 [MH^+]; found: 266.1393.

*Methyl benzo[d][1,3]dioxol-5-yl(but-3-en-1-yl)carbamate (**6ad**)*



Prepared from methyl benzo[*d*][1,3]dioxol-5-ylcarbamate **L** (0.72 g, 3.7 mmol), anhydrous K_2CO_3 (0.49 g, 3.7 mmol), powder NaOH (0.57 g, 14.9 mmol) and ^{n}Bu$_4$NHSO$_4$ (60.0 mg, 0.19 mmol) in toluene (45 mL). The mixture was stirred for 1 h at room temperature and then heated at 80 °C for 15 min. Afterwards, a solution of but-3-en-1-yl 4-methylbenzenesulfonate (1.3 g, 5.6 mmol) in toluene (5 mL) was added, and the reaction mixture was heated at 80 °C for 28 h. After work-up, the crude reaction product was purified by flash column chromatography (silica gel, hexane/AcOEt 7/3) affording **6ad** as an oil (0.79 g, 85%): IR (ATR): ν (cm^{-1}) = 1700 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.20-2.34 (m, 2H, $NCH_2C\underline{H}_2$), 3.60-3.70 (m, 5H, CO_2CH_3, NCH_2), 4.98-5.09 (m, 2H, $CH=C\underline{H}_2$), 5.73 (ddt, *J* = 17.0 Hz, 10.2 Hz, 6.8 Hz, 1 H, $C\underline{H}=CH_2$), 5.95 (s, 2H, OCH_2O), 6.59-6.66 (m, 2H, H_2, H_5), 6.75 (d, *J* = 8.1 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 32.6 ($NCH_2\underline{C}H_2$), 50.0 ($CO_2\underline{C}H_3$), 52.8 (NCH_2), 101.5 (OCH_2O), 108.1 (C_2), 109.0 (C_5), 116.8 (C_6), 120.8 ($CH=\underline{C}H_2$), 135.1 (C_1), 135.5 ($\underline{C}H=CH_2$), 146.3 (C_4), 147.8 (C_3), 156.2 (CO); MS (EI): *m/z* (%): 249.1 (M^+, 40), 209.1 (11), 208.1 (100), 176.1 (9), 164.1 (21), 149.1 (65), 136.1 (27), 106.1 (13); HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NO_4$: 250.1079 [MH^+]; found: 250.1092.

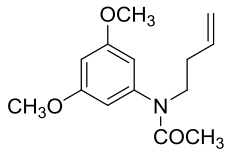
*Methyl but-3-en-1-yl(3,5-dimethylphenyl)carbamate (**6ae**)*



Prepared from methyl (3,5-dimethylphenyl)carbamate **M** (0.87 g, 4.9 mmol), anhydrous K_2CO_3 (0.70 g, 4.9 mmol), powder NaOH (0.80 g, 19.5 mmol) and ^{n}Bu$_4$NHSO$_4$ (85.0 mg, 0.25 mmol) in toluene (58.5 mL). The mixture was stirred for 1 h at room temperature and then, it was heated at 80 ºC for 15 min. Afterwards, a solution of but-3-en-1-yl 4-methylbenzenesulfonate (1.8 g, 7.8 mmol) in toluene (7 mL) was added, and the reaction

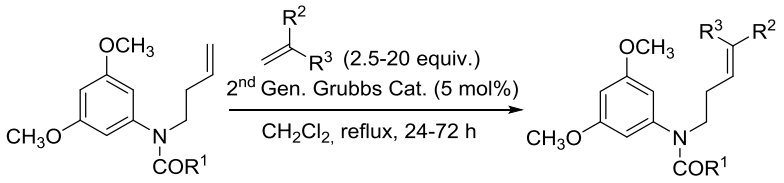
mixture was heated at 80 ^{o}C for 28 h. After work-up, the crude reaction product was purified by flash column chromatography (silica gel, hexane/AcOEt 7/3) affording **6ae** as an oil (0.87 g, 76%): IR (ATR) ν (cm^{-1}) = 1700 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.19-2.39 (m, 8H, $NCH_2C\underline{H}_2$, 2 x CH_3), 3.62-3.76 (m, 5H, CO_2CH_3, NCH_2), 4.99-5.10 (m, 2H, $CH=C\underline{H}_2$), 5.76 (ddt, *J* = 17.1 Hz, 10.4 Hz, 6.8 Hz, 1 H, $C\underline{H}=CH_2$), 6.80 (s, 2H, H_2, H_6), 6.90 (s, 1H, H_4); ^{13}C NMR ($CDCl_3$): δ (75.5 MHz, ppm) = 21.2 (2 × CH_3), 32.7 ($NCH_2\underline{C}H_2$), 49.9 ($CO_2\underline{C}H_3$), 52.8 (NCH_2), 116.6 ($CH=\underline{C}H_2$), 125.2 (C_2, C_6), 128.6 (C_4), 135.2 ($\underline{C}H=CH_2$), 138.6 (C_3, C_5), 141.5 (C_1), 156.2 (CO); MS (EI): *m/z* (%): 233.1 (M^+, 12), 192.1 (100), 148.1 (28), 133.1 (26), 121.1 (18), 105.1 (25); HRMS (ESI): *m/z* calcd. for $C_{14}H_{20}NO_2$: 234.1494 [MH^+]; found: 234.1503.

*N-(But-3-en-1-yl)-N-(3,5-dimethoxyphenyl)acetamide (**6ba**)*



Prepared from *N*-(3,5-dimethoxyphenyl)acetamide **N** (2.1 g, 10.5 mmol), anhydrous K_2CO_3 (1.5 g, 10.5 mmol), powdered NaOH (1.7 g, 42.0 mmol) and $^{n}Bu_4NHSO_4$ (0.18 g, 0.53 mmol) in toluene (31.5 mL). The mixture was stirred for 1 h at room temperature and then, it was heated at 80 ºC for 15 min. Afterwards, a solution of but-3-en-1-yl 4-methylbenzenesulfonate (3.8 g, 16.8 mmol) in toluene (9.5 mL) was added, and the reaction was heated at 80 ºC for 4 h. After work-up, the crude reaction product was purified by flash column chromatography (silica gel, hexane/AcOEt 6/4), affording **6ba** as an oil (1.7 g, 66%): IR (ATR): ν (cm^{-1}) = 1656 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.80 (s, 3H, $COCH_3$), 2.18-2.32 (m, 2H, $NCH_2C\underline{H}_2$), 3.65-3.72 (m, 2H, $NC\underline{H}_2CH_2$), 3.74 (s, 6H, 2 × OCH_3), 4.95-5.08 (m, 2H, $CH=C\underline{H}_2$), 5.69 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, $C\underline{H}=CH_2$), 6.25 (d, *J* = 2.2 Hz, 2H, H_2, H_6), 6.37 (t, *J* = 2.2 Hz, 1H, H_4); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.4 ($CO\underline{C}H_3$), 32.2 ($NCH_2\underline{C}H_2$), 47.8 ($N\underline{C}H_2CH_2$), 55.3 (2 × OCH_3), 99.4 (C_4), 106.4 (C_2, C_6), 116.4 ($CH=\underline{C}H_2$), 135.3 ($\underline{C}H=CH_2$), 144.5 (C_1), 161.3 (C_3, C_5), 169.8 ($\underline{C}O$); MS (EI): *m/z* (%): 249.1 (M^+, 6), 195.1 (12), 167.1 (10), 166.1 (100); HRMS (CI): *m/z* calcd. for $C_{14}H_{20}NO_3$: 250.1443 [MH^+]; found: 250.1455.

3.6. General procedure for the cross metathesis reaction of *N*-butenylanilines 6aa and 6ba. Synthesis of 7aa-7bf

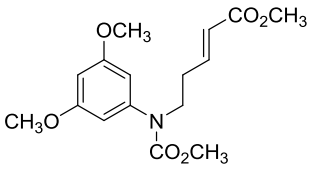


6aa, $R^1 = OCH_3$
6ba, $R^1 = CH_3$

7aa, $R^1 = OCH_3$, $R^2 = CO_2CH_3$, $R^3 = H$
7ba, $R^1 = CH_3$, $R^2 = CO_2CH_3$, $R^3 = H$
7ab, $R^1 = OCH_3$, $R^2 = CO_2(CH_2)_{11}CH_3$, $R^3 = H$
7ac, $R^1 = OCH_3$, $R^2 = CO_2CH_2CF_3$, $R^3 = H$
7ad, $R^1 = OCH_3$, $R^2 = CO_2Bn$, $R^3 = H$
7ae, $R^1 = OCH_3$, $R^2 = CO_2CH_3$, $R^3 = CH_3$
7af, $R^1 = OCH_3$, $R^2 = SO_2Ph$, $R^3 = H$
7bf, $R^1 = CH_3$, $R^2 = SO_2Ph$, $R^3 = H$

Over a solution of the corresponding *N*-but-3-en-1-ylaniline **6aa** or **6ba** (1 mmol) in dry CH_2Cl_2 (29 mL) under argon atmosphere, the corresponding acrylate (10 or 20 mmol) or phenyl vinyl sulfone (2.5 mmol) was added. The mixture was stirred, and then, a solution of 2nd generation Grubbs catalyst (0.05 mmol) in dry CH_2Cl_2 (8 mL) was added *via cannula*. The mixture was heated under reflux for 72 or 24 h, and every 24 h additional amounts of the catalyst (5 mol%) were added. Afterwards, the mixture was allowed to cool down to room temperature and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, hexane/AcOEt 6/4) afforded the corresponding products **7aa-7bf**.

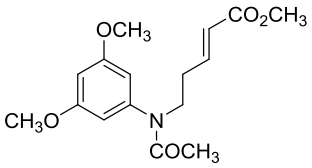
*Methyl (E)-5-((3,5-dimethoxyphenyl)(methoxycarbonyl)amino)pent-2-enoate (**7aa**)*



Prepared from methyl but-3-en-1-yl(3,5-dimethoxyphenyl)-carbamate **6aa** (1.1 g, 4.1 mmol) and methyl acrylate (7.4 mL, 81.8 mmol) in dry CH_2Cl_2 (118 mL), as well as a solution of 2nd generation Grubbs catalyst (0.17 g, 0.20 mmol) in dry CH_2Cl_2 (33 mL). The reaction mixture was heated under reflux for 72 h and additional amounts of the catalyst (0.17 g, 0.20 mmol) were added every 24 h. After purification by flash column chromatography, **7aa** was obtained as a solid (1.2 g, 88%): mp (CH_2Cl_2) 68-70 ºC; IR (ATR): ν (cm^{-1}) = 1727 (CO_2CH_3), 1691 (NCO_2CH_3); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.40-2.52 (m, 2H, $NCH_2C\underline{H}_2$),

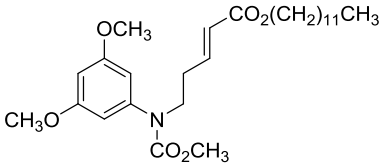
3.62-3.91 (m, 14H, 2 × OCH_3, CO_2CH_3, NCO_2CH_3, NCH_2CH_2), 5.82-5.91 (m, 1H, CO-CH=CH), 6.32 (d, *J* = 2.1 Hz, 2H, H_2, H_6), 6.37 (t, *J* = 2.1 Hz, 1H, H_4), 6.88 (dt, *J* = 15.7, 7.3 Hz, 1H, CO-CH=CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 31.2 (NCH_2CH_2), 48.9 (NCH_2CH_2), 51.5 (CO_2CH_3), 53.0 (CO_2CH_3), 55.4 (2 × OCH_3), 99.1 (C_4), 106.8 (C_2, C_6), 122.8 (CO-CH=CH), 143.1 (C_1), 145.4 (CO-CH=CH), 155.8 (NCO_2CH_3), 161.0 (C_3, C_5), 166.6 (CO_2CH_3); MS (EI): *m/z* (%): 323.1 (M^+, 11), 250.1 (18), 225.1 (13), 224.1 (100), 211.1 (18), 180.1 (21), 165.1 (19), 152.1 (36); HRMS (ESI): *m/z* calcd. for $C_{16}H_{22}NO_6$: 324.1447 [MH^+]; found: 324.1458.

*Methyl (E)-5-(N-(3,5-dimethoxyphenyl)acetamido)pent-2-enoate (**7ba**)*



Prepared from *N*-(but-3-en-1-yl)-*N*-(3,5-dimethoxyphenyl)acetamide **6ba** (0.15 g, 0.59 mmol) and methyl acrylate (1.1 mL, 11.7 mmol) in dry CH_2Cl_2 (17 mL), as well as a solution of 2nd generation Grubbs catalyst (24.8 mg, 0.029 mmol) in dry CH_2Cl_2 (4.7 mL). The reaction mixture was heated under reflux for 72 h and additional amounts of the catalyst (24.8 mg, 0.029 mmol) were added every 24 h. After purification by flash column chromatography, **7ba** was obtained as a solid (0.17 g, 91%): mp (CH_2Cl_2) 63-65 ºC; IR (ATR): ν (cm^{-1}) = 1724 (CO_2CH_3), 1656 ($COCH_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.87 (s, 3H, $COCH_3$), 2.40-2.53 (m, 2H, NCH_2CH_2), 3.60-3.86 (m, 11H, 2 × OCH_3, CO_2CH_3, NCH_2CH_2), 5.84 (d, *J* = 15.7 Hz, 1H, CO-CH=CH), 6.27 (d, *J* = 2.1 Hz, 2H, H_2, H_6), 6.43 (t, *J* = 2.1 Hz, 1H, H_4), 6.87 (dt, *J* = 15.7, 7.7 Hz, 1H, CO-CH=CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.4 ($COCH_3$), 31.7 (NCH_2CH_2), 47.2 (NCH_2CH_2), 51.3 (CO_2CH_3), 55.4 (2 × OCH_3), 99.6 (C_4), 106.3 (C_2, C_6), 122.6 (CO-CH=CH), 144.3 (C_1), 145.6 (CO-CH=CH), 161.4 (C_3, C_5), 166.5 (CO_2CH_3), 170.1 ($NCOCH_3$); MS (EI): *m/z* (%): 307.2 (M^+, 12), 234.1 (34), 208.1 (10), 195.1 (15), 167.2 (24), 166.2 (100), 153.1 (12); HRMS (ESI): *m/z* calcd. for $C_{16}H_{22}NO_5$: 308.1498 [MH^+]; found: 308.1507.

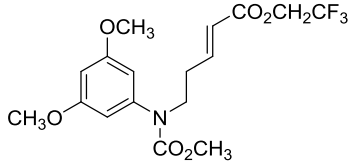
*Dodecyl (E)-5-((3,5-dimethoxyphenyl)(methoxycarbonyl)amino)pent-2-enoate (**7ab**)*



Prepared from methyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate **6aa** (0.29 g, 1.1 mmol) and lauryl acrylate (3.0 mL, 11.0 mmol) in dry CH_2Cl_2 (31.9 mL), as well as a solution of 2nd generation Grubbs catalyst (46.8 mg, 0.055 mmol) in dry CH_2Cl_2 (8.9 mL). The reaction mixture was heated under reflux for 72 h and additional amounts of the catalyst (46.8 mg, 0.055 mmol) were added every 24 h. After purification by flash column chromatography, **7ab** was obtained as an oil

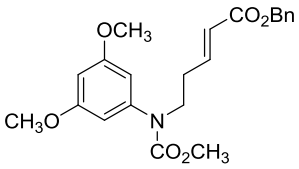
(0.53 g, quant.): IR (ATR): ν (cm^{-1}) = 1713 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.82 (t, *J* = 6.6 Hz, 3H, CH_3), 1.15-1.33 (m, 18H, $OCH_2CH_2(CH_2)_9CH_3$), 1.52-1.64 (m, 2H, $CO_2CH_2CH_2$), 2.36-2.46 (m, 2H, NCH_2CH_2), 3.53-3.80 (m, 11H, 2 × OCH_3, NCO_2CH_3, NCH_2CH_2), 4.04 (t, *J* = 6.7 Hz, 2H, CO_2CH_2), 5.79 (d, *J* = 15.7 Hz, 1H, CO-CH=CH), 6.28 (d, *J* = 1.8 Hz, 2H, H_2, H_6), 6.29-6.33 (m, 1H, H_4), 6.67-6.96 (m, 1H, CO-CH=CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.7 (CH_3), 22.7 (CH_3CH_2), 25.9 ($CO_2CH_2CH_2CH_2$), 28.6, 29.2, 29.3, 29.5, 29.6, 29.7 (7 × CH_2), 31.2 (NCH_2CH_2), 31.9 ($CH_3CH_2CH_2$), 48.9 (NCH_2CH_2), 52.9 (CO_2CH_3), 55.3 (2 × OCH_3), 64.4 (CO_2CH_2), 99.0 (C_4), 106.8 (C_2, C_6), 123.3 (CO-CH=CH), 143.1 (C_1), 145.0 (CO-CH=CH), 155.8 (NCO_2CH_3), 161.0 (C_3, C_5), 166.2 (CO_2CH_2); MS (ESI): *m/z* (%): 479.3 (MH^+ + 1, 25), 478.3 (MH^+, 100); HRMS (ESI): *m/z* calcd. for $C_{27}H_{44}NO_6$: 478.3169 [MH^+]; found: 478.3171.

*2,2,2-Trifluoroethyl (E)-5-((3,5-dimethoxyphenyl)(methoxycarbonyl)amino)pent-2-enoate (**7ac**)*



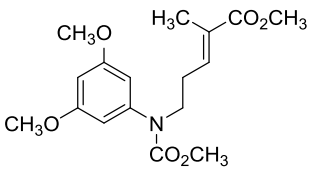
Prepared from methyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate **6aa** (0.30 g, 1.1 mmol) and 2,2,2-trifluoroethyl acrylate (1.4 mL, 11.2 mmol) in dry CH_2Cl_2 (32.4 mL), as well as a solution of 2nd generation Grubbs catalyst (47.6 mg, 0.056 mmol) in dry CH_2Cl_2 (9 mL). The reaction mixture was heated under reflux for 72 h and additional amounts of the catalyst (47.6 mg, 0.056 mmol) were added every 24 h. After purification by flash column chromatography, **7ac** was obtained as an oil (0.41 g, 94%): IR (ATR): ν (cm^{-1}) = 1739 (CO_2CH_2), 1701 (NCO_2CH_3); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.45-2.57 (m, 2H, NCH_2CH_2), 3.56-3.91 (m, 11H, 2 × OCH_3, NCO_2CH_3, NCH_2CH_2), 4.49 (q, *J* = 8.5 Hz, 2H, $CO_2CH_2CF_3$), 5.90 (d, *J* = 15.7 Hz, 1H, CO-CH=CH), 6.31 (d, *J* = 1.9 Hz, 2H, H_2, H_6), 6.36-6.39 (m, 1H, H_4), 7.01 (dt, *J* = 15.7, 7.1 Hz, 1H, CO-CH=CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 31.4 (NCH_2CH_2), 48.7 (NCH_2CH_2), 52.9 (CO_2CH_3), 55.3 (2 × OCH_3), 60.0 (q, *J* = 36.6 Hz, $CO_2CH_2CF_3$), 99.0 (C_4), 106.8 (C_2, C_6), 121.2 (CO-CH=CH), 123.0 (q, *J* = 275.8 Hz, CF_3), 143.0 (C_1), 148.3 (CO-CH=CH), 155.8 (NCO_2CH_3), 160.9 (C_3, C_5), 164.2 (CO_2CH_2); MS (EI): *m/z* (%): 392.2 (M^+ + 1, 4), 391.2 (M^+, 20), 250.1 (19), 225.1 (14), 224.2 (100), 211.1 (15), 180.1 (23), 165.1 (19), 152.1 (35); HRMS (ESI): *m/z* calcd. for $C_{17}H_{21}NO_6F_3$: 392.1321 [MH^+]; found: 392.1329.

*Benzyl (E)-5-((3,5-dimethoxyphenyl)(methoxycarbonyl)amino)pent-2-enoate (**7ad**)*



Prepared from methyl but-3-en-1-yl(3,5-dimethoxyphenyl)-carbamate **6aa** (0.24 g, 0.92 mmol) and benzyl acrylate (1.4 mL, 9.2 mmol) in dry CH_2Cl_2 (26.5 mL), as well as a solution of 2nd generation Grubbs catalyst (38.9 mg, 0.046 mmol) in dry CH_2Cl_2 (7.4 mL). The reaction mixture was heated under reflux for 24 h and after purification by flash column chromatography, **7ad** was obtained as an oil (0.32 g, 86%): IR (ATR): ν (cm^{-1}) = 1706 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.43-2.53 (m, 2H, $NCH_2C\underline{H}_2$), 3.64-3.81 (m, 11H, $NC\underline{H}_2CH_2$, NCO_2CH_3, 2 × OCH_3), 5.16 (s, 2H, $C\underline{H}_2Ph$), 5.86-5.94 (m, 1H, CO-C<u>H</u>=CH), 6.33 (d, *J* = 2.2 Hz, 2H, H_2, H_6), 6.39 (t, *J* = 2.2 Hz, 1H, H_4), 6.94 (dt, *J* = 15.7, 7.1 Hz, 1H, CO-CH=C<u>H</u>), 7.22-7.40 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 31.3 ($NCH_2\underline{C}H_2$), 48.9 ($N\underline{C}H_2CH_2$), 53.0 ($CO_2\underline{C}H_3$), 55.6 (2 × OCH_3), 66.1 ($\underline{C}H_2Ph$), 99.1 (C_4), 106.8 (C_2, C_6), 122.9 (CO-<u>C</u>H=CH), 128.1 ($C_{2'}$,$C_{6'}$), 128.2 ($C_{4'}$), 128.6 ($C_{3'}$,$C_{5'}$), 136.1 ($C_{1'}$), 143.1 (C_1), 145.9 (CO-CH=<u>C</u>H), 155.8 ($N\underline{C}O_2CH_3$), 161.0 (C_3, C_5), 165.9 ($\underline{C}O_2CH_2$); MS (EI): *m/z* (%): 400.2 (M^+ + 1, 2), 399.2 (M^+, 7), 308.1 (24), 250.1 (16), 248.1 (19), 225.1 (13), 224.1 (100), 211.1 (13), 180.1 (25), 165.1 (19), 152,1 (37), 91.1 (49); HRMS (ESI): *m/z* calcd. for $C_{22}H_{26}NO_6$: 400.1760 [MH^+]; found: 400.1760.

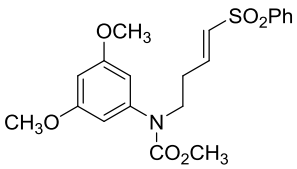
*Methyl (E)-5-((3,5-dimethoxyphenyl)(methoxycarbonyl)amino)-2-methylpent-2-enoate (**7ae**)*



Prepared from methyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate **6aa** (0.36 g, 1.4 mmol) and methyl methacrylate (2.9 mL, 27.3 mmol) in dry CH_2Cl_2 (39.4 mL), as well as a solution of 2nd generation Grubbs catalyst (57.9 mg, 0.068 mmol) in dry CH_2Cl_2 (11 mL). The reaction mixture was heated under reflux for 72 h and additional amounts of the catalyst (57.9 mg, 0.068 mmol) were added every 24 h. After purification by flash column chromatography, **7ae** was obtained as an oil (0.42 g, 92%): IR (ATR): ν (cm^{-1}) = 1706 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.76 (s, 3H, $C\underline{H}_3C$=CH), 2.36-2.46 (m, 2H, $NCH_2C\underline{H}_2$), 3.56-3.80 (m, 14H, 2 × OCH_3, NCO_2CH_3, CO_2CH_3, $NC\underline{H}_2CH_2$), 6.29 (d, *J* = 1.5 Hz, 2H, H_2, H_6), 6.31-6.35 (m, 1H, H_4), 6.61-6.69 (m, 1H, CO-C(CH_3)=C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 12.5 (CH_3), 27.8 ($NCH_2\underline{C}H_2$), 49.2 ($N\underline{C}H_2CH_2$), 51.7 ($CO_2\underline{C}H_3$), 52.9 ($CO_2\underline{C}H_3$), 55.3 (2 × OCH_3), 98.9 (C_4), 106.7 (C_2, C_6), 129.5 (CO-<u>C</u>(CH_3)=CH), 138.2 (CO-C(CH_3)=<u>C</u>H), 143.2 (C_1), 155.8 ($N\underline{C}O_2CH_3$), 160.9 (C_3, C_5), 168.2 ($\underline{C}O_2CH_3$); MS (EI): *m/z* (%): 338.2 (M^+ + 1, 2), 337.2

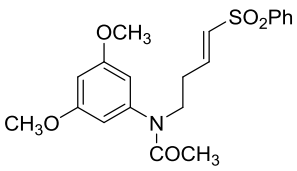
(M^+, 10), 305.1 (13), 225.1 (16), 224.2 (100), 211.1 (16), 180.1 (24), 165.1 (18), 152.1 (37); HRMS (ESI): *m/z* calcd. for $C_{17}H_{24}NO_6$: 338.1604 [MH^+]; found: 338.1604.

*Methyl (E)-(3,5-dimethoxyphenyl)(4-(phenylsulfonyl)but-3-en-1-yl)carbamate (**7af**)*



Prepared from methyl but-3-en-1-yl(3,5-dimethoxyphenyl)-carbamate **6aa** (0.12 g, 0.45 mmol) and phenyl vinyl sulfone (0.18 g, 1.1 mmol) in dry CH_2Cl_2 (13 mL), as well as a solution of 2nd generation Grubbs catalyst (19.1 mg, 0.023 mmol) in dry CH_2Cl_2 (3.7 mL). The reaction mixture was heated under reflux for 72 h and additional amounts of the catalyst (19.1 mg, 0.023 mmol) were added every 24 h. After purification by flash column chromatography, **7af** was obtained as an oil (0.13 g, 71%): IR (ATR): ν (cm^{-1}) = 1702 (C=O), 1229, 1157 (R-SO_2-R); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.43-2.54 (m, 2H, $NCH_2C\underline{H}_2$), 3.65 (s, 3H, CO_2CH_3), 3.70-3.86 (m, 8H, $NC\underline{H}_2CH_2$, 2 × OCH_3), 6.25 (d, *J* = 2.2 Hz, 2H, H_2, H_6), 6.30-6.42 (m, 2H, H_4, $CH=C\underline{H}$-SO_2Ph), 6.91 (dt, *J* = 15.2, 6.9 Hz, 1H, $C\underline{H}$=CH-SO_2Ph), 7.46-7.66 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$), 7.76-7.91 (m, 2H, $H_{3'}$, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 30.4 ($NCH_2\underline{C}H_2$), 48.4 ($N\underline{C}H_2CH_2$), 53.1 ($CO_2\underline{C}H_3$), 55.4 (2 × OCH_3), 99.1 (C_4), 105.7 (C_2, C_6), 127.6 ($C_{2'}$, $C_{6'}$), 129.3 ($C_{3'}$, $C_{5'}$), 132.2 ($C_{4'}$), 133.4 ($\underline{C}H$=CH-SO_2Ph), 140.4 ($C_{1'}$), 142.7 (C_1), 143.1 (CH=$\underline{C}H$-SO_2Ph), 155.8 (CO), 161.0 (C_3, C_5); MS (ESI): *m/z* (%): 407.1 (MH^+ + 1, 20), 406.1 (MH^+, 100), 374.1 (1); HRMS (ESI): *m/z* calcd. for $C_{20}H_{24}NO_6S$: 406.1324 [MH^+]; found: 406.1326.

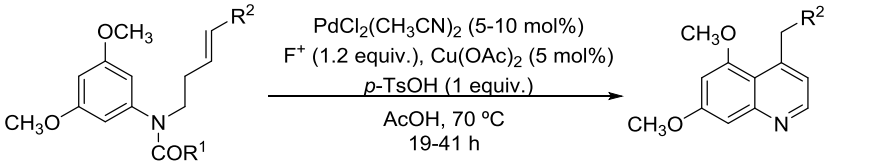
*(E)-N-(3,5-dimethoxyphenyl)-N-(4-(phenylsulphonyl)but-3-en-1-yl)acetamide (**7bf**)*



Prepared from *N*-(but-3-en-1-yl)-*N*-(3,5-dimethoxyphenyl)-acetamide **6ba** (0.15 g, 0.59 mmol) and phenyl vinyl sulfone (0.25 g, 1.5 mmol) in dry CH_2Cl_2 (17 mL), as well as a solution of 2nd generation Grubbs catalyst (25.0 mg, 0.029 mmol) in dry CH_2Cl_2 (4.7 mL). The reaction mixture was heated under reflux for 72 h and additional amounts of the catalyst (25.0 mg, 0.029 mmol) were added every 24 h. After purification by flash column chromatography, **7bf** was obtained as an oil (0.18 g, 77%): IR (ATR): ν (cm^{-1}) = 1652 (C=O), 1311, 1143 (R-SO_2-R); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.84 (s, 3H, $COCH_3$), 2.43-2.57 (m, 2H, $NCH_2C\underline{H}_2$), 3.71-3.89 (m, 8H, $NC\underline{H}_2CH_2$, 2 × OCH_3), 6.23 (d, *J* = 2.2 Hz, 2H, H_2, H_6), 6.31-6.49 (m, 2H, H_4, $CH=C\underline{H}$-SO_2Ph), 6.92 (dt, *J* = 14.8, 6.8 Hz, 1H, $C\underline{H}$=CH-SO_2Ph), 7.43-7.67 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$), 7.76-7.95 (m, 2H, $H_{3'}$, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.5 ($CO\underline{C}H_3$), 29.9 ($NCH_2\underline{C}H_2$), 46.7 ($N\underline{C}H_2CH_2$), 55.5 (2 × OCH_3), 99.8 (C_4), 106.2 (C_2, C_6), 127.6

($C_{2'}$, $C_{6'}$), 129.3 ($C_{3'}$, $C_{5'}$), 132.2 ($C_{4'}$), 133.4 (<u>C</u>H=CH-SO_2Ph), 140.5 ($C_{1'}$), 143.4 (CH=<u>C</u>H-SO_2Ph), 144.2 (C_1), 161.6 (C_3, C_5), 170.5 (<u>C</u>O); MS (CI): *m/z* (%): 391.1 (MH^+ + 1, 20), 390.1 (MH^+, 79), 348.1 (22), 250.1 (26), 249.1 (16), 248.1 (67), 247.1 (14), 232.1 (16), 231.1 (13), 208.1 (12), 206.1 (21), 197.1 (17), 196.1 (99), 195.1 (100), 180.1 (11), 166.1 (29), 153.1 (15), 125.0 (17), 111.0 (42), 110.0 (19); HRMS (CI): *m/z* calcd. for $C_{20}H_{24}NO_5S$: 390.1375 [MH^+]; found: 390.1378.

3.7. General procedure for the Pd(II)-catalyzed cyclization of esters 7aa-7ad. Synthesis of 4-substituted quinolines 8a-8d

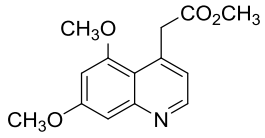


7aa, $R^1 = OCH_3$, $R^2 = CO_2CH_3$
7ba, $R^1 = CH_3$, $R^2 = CO_2CH_3$
7ab, $R^1 = OCH_3$, $R^2 = CO_2(CH_2)_{11}CH_3$
7ac, $R^1 = OCH_3$, $R^2 = CO_2CH_2CF_3$
7ad, $R^1 = OCH_3$, $R^2 = CO_2Bn$

8a, $R^2 = CO_2CH_3$
8b, $R^2 = CO_2(CH_2)_{11}CH_3$
8c, $R^2 = CO_2CH_2CF_3$
8d, $R^2 = CO_2Bn$

Over a solution of the corresponding ester **7aa-7ad** (1 mmol) in AcOH (11 mL), *p*-TsOH (1 mmol), *N*-fluoro-2,4,6-trimethylpyridinium triflate (F^+) (1.2 mmol), $Cu(OAc)_2$ (0.05 mmol) and $PdCl_2(CH_3CN)_2$ (0.05 or 0.1 mmol) were added. The mixture was stirred at 70 °C for 19-41 h, and then the solvent was removed under vacuum. The residue was dissolved in AcOEt (5 mL) and it was washed with a 2 M aqueous solution of Na_2CO_3 (2 × 10 mL) and brine (2 × 10 mL). The aqueous phase was re-extracted with AcOEt (10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, hexane/AcOEt) afforded the corresponding quinolines **8a-8d**.

*Methyl 2-(5,7-dimethoxyquinolin-4-yl)acetate (**8a**)*



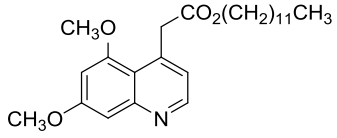
*This compound could be prepared starting from two different substrates, **7aa** and **7ba**, alternatively:*

Prepared from methyl *(E)*-5-[(3,5-dimethoxyphenyl)(methoxy-carbonyl)amino]pent-2-enoate **7aa** (93.3 mg, 0.29 mmol), *p*-TsOH (54.9 mg, 0.29 mmol), F^+ (0.10 g, 0.35 mmol), $Cu(OAc)_2$ (2.6 mg, 0.014 mmol) and $PdCl_2(CH_3CN)_2$ (3.7 mg, 0.014 mmol) in AcOH (3.2 mL). The mixture was stirred at 70 °C for

19 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 2/8), **8a** was obtained as a solid (40.8 mg, 54%): mp (CH_2Cl_2) 77-80 °C; IR (ATR): ν (cm^{-1}) = 1735 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.67 (s, 3H, CO_2CH_3), 3.83 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.09 (s, 2H, $C\underline{H}_2CO_2CH_3$), 6.49 (d, *J* = 2.2 Hz, 1H, H_6), 6.95 (d, *J* = 4.4 Hz, 1H, H_3), 7.02 (d, *J* = 2.2 Hz, 1H, H_8), 8.67 (d, *J* = 4.4 Hz, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 42.8 ($\underline{C}H_2CO_2CH_3$), 51.8 ($CO_2\underline{C}H_3$), 55.2 (OCH_3), 55.5 (OCH_3), 99.0 (C_6), 100.9 (C_8), 116.0 (C_{4a}), 122.2 (C_3), 140.2 (C_4), 150.4 (C_2), 151.6 (C_{8a}), 157.2 (C_5), 160.5 (C_7), 171.4 (CO); MS (EI): *m/z* (%): 262.1 (M^+ + 1, 17), 261.2 (M^+, 100), 229.1 (12), 202.1 (10), 186.1 (19), 172.1 (36); HRMS (ESI): *m/z* calcd. for $C_{14}H_{16}NO_4$: 262.1079 [MH^+]; found: 262.1091.

Prepared from methyl *(E)*-5-[*N*-(3,5-dimethoxyphenyl)acetamido]pent-2-enoate **7ba** (86.9 mg, 0.28 mmol), *p*-TsOH (53.8 mg, 0.28 mmol), F^+ (98.3 mg, 0.34 mmol), $Cu(OAc)_2$ (2.6 mg, 0.014 mmol) and $PdCl_2(CH_3CN)_2$ (3.7 mg, 0.014 mmol) in AcOH (3.1 mL). The mixture was stirred at 70 °C for 24 h and an additional amount of the catalyst (3.7 mg, 0,014 mmol) was added. The reaction was further stirred for 17.5 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 2/8), **8a** was obtained as a solid (39.7 mg, 54%).

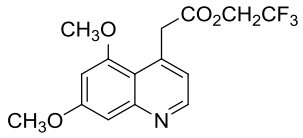
*Dodecyl 2-(5,7-dimethoxyquinolin-4-yl)acetate (**8b**)*



Prepared from dodecyl *(E)*-5-[(3,5-dimethoxyphenyl) (methoxycarbonyl)amino]pent-2-enoate **7ab** (0.14 g, 0.29 mmol), *p*-TsOH (54.3 mg, 0.29 mmol), F^+ (99.1 mg, 0.34 mmol), $Cu(OAc)_2$ (3.1 mg, 0.017 mmol) and $PdCl_2(CH_3CN)_2$ (4.4 mg, 0.017 mmol) in AcOH (3.2 mL). The mixture was stirred at 70 °C for 21 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 3/7), **8b** was obtained as a solid (59.5 mg, 50%): mp (CH_2Cl_2) 54–56 °C; IR (ATR) ν (cm^{-1}) = 1731 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.87 (t, *J* = 6.7 Hz, 3H, $C\underline{H}_3$), 1.10–1.35 (m, 18H, $OCH_2CH_2(C\underline{H}_2)_9CH_3$), 1.42–1.64 (m, 2H, $CO_2CH_2C\underline{H}_2$), 3.83 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.05 (t, *J* = 6.7 Hz, 2H, CO_2CH_2), 4.09 (s, 2H, $C\underline{H}_2CO_2CH_2$), 6.49 (d, *J* = 1.7 Hz, 1H, H_6), 6.96 (d, *J* = 4.1 Hz, 1H, H_3), 7.08 (d, *J* = 1.7 Hz, 1H, H_8), 8.67 (br s, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.1 (CH_3), 22.7 ($CH_3\underline{C}H_2$), 25.9 ($CO_2CH_2CH_2\underline{C}H_2$), 28.6, 29.2, 29.3, 29.5, 29.6, 29.7 (7 × $\underline{C}H_2$), 31.9 ($CH_3CH_2\underline{C}H_2$), 43.2 ($\underline{C}H_2CO_2CH_2$), 55.2 (OCH_3), 55.5 (OCH_3), 64.9 ($CO_2\underline{C}H_2$), 99.0 (C_6), 100.9 (C_8), 116.0 (C_{4a}), 122.2 (C_3), 140.5 (C_4), 150.4 (C_2), 151.6 (C_{8a}), 157.2 (C_5), 160.5 (C_7), 171.0 (CO); MS (EI): *m/z* (%): 416.3 (M^+ + 1, 8), 415.3 (M^+, 30), 386.3 (24), 372.2 (23), 358.2 (21), 344.2 (18), 330.2 (18), 316.2 (21), 302.1 (21), 248.1 (12), 247.1 (10), 204.1 (11), 203.1 (72), 202.1 (25), 189.1 (10),

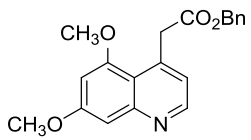
188.1 (100), 173.1 (18), 172.1 (56), 129.0 (10), 57.1 (12), 55.1 (19); HRMS (ESI): *m/z* calcd. for $C_{25}H_{38}NO_4$: 416.2801 [MH^+]; found: 416.2809.

*2,2,2-Trifluoroethyl 2-(5,7-dimethoxyquinolin-4-yl)acetate (**8c**)*



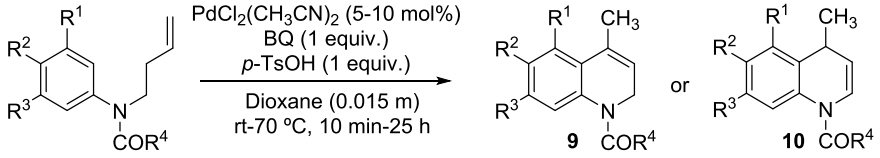
Prepared from 2,2,2-trifluoroethyl *(E)*-5-[(3,5-dimethoxyphenyl)(methoxycarbonyl)amino]pent-2-enoate **7ac** (0.15 g, 0.39 mmol), *p*-TsOH (73.4 mg, 0.39 mmol), F^+ (0.13 g, 0.46 mmol), $Cu(OAc)_2$ (3.5 mg, 0.019 mmol) and $PdCl_2(CH_3CN)_2$ (5.0 mg, 0.019 mmol) in AcOH (4.3 mL). The mixture was stirred at 70 °C for 21 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 2/8), **8c** was obtained as a solid (58.3 mg, 46%): mp (CH_2Cl_2) 95-97 °C; IR (ATR): ν (cm^{-1}) = 1745 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.81 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.19 (s, 2H, $C\underline{H_2}CO_2CH_2$), 4.48 (q, *J* = 8.5 Hz, 2H, $CO_2C\underline{H_2}CF_3$), 6.50 (d, *J* = 2.2 Hz, 1H, H_6), 6.95 (d, *J* = 4.4 Hz, 1H, H_3), 7.06 (d, *J* = 2.2 Hz, 1H, H_8), 8.67 (d, *J* = 4.4 Hz, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 42.2 ($\underline{C}H_2CO_2CH_2$), 55.3 (OCH_3), 55.6 (OCH_3), 60.5 (q, *J* = 36.6 Hz, $CO_2\underline{C}H_2CF_3$), 99.3 (C_6), 100.8 (C_8), 115.8 (C_{4a}), 122.3 (C_3), 112.9 (q, *J* = 275.8 Hz, CF_3), 139.2 (C_4), 150.3 (C_2), 151.5 (C_{8a}), 157.0 (C_5), 160.7 (C_7), 169.5 (CO); MS (EI): *m/z* (%): 330.1 (M^+ + 1, 17), 329.1 (M^+, 100), 186 (21), 172.1 (27); HRMS (ESI): *m/z* calcd. for $C_{15}H_{15}F_3NO_4$: 330.0953 [MH^+]; found: 330.0956.

*Benzyl 2-(5,7-dimethoxyquinolin-4-yl)acetate (**8d**)*



Prepared from benzyl *(E)*-5-[(3,5-dimethoxyphenyl)-(methoxycarbonyl)amino]pent-2-enoate **7ad** (0.11 g, 0.28 mmol), *p*-TsOH (53.9 mg, 0.28 mmol), F^+ (98.3 mg, 0.34 mmol), $Cu(OAc)_2$ (2.6 mg, 0.014 mmol) and $PdCl_2(CH_3CN)_2$ (3.7 mg, 0.014 mmol) in AcOH (3.1 mL). The mixture was stirred at 70 °C for 21 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 2/8), **8d** was obtained as an oil (58.9 mg, 62%): IR (ATR): ν (cm^{-1}) = 1735 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.54 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.12 (s, 2H, $C\underline{H_2}CO_2CH_2Ph$), 5.12 (s, 2H, $C\underline{H_2}Ph$) 6.41 (d, *J* = 2.3 Hz, 1H, H_6), 6.97 (d, *J* = 4.5 Hz, 1H, H_3), 7.06 (d, *J* = 2.3 Hz, 1H, H_8), 7.14-7.49 (m, 5H, Ph), 8.67 (d, *J* = 4.5 Hz, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 43.1 ($\underline{C}H_2CO_2CH_2Ph$), 54.9 ($OCH_3$), 55.5 ($OCH_3$), 66.3 ($\underline{C}H_2Ph$), 99.0 ($C_6$), 100.8 ($C_8$), 116.0 ($C_{4a}$), 122.3 ($C_3$), 128.2 ($C_{2'}$, $C_{6'}$), 128.5 ($C_{3'}$, $C_{4'}$, $C_{5'}$), 136.0 ($C_{1'}$), 140.2 (C_4), 150.4 (C_2), 151.6 (C_{8a}), 157.1 (C_5), 160.5 (C_7), 170.7 (CO); MS (EI): *m/z* (%): 338.1 (M^+ + 1, 20), 337.1 (M^+, 92), 172.1 (47), 91.1 (100); HRMS (ESI): *m/z* calcd. for $C_{20}H_{20}NO_4$: 338.1392 [MH^+]; found: 338.1418.

3.8. General procedure for the Pd(II)-catalyzed cyclization of *N*-protected butenylanilines 6aa-6ba. Synthesis of dihydroquinolines 9aa-9ba and 10ae

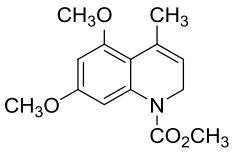


6aa-6ba

9aa, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = OCH_3$
9ba, $R^1 = R^3 = OCH_3$, $R^2 = H$, $R^4 = CH_3$
9ab, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = OCH_3$
10ae, $R^1 = R^3 = CH_3$, $R^2 = H$, $R^4 = OCH_3$

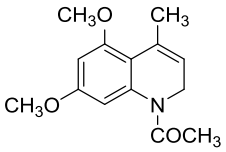
Over a solution of the corresponding *N*-substituted but-3-en-1-ylaniline **6aa-6ba** (1 mmol) in dioxane (66.7 mL), *p*-TsOH (1 mmol), benzoquinone (1 mmol) and $PdCl_2(CH_3CN)_2$ (0.05 or 0.1 mmol) were added. The reaction mixture was stirred for 10 min-25 h at room temperature or at 70 °C. Afterwards, water was added to quench the reaction and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, hexane/AcOEt) afforded the corresponding 1,2-dihydroquinolines **9aa-9ba** or 1,4-dihydroquinoline **10ae.**

*Methyl 5,7-dimethoxy-4-methylquinoline-1(2H)-carboxylate (**9aa**)*[31]



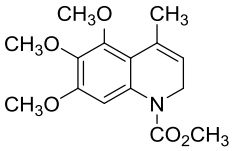
Prepared from methyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate **6aa** (0.11 g, 0.40 mmol), *p*-TsOH (77.5 mg, 0.40 mmol), benzoquinone (44.1 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (5.3 mg, 0.020 mmol) in dioxane (26.7 mL). The reaction mixture was stirred for 10 min at 70 °C and after work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 8/2), **9aa** was obtained as an oil (94.2 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.16 (d, *J* = 1.3 Hz, 3H, CH_3) 3.77 (s, 3H, CO_2CH_3), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.10–4.15 (m, 2H, 2 × H_2), 5.64 (td, *J* = 4.8, 1.3 Hz, 1H, H_3), 6.29 (d, *J* = 2.4 Hz, 1H, H_6), 6.80 (br s, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.9 (CH_3), 42.7 (C_2), 53.0 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.5 (OCH_3), 96.1 (C_6), 101.4 (C_8), 113.6 (C_{4a}), 119.9 (C_3), 132.7 (C_4), 139.4 (C_{8a}), 154.4 (CO), 158.0 (C_5), 159.0 (C_7).

*1-(5,7-Dimethoxy-4-methylquinolin-1(2H)-yl)ethanone (**9ba**)*



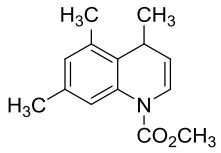
Prepared from *N*-(but-3-en-1-yl)-*N*-(3,5-dimethoxyphenyl) acetamide **6ba** (0.12 g, 0.46 mmol), *p*-TsOH (88.1 mg, 0.46 mmol), benzoquinone (50.1 mg, 0.46 mmol) and $PdCl_2(CH_3CN)_2$ (6.0 mg, 0.023 mmol) in dioxane (30.7 mL). The reaction mixture was stirred for 25 h at rt, and after work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 6/4), **9ba** was obtained as a mixture of rotamers in a 6:4 ratio and as an oil (71.2 mg, 62%): IR (ATR): ν (cm^{-1}) = 1699 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.19 (s, 3H, CH_3, both rotamers), 2.23 (s, 3H, $COCH_3$, both rotamers), 3.83 (s, 6H, 2 × OCH_3, both rotamers), 4.21 (br s, 2H, 2 × H_2, both rotamers), 5.71 (br s, 1H, H_3, both rotamers), 6.36 (br s, major rotamer: 2H, H_6, H_8; minor rotamer: 1H, H_6), 6.75 (s, 1H, H_8, minor rotamer); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.9 (CH_3, both rotamers), 22.7 ($CO\underline{C}H_3$, both rotamers), 40.9 (C_2, both rotamers), 55.4 (OCH_3, both rotamers), 55.5 (OCH_3, both rotamers), 96.5 (C_6, both rotamers), 102.3 (C_8, major rotamer), 114.1 (C_{4a}, both rotamers), 116.1 (C_8, minor rotamer), 122.2 (C_3, both rotamers), 132.2 (C_4, both rotamers), 139.9 (C_{8a}, minor rotamer), 149.84 (C_{8a}, major rotamer), 157.8 (C_5, both rotamers), 158.8 (C_7, both rotamers), 169.7 (CO, both rotamers); MS (EI): *m/z* (%): 248.1 (M^+ + 1, 3), 247.1 (M^+, 18), 205.1 (15), 204.1 (100), 203.1 (10), 190.1 (28), 189.1 (19); HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}NO_3$: 248.1287 [MH^+]; found: 248.1294.

*Methyl 5,6,7-trimethoxy-4-methylquinoline-1(2H)-carboxylate (**9ab**)*



Prepared from methyl but-3-en-1-yl(3,4,5-trimethoxyphenyl)-carbamate **6ab** (0.11 g, 0.36 mmol), *p*-TsOH (70.0 mg, 0.36 mmol), benzoquinone (40.0 mg, 0.36 mmol) and $PdCl_2(CH_3CN)_2$ (9.5 mg, 0.036 mmol) in dioxane (24 mL). The reaction mixture was stirred for 2 h at 70 °C, and after work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 6/4), **9ab** was obtained as an oil (42.0 mg, 40%): IR (ATR): ν (cm^{-1}) = 1685 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.18 (s, 3H, CH_3), 3.77 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.11 (br s, 2H, 2 × H_2), 5.69 (br s, 1H, H_3), 6.98 (br s, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.3 (CH_3), 42.6 (C_2), 53.0 ($CO_2\underline{C}H_3$), 56.0 (OCH_3), 60.8 (OCH_3), 61.1 (OCH_3), 104.3 (C_8), 117.8 (C_{4a}), 121.2 (C_3), 132.2 (C_4), 133.5 (C_{8a}), 139.8 (C_6), 150.8 (C_5), 151.9 (C_7), 154.5 (CO); MS (EI): *m/z* (%): 293.1 (M^+, 69), 278.1 (100), 262.1 (8), 234.1 (40), 218.1 (24), 207.1 (27), 204.1 (21), 190.1 (17), 176.1 (13); HRMS (ESI): calcd. for $C_{15}H_{20}NO_5$: 294.1341 [MH^+]; found: 294.1361.

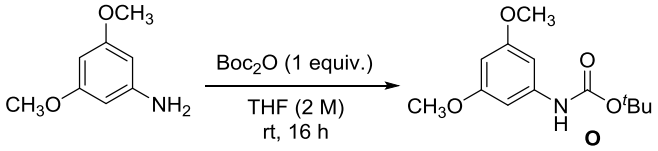
*Methyl 4,5,7-trimethylquinoline-1(4H)-carboxylate (**10ae**)*



Prepared from methyl but-3-en-1-yl(3,5-dimethylphenyl)carbamate **6ae** (0.11 g, 0.47 mmol), *p*-TsOH (91.1 mg, 0.47 mmol), benzoquinone (52.0 mg, 0.47 mmol) and $PdCl_2(CH_3CN)_2$ (12.4 mg, 0.047 mmol) in dioxane (31.3 mL). The reaction mixture was stirred for 24 h at 70 °C, and after work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 9/1) **10ae** was obtained as an oil (34.4 mg, 32%): IR (ATR): ν (cm^{-1}) = 1730 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.16 (d, *J* = 6.9 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.44–3.52 (m, 1H, H_4), 3.87 (s, 3H, OCH_3), 5.48 (t, *J* = 6.9 Hz, 1H, H_3), 6.84 (s, 1H, H_6), 6.95 (d, *J* = 6.9 Hz, 1H, H_2), 7.62 (s, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 18.7 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 29.0 (C_4), 53.1 (OCH_3), 116.3 (C_3), 120.3 (C_8), 125.9 (C_6), 127.8 (C_{4a}), 129.4 (C_2), 134.6 (C_{8a}), 135.3 (C_7), 136.1 (C_5), 153.3 (CO); MS (EI): *m/z* (%): 231.1 (M^+, 65), 215.1 (100), 199.1 (8), 171.1 (84), 156.1 (21); HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}NO_2$: 232.1338 [MH^+]; found: 232.1344.

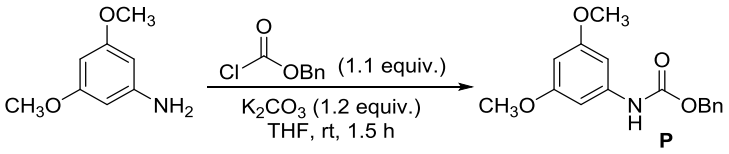
4. INTRAMOLECULAR PALLADIUM(II)-CATALYZED 6-*ENDO* C-H ALKENYLATION DIRECTED BY THE REMOTE *N*-PROTECTING GROUP. MECHANISTIC INSIGHT AND APPLICATION TO THE SYNTHESIS OF DIHYDROQUINOLINES

4.1. Synthesis of *tert*-butyl (3,5-dimethoxyphenyl)carbamate (O)[40]



A solution of commercially available 3,5-dimethoxyaniline (1.7 g, 10.8 mmol) and Boc_2O (2.4 g, 10.8 mmol) in dry THF (5.4 mL) was stirred under argon atmosphere and at room temperature for 16 h. Afterwards, the solvent was evaporated and the residue purified by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1). That way, **O** was obtained as a solid (2.5 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.59 (s, 9H, 3 × CH_3), 3.77 (s, 6H, 2 × OCH_3), 6.16 (t, *J* = 2.2 Hz, 1H, H_4), 6.49 (br s, 1H, NH), 6.60 (d, *J* = 2.2 Hz, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.3 (3 × CH_3), 55.4 (2 × OCH_3), 80.6 ($\underline{C}(CH_3)_3$), 95.5 (C_2, C_6), 96.7 (C_4), 140.2 (C_1), 152.2 (CO), 161.1 (C_3, C_5).

4.2. Synthesis of benzyl (3,5-dimethoxyphenyl)carbamate (P)[41]

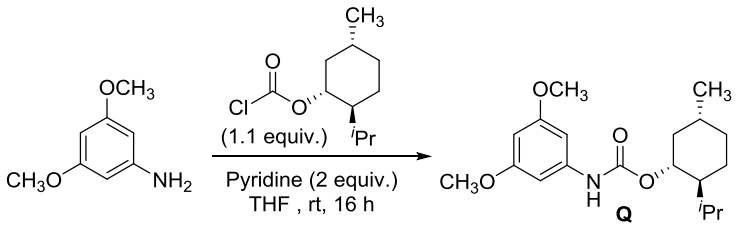


Over a solution of commercially available 3,5-dimethoxyaniline (1.0 g, 6.6 mmol) in dry THF (55 mL), K_2CO_3 (1.1 g, 7.9 mmol) and benzyl chloroformate (1.0 mL, 7.2 mmol) were added under argon atmosphere. The reaction was stirred at room temperature for 1.5 h and then, water was added. The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **P** as a solid (1.8 g, 95%):

[40] Guissart, C.; Dolbois, A.; Tresse, C.; Saint-Auret, S. ; Evano, G. ; Blanchard, N. *Synlett* **2016**, *27*, 2575.
[41] Sultane, P.R.; Mete, T.B.; Bhat, R.G. *Tetrahedron Lett.* **2015**, *56*, 2067.

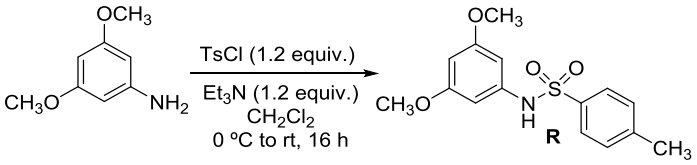
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.76 (s, 6H, 2 × OCH_3), 5.19 (s, 2H, OCH_2Ph), 6.20 (t, *J* = 2.2 Hz, 1H, H_4), 6.64 (d, *J* = 2.2 Hz, 2H, H_2, H_6), 6.84 (br s, 1H, NH), 7.31-7.43 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 55.4 (2 × OCH_3), 67.0 (OCH_2Ph), 95.9 (C_2, C_6), 97.0 (C_4), 128.3 ($C_{2'}$, $C_{6'}$), 128.4 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 136.0 ($C_{1'}$), 139.7 (C_1), 153.2 (CO), 161.2 (C_3, C_5).

4.3. (*1R,2S,5R*)-2-Isopropyl-5-methylcyclohexyl (3,5-dimethoxyphenyl)carbamate (Q)



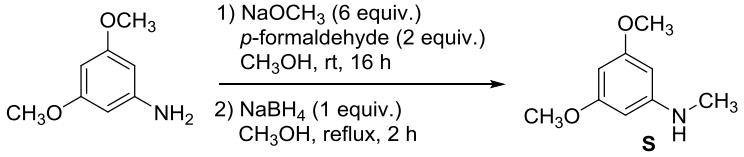
Over a solution of commercially available 3,5-dimethoxyaniline (0.67 g, 4.4 mmol) and pyridine (0.70 mL, 8.8 mmol) in dry THF (20 mL) under argon atmosphere, (1*R*)-(-)-menthyl chloroformate (1.1 mL, 4.8 mmol) was added dropwise. The reaction was stirred for 16 h at room temperature and afterwards the solvent was removed under reduced pressure. The crude reaction was dissolved in CH_2Cl_2 (30 mL) and washed with a 10% aqueous solution of HCl (2 × 15 mL) and with water (15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) affording **Q** as a solid (1.1 g, 75%): mp (CH_2Cl_2) 89-91 ºC; IR (ATR): ν (cm^{-1}) = 3357 (N-H), 1739 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.75-0.91 (m, 10H, 3 × CH_3, $(CH_3)_2CH$), 0.93-1.13 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.24-1.38 (m, 1H, 1 × $H_{6'}$), 1.38-1.57 (m, 1H, $H_{5'}$), 1.60-1.70 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.88-2.02 (m, 1H, 1 × $H_{6'}$), 2.02-2.11 (m, 1H, $H_{2'}$), 3.74 (s, 6H, 2 × OCH_3), 4.62 (td, *J* = 10.8, 4.3 Hz, $H_{1'}$), 6.16 (t, *J* = 2.2 Hz, 1H, H_4), 6.66 (d, *J* = 2.2 Hz, 2H, H_2, H_6), 6.91 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.4 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.5 ($C_{3'}$), 26.2 ($(CH_3)_2CH$), 31.4 ($C_{5'}$), 34.2 ($C_{4'}$), 41.3 ($C_{6'}$), 47.2 ($C_{2'}$), 55.3 (2 × OCH_3), 75.1 ($C_{1'}$), 95.7 (C_2, C_6), 96.7 (C_4), 140.2 (C_1), 153.4 (CO), 161.1 (C_3, C_5); MS (ESI): *m/z* (%): 359.2 (MNa^+ + 1, 16), 358.2 (MNa^+, 100), 336.2 (6), 199.1 (2), 198.1 (18), 176.1 (1); HRMS (ESI): *m/z* calcd. for $C_{19}H_{29}NO_4Na$: 358.1994 [MNa^+]; found: 358.1993. $[\alpha]_D^{20}$ = -118.4 (c = 0.12 g/100 mL in CH_2Cl_2).

4.4. Synthesis of *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (R)[42]



To a solution of commercially available 3,5-dimethoxyaniline (1.6 g, 10.7 mmol) and Et_3N (1.8 mL, 12.9 mmol) in dry CH_2Cl_2 (20 mL), TsCl (2.5 g, 12.9 mmol) was added at 0 ºC and under argon atmosphere. The mixture was stirred at room temperature for 16 h. Afterwards, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (20 mL) and it was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3) affording **R** as a solid (2.9 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.36 (s, 3H, CH_3), 3.69 (s, 6H, 2 × OCH_3), 6.16 (t, *J* = 2.2 Hz, 1H, H_4), 6.28 (d, *J* = 2.2 Hz, H_2, H_6), 7.19-7.24 (m, 2H, $H_{3'}$, $H_{5'}$), 7.30 (br s, 1H, NH), 7.70-7.78 (m, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.5 (CH_3), 55.3 (2 × OCH_3), 97.1 (C_4), 98.9 (C_2, C_6), 127.3 ($C_{2'}$, $C_{6'}$), 129.6 ($C_{3'}$, $C_{5'}$), 135.9 ($C_{1'}$), 138.4 ($C_{4'}$), 143.9 (C_1), 161.1 (C_3, C_5).

4.5. Synthesis of 3,5-dimethoxy-*N*-methylaniline (S)[43]

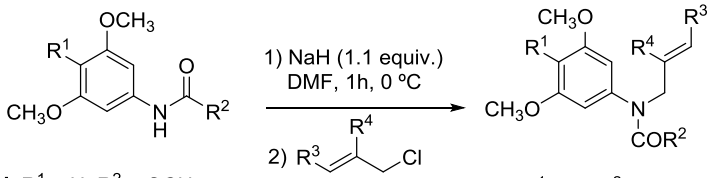


Commercially available 3,5-dimethoxyaniline (3.0 g, 19.3 mmol) was added over a solution of $NaOCH_3$ (6.6 g, 0.12 mol) in CH_3OH (30 mL). The mixture was stirred and a solution of *p*-formaldehyde (1.2 g, 38.6 mmol) in CH_3OH (18 mL) was added. The mixture was stirred at room temperature overnight, and then, $NaBH_4$ (0.75 g, 19.3 mmol) was added portionwise. The reaction was heated under reflux for 2 h and after that it was allowed to cool down to room temperature and treated with an aqueous solution of KOH 1M (10 mL). The mixture

[42] Lee, D.; Chang, S. *Chem. Eur. J.* **2015**, *21*, 5364.
[43] Fors, B.P.; Watson, D.A.; Biscoe, M.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2008**, *130*, 13552.

was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic extracts were dried (Na_2SO_4) and then concentrated *in vacuo*. Flash column chromatography (silica gel, petroleum ether/AcOEt 6/4) afforded aniline **S** as an oil (2.95 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.79 (s, 3H, NCH_3), 3.78 (s, 6H, 2 × OCH_3), 4.01 (s, 1H, NH), 5.84 (d, *J* = 2.0 Hz, 2H, H_2, H_6), 5.96 (t, *J* = 2.0 Hz, 1H, H_4); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 30.0 (NCH_3), 54.5 (2 × OCH_3), 89.0 (C_4), 91.2 (C_2, C_6), 151.1 (C_1), 161.3 (C_3, C_5).

4.6. General procedure for the alkylation of *N*-protected anilines I, J, N and O-Q. Synthesis of *N*-protected *N*-allylanilines 11aa-11gc

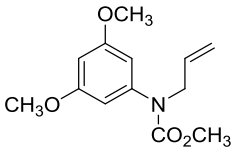


I, R^1 = H, R^2 = OCH_3
J, R^1 = OCH_3, R^2 = OCH_3
N, R^1 = H, R^2 = CH_3
O, R^1 = H, R^2 = O^{t}Bu
P, R^1 = H, R^2 = OBn
Q, R^1 = H, R^2 = O(-)Menthyl

11aa, R^1 = H, R^2 = OCH_3, R^3 = H, R^4 = H
11ab, R^1 = H, R^2 = OCH_3, R^3 = CH_3, R^4 = H
11ac, R^1 = H, R^2 = OCH_3, R^3 = Ph, R^4 = H
11am, R^1 = H, R^2 = OCH_3, R^3 = H, R^4 = CH_3
11baa, R^1 = OCH_3, R^2 = OCH_3, R^3 = H, R^4 = H
11ba, R^1 = H, R^2 = O^{t}Bu, R^3 = H, R^4 = H
11bc, R^1 = H, R^2 = O^{t}Bu, R^3 = Ph, R^4 = H
11ca, R^1 = H, R^2 = OBn, R^3 = H, R^4 = H
11da, R^1 = H, R^2 = CH_3, R^3 = H, R^4 = H
11ga, R^1 = H, R^2 = O(-)Menthyl, R^3 = H, R^4 = H
11gb, R^1 = H, R^2 = O(-)Menthyl, R^3 = CH_3, R^4 = H
11gc, R^1 = H, R^2 = O(-)Menthyl, R^3 = Ph, R^4 = H

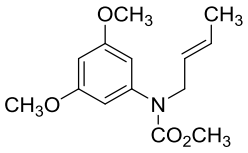
Over a solution of the corresponding *N*-protected aniline **I, J, N and O-Q** (1 mmol) in dry DMF (15 mL) at 0 ºC under argon atmosphere, NaH (60 % in mineral oil) (1.1 mmol) was added. The reaction was stirred at 0 ºC for 1 h, and afterwards, the corresponding allyl chloride (1.2 mmol) was added. Then, the reaction was allowed to warm up to room temperature and stirred for 3-7.5 h. Afterwards, water (20 mL) was added and the aqueous layer was extracted with AcOEt (3 × 15 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, petroleum ether/AcOEt) afforded the corresponding *N*-substituted *N*-allylanilines **11aa-11gc**.

*Methyl allyl(3,5-dimethoxyphenyl)carbamate (**11aa**)*



Prepared from methyl (3,5-dimethoxyphenyl)carbamate **I** (0.64 g, 3.0 mmol), NaH (60% in mineral oil) (0.13 g, 3.3 mmol) and allyl chloride (0.30 mL, 3.6 mmol). The reaction mixture was stirred at room temperature for 3 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 7/3) **11aa** was obtained as an oil (0.69 g, 91%): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.64 (s, 3H, CO_2CH_3), 3.69 (s, 6H, 2 × OCH_3), 4.15-4.21 (m, 2H, NCH_2), 5.05- 5.17 (m, 2H, CH=C$\underline{H}_2$), 5.86 (ddt, *J* = 17.0, 10.2, 5.8 Hz, 1H, C$\underline{H}$=CH_2), 6.30 (t, *J* = 2.2 Hz, 1H, H_4), 6.36 (d, *J* = 2.2 Hz, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.7 ($CO_2\underline{C}H_3$), 53.2 (NCH_2), 55.2 (2 × OCH_3), 98.5 (C_2, C_6), 105.2 (C_4), 116.9 (CH=$\underline{C}H_2$), 133.9 ($\underline{C}$H=CH_2), 143.7 (C_1), 155.6 (CO), 160.7 (C_3, C_5); MS (EI): *m/z* (%): 252.1 (M^+ + 1, 14), 251.1 (M^+, 93), 237.1 (13), 236.1 (100), 222.1 (14), 192.1 (32), 190.1 (21), 179.0 (10), 177.1 (22), 176.1 (54), 162.0 (19), 161.1 (20), 160.1 (10), 150.0 (10), 146.0 (10); HRMS (CI): *m/z* calcd. for $C_{13}H_{18}NO_4$: 252.1236 [MH^+]; found: 252.1234.

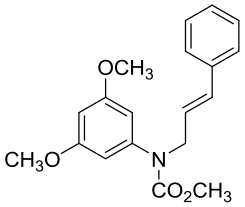
*Methyl (E)-but-2-en-1-yl(3,5-dimethoxyphenyl)carbamate (**11ab**)*



Prepared from methyl (3,5-dimethoxyphenyl)carbamate **I** (0.46 g, 2.2 mmol), NaH (60% in mineral oil) (96.7 mg, 2.4 mmol) and (*E*)-1-chlorobut-2-ene (0.26 mL, 2.6 mmol). The reaction mixture was stirred at room temperature for 7 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 8/2) **11ab** was obtained as an oil and as a mixture of rotamers in a 75:25 ratio (0.51 g, 88%): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.57 (d, *J* = 6.0 Hz, 3H, CH_3, minor rotamer), 1.64-1.68 (m, 3H, CH_3, major rotamer), 3.69 (s, 3H, CO_2CH_3, both rotamers), 3.76 (s, 6H, 2 × OCH_3, both rotamers), 4.07-4.22 (m, 2H, NCH_2, major rotamer), 4.27 (d, *J* = 6.3 Hz, NCH_2, minor rotamer), 5.53-5.62 (m, 2H, CH=CH, both rotamers), 6.33-6.40 (m, 3H, H_2, H_6, H_4, both rotamers); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 12.8 (CH_3, minor rotamer), 17.7 (CH_3, major rotamer), 47.2 (NCH_2, minor rotamer), 52.6 (NCH_2, major rotamer), 52.8 ($CO_2\underline{C}H_3$, both rotamers), 55.3 (2 × OCH_3, both rotamers), 98.6 (C_4, major rotamer), 98.7 (C_4, minor rotamer), 105.5 (C_2, C_6, both rotamers), 126.1 (CH=$\underline{C}$HCH$_3$, minor rotamer), 126.5 (CH=$\underline{C}$HCH$_3$, major rotamer), 127.1 ($\underline{C}$H=CHCH$_3$, minor rotamer), 128.6 ($\underline{C}$H=CHCH$_3$, major rotamer), 143.8 (C_1, both rotamers), 155.7 (CO, major rotamer), 155.8 (CO, minor rotamer), 160.7 (C_3, C_5, minor rotamer), 160.8 (C_3, C_5, major rotamer); MS (EI): *m/z* (%): 266.2 (M^+ + 1, 8), 265.2 (M^+, 49), 250.1 (10), 237.1 (15), 236.1 (100), 224.1 (14), 211.1 (16), 206.2 (23), 190.1 (39), 180.1 (14), 179.1 (24), 178.1 (11), 176.1

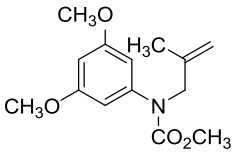
(23), 175.1 (20), 150.1 (30), 55.1 (21); HRMS (ESI): *m/z* calcd. for $C_{14}H_{20}NO_4$: 266.1392 [MH^+]; found: 266.1403.

*Methyl cinnamyl(3,5-dimethoxyphenyl)carbamate (**11ac**)*



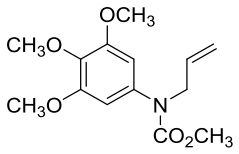
Prepared from methyl (3,5-dimethoxyphenyl)carbamate **I** (0.30 g, 1.4 mmol), NaH (60% in mineral oil) (62.9 mg, 1.6 mmol) and cinnamyl chloride (0.24 mL, 1.7 mmol). The reaction mixture was stirred at room temperature for 3 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 7/3) **11ac** was obtained as an oil (0.45 g, 70%): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.74 (s, 9H, 2 × OCH_3, CO_2CH_3), 4.40 (d, *J* = 6.2 Hz, 2H, NCH_2), 6.07-6.60 (m, 5H, CH=CH, H_2, H_4, H_6), 7.12-7.41 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.9 (NCH_2), 53.0 ($CO_2\underline{C}H_3$), 55.4 (2 × OCH_3), 98.8 (C_2, C_6), 105.5 (C_4), 125.1 (CH=$\underline{C}$HPh), 126.5 ($C_{2'}$, $C_{6'}$), 127.7 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 132.6 ($\underline{C}$H=CHPh), 136.7 ($C_{1'}$), 143.7 (C_1), 155.9 (CO), 160.9 (C_3, C_5); MS (EI): *m/z* (%): 328.2 (M^+ + 1, 3), 327.2 (M^+, 16), 252.1 (17), 237.1 (10), 236.1 (56), 118.1 (10), 117.1 (100), 115.1 (35), 91.1 (16); HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}NO_4$: 328.1549 [MH^+]; found: 328.1565.

*Methyl (3,5-dimethoxyphenyl)(2-methylallyl)carbamate (**11am**)*



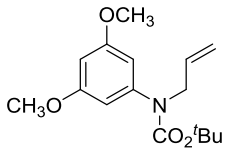
Prepared from methyl (3,5-dimethoxyphenyl)carbamate **I** (0.22 g, 1.1 mmol), NaH (60% in mineral oil) (46.3 mg, 1.2 mmol) and 3-chloro-2-methylprop-1-ene (0.12 mL, 1.3 mmol). The reaction mixture was stirred at room temperature for 3 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 6/4) **11am** was obtained as an oil (0.25 g, 89%): IR (ATR): ν (cm^{-1}) = 1706 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.75 (s, 3H, CH_3), 3.71 (s, 3H, CO_2CH_3), 3.76 (s, 6H, 2 × OCH_3), 4.18 (s, 2H, NCH_2), 4.80-4.88 (m, 2H, CH_3C=C$\underline{H_2}$), 6.30-6.36 (m, 1H, H_4), 6.41 (d, *J* = 1.5 Hz, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 20.1 (CH_3), 53.0 ($CO_2\underline{C}H_3$), 55.4 (2 × OCH_3), 56.2 (NCH_2), 98.2 (C_2, C_6), 104.9 (C_4), 112.0 (CH_3C=$\underline{C}H_2$), 141.2 ($CH_3\underline{C}$=CH_2), 143.9 (C_1), 156.0 (CO), 160.6 (C_3, C_5); MS (EI): *m/z* (%): 266.2 (M^+ + 1, 13), 265.2 (M^+, 80), 251.2 (15), 250.2 (100), 206.2 (19), 192.1 (13), 191.1 (22), 190.1 (56), 189.1 (11), 176.1 (17), 175.1 (26), 55.1 (10); HRMS (ESI): *m/z* calcd. for $C_{14}H_{20}NO_4$: 266.1392 [MH^+]; found: 266.1401.

*Methyl allyl(3,4,5-dimethoxyphenyl)carbamate (**11baa**)*



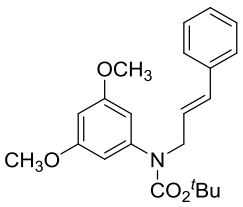
Prepared from methyl (3,4,5-dimethoxyphenyl)carbamate **J** (0.25 g, 1.0 mmol), NaH (60% in mineral oil) (45.9 mg, 1.2 mmol) and allyl chloride (0.10 mL, 1.3 mmol). The reaction mixture was stirred at room temperature for 5 h. After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3) **11baa** was obtained as an oil (0.27 g, 91%): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.63 (s, 3H, OCH_3), 3.73 (s, 6H, 2 × OCH_3), 3.74 (s, 3H, OCH_3), 4.13 (d, *J* = 5.9 Hz, 2H, NCH_2), 5.03- 5.14 (m, 2H, CH=C$\underline{H_2}$), 5.78-5.93 (m, 1H, C$\underline{H}$=CH_2), 6.37 (s, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.8 ($CO_2\underline{C}H_3$), 53.5 (NCH_2), 56.0 (2 × OCH_3), 60.7 (OCH_3), 104.5 (C_2, C_6), 117.1 (CH=$\underline{C}H_2$), 133.9 ($\underline{C}$H=CH_2), 136.6 (C_1), 137.8 (C_4), 153.1 (C_3, C_5), 155.8 (CO); MS (ESI): *m/z* (%): 305.1 (MNa^+ + 1, 11), 304.1 (MNa^+, 100), 283.1 (MH^+ + 1, 4), 282.1 (MH^+, 31), 281.1 (3), 274.3 (2), 251.1 (9), 250.1 (84), 210.1 (2), 209.1 (25); HRMS (ESI): *m/z* calcd. for $C_{14}H_{19}NO_5Na$: 304.1161 [MNa^+]; found: 304.1169.

*tert-Butyl allyl(3,5-dimethoxyphenyl)carbamate (**11ba**)*



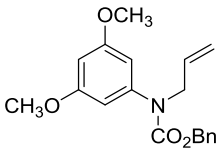
Prepared from *tert*-butyl (3,5-dimethoxyphenyl)carbamate **O** (0.47 g, 1.9 mmol), NaH (60% in mineral oil) (82.0 mg, 2.1 mmol) and allyl chloride (0.18 mL, 2.2 mmol). The reaction mixture was stirred at room temperature for 4 h. After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) **11ba** was obtained as an oil (0.39 g, 72%): IR (ATR): ν (cm^{-1}) = 1699 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.46 (s, 9H, 3 × CH_3), 3.76 (s, 6H, 2 × OCH_3), 4.20 (d, *J* = 5.5 Hz, 2H, NCH_2), 5.07- 5.23 (m, 2H, CH=C$\underline{H_2}$), 5.92 (qd, 1H, *J* = 10.6, 5.5 Hz, C$\underline{H}$=CH_2), 6.31 (t, *J* = 2.0 Hz, 1H, H_4), 6.42 (d, *J* = 2.0 Hz, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.3 (3 × CH_3), 53.0 (NCH_2), 55.3 (2 × OCH_3), 80.4 ($\underline{C}(CH_3)_3$), 97.9 (C_4), 104.8 (C_2, C_6), 116.3 (CH=$\underline{C}H_2$), 134.4 ($\underline{C}$H=CH_2), 144.4 (C_1), 154.2 (CO), 160.5 (C_3, C_5); MS (ESI): *m/z* (%): 294.2 (MH^+, 6), 240.1 (1), 239.1 (13), 238.1 100), 220.1 (7), 194.1 (3); HRMS (ESI): *m/z* calcd. for $C_{16}H_{24}NO_4$: 294.1705 [MH^+]; found: 294.1715.

*tert-Butyl cinnamyl(3,5-dimethoxyphenyl)carbamate (**11bc**)*



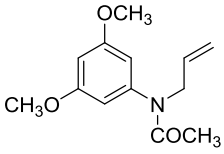
Prepared from *tert*-butyl (3,5-dimethoxyphenyl)carbamate **O** (0.63 g, 2.5 mmol), NaH (60% in mineral oil) (0.11 g, 2.8 mmol) and cinammyl chloride (0.42 mL, 3.0 mmol). The reaction mixture was stirred at room temperature for 7.5 h. After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) **11bc** was obtained as a solid (0.91 g, 98%): mp (CH_2Cl_2) 63-64 ºC; IR (ATR): ν (cm^{-1}) = 1685 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.48 (s, 9H, 3 × CH_3), 3.76 (s, 6H, 2 × OCH_3), 4.40 (d, *J* = 6.2 Hz, 2H, NCH_2), 6.22-6.38 (m, 2H, C<u>H</u>=CHPh, H_4), 6.39-6.57 (m, 3H, CH=C<u>H</u>Ph, H_2, H_6), 7.18-7.42 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.3 (3 × CH_3), 52.6 (NCH_2), 55.4 (2 × OCH_3), 80.5 (<u>C</u>(CH_3)$_3$), 98.1 (C_4), 105.0 (C_2, C_6), 125.8 (CH=<u>C</u>HPh), 126.4 ($C_{2'}$, $C_{6'}$), 127.5 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 131.9 (<u>C</u>H=CHPh), 136.9 ($C_{1'}$), 144.6 (C_1), 154.3 (CO), 160.6 (C_3, C_5); MS (ESI): *m/z* (%): 370.2 (MH^+, 6), 348.1 (2), 315.1 (15), 314.1 (100), 210.1 (2), 166.1 (5); HRMS (ESI): *m/z* calcd. for $C_{22}H_{28}NO_4$: 370.2018 [MH^+]; found: 370.2024.

*Benzyl allyl(3,5-dimethoxyphenyl)carbamate (**11ca**)*



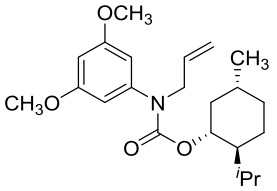
Prepared from benzyl (3,5-dimethoxyphenyl)carbamate **P** (0.40 g, 1.4 mmol), NaH (60% in mineral oil) (61.9 mg, 1.6 mmol) and allyl chloride (0.14 mL, 1.7 mmol). The reaction mixture was stirred at room temperature for 5 h. After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) **11ca** was obtained as an oil (0.40 g, 86%): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.76 (s, 6H, 2 × OCH_3), 4.28 (dt, *J* = 5.8, 1.4 Hz, 2H, NCH_2), 5.12- 5.24 (m, 4H, $CO_2C\underline{H}_2Ph$, CH=C<u>H</u>$_2$), 5.85-6.03 (m, 1H, C<u>H</u>=CH_2), 6.37 (t, *J* = 2.2 Hz, 1H, H_4), 6.43 (d, *J* = 2.2 Hz, 2H, H_2, H_6), 7.25-7.41 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 53.3 (NCH_2), 55.3 (2 × OCH_3), 67.3 ($CO_2\underline{C}H_2Ph$), 98.8 (C_4), 105.1 (C_2, C_6), 117.1 (CH=<u>C</u>H_2), 127.8 ($C_{2'}$, $C_{6'}$), 127.9 ($C_{4'}$), 128.4 ($C_{3'}$, $C_{5'}$), 133.9 (<u>C</u>H=CH_2), 136.6 ($C_{1'}$), 143.8 (C_1), 155.1 (CO), 160.7 (C_3, C_5); MS (ESI): *m/z* (%): 329.2 (MH^+ + 1, 17), 328.2 (MH^+, 93), 310.1 (1), 284.2 (3), 250.1 (2), 220.1 (1), 206.1 (1); HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}NO_4$: 328.1541 [MH^+]; found: 328.1558.

*N-Allyl-N-(3,5-dimethoxyphenyl)acetamide (**11da**)*



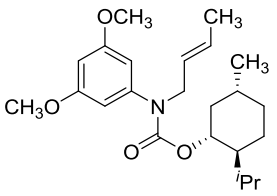
Prepared from *N*-(3,5-dimethoxyphenyl)acetamide **N** (0.28 g, 1.4 mmol), NaH (60% in mineral oil) (62.9 mg, 1.6 mmol) and allyl chloride (0.14 mL, 1.7 mmol). The reaction mixture was stirred at room temperature for 3 h. After work-up and purification by flash column chromatography (silica gel, hexane/AcOEt 5/5) **11da** was obtained as an oil (0.32 g, 97%): IR (ATR): ν (cm^{-1}) = 1652 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.80 (s, 3H, $COCH_3$), 3.67 (s, 6H, 2 × OCH_3), 4.26 (d, *J* = 6.2 Hz, 2H, NCH_2), 5.02-5.20 (m, 2H, CH=C$\underline{H}_2$), 5.87 (ddt, *J* = 16.8, 10.7, 6.2 Hz, 1H, C$\underline{H}$=CH_2), 6.31 (d, *J* = 2.1 Hz, 2H, H_2, H_6), 6.42 (t, *J* = 2.1 Hz, 1H, H_4); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.5 ($COCH_3$), 51.8 (NCH_2), 55.4 (2 × OCH_3), 99.5 (C_4), 106.4 (C_2, C_6), 117.7 (CH=$\underline{C}H_2$), 133.3 ($\underline{C}$H=CH_2), 144.7 (C_1), 161.2 (C_3, C_5), 169.9 (CO); MS (EI): *m/z* (%): 236.1 (M^+ + 1, 13), 235.1 (M^+, 84), 220.1 (22), 194.1 (10), 193.1 (83), 192.1 (100), 179.1 (14), 178.1 (98), 177.1 (13), 176.0 (23), 166.1 (38), 164.1 (22), 163.0 (11), 162.0 (22), 161.0 (13), 148.0 (10), 147.0 (10), 138.0 (14), 137.0 (11), 122.0 (11); HRMS (CI): *m/z* calcd. for $C_{13}H_{18}NO_3$: 236.1287 [MH^+]; found: 236.1294.

*(1R,2S,5R)-2-Isoprpyl-5-methylcyclohexyl allyl(3,5-dimethoxyphenyl)carbamate (**11ga**)*



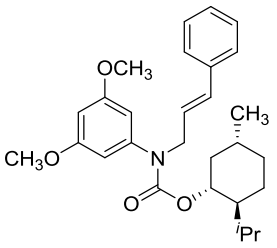
Prepared from (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (3,5-dimethoxyphenyl)carbamate **Q** (0.45 g, 1.4 mmol), NaH (60% in mineral oil) (59.6 mg, 1.5 mmol) and allyl chloride (0.13 mL, 1.6 mmol). The reaction mixture was stirred at room temperature for 4 h. After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) **11ga** was obtained as an oil (0.37 g, 72%): IR (ATR): ν (cm^{-1}) = 1700 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.73-0.93 (m, 10H, 3 × CH_3, $(CH_3)_2C\underline{H}$), 0.93-1.14 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.22-1.38 (m, 1H, 1 × $H_{6'}$), 1.39-1.57 (m, 1H, $H_{5'}$), 1.58-1.71 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.86-1.99 (m, 1H, 1 × $H_{6'}$), 2.05-2.16 (m, 1H, $H_{2'}$), 3.76 (s, 6H, 2 × OCH_3), 4.23 (d, *J* = 5.6 Hz, 2H, NCH_2), 4.62 (td, *J* = 10.8, 4.3 Hz, 1H, $H_{1'}$), 5.11-5.22 (m, 2H, CH=C$\underline{H}_2$), 5.84-6.00 (m, 1H, C$\underline{H}$=CH_2), 6.32 (t, *J* = 2.2 Hz, H_4), 6.42 (d, *J* = 2.2 Hz, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.3 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.4 ($C_{3'}$), 26.2 ($(CH_3)_2\underline{C}H$), 31.4 ($C_{5'}$), 34.3 ($C_{4'}$), 41.2 ($C_{6'}$), 47.1 ($C_{2'}$), 53.1 (NCH_2), 55.3 (2 × OCH_3), 75.8 ($C_{1'}$), 98.4 (C_2, C_6), 104.9 (C_4), 116.7 (CH=$\underline{C}H_2$) 134.2 ($C\underline{H}$=CH_2) 144.2 (C_1), 155.0 (CO), 160.6 (C_3, C_5); MS (ESI): *m/z* (%): 377.3 (MH^+ + 1, 4), 376.2 (MH^+, 23), 372.1 (3), 371.1 (9), 355.3 (2), 239.1 (9), 238.1 (87), 220.1 (13) 194.1 (7); HRMS (ESI): *m/z* calcd. for $C_{22}H_{34}NO_4$: 376.2488 [MH^+]; found: 376.2491; $[\alpha]_D^{20}$ = -36.9 (c = 0.28 g/100 mL in CH_2Cl_2).

*(1R,2S,5R)-2-Isoprpyl-5-methylcyclohexyl ((E)-but-2-en-1-yl)(3,5-dimethoxyphenyl)carbamate (**11gb**)*



Prepared from (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (3,5-dimethoxyphenyl)carbamate **Q** (0.42 g, 1.3 mmol), NaH (60% in mineral oil) (55.4 mg, 1.4 mmol) and crotyl chloride (0.15 mL, 1.5 mmol). The reaction mixture was stirred at room temperature for 7 h. After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) **11gb** was obtained as an oil (0.40 g, 82%): IR (ATR): ν (cm^{-1}) = 1695 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.77-0.92 (m, 10H, 3 × CH_3, $(CH_3)_2C\underline{H}$), 0.92-1.09 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.24-1.36 (m, 1H, 1 × $H_{6'}$), 1.42-1.54 (m, 1H, $H_{5'}$), 1.57-1.66 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.67 (d, *J* = 4.0 Hz, 3H, CH=CH$\underline{CH_3}$), 1.86-1.96 (m, 1H, 1 × $H_{6'}$), 2.07-2.15 (m, 1H, $H_{2'}$), 3.77 (s, 6H, 2 × OCH_3), 4.09-4.34 (m, 2H, NCH_2), 4.61-4.72 (td, *J* = 10.8, 4.3 Hz, 1H, $H_{1'}$), 5.49-5.65 (m, 2H, CH=CH), 6.32 (t, *J* = 2.0 Hz, 1H, H_4), 6.40 (s, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.3 (CH_3), 17.7 (CH=$\underline{CH}CH_3$), 20.9 (CH_3), 22.1 (CH_3), 23.4 ($C_{3'}$), 26.2 ($(CH_3)_2\underline{C}H$), 31.4 ($C_{5'}$), 34.3 ($C_{4'}$), 41.3 ($C_{6'}$), 47.2 ($C_{2'}$), 52.5 (NCH_2), 55.4 (2 × OCH_3), 75.7 ($C_{1'}$), 98.4 (C_2, C_6), 105.1 (C_4), 126.8 (CH=$\underline{C}HCH_3$), 128.2 ($\underline{C}H$=$CHCH_3$), 144.3 (C_1), 155.0 (CO), 160.5 (C_3, C_5); MS (ESI): *m/z* (%): 413.2 (MNa^+ + 1, 19), 412.2 (MNa^+, 100), 390.3 (3), 252.1 (5), 102.1 (5); HRMS (ESI): *m/z* calcd. for $C_{23}H_{35}NO_4Na$: 412.2464 [MNa^+]; found: 412.2455; $[\alpha]_D^{20}$ = -42.9 (c = 0.074 g/100 mL in CH_2Cl_2).

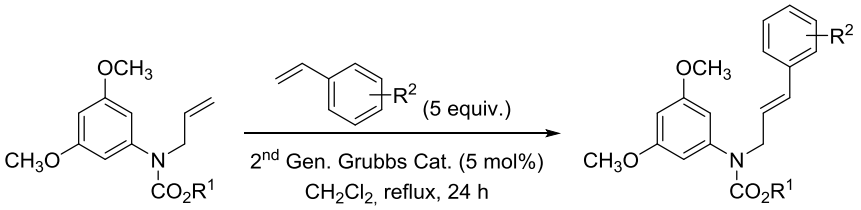
*(1R,2S,5R)-2-Isoprpyl-5-methylcyclohexyl cinnamyl(3,5-dimethoxyphenyl)carbamate (**11gc**)*



Prepared from (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (3,5-dimethoxyphenyl)carbamate **Q** (0.21 g, 0.64 mmol), NaH (60% in mineral oil) (28.1 mg, 0.70 mmol) and cinnamyl chloride (0.11 mL, 0.77 mmol). The reaction mixture was stirred at room temperature for 7 h. After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) **11gc** was obtained as an oil (0.21 g, 71%): IR (ATR): ν (cm^{-1}) = 1695 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.77-0.94 (m, 10H, 3 × CH_3, $(CH_3)_2C\underline{H}$), 0.94-1.15 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.26-1.39 (m, 1H, 1 × $H_{6'}$), 1.41-1.58 (m, 1H, $H_{5'}$), 1.60-1.75 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.88-2.06 (m, 1H, 1 × $H_{6'}$), 2.10-2.20 (m, 1H, $H_{2'}$), 3.75 (s, 6H, 2 × OCH_3), 4.31-4.49 (m, 2H, NCH_2), 4.66 (td, *J* = 10.8, 4.3 Hz, 1H, $H_{1'}$), 6.25-6.37 (m, 2H, C$\underline{H}$=CHPh, H_4), 6.43-6.54 (m, 3H, CH=C$\underline{H}$Ph, H_2, H_6), 7.19-7.38 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.3 (CH_3), 20.8 (CH_3), 22.1 (CH_3), 23.4 ($C_{3'}$), 26.3 ($(CH_3)_2\underline{C}H$), 31.4 ($C_{5'}$), 34.3 ($C_{4'}$), 41.3 ($C_{6'}$), 47.2 ($C_{2'}$), 52.7 (NCH_2), 55.4 (2 × OCH_3), 75.9 ($C_{1'}$),

98.6 (C_2, C_6), 105.0 (C_4), 125.5 (CH=CHPh), 126.4 ($C_{2''}$, $C_{6''}$), 127.6 ($C_{4''}$), 128.5 ($C_{3''}$, $C_{5''}$), 132.1 (CH=CHPh), 136.8 ($C_{1''}$), 144.2 (C_1), 155.1 (CO), 160.7 (C_3, C_5); MS (ESI): *m/z* (%): 475.3 (MNa^+ + 1, 21), 474.3 (MNa^+, 77), 453.3 (2), 452.3 (6), 314.1 (10), 166.1 (2); HRMS (ESI): *m/z* calcd. for $C_{28}H_{37}NO_4Na$: 474.2620 [MNa^+]; found: 474.2623; $[\alpha]_D^{20}$ = -95.2 (c = 0.11 g/100 mL in CH_2Cl_2).

4.7. General procedure for the metathesis reaction of allyl(3,5-dimethoxyphenyl) carbamates 11aa and 11ga. Synthesis of carbamates 11ad-11gl



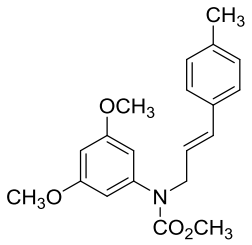
11aa, R^1 = CH_3
11ga, R^1 = (-)Menthyl

11ad, R^1 = CH_3, R^2 = 4-CH_3
11ae, R^1 = CH_3, R^2 = 3-CH_3
11af, R^1 = CH_3, R^2 = 2-CH_3
11ah, R^1 = CH_3, R^2 = 3-OCH_3
11ai, R^1 = CH_3, R^2 = 4-Ph
11aj, R^1 = CH_3, R^2 = 4-^{t}Bu
11ak, R^1 = CH_3, R^2 = 4-F
11al, R^1 = CH_3, R^2 = 2,3-(CH=CH-CH=CH)
11gl, R^1 = (-)Menthyl, R^2 = 2,3-(CH=CH-CH=CH)

Two different procedures were employed depending on the styrene used:

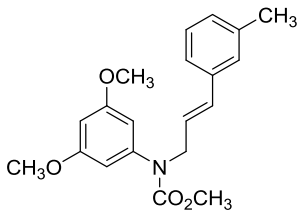
When a liquid styrene was used, a solution of allyl(3,5-dimethoxyphenyl)carbamate **11aa** or **11ga** (1 mmol) and the corresponding styrene (5 mmol) in dry CH_2Cl_2 (2.3 mL) was added *via cannula* over a solution of 2nd generation Grubbs catalyst (0.05 mmol) in dry CH_2Cl_2 (1.1 mL) under argon atmosphere. On the other hand, when a solid styrene was employed, a solution of 2nd generation Grubbs catalyst (0.05 mmol) in dry CH_2Cl_2 (1.1 mL) was added *via cannula* over a solution of allyl(3,5-dimethoxyphenyl)carbamate **11aa** or **11ga** (1mmol) and the corresponding styrene (5 mmol) in dry CH_2Cl_2 (2.3 mL) under argon atmosphere. In both cases, the reaction mixture was stirred at reflux for 24 h and, after allowing it to cool down to room temperature, the volatile compounds were evaporated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt). That way, the corresponding carbamates **11ad-11gl** were obtained.

*Methyl (E)-(3,5-dimethoxyphenyl)(3-(p-tolyl)allyl)carbamate (**11ad**)*



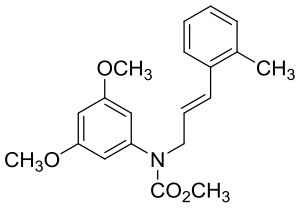
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.28 g, 1.1 mmol) and 4-methylstyrene (0.74 mL, 5.7 mmol) in dry CH_2Cl_2 (2.6 mL) and 2nd Generation Grubbs Catalyst (48.0 mg, 0.056 mmol) in dry CH_2Cl_2 (1.3 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **11ad** as a solid (0.27 g, 70%): mp (CH_2Cl_2) 93-95 ºC; IR (ATR): ν (cm^{-1}) = 1690 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (s, 3H, CH_3), 3.74 (s, 3H, CO_2CH_3), 3.76 (s, 6H, 2 × OCH_3), 4.38 (d, *J* = 6.3 Hz, 2H, NCH_2), 6.26 (dt, *J* = 15.9, 6.3 Hz, 1H, $CH_2C\underline{H}$=CH), 6.37 (t, *J* = 2.2 Hz, 1H, H_4), 6.40-6.50 (m, 3H, CH_2CH=C<u>H</u>, H_2, H_6), 7.11 (d, *J* = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.26 (d, *J* = 8.0 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.2 (CH_3), 53.0 (NCH_2, $CO_2\underline{C}H_3$), 55.4 (2 × OCH_3), 98.8 (C_2, C_6), 105.5 (C_4), 124.0 ($CH_2CH=\underline{C}H$), 126.4 ($C_{2'}$, $C_{6'}$), 129.2 ($C_{3'}$, $C_{5'}$), 132.5 ($CH_2\underline{C}H$=CH), 133.9 ($C_{4'}$), 137.5 ($C_{1'}$), 143.7 (C_1), 155.8 (CO), 160.8 (C_3, C_5); MS (ESI): *m/z* (%): 343.2 (MH^+ + 1, 17), 342.2 (MH^+, 100), 310.1 (1), 224.1 (7), 131.1 (3); HRMS (ESI): *m/z* calcd. for $C_{20}H_{24}NO_4$: 342.1705 [MH^+]; found: 342.1711.

*Methyl (E)-(3,5-dimethoxyphenyl)(3-(m-tolyl)allyl)carbamate (**11ae**)*



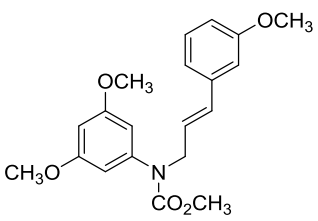
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.37 g, 1.5 mmol) and 3-methylstyrene (0.99 mL, 7.4 mmol) in dry CH_2Cl_2 (3.4 mL) and 2nd generation Grubbs catalyst (63.2 mg, 0.074 mmol) in dry CH_2Cl_2 (1.7 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **11ae** as an oil (0.31 g, 61%): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.36 (s, 3H, CH_3), 3.75 (s, 3H, CO_2CH_3), 3.76 (s, 6H, 2 × OCH_3), 4.39 (d, *J* = 6.1 Hz, 2H, NCH_2), 6.22-6.50 (m, 5H, H_2, H_4, H_6, $CH_2C\underline{H}$=C<u>H</u>), 6.99-7.29 (m, 4H, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.4 (CH_3), 53.0 (NCH_2, $CO_2\underline{C}H_3$), 55.4 (2 × OCH_3), 98.8 (C_2, C_6), 105.4 (C_4), 123.6 ($C_{6'}$), 124.8 ($CH_2CH=\underline{C}H$), 127.1 ($C_{2'}$), 128.4 ($C_{4'}$,$C_{5'}$), 132.7 ($CH_2\underline{C}H$=CH), 136.6 ($C_{3'}$), 138.1 ($C_{1'}$), 143.7 (C_1), 155.8 (CO), 160.8 (C_3, C_5); MS (ESI): *m/z* (%): 343.2 (MH^+ + 1, 18), 342.2 (MH^+, 100), 310.1 (1), 224.1 (12), 131.1 (2); HRMS (ESI): *m/z* calcd. for $C_{20}H_{24}NO_4$: 342.1705 [MH^+]; found: 342.1714.

*Methyl (E)-(3,5-dimethoxyphenyl)(3-(o-tolyl)allyl)carbamate (**11af**)*



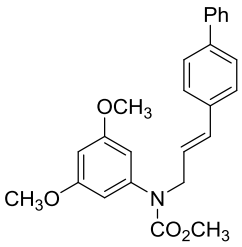
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.34 g, 1.4 mmol) and 2-methylstyrene (0.91 mL, 6.9 mmol) in dry CH_2Cl_2 (3.1 mL) and 2nd generation Grubbs catalyst (57.5 mg, 0.068 mmol) in dry CH_2Cl_2 (1.5 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **11af** as an oil (0.35 g, 75%): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.28 (s, 3H, CH_3), 3.74 (s, 3H, CO_2CH_3), 3.77 (s, 6H, 2 × OCH_3), 4.41 (dd, *J* = 6.4, 1.4 Hz, 2H, NCH_2), 6.15 (dt, *J* = 15.7, 6.4 Hz, 1H, $CH_2C\underline{H}$=CH), 6.38 (t, *J* = 2.3 Hz, 1H, H_4), 6.43 (d, *J* = 2.3 Hz, 2H, H_2, H_6), 6.68 (d, *J* = 15.7 Hz, 1H, CH_2CH=C$\underline{H}$), 7.10-7.19 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.37-7.43 (m, 1H, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.7 (CH_3), 53.0 (NCH_2, $CO_2\underline{C}H_3$), 55.4 (2 × OCH_3), 98.8 (C_2, C_6), 105.5 (C_4), 125.9 ($C_{5'}$), 126.1, 126.4 ($C_{6'}$, CH_2CH=$\underline{C}$H), 127.5 ($C_{3'}$), 130.2 ($C_{4'}$), 130.8 ($CH_2\underline{C}H$=CH), 135.4 ($C_{2'}$), 136.0 ($C_{1'}$), 143.6 (C_1), 155.8 (CO), 160.8 (C_3, C_5); MS (ESI): *m/z* (%): 343.2 (MH^+ + 1, 16), 342.2 (MH^+, 100), 225.1 (1), 224.1 (13), 131.1 (3); HRMS (ESI): *m/z* calcd. for $C_{20}H_{24}NO_4$: 342.1705 [MH^+]; found: 342.1712.

*Methyl (E)-(3,5-dimethoxyphenyl)(3-(3-methoxyphenyl)allyl)carbamate (**11ah**)*



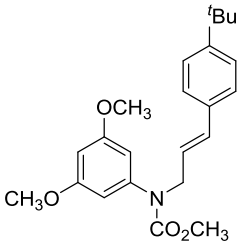
Prepared from methyl allyl(3,5-dimethoxyphenyl)-carbamate **11aa** (0.13 g, 0.50 mmol) and 3-vinylanisole (0.35 mL, 2.5 mmol) in dry CH_2Cl_2 (1.1 mL) and 2nd generation Grubbs catalyst (21.4 mg, 0.025 mmol) in dry CH_2Cl_2 (0.6 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **11ah** as an oil (0.11 g, 61%): IR (ATR): ν (cm^{-1}) = 1706 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.73 (s, 3H, CO_2CH_3), 3.75 (s, 6H, 2 × OCH_3), 3.80 (s, 3H, OCH_3), 4.38 (d, *J* = 5.9 Hz, 2H, NCH_2), 6.21-6.53 (m, 5H, H_2, H_4, H_6, $CH_2C\underline{H}$=C$\underline{H}$), 6.76-6.82 (m, 1H, $H_{4'}$), 6.87-6.91 (m, 1H, $H_{2'}$), 6.92-6.98 (m, 1H, $H_{6'}$), 7.17-7.27 (m, 1H, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.9 (NCH_2), 53.0 ($CO_2\underline{C}H_3$), 55.2 (OCH_3), 55.4 (2 × OCH_3), 98.8 (C_2, C_6), 105.4 (C_4), 111.8 ($C_{2'}$), 113.3 ($C_{4'}$), 119.1 ($C_{6'}$), 125.4 (CH_2CH=$\underline{C}$H), 129.5 ($C_{5'}$), 132.5 ($CH_2\underline{C}H$=CH), 138.2 ($C_{1'}$), 143.7 (C_1), 155.8 (CO), 159.8 ($C_{3'}$), 160.8 (C_3, C_5); MS (ESI): *m/z* (%): 359.2 (MH^+ + 1, 18), 358.2 (MH^+, 100), 326.2 (1), 323.2 (1), 225.1 (1), 224.1 (15), 147.1 (2); HRMS (ESI): *m/z* calcd. for $C_{20}H_{24}NO_5$: 358.1654 [MH^+]; found: 358.1664.

*Methyl (E)-(3-([1,1´-biphenyl]-4-yl)allyl)(3,5-dimethoxyphenyl)carbamate (**11ai**)*



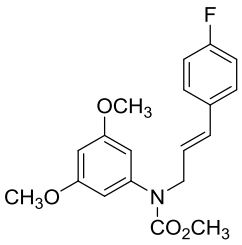
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.35 g, 1.4 mmol) and 4-vinylbiphenyl (1.3 g, 7.1 mmol) in dry CH_2Cl_2 (3.2 mL) and 2nd generation Grubbs catalyst (59.8 mg, 0.070 mmol) in dry CH_2Cl_2 (1.6 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **11ai** as a solid (0.23 g, 40%): mp (CH_2Cl_2) 122-125 ºC; IR (ATR): ν (cm^{-1}) = 1706 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.76 (s, 3H, CO_2CH_3), 3.77 (s, 6H, 2 × OCH_3), 4.42 (dd, *J* = 6.2, 0.9 Hz, 2H, NCH_2), 6.28-6.58 (m, 5H, CH_2CH=C<u>H</u>, H_2, H_4, H_6), 7.30-7.38 (m, 1H, $H_{4''}$), 7.40-7.48 (m, 4H, $H_{2'}$, $H_{6'}$, $H_{3''}$, $H_{5''}$), 7.53-7.63 (m, 4H, $H_{3'}$, $H_{5'}$, $H_{2''}$, $H_{6''}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 53.0 (NCH_2, CO_2CH_3), 55.4 (2 × OCH_3), 98.8 (C_2, C_6), 105.5 (C_4), 125.2 (CH_2CH=C<u>H</u>), 126.9 ($C_{2'}$, $C_{6'}$), 127.0 ($C_{3'}$, $C_{5'}$), 127.2 ($C_{2''}$, $C_{6''}$), 127.3 ($C_{4''}$), 128.8 ($C_{3''}$, $C_{5''}$), 132.2 (CH_2C<u>H</u>=CH), 135.7 ($C_{1'}$), 140.4 ($C_{4'}$), 140.6 ($C_{1''}$), 143.7 (C_1), 155.9 (CO), 160.8 (C_3, C_5); MS (ESI): *m/z* (%): 405.2 (MH^+ + 1, 21), 404.2 (MH^+, 100), 224.1 (5), 194.1 (1), 193.1 (8); HRMS (ESI): *m/z* calcd. for $C_{25}H_{26}NO_4$: 404.1862 [MH^+]; found: 404.1859.

*Methyl (E)-(3-(4-(tert-butyl)phenyl)allyl)(3,5-dimethoxyphenyl)carbamate (**11aj**)*



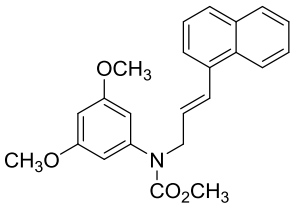
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.25 g, 1.0 mmol) and 4-*tert*-butylstyrene (0.92 mL, 5.0 mmol) in dry CH_2Cl_2 (2.3 mL) and 2nd generation Grubbs catalyst (42.6 mg, 0.050 mmol) in dry CH_2Cl_2 (1.1 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **11aj** as a solid (0.26 g, 67 %): mp (CH_2Cl_2) 108-111 ºC; IR (ATR): ν (cm^{-1}) = 1706 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.31 (s, 9H, 3 × CH_3), 3.73 (s, 3H, CO_2CH_3), 3.76 (s, 6H, 2 × OCH_3), 4.37 (d, *J* = 5.9 Hz, 2H, NCH_2), 6.15-6.57 (m, 5H, CH_2CH=C<u>H</u>, H_2, H_4, H_6), 7.20-7.39 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 31.3 (3 × CH_3), 34.4 (<u>C</u>(CH_3)$_3$), 53.0 (NCH_2, CO_2CH_3), 55.4 (2 × OCH_3), 98.7 (C_2, C_6), 105.4 (C_4), 124.2 (CH_2CH=C<u>H</u>), 125.5 ($C_{2'}$, $C_{6'}$), 126.2 ($C_{3'}$, $C_{5'}$), 132.4 (CH_2C<u>H</u>=CH), 133.9 ($C_{1'}$), 143.7 (C_1), 150.8 ($C_{4'}$), 155.8 (CO), 160.8 (C_3, C_5); MS (ESI): *m/z* (%): 385.2 (MH^+ + 1, 17), 384.2 (MH^+, 86), 352.2 (3), 250.1 (2), 225.1 (3), 224.1 (35), 192.1 (3), 174.1 (2), 173.1 (20), 117.1 (2); HRMS (ESI): *m/z* calcd. for $C_{23}H_{30}NO_4$: 384.2175 [MH^+]; found: 384.2183.

*Methyl (E)-(3,5-dimethoxyphenyl)(3-(4-fluorophenyl)allyl)carbamate (**11ak**)*



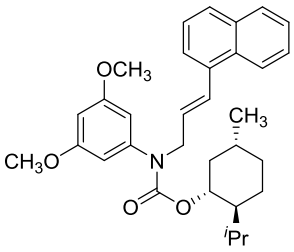
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.31 g, 1.3 mmol) and 4-fluorostyrene (0.74 mL, 6.2 mmol) in dry CH_2Cl_2 (2.8 mL) and 2nd generation Grubbs catalyst (52.9 mg, 0.062 mmol) in dry CH_2Cl_2 (1.4 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **11ak** as a solid (0.24 g, 56%): mp (CH_2Cl_2) 90-91 ºC; IR (ATR): ν = 1695 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.73 (s, 3H, CO_2CH_3), 3.75 (s, 6H, 2 × OCH_3), 4.36 (dd, *J* = 6.3, 1.1 Hz, 2H, NCH_2), 6.21 (dt, *J* = 15.8, 6.3 Hz, 1H, CH_2CH=CH), 6.37 (t, *J* = 2.2 Hz, 1H, H_4), 6.39-6.49 (m, 3H, CH_2CH=C<u>H</u>, H_2, H_6), 6.93-7.02 (m, 2H, $H_{3'}$, $H_{5'}$), 7.27-7.34 (m, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.9 (NCH_2), 53.0 (CO_2CH_3), 55.4 (2 × OCH_3), 98.7 (C_2, C_6), 105.5 (C_4), 115.4 (d, *J* = 21.6 Hz, $C_{3'}$, $C_{5'}$), 124.8 (d, *J* = 2.0 Hz, CH_2CH=C<u>H</u>), 128.0 (d, *J* = 8.7 Hz, $C_{2'}$, $C_{6'}$), 131.4 (CH_2CH=CH), 132.9 (d, *J* = 3.8 Hz, $C_{1'}$), 143.7 (C_1), 155.8 (CO), 160.8 (C_3, C_5), 162.3 (d, *J* = 247.4 Hz, $C_{4'}$); MS (ESI): *m/z* (%): 347.1 (MH^+ + 1, 18), 346.1 (MH^+, 100), 314.1 (2), 225.1 (1), 224.1 (12), 135.1 (2); HRMS (ESI): *m/z* calcd. for $C_{19}H_{21}FNO_4$: 346.1455 [MH^+]; found: 346.1453.

*Methyl (E)-(3,5-dimethoxyphenyl)(3-(naphthalen-1-yl)allyl)carbamate (**11al**)*



Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.30 g, 1.2 mmol) and 1-vinylnaphthalene (0.90 mL, 6.1 mmol) in dry CH_2Cl_2 (2.8 mL) and 2nd generation Grubbs catalyst (51.4 mg, 0.061 mmol) in dry CH_2Cl_2 (1.4 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **11al** as an oil (0.32 g, 70%): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.78 (s, 3H, CO_2CH_3), 3.80 (s, 6H, 2 × OCH_3), 4.55 (d, *J* = 6.4 Hz, 2H, NCH_2), 6.35 (dt, *J* = 15.9, 6.6 Hz, 1H, CH_2CH=CH), 6.45 (t, *J* = 2.0 Hz, 1H, H_4), 6.54 (d, *J* = 2.0 Hz, 2H, H_2, H_6), 7.26 (d, *J* = 15.9 Hz, 1H, CH_2CH=C<u>H</u>), 7.42-7.46 (m, 1H, $H_{6'}$), 7.46-7.54 (m, 2H, $H_{3'}$, $H_{7'}$), 7.56-7.61 (m, 1H, $H_{2'}$), 7.76-7.82 (m, 1H, $H_{8'}$), 7.83-7.89 (m, 1H, $H_{5'}$), 7.96-8.05 (m, 1H, $H_{4'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 53.1 (NCH_2, CO_2CH_3), 55.5 (2 × OCH_3), 99.0 (C_2, C_6), 105.7 (C_4), 123.9 ($C_{2'}$), 124.1 ($C_{8'}$), 125.7 ($C_{6'}$), 125.9 ($C_{7'}$), 126.1 ($C_{3'}$), 128.1 ($C_{4'}$), 128.3, 128.6 ($C_{5'}$, CH_2CH=C<u>H</u>), 130.4 (CH_2CH=CH), 131.2 ($C_{8a'}$), 133.6 ($C_{4a'}$) 134.6 ($C_{1'}$), 143.7 (C_1), 155.9 (CO), 161.0 (C_3, C_5); MS (ESI): *m/z* (%): 401.2 (MNa^+ + 1, 20), 400.2 (MNa^+, 100), 379.2 (MH^+ + 1, 18), 378.2 (MH^+, 94), 346.1 (7), 269.2 (5), 251.1 (3), 250.1 (18), 225.1 (6), 224.1 (70), 168.1 (7), 167.1 (65); HRMS (ESI): *m/z* calcd. for $C_{23}H_{24}NO_4$: 378.1705 [MH^+]; found: 378.1703.

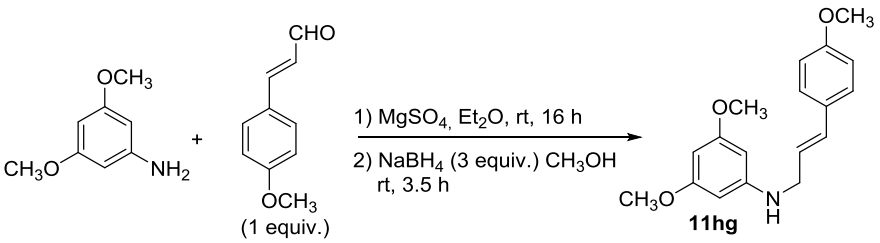
*(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl (3,5-dimethoxyphenyl)((E)-3-(naphthalene-1-yl) allyl)carbamate (**11gl**)*



Prepared from (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl allyl(3,5-dimethoxyphenyl) carbamate **11ga** (0.28 g, 0.74 mmol) and 1-vinylnaphthalene (0.55 mL, 3.7 mmol) in dry CH_2Cl_2 (1.7 mL) and 2nd generation Grubbs catalyst (31.5 mg, 0.037 mmol) in dry CH_2Cl_2 (0.84 mL). Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **11gl** as an oil (0.23 g, 62%): IR (ATR): ν (cm^{-1}) = 1700 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.78-0.93 (m, 10H, 3 × CH_3, $(CH_3)_2$C<u>H</u>), 0.96-1.16 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.29-1.40 (m, 1H, 1 × $H_{6'}$), 1.42-1.55 (m, 1H, $H_{5'}$), 1.61-1.74 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.89-2.04 (m, 1H, 1 × $H_{6'}$), 2.11-2.23 (m, 1H, $H_{2'}$), 3.77 (s, 6H, 2 × OCH_3), 4.52 (dd, *J* = 6.1, 1.2 Hz, 2H, NCH_2), 4.69 (td, *J* = 10.8, 4.3 Hz, 1H, $H_{1'}$), 6.19-6.58 (m, 4H, CH_2C<u>H</u>=CH, H_2, H_4, H_6), 7.23 (d, *J* = 15.7 Hz, 1H, CH_2CH=C<u>H</u>), 7.41-7.62 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{6'}$, $H_{7'}$), 7.74-7.92 (m, 2H, $H_{5'}$, $H_{8'}$), 7.97-8.07 (m, 1H, $H_{4'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.4 (CH_3), 20.8 (CH_3), 22.1 (CH_3), 23.4 ($C_{3'}$), 26.3 ($(CH_3)_2$<u>C</u>H), 31.4 ($C_{5'}$), 34.3 ($C_{4'}$), 41.3 ($C_{6'}$), 47.2 ($C_{2'}$), 52.8 (NCH_2), 55.4 (2 × OCH_3), 76.0 ($C_{1'}$), 98.8 (C_2, C_6), 105.2 (C_4), 123.9 ($C_{2''}$), 124.0 ($C_{8''}$), 125.6 ($C_{6''}$), 125.8 ($C_{7''}$), 126.0 ($C_{3''}$), 127.9 ($C_{4''}$), 128.5 ($C_{5''}$), 128.7 (CH_2CH=<u>C</u>H), 129.8 (CH_2<u>C</u>H=CH), 131.2 ($C_{8a''}$), 133.6 ($C_{4a''}$) 134.7 ($C_{1''}$), 144.1 (C_1), 155.1 (CO), 160.7 (C_3, C_5); MS (ESI): *m/z* (%): 503.3 (MH^+ + 1, 11), 502.3 (MH^+, 36), 380.1 (4), 366.2 (3), 365.2 (20), 364.2 (100), 348.2 (2), 237.1 (2), 236.1 (13), 210.1 (8), 167.1 (4), 166.1 (2); HRMS (ESI): *m/z* calcd. for $C_{32}H_{40}NO_4$: 502.2957 [MH^+]; found: 502.2961; $[\alpha]_D^{20}$ = -114.2 (c = 0.053 g/100 mL in CH_2Cl_2).

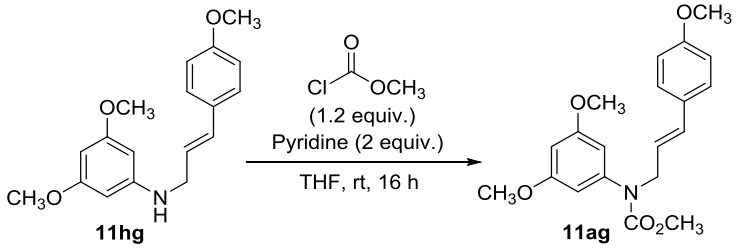
4.8. Synthesis of methyl *(E)*-(3,5-dimethoxyphenyl)(3-(4-methoxyphenyl)allyl)carbamate (11ag)

*4.8.1. Step 1: Reductive amination. Synthesis of (E)-3,5-dimethoxy-N-(3-(4-methoxyphenyl)-allyl)aniline (**11hg**)*



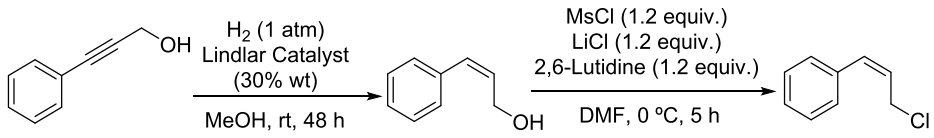
Over a solution of commercially available 3,5-dimethoxyaniline (0.53 g, 3.5 mmol) in dry Et_2O (17 mL), *trans-p*-methoxycinnamaldehyde (0.56 g, 3.5 mmol) and anhydrous $MgSO_4$ (4 g) were added under argon atmosphere. The reaction mixture was stirred at room temperature for 16 h, it was filtered and the solvent was evaporated *in vacuo*. The crude imine was dissolved in dry MeOH (23 mL) and $NaBH_4$ (0.39 g, 10.4 mmol) was added portionwise under argon atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for 3.5 h. Afterwards, a 1 M NaOH aqueous solution (15 mL) was added to quench the reaction and it was diluted with water (20 mL). The mixture was extracted with AcOEt (3 × 15 mL), the combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. Flash column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **11hg** as an oil (0.64 g, 62%): IR (ATR): ν (cm^{-1}) = 3408 (N-H); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.77 (s, 6H, 2 × OCH_3), 3.81 (s, 3H, OCH_3), 3.84-3.96 (m, 3H, NH, NCH_2), 5.88 (d, *J* = 2.1 Hz, 2H, H_2, H_6), 5.93 (t, *J* = 2.1 Hz, 1H, H_4), 6.18 (dt, *J* = 15.8, 5.7 Hz, 1H, CH_2CH=CH), 6.57 (d, *J* = 15.8 Hz, 1H, CH_2CH=C<u>H</u>), 6.87 (d, *J* = 8.8 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.32 (d, *J* = 8.8 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 46.3 (NCH_2), 55.2 (OCH_3), 55.3 (2 × OCH_3), 89.9 (C_4), 91.9 (C_2, C_6), 114.0 ($C_{3'}$, $C_{5'}$), 124.6 (CH_2CH=<u>C</u>H), 127.5 ($C_{2'}$, $C_{6'}$), 129.7 ($C_{1'}$), 131.2 (CH_2<u>C</u>H=CH), 150.1 (C_1), 159.2 ($C_{4'}$), 161.8 (C_3, C_5); MS (ESI): *m/z* (%): 301.2 (MH^+ + 1, 6), 300.2 (MH^+, 37), 299.1 (6), 298.1 (44), 148.1 (7), 147.1 (100), 132.1 (1), 117.1 (1), 91.1 (5); HRMS (ESI): *m/z* calcd. for $C_{18}H_{22}NO_3$: 300.1600 [MH^+]; found: 300.1600.

*4.8.2. Step 2: N-Protection. Synthesis of methyl (E)-(3,5-dimethoxyphenyl)(3-(4-methoxyphenyl)allyl)carbamate (**11ag**)*

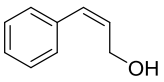


Over a solution of *(E)*-3,5-dimethoxy-*N*-(3-(4-methoxyphenyl)allyl)aniline **11hg** (0.51 g, 1.7 mmol) and freshly distilled pyridine (0.27 mL, 3.4 mmol) in dry THF (20 mL), methyl chloroformate (0.16 mL, 2.1 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 16 h and afterwards, the solvent was evaporated under reduced pressure. The crude reaction was dissolved in CH_2Cl_2 (30 mL) and washed with a 10% aqueous solution of HCl (2 × 15 mL) and with water (15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **11ag** as an oil (0.54 g, 89%): IR (ATR): ν (cm^{-1}) = 1695 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.72 (s, 3H, CO_2CH_3), 3.74 (s, 6H, 2 × OCH_3), 3.77 (s, 3H, OCH_3), 4.32 (d, *J* = 6.4 Hz, 2H, NCH_2), 6.16 (dt, *J* = 15.8, 6.4 Hz, 1H, CH_2CH=CH), 6.33-6.48 (m, 4H, H_2, H_4, H_6, CH_2CH=C<u>H</u>), 6.83 (d, *J* = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.28 (d, *J* = 8.7 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.9 (CO_2<u>C</u>H_3), 53.0 (NCH_2), 55.2 (OCH_3), 55.4 (2 × OCH_3), 98.8 (C_2, C_6), 105.5 (C_4), 114.0 ($C_{3'}$, $C_{5'}$), 122.8 (CH_2CH=<u>C</u>H), 127.6 ($C_{2'}$, $C_{6'}$), 129.5 ($C_{1'}$), 132.1 (CH_2<u>C</u>H=CH), 143.8 (C_1), 155.8 (CO), 159.3 ($C_{4'}$), 160.8 (C_3, C_5); MS (ESI): *m/z* (%): 381.2 (MNa^+ + 1, 16), 380.1 (MNa^+, 96), 359.2 (MH^+ + 1, 10), 358.2 (MH^+, 60), 357.2 (3), 326.1 (3), 250.1 (4), 225.1 (3), 224.1 (30), 148.1 (5), 147.1 (66); HRMS (ESI): *m/z* calcd. for $C_{20}H_{23}NO_5Na$: 380.1474 [MNa^+]; found: 380.1473.

4.9. Synthesis of *(Z)*-(3-chloroprop-1-en-1-yl)benzene

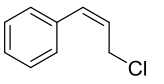


(Z)-3-Phenylprop-2-en-1-ol[44]



To a solution of 3-phenyl-2-propyn-1-ol (1.1 mL, 4.6 mmol) in dry MeOH (18.3 mL), Lindlar catalyst (0.18 g, 30% wt.) was added under argon atmosphere. The reaction flask was evacuated and refilled with H_2 three times and it was stirred vigorously for 48 h under hydrogen atmosphere (balloon). Afterwards, the reaction mixture was filtered through celite and washed with AcOEt (3 × 20 mL) and the solvent was evaporated *in vacuo* affording *(Z)*-3-phenylprop-2-en-1-ol (with 8% of the over-reduced product) as an oil without further purification (0.58 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.78 (br s, 1H, OH), 4.45 (dd, *J* = 6.4, 1.7 Hz, 2H, C$\underline{H_2}$OH), 5.79-5.97 (m, 1H, C$\underline{H}$=CHPh), 6.57 (d, *J* = 11.8 Hz, 1H, CH=C$\underline{H}$Ph), 7.20-7.42 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 59.6 (CH_2OH), 127.3 (C_4), 128.3 (C_2, C_6), 128.8 (C_3, C_5), 130.8 ($\underline{C}$H=CHPh), 131.4 (CH=$\underline{C}$HPh), 136.6 (C_1).

(Z)-(3-Chloroprop-1-en-1-yl)benzene[44]

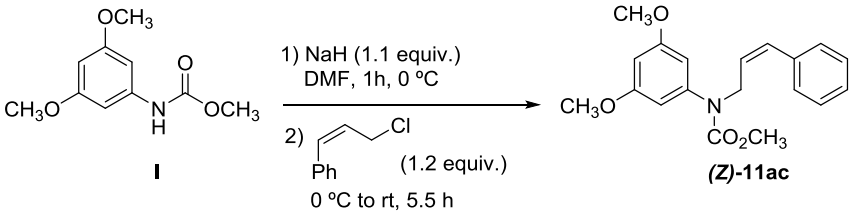


A solution of LiCl (0.22 g, 5.2 mmol) in dry DMF (5 mL) was stirred for 10 minutes at 0 ºC and under argon atmosphere. To that mixture, a solution of *(Z)*-3-phenylprop-2-en-1-ol (0.58 g, 4.3 mmol) in dry DMF (5 mL) was added *via cannula*, followed by the slow addition of anhydrous 2,6-lutidine (0.61 mL, 5.2 mmol) and methanesulfonyl chloride (0.40 mL, 5.2 mmol). The reaction mixture was stirred at 0 ºC for 5 h. After that, the mixture was diluted with Et_2O (20 mL) and washed with water (10 mL). The aqueous phase was extracted with Et_2O (10 mL) and the combined organic extracts were dried (Na_2SO_4). The volatiles were evaporated at reduced pressure and the residue was purified by flash column chromatography (silica gel, ^{n}pentane) affording *(Z)*-(3-chloroprop-1-en-1-yl)benzene (with 8% of the over-reduced counterpart) as an oil (0.40 g, 60%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.31 (dd, *J* = 8.2, 0.8 Hz, 2H, C$\underline{H_2}$Cl), 5.94 (dt, *J* = 11.3, 8.2 Hz, 1H, C$\underline{H}$=CHPh), 6.70 (d, *J* = 11.3 Hz, 1H, CH=C$\underline{H}$Ph), 7.27-7.46 (m, 5H, Ph); ^{13}C

[44] Jiang, T.; Huynh, K.; Livinghouse, T. *Synlett* **2013**, *24*, 193.

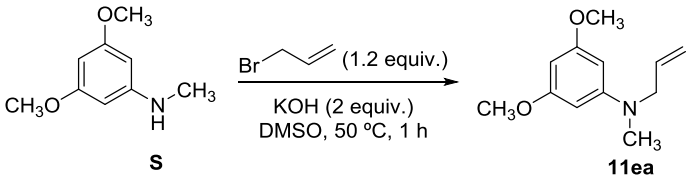
NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 40.9 (CH_2Cl), 127.0 (C̲H=CHPh), 127.7 (C_4), 128.5 (C_2, C_6), 128.8 (C_3, C_5), 133.5 (CH=C̲HPh), 135.7 (C_1).

4.10. Synthesis of methyl *(Z)*-(3,5-dimethoxyphenyl)(3-phenylallyl)carbamate [*(Z)*-11ac]



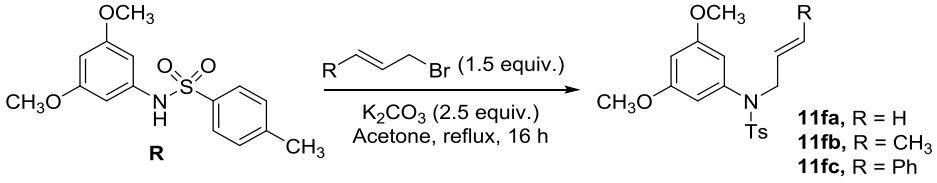
Over a solution of methyl (3,5-dimethoxyphenyl)carbamate **I** (0.45 g, 2.1 mmol) in dry DMF (10 mL) at 0 ºC under argon atmosphere, NaH (60 % in mineral oil) (93.5 mg, 2.3 mmol) was added. The reaction was stirred at 0 ºC for 1 h, and afterwards, a solution of *(Z)*-(3-chloroprop-1-en-1-yl)benzene (0.39 g, 2.5 mmol) in dry DMF (5 mL) was added *via cannula*. Then, the reaction was allowed to warm up to room temperature and stirred for 5.5 h. Afterwards, water (20 mL) was added and the aqueous layer was extracted with AcOEt (3 × 15 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded ***(Z)*-11ac** (with 8 % of the over-reduced counterpart) as a solid (0.54 g, 78%): mp (CH_2Cl_2) 65-67 ºC; IR (ATR): ν (cm^{-1}) = 1690 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.72 (s, 6H, 2 × OCH_3), 3.74 (s, 3H, CO_2CH_3), 4.60 (dd, *J* = 6.3, 1.8 Hz, 2H, NCH_2), 5.84 (dt, *J* = 12.0, 6.3 Hz, 1H, C̲H=CHPh), 5.35-5.38 (m, 1H, H_4), 6.39 (d, *J* = 2.0 Hz, 2H, H_2, H_6), 6.58 (d, *J* = 12.0 Hz, 1H, CH=C̲HPh), 7.11-7.35 (m, 5H, Ph); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ (ppm) = 48.7 (NCH_2), 53.0 (CO_2C̲H_3), 55.3 (2 × OCH_3), 98.8 (C_2, C_6), 105.1 (C_4), 127.1 (CH=C̲HPh), 128.3 ($C_{2'}$, $C_{6'}$), 128.7 ($C_{4'}$), 128.8 ($C_{3'}$, $C_{5'}$), 131.1 (C̲H=CHPh), 136.5 ($C_{1'}$), 143.5 (C_1), 155.8 (CO), 160.8 (C_3, C_5); MS (ESI): *m/z* (%): 329.2 (MH^+ + 1, 10), 328.2 (MH^+, 60), 301.1 (6), 297.1 (2), 296.1 (11), 268.1 (2), 225.1 (9), 224.1 (100), 118.1 (2), 117.1 (19); HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}NO_4$: 328.1549 [MH^+]; found: 328.1548.

4.11. Synthesis of *N*-allyl-3,5-dimethoxy-*N*-methylaniline (11ea)



Over a solution of 3,5-dimethoxy-*N*-methylaniline **S** (0.20 g, 1.2 mmol) in DMSO (5 mL), powder KOH (0.14 g, 2.5 mmol) was added. After 15 min, allyl bromide (0.13 mL, 1.5 mmol) was added dropwise at room temperature and the reaction was heated at 50 ºC for 1 h. Then, water (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **11ea** as an oil (0.15 g, 60%); IR (ATR): ν (cm^{-1}) = 1612 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.94 (s, 3H, NCH_3), 3.79 (s, 6H, 2 × OCH_3), 3.91 (dt, *J* = 5.1, 1.6 Hz, 2H, NCH_2), 5.15-5.21 (m, 2H, CH=C$\underline{H}_2$), 5.85 (ddt, *J* = 17.0, 10.2, 5.1 Hz, 1H, C$\underline{H}$=CH_2), 5.93 (s, 3H, H_2, H_4, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 38.2 (NCH_3), 55.2 (NCH_2), 55.3 (2 × OCH_3), 88.6 (C_4), 91.8 (C_2, C_6), 116.2 (CH=$\underline{C}H_2$), 133.8 ($\underline{C}$H=CH_2), 151.4 (C_1), 161.6 (C_3, C_5); MS (CI): *m/z* (%): 209.1 (MH^+ + 1, 12), 208.1 (MH^+, 97), 207.1 (100), 206.1 (16), 192.1 (23), 176.1 (32); HRMS (CI): *m/z* calcd. for $C_{12}H_{18}NO_2$: 208.1338 [MH^+]; found: 208.1320.

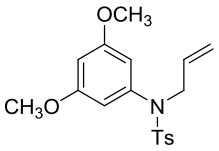
4.12 General procedure for the alkylation of *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (R). Synthesis of sulfonamides 11fa-11fc



Over a solution of *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide **R** (1 mmol) in dry acetone (20 mL), K_2CO_3 (2.5 mmol) and the corresponding allyl bromide (1.5 mmol) were added under argon atmosphere. The reaction mixture was heated at reflux for 16 h and then, it was allowed to cool down to room temperature. Afterwards, CH_2Cl_2 (20 mL) was added and the mixture was washed with water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried (Na_2SO_4) and

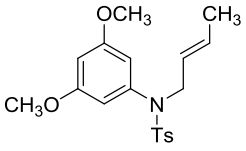
concentrated *in vacuo*. Flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded the corresponding *N*-allyl-*N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamides **11fa-11fc**.

*N-Allyl-N-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (**11fa**)*



Prepared from *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide **R** (0.40 g, 1.3 mmol), K_2CO_3 (0.45 g, 3.3 mmol) and allyl bromide (0.17 mL, 2.0 mmol). After work-up and purification by flash column chromatography **11fa** was obtained as a solid (0.41 g, 89%): mp (CH_2Cl_2) 82-84 ºC; IR (ATR): ν (cm^{-1}) = 1343, 1153 (Ar-SO_2-NR_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.42 (s, 3H, CH_3), 3.70 (s, 6H, 2 × OCH_3), 4.13 (d, *J* = 6.1 Hz, 2H, NCH_2), 5.00-5.18 (m, 2H, CH=CH_2), 5.64-5.86 (m, 1H, CH=CH_2), 6.21 (d, *J* = 1.8 Hz, 2H, H_2, H_6), 6.37 (t, *J* = 1.8 Hz, 1H, H_4), 7.26 (d, *J* = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.55 (d, *J* = 8.0 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.5 (CH_3), 53.6 (NCH_2), 55.4 (2 × OCH_3), 100.0 (C_4), 107.0 (C_2, C_6), 118.7 (CH=CH_2), 127.8 ($C_{2'}$, $C_{6'}$), 129.4 ($C_{3'}$, $C_{5'}$), 132.8 (CH=CH_2), 135.5 ($C_{1'}$), 140.9 ($C_{4'}$), 143.5 (C_1), 160.6 (C_3, C_5); MS (ESI): *m/z* (%): 371.1 (MNa^+ + 1, 16), 370.1 (MNa^+, 100), 349.1 (MH^+ + 1, 8), 348.1 (MH^+, 52), 283.2 (4), 194.1 (5), 193.1 (57), 178.1 (2); HRMS (ESI): *m/z* calcd. for $C_{18}H_{21}NO_4SNa$: 370.1089 [MNa^+]; found: 370.1091.

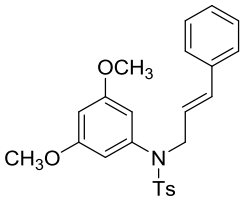
*(E)-N-(But-2-en-1-yl)-N-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (**11fb**)*



Prepared from *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide **R** (0.30 g, 0.98 mmol), K_2CO_3 (0.34 g, 2.5 mmol) and crotyl bromide (0.18 mL, 1.5 mmol). After work-up and purification by flash column chromatography **11fb** was obtained as a solid and as a mixture of rotamers in a 83:17 ratio (0.30 g, 83%): mp (CH_2Cl_2) 101-102 ºC; IR (ATR): ν (cm^{-1}) = 1285, 1160 (Ar-SO_2-NR_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.49-1.54 (m, 3H, CH=CHCH_3, minor rotamer), 1.55-1.59 (m, 3H, CH=CHCH_3, major rotamer), 2.41 (s, 3H, CH_3, both rotamers), 3.70 (s, 6H, 2 × OCH_3, both rotamers), 4.02-4.09 (m, 2H, NCH_2, major rotamer), 4.14-4.20 (m, 2H, NCH_2, minor rotamer), 5.30-5.58 (m, 2H, CH=CH, both rotamers), 6.19 (d, *J* = 2.3 Hz, 2H, H_2, H_6, major rotamer), 6.21 (d, *J* = 2.3 Hz, 2H, H_2, H_6, minor rotamer), 6.36 (t, *J* = 2.3 Hz, 1H, H_4, both rotamers), 7.25 (d, *J* = 8.3 Hz, $H_{3'}$, $H_{5'}$, both rotamers), 7.54 (d, *J* = 8.3 Hz, $H_{2'}$, $H_{6'}$, both rotamers); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 12.9 (CH=CHCH_3, minor rotamer), 17.7 (CH=CHCH_3, major rotamer), 21.5 (CH_3, both rotamers), 47.4 (NCH_2, minor rotamer), 53.1 (NCH_2, major rotamer), 55.4 (2 × OCH_3, both rotamers), 100.0 (C_4, both rotamers), 106.9 (C_2, C_6, minor rotamer), 107.1 (C_2, C_6, major rotamer), 124.7 (CH=C$H$$CH_3$, minor rotamer), 125.5 (CH=C$H$$CH_3$, major rotamer), 127.8 ($C_{2'}$,

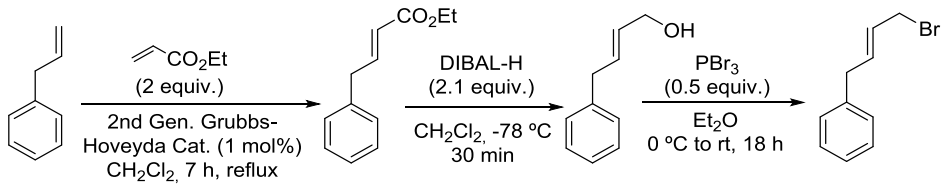
$C_{6'}$, major rotamer), 128.4 ($C_{2'}$, $C_{6'}$, minor rotamer), 129.3 ($C_{3'}$, $C_{5'}$, major rotamer), 129.4 ($C_{3'}$, $C_{5'}$, minor rotamer), 130.2 (C̲H=CHCH$_3$, both rotamers), 135.8 ($C_{1'}$, both rotamers), 141.1 ($C_{4'}$, both rotamers), 143.3 (C_1, both rotamers), 160.5 (C_3, C_5, both rotamers); MS (ESI): *m/z* (%): 385.1 (MNa^+ + 1, 16), 384.1 (MNa^+, 100), 363.1 (MH^+ + 1, 13), 362.1 (MH^+, 78), 320.1 (10), 309.1 (3), 308.1 (24), 256.1 (2), 208.1 (6), 207.1 (59), 178.1 (2); HRMS (ESI): *m/z* calcd. for $C_{19}H_{23}NO_4SNa$: 384.1246 [MNa^+]; found: 384.1241.

*N-Cinnamyl-N-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (**11fc**)*

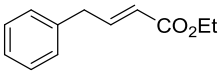


Prepared from *N*-(3,5-dimethoxyphenyl)-4-methylbenzene-sulfonamide **R** (0.27 g, 0.87 mmol), K_2CO_3 (0.30 g, 2.2 mmol) and cinnamyl bromide (0.26 g, 1.3 mmol). After work-up and purification by flash column chromatography **11fc** was obtained as a solid (0.21 g, 58%): mp (CH_2Cl_2) 123-126 ºC; IR (ATR): ν (cm^{-1})= 1345, 1155 (Ar-SO_2-NR_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.41 (s, 3H, CH_3), 3.68 (s, 6H, 2 × OCH_3), 4.32 (dd, *J* = 6.5, 1.0 Hz, 2H, NCH_2), 6.14 (dt, 1H, *J* = 15.8, 6.5 Hz, C̲H=CHPh), 6.28 (d, *J* = 2.2 Hz, 2H, H_2, H_6), 6.38 (t, *J* = 2.2 Hz, 1H, H_4), 6.43 (d, 1H, *J* = 15.8 Hz, CH=C̲HPh), 7.17-7.30 (m, 7H, Ph, $H_{3'}$, $H_{5'}$), 7.61 (d, *J* = 8.3 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.6 (CH_3), 53.4 (NCH_2), 55.4 (2 × OCH_3), 100.1 (C_4), 107.1 (C_2, C_6), 124.2 (CH=C̲HPh), 126.5 ($C_{2''}$, $C_{6''}$), 127.8 ($C_{2'}$, $C_{6'}$, $C_{4''}$), 128.6 ($C_{3''}$, $C_{5''}$), 129.5 ($C_{3'}$, $C_{5'}$), 133.7 (C̲H=CHPh), 135.7 ($C_{1'}$), 136.4 ($C_{1''}$), 141.1 ($C_{4'}$), 143.6 (C_1), 160.7 (C_3, C_5); MS (ESI): *m/z* (%): 447.2 (MNa^+ + 1, 12), 446.1 (MNa^+, 53), 441.2 (10), 426.2 (6), 425.2 (MH^+ + 1, 21), 424.2 (MH^+, 100), 320.1 (5), 308.1 (1), 270.1 (5), 269.1 (32), 118.1 (6), 117.1 (89); HRMS (ESI): *m/z* calcd. for $C_{24}H_{25}NO_4SNa$: 446.1402 [MNa^+]; found: 446.1397.

4.13. Synthesis of *(E)*-(4-bromobut-2-en-1-yl)benzene

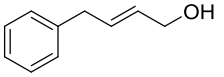


Ethyl (E)-4-phenylbut-2-enoate[45]



To a solution of 2nd generation Grubbs-Hoveyda catalyst (47.3 mg, 0.075 mmol) in dry CH_2Cl_2 (30.2 mL), allyl benzene (1.0 mL, 7.5 mmol) and ethyl acrylate (1.7 mL, 15.1 mmol) were added under argon atmosphere. The reaction mixture was stirred for 7 h at reflux and it was allowed to cool down to room temperature. The solvent was evaporated *in vacuo* and the obtained residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 95/5), affording ethyl *(E)*-4-phenylbut-2-enoate as an oil (1.2 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.27 (t, *J* = 7.0 Hz, 3H, CH_3), 3.51 (d, *J* = 7.0 Hz, 2H, PhC$\underline{H}_2$), 4.17 (q, *J* = 7.0 Hz, 2H, OCH_2), 5.81 (d, *J* = 15.5 Hz, 1H, CH=C$\underline{H}CO_2$Et), 7.10 (dt, *J* = 15.5, 7.0 Hz, 1H, C$\underline{H}$=CHCO$_2$Et), 7.16-7.32 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.2 ($CH_2\underline{C}H_3$), 38.4 (Ph$\underline{C}H_2$), 60.2 (OCH_2), 122.3 (CH=$\underline{C}$HCO$_2$Et), 126.6 (C_4), 128.6 (C_3, C_5), 128.7 (C_2, C_6), 137.2 (C_1), 147.2 ($\underline{C}$H=CHCO$_2$Et), 166.4 (CO).

(E)-4-Phenylbut-2-en-1-ol[45]

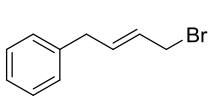


To a solution of ethyl *(E)*-4-phenylbut-2-enoate (1.0 g, 5.3 mmol) in dry CH_2Cl_2 (15.0 mL), DIBAL-H (1 M in THF) (23.3 mL, 23.3 mmol) was added dropwise at -78 ºC and under argon atmosphere. The solution was stirred at that temperature for 30 minutes and the reaction was quenched by addition of water (5 mL) and AcOEt (5 mL). The mixture was vigorously stirred at room temperature for 1 h and it was filtered through Celite®. The organic phase was washed with water and the aqueous phase was extracted with AcOEt (15 mL). The combined organic phases were washed with brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded *(E)*-4-phenylbut-2-en-1-ol as an oil (0.67 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.08 (br s, 1H, OH),

[45] Race, N.; Bower, J. *Org. Lett.* **2013**, *15*, 4616.

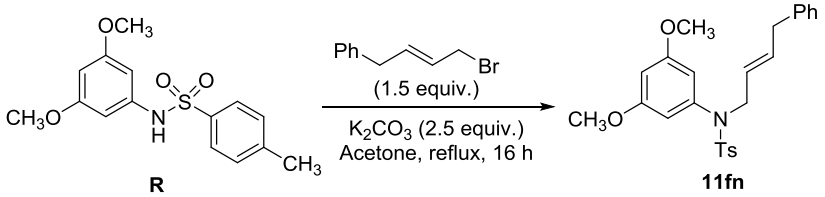
3.44 (d, *J* = 6.5 Hz, 2H, PhC<u>H</u>$_2$), 4.12 (d, *J* = 5.3 Hz, 2H, C<u>H</u>$_2$OH), 5.66-5.99 (m, 2H, CH=CH), 7.19-7.47 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 38.8 (Ph<u>C</u>H$_2$), 62.2 (CH_2OH), 126.2 (C_4), 128.6 (C_3, C_5), 128.7 (C_2, C_6), 130.5 (<u>C</u>H=CHCH$_2$OH), 131.2 (CH=<u>C</u>HCH$_2$OH), 140.2 (C_1).

(E)-(4-Bromobut-2-en-1-yl)benzene[45]



Over a solution of *(E)*-4-phenylbut-2-en-1-ol (0.66 g, 4.5 mmol) in dry Et_2O (4.9 mL), PBr_3 (0.21 mL, 2.2 mmol) was added dropwise at 0 ºC and under argon atmosphere. The mixture was allowed to warm up to room temperature and stirred for 18 h. Afterwards, the reaction was quenched by careful pouring in ice-water (18.0 mL) and extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with water (15 mL), a saturated aqueous solution of $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered through a short pad of silica, obtaining *(E)*-(4-bromobut-2-en-1-yl)benzene (0.77 g, 82%) as an oil and without further purification: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.45 (d, *J* = 6.6 Hz, 2H, PhC<u>H</u>$_2$), 4.01 (d, *J* = 7.4 Hz, 2H, C<u>H</u>$_2$Br), 5.74-6.04 (m, 2H, CH=CH), 7.15-7.45 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 33.0 (CH_2Br), 38.8 (Ph<u>C</u>H$_2$), 126.4 (C_4), 127.7 (CH=<u>C</u>HCH$_2$Br), 128.6 (C_3, C_5), 128.7 (C_2, C_6), 134.9 (<u>C</u>H=CHCH$_2$Br), 139.4 (C_1).

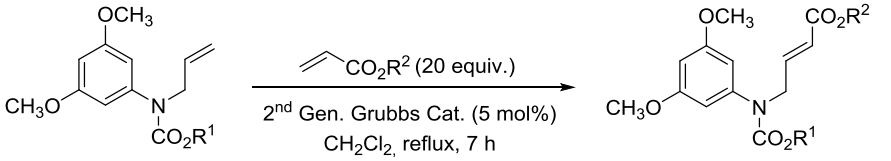
4.14. Synthesis of *(E)-N*-(3,5-dimethoxyphenyl)-4-methyl-*N*-(4-phenylbut-2-en-1-yl)-benzene sulfonamide (11fn)



Over a solution of *N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide **R** (0.30 g, 0.99 mmol) in dry acetone (20 mL), K_2CO_3 (0.34 g, 2.5 mmol) and *(E)*-(4-bromobut-2-en-1-yl)benzene (0.31 g, 1.5 mmol) were added under argon atmosphere. The reaction mixture was heated at reflux for 16 h and then, it was allowed to cool down to room temperature. Afterwards, CH_2Cl_2 (20 mL) was added and the mixture was washed with water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **11fn** as an oil (0.40 g, 92%): IR (ATR): ν (cm^{-1}) = 1360,

1170 (Ar-SO_2-NR_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.41 (s, 3H, CH_3), 3.26 (d, *J* = 6.6 Hz, 2H, $C\underline{H}_2Ph$), 3.67 (s, 6H, 2 × OCH_3), 4.16 (d, *J* = 6.4 Hz, 2H, NCH_2), 5.38-5.71 (m, 2H, CH=CH), 6.24 (d, *J* = 2.3 Hz, 2H, H_2, H_6), 6.42 (t, *J* = 2.3 Hz, 1H, H_4), 6.84-6.99 (m, 2H, $H_{2''}$, $H_{6''}$), 7.10-7.30 (m, 5H, $H_{3'}$, $H_{5'}$, $H_{3''}$, $H_{4''}$, $H_{5''}$), 7.58 (d, *J* = 8.3 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.6 (CH_3), 38.4 ($\underline{C}H_2Ph$), 53.0 (NCH_2), 55.4 (2 × OCH_3), 100.2 (C_4), 107.3 (C_2, C_6), 126.0 ($C_{4''}$), 126.1 (CH=$\underline{C}$HBn), 127.8 ($C_{2'}$, $C_{6'}$), 128.4 ($C_{3''}$, $C_{5''}$), 128.5 ($C_{2''}$, $C_{6''}$), 129.5 ($C_{3'}$, $C_{5'}$), 134.1 ($\underline{C}$H=CHBn), 135.7 ($C_{1'}$), 139.7 ($C_{4'}$), 140.9 ($C_{1''}$), 143.5 (C_1), 160.7 (C_3, C_5); MS (ESI): *m/z* (%): 439.2 (MH^+ + 1, 23), 438.2 (MH^+, 100), 320.1 (4), 309.1 (4), 308.1 (25), 284.2 (3) 283.2 (19) 132.1 (2), 131.1 (22); HRMS (ESI): *m/z* calcd. for $C_{25}H_{28}NO_4S$: 438.1739 [MH^+]; found: 438.1746.

4.15. General procedure for the metathesis reaction of carbamates 11aa and 11ba. Synthesis of esters 12aa-12ba

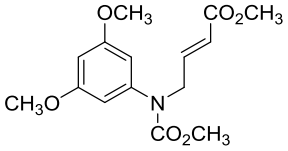


11aa, R^1 = CH_3
11ba, R^1 = ^{t}Bu

12aa, R^1 = CH_3, R^2 = CH_3
12ab, R^1 = CH_3, R^2 = Et
12ac, R^1 = CH_3, R^2 = ^{n}Bu
12ad, R^1 = CH_3, R^2 = ^{t}Bu
12ae, R^1 = CH_3, R^2 = Bn
12ba, R^1 = ^{t}Bu, R^2 = CH_3

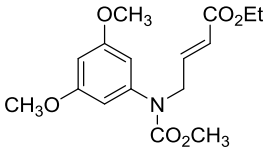
To a solution of the corresponding carbamate **11aa** or **11ba** (1 mmol) and acrylate (20 mmol) in dry CH_2Cl_2 (28.9 mL), a solution of 2nd generation Grubbs catalyst (0.05 mmol) in dry CH_2Cl_2 (8.1 mL) was added *via cannula*, under argon atmosphere. The reaction mixture was stirred at reflux for 7 h and it was allowed to cool down to room temperature. Afterwards, the solvent was evaporated *in vacuo* and purification by flash column chromatography (silica gel, petroleum ether/AcOEt) afforded esters **12aa-12ba.**

*Methyl (E)-4-((3,5-dimethoxyphenyl)(methoxycarbonyl)amino)but-2-enoate (**12aa**)*



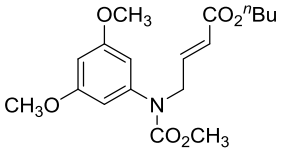
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.24 g, 0.95 mmol) and methyl acrylate (1.7 mL, 18.9 mmol) in dry CH_2Cl_2 (27.3 mL) and 2nd generation Grubbs catalyst (40.2 mg, 0.047 mmol) in dry CH_2Cl_2 (7.6 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **12aa** was obtained as an oil (0.27 g, 91%): IR (ATR): ν (cm^{-1}) = 1710 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.67 (s, 3H, CO_2CH_3), 3.68 (s, 3H, CO_2CH_3), 3.71 (s, 6H, 2 × OCH_3), 4.33 (dd, *J* = 5.5, 1.7 Hz, 2H, NCH_2), 5.90 (dt, *J* = 15.7, 1.7 Hz, 1H, CH=C<u>H</u>CO_2CH_3), 6.26-6.38 (m, 3H, H_2, H_4, H_6), 6.92 (dt, *J* = 15.7, 5.5 Hz, 1H, C<u>H</u>=CHCO_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 51.5 (NCH_2), 51.6 (CO_2<u>C</u>H_3), 53.1 (CO_2<u>C</u>H_3), 55.3 (2 × OCH_3), 98.7 (C_2, C_6), 105.0 (C_4), 122.2 (CH=<u>C</u>HCO_2CH_3), 143.3 (C_1), 143.4 (<u>C</u>H=CHCO_2CH_3), 155.5 (N<u>C</u>O_2CH_3), 160.9 (C_3, C_5), 166.3 (<u>C</u>O_2CH_3); MS (ESI): *m/z* (%): 311.1 (MH^+ + 1, 12), 310.1 (MH^+, 100), 279.1 (2), 278.1 (23); HRMS (ESI): *m/z* calcd. for $C_{15}H_{20}NO_6$: 310.1291 [MH^+]; found: 310.1300.

*Ethyl (E)-4-((3,5-dimethoxyphenyl)(methoxycarbonyl)amino)but-2-enoate (**12ab**)*



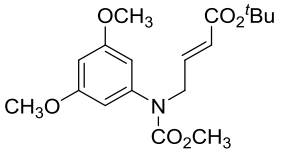
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.26 g, 1.04 mmol) and ethyl acrylate (2.3 mL, 20.8 mmol) in dry CH_2Cl_2 (30.1 mL) and 2nd generation Grubbs catalyst (44.2 mg, 0.052 mmol) in dry CH_2Cl_2 (8.4 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **12ab** was obtained as an oil (0.33 g, 99%): IR (ATR): ν (cm^{-1}) = 1710 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.26 (t, *J* = 7.1 Hz, CH_3), 3.70 (s, 3H, CO_2CH_3), 3.75 (s, 6H, 2 × OCH_3), 4.16 (q, *J* = 7.1 Hz, 2H, O<u>C</u>H_2CH_3), 4.36 (dd, *J* = 5.5, 1.7 Hz, 2H, NCH_2), 5.92 (dt, *J* = 15.7, 1.7 Hz, 1H, CH=C<u>H</u>CO_2CH_2), 6.28-6.41 (m, 3H, H_2, H_4, H_6), 6.92 (dt, *J* = 15.7, 5.5 Hz, 1H, C<u>H</u>=CHCO_2CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.2 (CH_3), 51.6 (NCH_2), 53.2 (CO_2<u>C</u>H_3), 55.4 (2 × OCH_3), 60.5 (O<u>C</u>H_2CH_3), 98.7 (C_2, C_6), 105.0 (C_4), 122.6 (CH=<u>C</u>HCO_2CH_2), 143.2 (<u>C</u>H=CHCO_2CH_2), 143.4 (C_1), 155.6 (N<u>C</u>O_2CH_3), 160.9 (C_3, C_5), 165.9 (<u>C</u>O_2Et); MS (ESI): *m/z* (%): 325.1 (MH^+ + 1, 14), 324.1 (MH^+, 100), 292.1 (7), 278.1 (9); HRMS (ESI): *m/z* calcd. for $C_{16}H_{22}NO_6$: 324.1447 [MH^+]; found: 324.1454.

*Butyl (E)-4-((3,5-dimethoxyphenyl)(methoxycarbonyl)amino)but-2-enoate (**12ac**)*



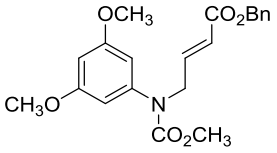
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.31 g, 1.25 mmol) and *n*-butyl acrylate (3.6 mL, 24.9 mmol) in dry CH_2Cl_2 (36.0 mL) and 2nd generation Grubbs catalyst (52.9 mg, 0.062 mmol) in dry CH_2Cl_2 (10.0 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **12ac** was obtained as an oil (0.40 g, 91%): IR (ATR): ν (cm^{-1})= 1710 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.88 (t, *J* = 7.3 Hz, CH_3), 1.25-1.45 (m, 2H, CH_2CH_3), 1.53-1.68 (m, 2H, OCH_2CH_2), 3.67 (s, 3H, CO_2CH_3), 3.71 (s, 6H, 2 × OCH_3), 4.08 (t, *J* = 6.7 Hz, 2H, OCH_2), 4.33 (dd, *J* = 5.4, 1.4 Hz, 2H, NCH_2), 5.89 (d, *J* = 15.7 Hz, 1H, $CH=CHCO_2CH_2$), 6.26-6.36 (m, 3H, H_2, H_4, H_6), 6.90 (dt, *J* = 15.7, 5.4 Hz, 1H, $CH=CHCO_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 13.7 (CH_3), 19.1 (CH_2CH_3), 30.6 (OCH_2CH_2), 51.6 (NCH_2), 53.1 (CO_2CH_3), 55.3 (2 × OCH_3), 64.3 (OCH_2), 98.7 (C_2, C_6), 105.1 (C_4), 122.6 ($CH=CHCO_2{}^nBu$), 143.2 ($CH=CHCO_2{}^nBu$), 143.4 (C_1), 155.6 (NCO_2CH_3), 160.9 (C_3, C_5), 166.0 ($CO_2{}^nBu$); MS (ESI): *m/z* (%): 353.2 (MH^+ + 1, 15), 352.2 (MH^+, 100), 320.2 (2), 278.1 (5). 220.1 (1); HRMS (ESI): *m/z* calcd. for $C_{18}H_{26}NO_6$: 352.1760 [MH^+]; found: 352.1761.

*tert-Butyl (E)-4-((3,5-dimethoxyphenyl)(methoxycarbonyl)amino)but-2-enoate (**12ad**)*



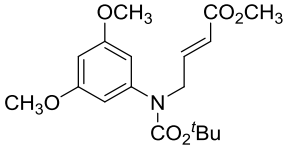
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.23 g, 0.91 mmol) and *tert*-butyl acrylate (2.7 mL, 18.3 mmol) in dry CH_2Cl_2 (26.4 mL) and 2nd generation Grubbs catalyst (38.8 mg, 0.046 mmol) in dry CH_2Cl_2 (7.4 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **12ad** was obtained as an oil (0.33 g, quant): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.44 (s, 9H, 3 × CH_3), 3.68 (s, 3H, CO_2CH_3), 3.73 (s, 6H, 2 × OCH_3), 4.32 (dd, *J* = 5.5, 1.7 Hz, 2H, NCH_2), 5.82 (dt, *J* = 15.7, 1.7 Hz, 1H, $CH=CHCO_2CH_2$), 6.28-6.38 (m, 3H, H_2, H_4, H_6), 6.81 (dt, *J* = 15.7, 5.5 Hz, 1H, $CH=CHCO_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.0 (3 × CH_3), 51.5 (NCH_2), 53.1 (CO_2CH_3), 55.3 (2 × OCH_3), 80.5 ($C(CH_3)_3$), 98.7 (C_2, C_6), 105.0 (C_4), 124.3 ($CH=CHCO_2{}^tBu$), 141.9 ($CH=CH\ CO_2{}^tBu$), 143.5 (C_1), 155.6 (NCO_2CH_3), 160.8 (C_3, C_5), 165.2 ($CO_2{}^tBu$); MS (ESI): *m/z* (%): 352.2 (MH^+, 11), 330.1 (2), 297.1 (12), 296.1 (100), 278.1 (6), 264.1 (1)220.1 (3); HRMS (ESI): *m/z* calcd. for $C_{18}H_{26}NO_6$: 352.1760 [MH^+]; found: 352.1760.

*Benzyl (E)-4-((3,5-dimethoxyphenyl)(methoxycarbonyl)amino)but-2-enoate (**12ae**)*



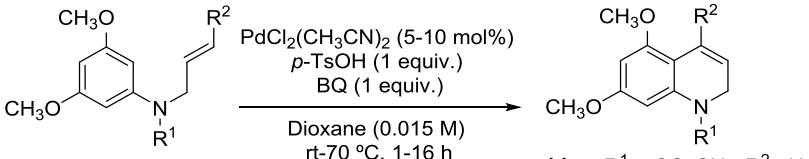
Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.20 g, 0.81 mmol) and benzyl acrylate (2.4 mL, 16.2 mmol) in dry CH_2Cl_2 (23.4 mL) and 2nd generation Grubbs catalyst (34.4 mg, 0.041 mmol) in dry CH_2Cl_2 (6.5 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **12ae** was obtained as an oil (0.26 g, 84%): IR (ATR): ν (cm^{-1}) = 1710 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.69 (s, 3H, CO_2CH_3), 3.71 (s, 6H, 2 × OCH_3), 4.37 (d, *J* = 4.1 Hz, 2H, NCH_2), 5.15 (s, 2H, $CO_2C\underline{H}_2Ph$), 5.99 (d, *J* = 15.7 Hz, 1H, CH=C<u>H</u>CO_2Bn), 6.35 (br s, 1H, H_4), 6.38 (br s, 2H, H_2, H_6), 6.91-7.08 (m, 1H, C<u>H</u>=$CHCO_2Bn$), 7.20-7.37 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 51.6 (NCH_2), 53.1 ($CO_2\underline{C}H_3$), 55.3 (2 × OCH_3), 66.3 ($CO_2\underline{C}H_2Ph$), 98.8 (C_2, C_6), 105.1 (C_4), 122.3 (CH=<u>C</u>HCO_2Bn), 128.2 ($C_{2'}$, $C_{4'}$, $C_{6'}$), 128.5 ($C_{3'}$, $C_{5'}$), 135.9 ($C_{1'}$), 143.4 (C_1), 144.0 (<u>C</u>H=$CHCO_2Bn$), 155.6 ($N\underline{C}O_2CH_3$), 160.9 (C_3, C_5), 165.7 ($\underline{C}O_2Bn$); MS (ESI): *m/z* (%): 409.1 (MNa^+ + 1, 17), 408.1 (MNa^+, 100), 387.2 (MH^+ + 1, 11), 386.2 (MH^+, 60), 369.2 (6), 368.1 (20), 355.1 (6), 354.1 (37), 341.2 (2), 340.2 (9), 336.1 (2), 326.1 (1), 308.1 (7), 278.1 (3); HRMS (ESI): *m/z* calcd. for $C_{21}H_{23}NO_6Na$: 408.1423 [MNa^+]; found: 408.1420.

*Methyl (E)-4-((tert-butoxycarbonyl)(3,5-dimethoxyphenyl)amino)but-2-enoate (**12ba**)*



Prepared from *tert*-butyl allyl(3,5-dimethoxyphenyl)carbamate **11ba** (0.26 g, 0.88 mmol) and methyl acrylate (1.6 mL, 17.5 mmol) in dry CH_2Cl_2 (25.3 mL) and 2nd generation Grubbs catalyst (37.2 mg, 0.044 mmol) in dry CH_2Cl_2 (7.1 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **12ba** was obtained as an oil (0.26 g, 86%): IR (ATR): ν (cm^{-1}) = 1699 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.44 (s, 9H, 3 × CH_3), 3.72 (s, 3H, CO_2CH_3), 3.75 (s, 6H, 2 × OCH_3), 4.34 (dd, *J* = 5.2, 1.8 Hz, 2H, NCH_2), 5.93 (dt, *J* = 15.7, 1.8 Hz, 1H, CH=C<u>H</u>CO_2CH_3), 6.30 (t, *J* = 2.2 Hz, 1H, H_4), 6.36 (d, *J* = 2.2 Hz, 2H, H_2, H_6), 6.97 (dt, *J* = 15.7, 5.2 Hz, 1H, C<u>H</u>=$CHCO_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.3 (3 × CH_3), 51.3 (NCH_2), 51.6 ($CO_2\underline{C}H_3$), 55.4 (2 × OCH_3), 81.0 ($\underline{C}(CH_3)_3$), 98.1 (C_4), 104.7 (C_2, C_6), 121.7 (CH=<u>C</u>HCO_2CH_3), 144.1 (C_1), 144.4 (<u>C</u>H=$CHCO_2CH_3$), 154.0 ($N\underline{C}O_2{}^t$Bu), 160.7 (C_3, C_5), 166.5 ($\underline{C}O_2CH_3$); MS (ESI): *m/z* (%): 375.2 (MNa^+ + 1, 7), 374.2 (MNa^+, 54), 352.2 (MH^+, 2), 296.1 (7), 286.1 (10), 253.1 (9), 252.1 (100), 220.1 (1); HRMS (ESI): *m/z* calcd. for $C_{18}H_{25}NO_6Na$: 374.1580 [MNa^+]; found: 374.1584.

4.16. General procedure for the Pd(II)-catalyzed intramolecular alkenylation reaction of *N*-protected allylanilines 11aa-11fb. Synthesis of 1,2-dihydroquinolines 14aa-14fb

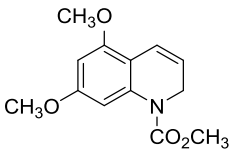


11aa-11fb

14aa, $R^1 = CO_2CH_3$, R^2= H
14ba, $R^1 = CO_2{}^tBu$, R^2= H
14ca, $R^1 = CO_2Bn$, R^2= H
14da, $R^1 = COCH_3$, R^2= H
14fa, R^1 = Ts, R^2= H
14fb, R^1 = Ts, $R^2 = CH_3$

To a solution of the corresponding *N*-ptotected allylaniline **11aa-11fb** (1 mmol) in 1,4-dioxane (66.7 mL), *p*-TsOH (1 mmol), benzoquinone (1 mmol) and $PdCl_2(CH_3CN)_2$ (0.05 or 0.1 mmol) were added and the reaction mixture was stirred at room temperature or 70 ºC for 1-16 h. Afterwards, water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt) affording the corresponding 1,2-dihydroquinolines **14aa-14fb.**

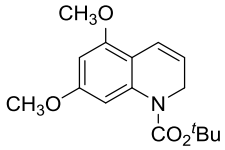
*Methyl 5,7-dimethoxyquinoline-1(2H)-carboxylate (**14aa**)*



Prepared from methyl allyl(3,5-dimethoxyphenyl)carbamate **11aa** (0.14 g, 0.57 mmol), *p*-TsOH (0.11 g, 0.57 mmol), benzoquinone (61.6 mg, 0.57 mmol) and $PdCl_2(CH_3CN)_2$ (7.4 mg, 0.028 mmol) in dioxane (38 mL). The reaction mixture was stirred for 16 h at room temperature and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **14aa** was obtained as an oil (0.12 g, 85%): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.78 (s, 3H, CO_2CH_3), 3.80 (s, 6H, 2 × OCH_3), 4.32 (dd, *J* = 4.3, 1.7 Hz, 2H, NCH_2), 5.82 (dt, *J* = 9.6, 4.3 Hz, 1H, H_3), 6.24 (d, *J* = 2.3 Hz, 1H, H_6), 6.76 (dt, *J* = 9.6, 1.7 Hz, 1H, H_4), 6.85 (br s, 1H, H_8); ^{13}C NMR (75.5 MHz, CDCl3): δ (ppm) = 43.2 (C_2), 53.0 (CO_2CH_3), 55.4 (OCH_3), 55.6 (OCH_3), 94.8 (C_6), 101.0 (C_8), 111.2 (C_{4a}), 120.7 (C_3), 120.8 (C_4), 138.2 (C_{8a}), 154.7 (CO), 155.6 (C_5), 159.4 (C_7); MS (EI): *m/z* (%): 250.1 (M^+ + 1, 12), 249.1 (M^+, 79), 248.1 (59), 234.1 (40), 218.1 (11), 191.1 (13), 190.1 (100), 189.1 (54), 175.1 (24), 174.1 (16), 160.1 (18), 159.1 (10), 146.1 (21),

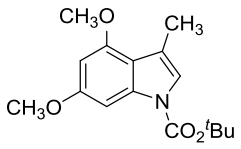
132.1 (12), 131.1 (11), 117.1 (12), 116.1 (12); HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NO_4$: 250.1079 [MH^+]; found: 250.1085.

*tert-Butyl 5,7-dimethoxyquinoline-1(2H)-carboxylate (**14ba**)*



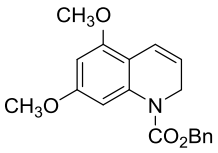
Prepared from *tert*-butyl allyl(3,5-dimethoxyphenyl)carbamate **11ba** (0.12 g, 0.40 mmol), *p*-TsOH (75.2 mg, 0.40 mmol), benzoquinone (42.3 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (10.3 mg, 0.040 mmol) in dioxane (26.3 mL). The reaction mixture was stirred for 1.5 h at room temperature and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **14ba** was obtained as an oil (67.3 mg, 58%): IR (ATR): ν (cm^{-1}) = 1649 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.52 (s, 9H, 3 × CH_3), 3.80 (s, 6H, 2 × OCH_3), 4.28 (dd, *J* = 4.3, 1.7 Hz, 2H, NCH_2), 5.82 (dt, *J* = 9.6, 4.3 Hz, 1H, H_3), 6.21 (d, *J* = 2.3 Hz, 1H, H_6), 6.72-6.79 (m, 1H, H_4), 6.82 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.4 (3 × CH_3), 42.8 (C_2), 55.4 (OCH_3), 55.6 (OCH_3), 81.1 ($C(CH_3)_3$), 94.5 (C_6), 101.1 (C_8), 111.2 (C_{4a}), 120.8 (C_3), 121.0 (C_4), 138.7 (C_{8a}), 153.1 (CO), 155.5 (C_5), 159.1 (C_7); MS (ESI): *m/z* (%): 314.1 (MNa^+, 12), 292.2 (MH^+, 5), 237.1 (9), 236.1 (100), 218.1 (1), 192.1 (5), 182.1 (2); HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}NO_4Na$: 314.1368 [MNa^+]; found: 314.1370.

*tert-Butyl 4,6-dimethoxy-2-methyl-1H-indole-1-carboxylate (**15ba**)*



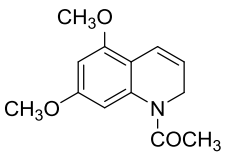
Obtained as a side-product in the reaction of *tert*-butyl allyl(3,5-dimethoxyphenyl)carbamate **11ba** (0.12 g, 0.40 mmol), *p*-TsOH (75.2 mg, 0.40 mmol), benzoquinone (42.3 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (10.3 mg, 0.040 mmol) in dioxane (26.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **15ba** was obtained as an oil (18.9 mg, 16%): IR (ATR): ν (cm^{-1}) = 1724 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.65 (s, 9H, 3 × CH_3), 2.35 (d, *J* = 1.3 Hz, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.30 (d, *J* = 2.0 Hz, 1H, H_5), 7.01-7.15 (m, 1H, H_2), 7.33-7.43 (m, 1H, H_7); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 12.3 (CH_3), 28.2 (3 × CH_3), 55.3 (OCH_3), 55.6 (OCH_3), 82.9 ($\underline{C}(CH_3)_3$), 91.4 (C_5), 94.2 (C_7), 114.8 (C_3), 116.7 (C_{3a}), 120.0 (C_2), 137.6 (C_{7a}), 149.9 (CO), 154.9 (C_6), 158.8 (C_4); MS (ESI): *m/z* (%): 292.2 (MH^+, 58), 291.1 (1), 238.1 (1), 237.1 (10), 236.1 (100); HRMS (ESI): *m/z* calcd. for $C_{16}H_{22}NO_4$: 292.1549 [MH^+]; found: 292.1557.

*Benzyl 5,7-dimethoxyquinoline-1(2H)-carboxylate (**14ca**)*



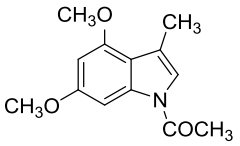
Prepared from benzyl allyl(3,5-dimethoxyphenyl)carbamate **11ca** (0.11 g, 0.33 mmol), *p*-TsOH (62.8 g, 0.33 mmol), benzoquinone (35.7 mg, 0.33 mmol) and $PdCl_2(CH_3CN)_2$ (8.6 mg, 0.033 mmol) in dioxane (22 mL). The reaction mixture was stirred for 3 h at room temperature and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **14ca** was obtained as an oil (71.5 mg, 67%): IR (ATR): ν (cm^{-1}) = 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.68 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.37 (d, *J* = 4.2 Hz, 2H, NCH_2), 5.24 (s, 2H, $C\underline{H_2}Ph$), 5.78-5.89 (m, 1H, H_3), 6.23 (d, *J* = 1.9 Hz, 1H, H_6), 6.73-6.85 (m, 2H, H_4, H_8), 7.28-7.44 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, CDCl3): δ (ppm) = 43.2 (C_2), 55.3 (OCH_3), 55.6 (OCH_3), 67.8 ($\underline{C}H_2Ph$), 95.1 (C_6), 100.7 (C_8), 111.2 (C_{4a}), 120.7 (C_3), 120.8 (C_4), 128.2 ($C_{2'}$, $C_{6'}$), 128.3 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 136.1 ($C_{1'}$), 138.1 (C_{8a}), 154.0 (CO), 155.6 (C_5), 159.3 (C_7); MS (ESI): *m/z* (%): 349.1 (MNa^+ + 1, 16), 348.1 (MNa^+, 100), 327.1 (MH^+ + 1, 9), 326.1 (MH^+, 54), 283.2 (6), 282.1 (38), 280.1 (4), 210.1 (1), 190.1 (7), 166.1 (6); HRMS (ESI): *m/z* calcd. for $C_{19}H_{19}NO_4Na$: 348.1212 [MNa^+]; found: 348.1215.

*1-(5,7-Dimethoxyquinolin-1(2H)-yl)ethan-1-one (**14da**)*



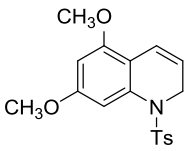
Prepared from *N*-allyl-*N*-(3,5-dimethoxyphenyl)acetamide **11da** (93.3 mg, 0.40 mmol), *p*-TsOH (75.4 mg, 0.40 mmol), benzoquinone (42.9 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (10.3 mg, 0.040 mmol) in dioxane (26.4 mL). The reaction mixture was stirred for 1 h at 70 ºC and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **14da** was obtained as an oil (78.2 mg, 85%): IR (ATR): ν (cm^{-1}) = 1659 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.22 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.29-4.41 (m, 2H, NCH_2), 5.88 (dt, *J* = 9.5, 4.2 Hz, 1H, H_3), 6.28 (d, *J* = 2.2 Hz, 1H, H_6), 6.36 (br s, 1H, H_8), 6.75 (dt, *J* = 9.5, 1.8 Hz, 1H, H_4); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.9 (CH_3), 41.4 (C_2), 55.5 (OCH_3), 55.7 (OCH_3), 95.2 (C_6), 102.0 (C_8), 112.1 (C_{4a}), 120.8 (C_3), 123.1 (C_4), 138.8 (C_{8a}), 155.8 (C_5), 159.2 (C_7), 170.1 (CO); MS (ESI): *m/z* (%): 257.1 (MNa^+ + 1, 8), 256.1 (MNa^+, 83), 235.1 (MH^+ + 1, 10), 234.1 (MH^+, 100), 192.1 (8); HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NO_3$: 234.1130 [MH^+]; found: 234.1133.

*1-(4,6-Dimethoxy-3-methyl-1H-indol-1-yl)ethan-1-one (**15da**)*



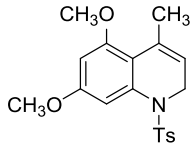
Obtained as a side-product in the reaction of *N*-allyl-*N*-(3,5-dimethoxyphenyl)acetamide **11da** (93.3 mg, 0.40 mmol), *p*-TsOH (75.4 mg, 0.40 mmol), benzoquinone (42.9 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (10.3 mg, 0.040 mmol) in dioxane (26.4 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **15da** was obtained as a solid (9.5 mg, 10 %): mp (CH_2Cl_2) 141-143 ºC; IR (ATR): ν (cm^{-1}) = 1685 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.36 (d, *J* = 1.3 Hz, 3H, CH_3), 2.55 (s, 3H, $COCH_3$), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.35 (d, *J* = 2.0 Hz, 1H, H_5), 6.88 (d, *J* = 1.3 Hz, 1H, H_2), 7.66 (d, *J* = 2.0 Hz, 1H, H_7); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 12.4 (CH_3), 24.1 ($CO\underline{C}H_3$), 55.3 (OCH_3), 55.8 (OCH_3), 92.9 (C_5), 95.2 (C_7), 114.7 (C_3), 118.9 (C_{3a}), 119.5 (C_2), 137.9 (C_{7a}), 154.7 (C_6), 159.5 (C_4), 168.7 (CO); MS (ESI): *m/z* (%): 235.1 (MH^+ + 1, 10), 234.1 (MH^+, 100), 233.1 (11), 193.1 (4), 192.1 (45), 191.1 (3); HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NO_3$: 234.1130 [MH^+]; found: 234.1138.

*5,7-Dimethoxy-1-tosyl-1,2-dihydroquinoline (**14fa**)*



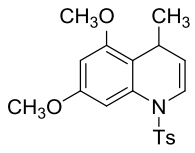
Prepared from *N*-allyl-*N*-(3,5-dimethoxyphenyl)-4-methylbenzene-sulfonamide **11fa** (0.11 g, 0.31 mmol), *p*-TsOH (58.4 g, 0.31 mmol), benzoquinone (33.2 mg, 0.31 mmol) and $PdCl_2(CH_3CN)_2$ (4.0 mg, 0.015 mmol) in dioxane (20.5 mL). The reaction mixture was stirred for 16 h at room temperature and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **14fa** was obtained as an oil (92.5 mg, 87%): IR (ATR): ν (cm^{-1}) = 1350, 1160 (Ar-SO_2-NR_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.33 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.37 (dd, *J* = 4.3, 1.6 Hz, 2H, NCH_2), 5.40 (dt, *J* = 9.6, 4.3 Hz, 1H, H_3), 6.22-6.36 (m, 2H, H_6, H_4), 6.93 (d, *J* = 2.3 Hz, 1H, H_8), 7.08 (d, *J* = 8.0 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.37 (d, *J* = 8.0 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, CDCl3): δ (ppm) = 21.5 (CH_3), 45.2 (C_2), 55.6 (2 × OCH_3), 96.9 (C_6), 102.9 (C_8), 112.5 (C_{4a}), 119.0 (C_3), 120.4 (C_4), 127.3 ($C_{2'}$, $C_{6'}$), 129.1 ($C_{3'}$, $C_{5'}$), 136.6 ($C_{1'}$), 136.9 ($C_{4'}$), 143.4 (C_{8a}) 155.7 (C_5), 159.6 (C_7); MS (ESI): *m/z* (%): 369.1 (MNa^+ + 1, 16), 368.1 (MNa^+, 100), 347.1 (MH^+ + 1, 14), 346.1 (MH^+, 89), 345.1 (28), 192.1 (3), 191.1 (33), 190.1 (48), 189.1 (4); HRMS (ESI): *m/z* calcd. for $C_{18}H_{19}NO_4SNa$: 368.0933 [MNa^+]; found: 368.0934.

*5,7-Dimethoxy-4-methyl-1-tosyl-1,2-dihydroquinoline (**14fb**)*



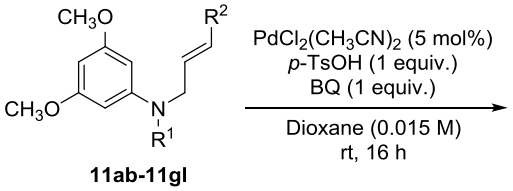
Prepared from *(E)-N*-(but-2-en-1-yl)-*N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide **11fb** (0.10 g, 0.28 mmol), *p*-TsOH (54.2 mg, 0.28 mmol), benzoquinone (30.8 mg, 0.28 mmol) and $PdCl_2(CH_3CN)_2$ (3.7 mg, 0.014 mmol) in dioxane (19.0 mL). The reaction mixture was stirred for 16 h at room temperature and after work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **14fb** was obtained as an oil (65.5 mg, 64%): IR (ATR): ν (cm^{-1}) = 1347, 1159 (Ar-SO_2-NR_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.58 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.10-4.22 (m, 2H, NCH_2), 5.03-5.14 (m, 1H, H_3), 6.33-6.40 (m, 1H, H_6), 6.90-6.97 (m, 1H, H_8), 7.05-7.14 (m, 2H, $H_{3'}$, $H_{5'}$), 7.30-7.38 (m, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.0 ($\underline{C}H_3$), 21.4 (CH_3), 45.2 (C_2), 55.5 (OCH_3), 55.6 (OCH_3), 98.3 (C_6), 103.6 (C_8), 115.0 (C_{4a}), 118.3 (C_3), 127.5 ($C_{2'}$, C_6), 128.9 ($C_{3'}$, $C_{5'}$), 132.2 (C_4), 136.7 ($C_{1'}$), 138.3 ($C_{4'}$), 143.1 (C_{8a}) 157.5 (C_5), 159.2 (C_7); MS (ESI): *m/z* (%): 383.1 (MNa^+ + 1, 7), 382.1 (MNa^+, 43), 361.1 (MH^+ + 1, 17), 360.1 (MH^+, 100), 359.1 (3), 205.1 (5), 204.1 (10); HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}NO_4S$: 360.1270 [MH^+]; found: 360.1272.

*5,7-Dimethoxy-4-methyl-1-tosyl-1,4-dihydroquinoline (**16fb**)*



Obtained as a side-product in the reaction of *(E)-N*-(but-2-en-1-yl)-*N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide **11fb** (0.10 g, 0.28 mmol), *p*-TsOH (54.2 mg, 0.28 mmol), benzoquinone (30.8 mg, 0.28 mmol) and $PdCl_2(CH_3CN)_2$ (3.7 mg, 0.014 mmol) in dioxane (19.0 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **16fb** was obtained as a solid (26.6 mg, 26%): mp (CH_2Cl_2) 106-108 ºC; IR (ATR): ν (cm^{-1}) = 1350, 1164 (Ar-SO_2-NR_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.39 (d, *J* = 6.8 Hz, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.35 (q, *J* = 6.4 Hz, 1H, H_4), 3.72 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.42 (dd, *J* = 7.5, 6.4 Hz, 1H, H_3), 6.29 (d, *J* = 2.3 Hz, 1H, H_6), 6.72 (d, *J* = 7.5 Hz, 1H, H_2), 7.14-7.24 (m, 3H, $H_{3'}$, $H_{5'}$, H_8), 7.53 (d, *J* = 8.3 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.5 (CH_3), 22.7 (CH_3), 26.4 (C_4), 55.4 (OCH_3), 55.6 (OCH_3), 96.7 (C_6), 99.3 (C_8), 115.5 (C_{4a}), 120.7 (C_3), 125.1 (C_2), 127.6 ($C_{2'}$, $C_{6'}$), 129.2 ($C_{3'}$, $C_{5'}$), 134.3 ($C_{1'}$), 135.9 ($C_{4'}$), 143.9 (C_{8a}), 157.1 (C_7), 158.7 (C_5); MS (ESI): *m/z* (%): 383.1 (MNa^+ + 1, 12), 382.1 (MNa^+, 20), 361.1 (MH^+ + 1, 4), 360.1 (MH^+, 100), 344.1 (4), 205.1 (5), 204.1 (28), 190.1 (20), 179.0 (2); HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}NO_4S$: 360.1270 [MH^+]; found: 360.1269.

4.17. General procedure for the Pd(II)-catalyzed intramolecular alkenylation reaction of *N*-protected allylanilines 11ab-11gl. Synthesis of 1,4-dihydroquinolines 16ab-16gl

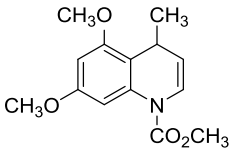


11ab-11gl

16ab, $R^1 = CO_2CH_3$, $R^2 = CH_3$
16ac, $R^1 = CO_2CH_3$, $R^2 = Ph$
16ad, $R^1 = CO_2CH_3$, $R^2 = 4(CH_3)C_6H_4$
16ae, $R^1 = CO_2CH_3$, $R^2 = 3(CH_3)C_6H_4$
16af, $R^1 = CO_2CH_3$, $R^2 = 2(CH_3)C_6H_4$
16ag, $R^1 = CO_2CH_3$, $R^2 = 4(OCH_3)C_6H_4$
16ah, $R^1 = CO_2CH_3$, $R^2 = 3(OCH_3)C_6H_4$
16ai, $R^1 = CO_2CH_3$, $R^2 = 4(Ph)C_6H_4$
16aj, $R^1 = CO_2CH_3$, $R^2 = 4(^t Bu)C_6H_4$
16ak, $R^1 = CO_2CH_3$, $R^2 = 4(F)C_6H_4$
16al, $R^1 = CO_2CH_3$, $R^2 = 1$-naphthyl
16bc, $R^1 = CO_2{}^t Bu$, $R^2 = Ph$
16fc, $R^1 = Ts$, $R^2 = Ph$
16fn, $R^1 = Ts$, $R^2 = CH_2Ph$
16gb, $R^1 = CO_2$(-)Menthyl, $R^2 = CH_3$
16gc, $R^1 = CO_2$(-)Menthyl, $R^2 = Ph$
16gl, $R^1 = CO_2$(-)Menthyl, $R^2 = 1$-naphthyl

To a solution of the corresponding *N*-protected allylaniline **11ab-11gl** (1 mmol) in 1,4-dioxane (66.7 mL), *p*-TsOH (1 mmol), benzoquinone (1 mmol) and $PdCl_2(CH_3CN)_2$ (0.05 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. Afterwards, water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The obtained residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt) affording 1,4-dihydroquinolines **16ab-16gl.**

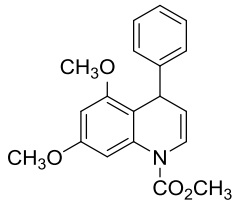
*Methyl 5,7-dimethoxy-4-methylquinoline-1(4H)-carboxylate (**16ab**)*



Prepared from methyl *(E)*-but-2-en-1-yl(3,5-dimethoxyphenyl)-carbamate **11ab** (0.11 g, 0.42 mmol), *p*-TsOH (79.8 mg, 0.42 mmol), benzoquinone (45.4 mg, 0.42 mmol) and $PdCl_2(CH_3CN)_2$ (5.4 mg, 0.021 mmol) in dioxane (28 mL). After work-up and purification by

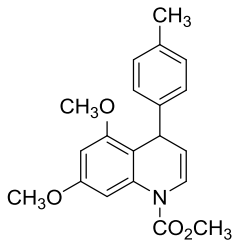
flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **16ab** was obtained as an oil (62.6 mg, 57%): IR (ATR): ν (cm^{-1}) = 1705 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.14 (d, *J* = 6.8 Hz, 3H, CH_3), 3.53-3.70 (m, 1H, H_4), 3.80 (s, 3H, CO_2CH_3), 3.86 (s, 6H, 2 × OCH_3), 5.28-5,44 (m, 1H, H_3), 6.30 (d, *J* = 2.2 Hz, 1H, H_6), 6.92 (d, *J* = 7.7 Hz, 1H, H_2), 7.29 (d, *J* = 2.2 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.1 (CH_3), 26.1 (C_4), 53.2 (CO_2CH_3), 55.4 (OCH_3), 55.5 (OCH_3), 95.5 (C_6), 98.1 (C_8), 114.6 (C_{4a}), 116.0 (C_3), 125.1 (C_2), 137.3 (C_{8a}), 153.2 (CO), 156.8 (C_7), 158.4 (C_5); MS (EI): *m/z* (%): 264.1 (M^+ + 1, 2), 263.1 (M^+, 10), 249.2 (34), 248.2 (100), 204.1 (13), 190.1 (11), 189.1 (64), 188.1 (14), 174.1 (13), 160.1 (19), 146.1 (15); HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}NO_4$: 264.1236 [MH^+]; found: 264.1251.

*Methyl 5,7-dimethoxy-4-phenylquinoline-1(4H)-carboxylate (**16ac**)*



Prepared from methyl cinnamyl(3,5-dimethoxyphenyl)carbamate **11ac** (98.8 mg, 0.30 mmol), *p*-TsOH (57.4 mg, 0.30 mmol), benzoquinone (32.6 mg, 0.30 mmol) and $PdCl_2(CH_3CN)_2$ (3.9 mg, 0.015 mmol) in dioxane (20.1 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **16ac** was obtained as a solid (76.0 mg, 77%): mp (CH_2Cl_2) 137-140 ºC; IR (ATR): ν (cm^{-1}) = 1727 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.70 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.82 (d, *J* = 6.0 Hz, 1H, H_4), 5.42-5.55 (m, 1H, H_3), 6.29 (s, 1H, H_6), 7.07 (d, *J* = 7.8 Hz, 1H, H_2), 7.11-7.28 (m, 5H, Ph), 7.43 (s, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 37.3 (C_4), 53.4 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.6 (OCH_3), 95.8 (C_6), 97.9 (C_8), 112.1 (C_{4a}), 113.9 (C_3), 125.2 (C_2), 126.2 ($C_{4'}$), 127.4 ($C_{2'}$, $C_{6'}$), 128.4 ($C_{3'}$, $C_{5'}$), 137.5 (C_{8a}), 144.8 ($C_{1'}$), 153.2 (CO), 157.2 (C_7), 159.0 (C_5); MS (EI): *m/z* (%): 326.1 (M^+ + 1, 4), 325.1 (M^+, 20), 249.1 (15), 248.1 (100), 189.1 (19); HRMS (ESI): *m/z* calcd. for $C_{19}H_{20}NO_4$: 326.1392 [MH^+]; found: 326.1400.

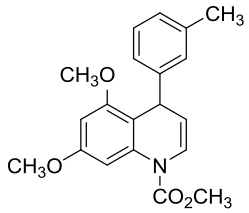
*Methyl 5,7-dimethoxy-4-(p-tolyl)quinoline-1(4H)-carboxylate (**16ad**)*



Prepared from methyl *(E)*-(3,5-dimethoxyphenyl)(3-(*p*-tolyl)allyl)carbamate **11ad** (0.12 g, 0.36 mmol), *p*-TsOH (67.8 mg, 0.36 mmol), benzoquinone (38.5 mg, 0.36 mmol) and $PdCl_2(CH_3CN)_2$ (4.6 mg, 0.018 mmol) in dioxane (23.8 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **16ad** was obtained as a solid (98.7 mg, 82%): mp (CH_2Cl_2) 105-106 ºC; IR (ATR): ν (cm^{-1}) = 1727 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.29 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.79 (d, *J* = 6.2 Hz, 1H, H_4), 5.48 (dd, *J* = 7.7, 6.2 Hz, 1H, H_3), 6.29 (d, *J* =

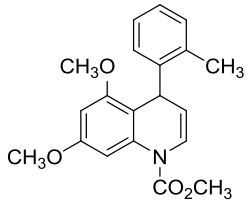
2.3 Hz, 1H, H_6), 6.98-7.13 (m, 5H, H_2, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$), 7.42 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.0 (CH_3), 36.8 (C_4), 53.3 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.6 (OCH_3), 95.8 (C_6), 97.9 (C_8), 112.3 (C_{4a}), 114.1 (C_3), 125.0 (C_2), 127.3 ($C_{3'}$, $C_{5'}$), 129.1 ($C_{2'}$, $C_{6'}$), 135.7 ($C_{4'}$), 137.5 (C_{8a}), 141.9 ($C_{1'}$), 153.2 (CO), 157.2 (C_7), 158.9 (C_5); MS (ESI): *m/z* (%): 341.2 (MH^+ + 1, 19), 340.2 (MH^+, 100), 339.1 (1), 248.1 (3); HRMS (ESI): *m/z* calcd. for $C_{20}H_{22}NO_4$: 340.1549 [MH^+]; found: 340.1553.

*Methyl 5,7-dimethoxy-4-(m-tolyl)quinoline-1(4H)-carboxylate (**16ae**)*



Prepared from methyl *(E)*-(3,5-dimethoxyphenyl)(3-(*m*-tolyl)allyl)carbamate **11ae** (0.11 g, 0.31 mmol), *p*-TsOH (59.0 mg, 0.31 mmol), benzoquinone (33.5 mg, 0.31 mmol) and $PdCl_2(CH_3CN)_2$ (4.0 mg, 0.016 mmol) in dioxane (20.7 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **16ae** was obtained as a solid (96.5 mg, 92%): mp (CH_2Cl_2) 101-102 ºC; IR (ATR): ν (cm^{-1}) = 1727 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.33 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.79 (d, *J* = 6.2 Hz, 1H, H_4), 5.48 (m, 1H, H_3), 6.30 (d, *J* = 2.1 Hz, 1H, H_6), 6.91-7.18 (m, 5H, H_2, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.43 (d, *J* = 2.1 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.5 (CH_3), 37.2 (C_4), 53.3 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.6 (OCH_3), 95.8 (C_6), 97.9 (C_8), 112.1 (C_{4a}), 114.0 (C_3), 124.4 ($C_{6'}$), 125.0 (C_2), 127.0 ($C_{4'}$), 128.1 ($C_{5'}$), 128.3 ($C_{2'}$), 137.6 (C_{8a}), 137.9 ($C_{3'}$), 144.8 ($C_{1'}$), 153.2 (CO), 157.3 (C_7), 159.0 (C_5); MS (ESI): *m/z* (%): 341.2 (MH^+ + 1, 18), 340.2 (MH^+, 100), 339.1 (1), 338.1 (1), 248.1 (2); HRMS (ESI): *m/z* calcd. for $C_{20}H_{22}NO_4$: 340.1549 [MH^+]; found: 340.1555.

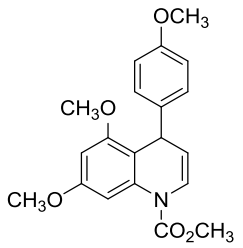
*Methyl 5,7-dimethoxy-4-(o-tolyl)quinoline-1(4H)-carboxylate (**16af**)*



Prepared from methyl *(E)*-(3,5-dimethoxyphenyl)(3-(*o*-tolyl)allyl)carbamate **11af** (0.11 g, 0.31 mmol), *p*-TsOH (59.6 mg, 0.31 mmol), benzoquinone (33.8 mg, 0.31 mmol) and $PdCl_2(CH_3CN)_2$ (4.1 mg, 0.016 mmol) in dioxane (20.9 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **16af** was obtained as a solid (87.6 mg, 82%): mp (CH_2Cl_2) 118-121 ºC; IR (ATR): ν (cm^{-1}) = 1724 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.53 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.01 (d, *J* = 5.9 Hz, 1H, H_4), 5.43 (m, 1H, H_3), 6.29 (d, *J* = 2.3 Hz, 1H, H_6), 6.77-7.17 (m, 5H, H_2, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.50 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (CH_3), 34.0 (C_4), 53.3 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.7 (OCH_3), 95.8 (C_6),

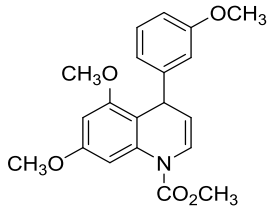
97.8 (C_8), 112.1 (C_{4a}), 112.5 (C_3), 124.6 ($C_{6'}$), 126.0 (C_2), 126.6 ($C_{4'}$), 127.5 ($C_{5'}$), 129.9 ($C_{3'}$), 134.6 ($C_{2'}$), 138.1 (C_{8a}), 143.6 ($C_{1'}$), 153.2 (CO), 157.3 (C_7), 159.0 (C_5); MS (ESI): *m/z* (%): 341.2 (MH^+ + 1, 17), 340.2 (MH^+, 100), 339.1 (1), 338.1 (1), 248.1 (2); HRMS (ESI): *m/z* calcd. for $C_{20}H_{22}NO_4$: 340.1549 [MH^+]; found: 340.1557.

*Methyl 5,7-dimethoxy-4-(4-methoxyphenyl)quinoline-1(4H)-carboxylate (**16ag**)*



Prepared from methyl *(E)*-(3,5-dimethoxyphenyl)(3-(4-methoxyphenyl)allyl)carbamate **11ag** (0.13 g, 0.37 mmol), *p*-TsOH (69.7 mg, 0.37 mmol), benzoquinone (39.6 mg, 0.37 mmol) and $PdCl_2(CH_3CN)_2$ (4.8 mg, 0.018 mmol) in dioxane (24.4 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **16ag** was obtained as a solid (98.7 mg, 82%): mp (CH_2Cl_2) 109-110 ºC; IR (ATR): ν (cm^{-1}) = 1727 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.71 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.77 (d, *J* = 6.2 Hz, 1H, H_4), 5.47 (dd, *J* = 7.7, 6.2 Hz, 1H, H_3), 6.29 (d, *J* = 2.3 Hz, 1H, H_6), 6.78 (d, *J* = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.06 (d, *J* = 7.7 Hz, 1H, H_2), 7.12 (d, *J* = 8.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.41 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 36.4 (C_4), 53.3 ($CO_2\underline{C}H_3$), 55.2 (OCH_3), 55.4 (OCH_3), 55.6 (OCH_3), 95.8 (C_6), 98.0 (C_8), 112.5 (C_{4a}), 113.8 ($C_{3'}$, $C_{5'}$), 114.2 (C_3), 125.0 (C_2), 128.4 ($C_{2'}$, $C_{6'}$), 137.1 ($C_{1'}$), 137.4 (C_{8a}), 153.2 (CO), 157.1 (C_7), 158.0 ($C_{4'}$), 158.9 (C_5); MS (ESI): *m/z* (%): 379.1 (MNa^+ + 1, 16), 378.1 (MNa^+, 100), 357.2 (MH^+ + 1, 17), 356.2 (MH^+, 99), 355.2 (8), 354.1 (2), 296.1 (2), 249.1 (2), 248.1 (16), 135.1 (4); HRMS (ESI): *m/z* calcd. for $C_{20}H_{21}NO_5Na$: 378.1317 [MNa^+]; found: 378.1324.

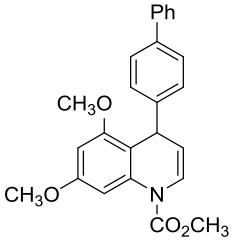
*Methyl 5,7-dimethoxy-4-(3-methoxyphenyl)quinoline-1(4H)-carboxylate (**16ah**)*



Prepared from methyl *(E)*-(3,5-dimethoxyphenyl)(3-(3-methoxyphenyl)allyl)carbamate **11ah** (57.6 mg, 0.16 mmol), *p*-TsOH (30.7 mg, 0.16 mmol), benzoquinone (17.4 mg, 0.16 mmol) and $PdCl_2(CH_3CN)_2$ (2.1 mg, 0.008 mmol) in dioxane (10.8 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **16ah** was obtained as a solid (46.1 mg, 81%): mp (CH_2Cl_2) 101-103 ºC; IR (ATR): ν (cm^{-1}) = 1720 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.71 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.80 (d, *J* = 6.2 Hz, 1H, H_4), 5.38-5.54 (m, 1H, H_3), 6.29 (d, *J* = 1.8 Hz, 1H, H_6), 6.65-7.18 (m, 5H, H_2, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.41 (d, *J* = 2.1 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 37.2 (C_4), 53.3 ($CO_2\underline{C}H_3$), 55.0 (OCH_3), 55.4 (OCH_3), 55.6 (OCH_3),

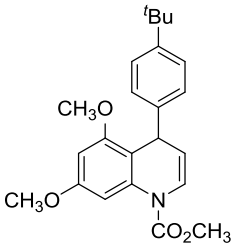
95.8 (C_6), 98.0 (C_8), 111.3 ($C_{4'}$), 112.0 (C_{4a}), 113.3 ($C_{2'}$), 113.8 (C_3), 119.8 ($C_{6'}$), 125.3 (C_2), 129.3 ($C_{5'}$), 137.5 (C_{8a}), 146.4 ($C_{1'}$), 153.1 (CO), 157.2 (C_7), 159.0 (C_5), 159.6 ($C_{3'}$); MS (ESI): *m/z* (%): 357.2 (MH^+ + 1, 16), 356.2 (MH^+, 100), 301.1 (2), 279.2 (1), 248.1 (1), 205.1 (1); HRMS (ESI): *m/z* calcd. for $C_{20}H_{22}NO_5$: 356.1498 [MH^+]; found: 356.1510.

*Methyl 4-([1,1´-biphenyl]-4-yl)-5,7-dimethoxyquinoline-1(4H)-carboxylate (**16ai**)*



Prepared from methyl (*E*)-(3-([1,1´-biphenyl]-4-yl)allyl)(3,5-dimethoxyphenyl)carbamate **11ai** (0.11 g, 0.28 mmol), *p*- TsOH (53.9 mg, 0.28 mmol), benzoquinone (30.7 mg, 0.28 mmol) and $PdCl_2(CH_3CN)_2$ (3.7 mg, 0.014 mmol) in dioxane (18.9 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **16ai** was obtained as a solid (82.6 mg, 73%): mp (CH_2Cl_2) 54-56 ºC; IR (ATR): ν (cm^{-1}) = 1724 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.74 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.89 (d, *J* = 6.2 Hz, 1H, H_4), 5.53 (dd, *J* = 7.7, 6.2 Hz, 1H, H_3), 6.33 (d, *J* = 2.3 Hz, 1H, H_6), 7.11 (d, *J* = 7.7 Hz, 1H, H_2), 7.20-7.71 (m, 10H, H_8, $H_{2'}$, $H_{3'}$, $H_{5'}$,$H_{6'}$, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 36.9 (C_4), 53.4 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.6 (OCH_3), 95.8 (C_6), 98.0 (C_8), 112.0 (C_{4a}), 113.8 (C_3), 125.4 (C_2), 127.0 ($C_{4''}$), 127.1 ($C_{2''}$, $C_{6''}$), 127.2 ($C_{3'}$, $C_{5'}$), 127.8 ($C_{2'}$, $C_{6'}$), 128.7 ($C_{3''}$, $C_{5''}$), 137.5 (C_{8a}), 139.1 ($C_{4'}$), 141.1 ($C_{1''}$), 143.9 ($C_{1'}$), 153.2 (CO), 157.2 (C_7), 159.1 (C_5); MS (ESI): *m/z* (%): 403.2 (MH^+ + 1, 21), 402.2 (MH^+, 100), 401.2 (1); HRMS (ESI): *m/z* calcd. for $C_{25}H_{24}NO_4$: 402.1705 [MH^+]; found: 402.1710.

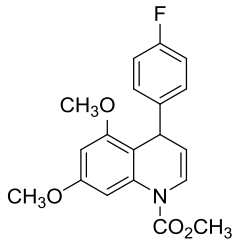
*Methyl 4-(4-(tert-butyl)phenyl)-5,7-dimethoxyquinoline-1(4H)-carboxylate (**16aj**)*



Prepared from methyl (*E*)-(3-(4-(*tert*-butyl)phenyl)allyl)(3,5-dimethoxyphenyl)carbamate **11aj** (91.5 mg, 0.24 mmol), *p*-TsOH (45.4 mg, 0.24 mmol), benzoquinone (25.8 mg, 0.24 mmol) and $PdCl_2(CH_3CN)_2$ (3.1 mg, 0.012 mmol) in dioxane (15.9 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **16aj** was obtained as a solid (79.1 mg, 87%): mp (CH_2Cl_2) 107-109 ºC; IR (ATR): ν (cm^{-1}) = 1724 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.29 (s, 9H, 3 × CH_3), 3.73 (s, 3H, CO_2CH_3), 3.83 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.82 (d, *J* = 6.3 Hz, 1H, H_4), 5.51 (dd, *J* = 7.7, 6.3 Hz, 1H, H_3), 6.30 (d, *J* = 2.3 Hz, 1H, H_6), 7.08 (d, *J* = 7.7 Hz, 1H, H_2), 7.15 (d, *J* = 8.3 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.26 (d, *J* = 8.3 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.41 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 31.4 (3 × CH_3), 34.3 ($\underline{C}(CH_3)_3$), 36.6 (C_4), 53.3 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.6 (OCH_3), 95.8 (C_6), 98.0 (C_8), 112.6 (C_{4a}), 114.2 (C_3), 125.3 (C_2, $C_{3'}$, $C_{5'}$), 127.0 ($C_{2'}$, $C_{6'}$), 137.5

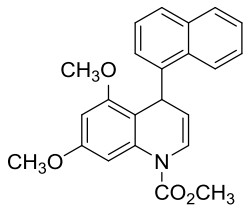
(C_{8a}), 141.6 ($C_{1'}$), 148.8 ($C_{4'}$), 153.2 (CO), 157.1 (C_7), 158.9 (C_5); MS (ESI): *m/z* (%): 383.2 (MH^+ + 1, 20), 382.2 (MH^+, 100), 381.2 (6), 380.2 (2), 350.2 (1), 249.1 (1), 248.1 (10); HRMS (ESI): *m/z* calcd. for $C_{23}H_{28}NO_4$: 382.2018 [MH^+]; found: 382.2019.

*Methyl 5,7-dimethoxy-4-(4-fluorophenyl)quinoline-1(4H)-carboxylate (**16ak**)*



Prepared from methyl *(E)*-(3,5-dimethoxyphenyl)(3-(4-fluorophenyl)allyl)carbamate **11ak** (0.11 mg, 0.31 mmol), *p*-TsOH (59.9 mg, 0.31 mmol), benzoquinone (34.0 mg, 0.31 mmol) and $PdCl_2(CH_3CN)_2$ (4.1 mg, 0.016 mmol) in dioxane (21.0 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **16ak** was obtained as a solid (77.5 mg, 72%): mp (CH_2Cl_2) 129-131 ºC; IR (ATR): ν (cm^{-1}) = 1724 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.73 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.82 (d, *J* = 6.2 Hz, 1H, H_4), 5.47 (dd, *J* = 7.7, 6.2 Hz, 1H, H_3), 6.31 (d, *J* = 2.3 Hz, 1H, H_6), 6.88-6.97 (m, 2H, $H_{2'}$, $H_{6'}$), 7.09 (d, *J* = 7.7 Hz, 1H, H_2), 7.14-7.21 (m, 2H, $H_{3'}$, $H_{5'}$), 7.45 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 36.5 (C_4), 53.4 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.6 (OCH_3), 95.8 (C_6), 98.0 (C_8), 112.0 (C_{4a}), 113.6 (C_3), 115.0 (d, *J* = 21.3 Hz, $C_{3'}$, $C_{5'}$), 125.3 (C_2), 128.9 (d, *J* = 8.0 Hz, $C_{2'}$, $C_{6'}$), 137.4 (C_{8a}), 140.6 (d, *J* = 3.1 Hz, $C_{1'}$), 153.1 (CO), 157.1 (C_7), 159.1 (C_5), 161.4 (d, *J* = 243.9 Hz, $C_{4'}$); MS (ESI): *m/z* (%): 345.1 (MH^+ + 1, 16), 344.1 (MH^+, 100), 301.1 (1); HRMS (ESI): *m/z* calcd. for $C_{19}H_{19}FNO_4$: 344.1298 [MH^+]; found: 344.1311.

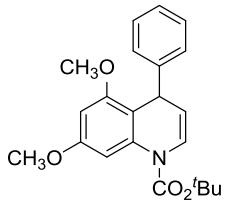
*Methyl 5,7-dimethoxy-4-(naphthalene-1-yl)quinoline-1(4H)-carboxylate (**16al**)*



Prepared from methyl (*E*)-(3,5-dimethoxyphenyl)(3-(naphthalen-1-yl)allyl)carbamate **11al** (72.0 mg, 0.19 mmol), *p*-TsOH (36.3 mg, 0.19 mmol), benzoquinone (20.6 mg, 0.19 mmol) and $PdCl_2(CH_3CN)_2$ (2.5 mg, 0.010 mmol) in dioxane (12.7 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **16al** was obtained as a solid (58.4 mg, 82%): mp (CH_2Cl_2) 140-142 ºC; IR (ATR): ν (cm^{-1}) = 1727 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.54 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.61-5.71 (m, 2H, H_3, H_4), 6.33 (d, *J* = 2.4 Hz, 1H, H_6), 6.92-7.00 (m, 2H, H_2, $H_{2'}$), 7.27-7.34 (m, 1H, $H_{7'}$), 7.47-7.55 (m, 2H, H_8, $H_{3'}$), 7.56-7.64 (m, 1H, $H_{6'}$), 7.67 (d, *J* = 8.2 Hz, $H_{4'}$), 7.84-7.91 (m, 1H, $H_{8'}$); 8.34 (d, *J* = 8.4 Hz, 1H, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 33.3 (C_4), 53.3 ($CO_2\underline{C}H_3$), 55.5 (OCH_3), 55.6 (OCH_3), 95.9 (C_6), 97.9 (C_8), 111.5 (C_{4a}), 113.0 (C_3), 123.4 ($C_{2'}$), 124.1 ($C_{8'}$), 125.0 (C_2), 125.4 ($C_{6'}$), 125.9 ($C_{7'}$), 126.1 ($C_{3'}$), 126.6 ($C_{4'}$), 128.9 ($C_{5'}$),

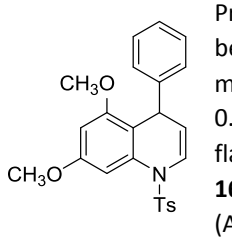
130.9 ($C_{8a'}$), 134.0 ($C_{4a'}$), 138.7 (C_{8a}), 141.2 ($C_{1'}$), 153.2 (CO), 157.3 (C_7), 159.3 (C_5); MS (ESI): *m/z* (%): 399.1 (MNa^+ + 1, 10), 398.1 (MNa^+, 53), 377.2 (MH^+ + 1, 19), 376.2 (MH^+, 100), 344.1 (3), 249.1 (3), 248.1 (25), 165.1 (5); HRMS (ESI): *m/z* calcd. for $C_{23}H_{22}NO_4$: 376.1549 [MH^+]; found: 376.1553.

*tert-Butyl 5,7-dimethoxy-4-phenylquinoline-1(4H)-carboxylate (**16bc**)*



Prepared from *tert*-butyl cinnamyl(3,5-dimethoxyphenyl)carbamate **11bc** (0.11 g, 0.29 mmol), *p*-TsOH (55.3 mg, 0.29 mmol), benzoquinone (31.4 mg, 0.29 mmol) and $PdCl_2(CH_3CN)_2$ (3.8 mg, 0.015 mmol) in dioxane (19.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **16bc** was obtained as a solid (77.4 mg, 73%): mp (CH_2Cl_2) 110-112 ºC; IR (ATR): ν (cm^{-1}) = 1727 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.61 (s, 9H, 3 × CH_3), 3.71 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.83 (d, *J* = 6.2 Hz, 1H, H_4), 5.45 (dd, *J* = 7.7, 6.2 Hz, 1H, H_3), 6.28 (d, *J* = 2.3 Hz, 1H, H_6), 7.06 (d, *J* = 7.7 Hz, 1H, H_2), 7.11-7.28 (m, 5H, Ph), 7.37 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.4 (3 × CH_3), 37.4 (C_4), 55.4 (OCH_3), 55.6 (OCH_3), 82.2 ($\underline{C}(CH_3)_3$), 95.5 (C_6), 98.4 (C_8), 112.4 (C_{4a}), 113.2 (C_3), 126.0 (C_2), 126.1 ($C_{4'}$), 127.5 ($C_{2'}$, $C_{6'}$), 128.4 ($C_{3'}$, $C_{5'}$), 137.9 (C_{8a}), 145.1 ($C_{1'}$), 151.6 (CO), 157.1 (C_7), 158.9 (C_5); MS (EI): *m/z* (%): 391.2 (MNa^+ + 1, 5), 390.2 (MNa^+, 27), 313.1 (16), 312.1 (100), 290.1 (14), 268.1 (7), 190.1 (6); HRMS (ESI): *m/z* calcd. for $C_{22}H_{25}NO_4Na$: 390.1681 [MNa^+]; found: 390.1684.

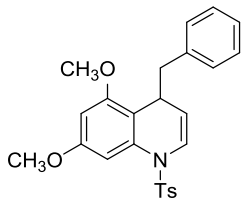
*5,7-Dimethoxy-4-phenyl-1-tosyl-1,4-dihydroquinoline (**16fc**)*



Prepared from *N*-cinnamyl-*N*-(3,5-dimethoxyphenyl)-4-methyl-benzenesulfonamide **11fc** (0.10 g, 0.25 mmol), *p*-TsOH (46.6 mg, 0.25 mmol), benzoquinone (26.5 mg, 0.25 mmol) and $PdCl_2(CH_3CN)_2$ (3.2 mg, 0.012 mmol) in dioxane (16.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/CH_2Cl_2 4/6), **16fc** was obtained as a solid (43.6 mg, 42%): mp (CH_2Cl_2) 161-163 ºC; IR (ATR): ν (cm^{-1}) = 1350, 1154 (Ar-SO_2-NR_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.42 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.64 (d, *J* = 5.6 Hz, 1H, H_4), 5.35-5.50 (m, 1H, H_3), 6.24 (s, 1H, H_6), 6.44-6.53 (m, 2H, $H_{2''}$, $H_{6''}$), 6.89-6.98 (m, 3H, H_2, $H_{3''}$, $H_{5''}$), 6.99-7.08 (m, 1H, $H_{4''}$), 7.18 (d, *J* = 7.9 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.42 (s, 1H, H_8) 7.63 (d, *J* = 7.9 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.6 (CH_3), 37.7 (C_4), 55.4 (OCH_3), 55.5 (OCH_3), 96.5 (C_6), 97.6 (C_8), 111.2 (C_{4a}), 115.7 (C_3), 124.1 ($C_{4''}$), 125.5 (C_2), 127.2 ($C_{2''}$, $C_{6''}$), 127.6 ($C_{3''}$, $C_{5''}$), 127.8 ($C_{2'}$, $C_{6'}$), 129.7 ($C_{3'}$, $C_{5'}$), 134.7 ($C_{1'}$), 136.1 ($C_{4'}$), 144.2 ($C_{1''}$), 144.9

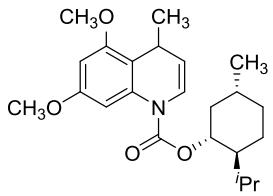
(C_{8a}), 157.9 (C_7), 159.4 (C_5); MS (ESI): *m/z* (%): 423.1 (MH^+ + 1, 21), 422.1 (MH^+, 100), 421.1 (1), 344.1 (3), 267.1 (5). 266.1 (8), 190.1 (2); HRMS (ESI): *m/z* calcd. for $C_{24}H_{24}NO_4S$: 422.1426 [MH^+]; found: 422.1431.

*4-Benzyl-5,7-dimethoxy-1-tosyl-1,4-dihydroquinoline (**16fn**)*



Prepared from *(E)-N*-(3,5-dimethoxyphenyl)-4-methyl-*N*-(4-phenylbut-2-en-1-yl)benzenesulfonamide **11fn** (0.10 g, 0.24 mmol), *p*-TsOH (44.8 mg, 0.24 mmol), benzoquinone (25.4 mg, 0.24 mmol) and $PdCl_2(CH_3CN)_2$ (3.1 mg, 0.012 mmol) in dioxane (15.7 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **16fn** was obtained as an oil (61.9 mg, 60%): IR (ATR): ν (cm^{-1}) = 1358, 1168 ($Ar\text{-}SO_2\text{-}NR_2$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.97-1.13 (m, 1H, 1 × C$\underline{H_2}$Ph), 2.34 (s, 3H, CH_3), 2.44-2.57 (m, 1H, 1 × C$\underline{H_2}$Ph), 3.51-3.61 (m, 1H, H_4), 3.71 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.24 (t, *J* = 6.7 Hz, 1H, H_3), 6.33 (s, 1H, H_6), 6.74 (d, *J* = 7.5 Hz, 1H, H_2), 6.90 (d, *J* = 7.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.13-7.33 (m, 6H, Ph, H_8), 7.64 (d, *J* = 7.5 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.6 (CH_3), 33.8 (C_4), 44.7 ($\underline{C}H_2$Ph), 55.5 (OCH_3), 55.6 (OCH_3), 96.7 (C_6), 99.4 (C_8), 114.2 (C_{4a}), 118.8 (C_3), 125.7 (C_2), 126.0 ($C_{4''}$), 127.7 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{3''}$, $C_{5''}$), 128.9 ($C_{2''}$, $C_{6''}$), 129.5 ($C_{3'}$, $C_{5'}$), 134.6 ($C_{1'}$), 136.3 ($C_{4'}$), 139.7 ($C_{1''}$), 144.3 (C_{8a}), 157.1 (C_7), 159.0 (C_5); MS (ESI): *m/z* (%): 459.1 (MNa^+ + 1, 22), 458.1 (MNa^+, 100), 437.2 (MH^+ + 1, 20), 436.2 (MH^+, 91), 346.1 (5), 345.1 (15), 344.1 (96), 280.1 (3); HRMS (ESI): *m/z* calcd. for $C_{25}H_{25}NO_4SNa$: 458.1402 [MNa^+]; found: 458.1406.

*(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 5,7-dimethoxy-4-methylquinoline-1(4H)-carboxylate (**16gb**)*

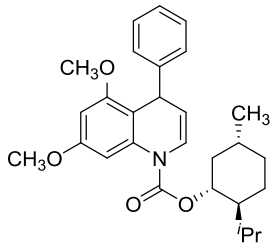


Prepared from (1*R*,2*S*,5*R*)-2-isoprpyl-5-methylcyclohexyl ((*E*)-but-2-en-1-yl)(3,5-dimethoxyphenyl) carbamate **11gb** (0.11 g, 0.28 mmol), *p*-TsOH (52.5 mg, 0.28 mmol), benzoquinone (29.8 mg, 0.28 mmol) and $PdCl_2(CH_3CN)_2$ (3.6 mg, 0.014 mmol) in dioxane (18.4 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 18/1), **16gb** was obtained as a mixture of diastereoisomers in a 58:42 ratio and as an oil (71.3 mg, 67%): IR (ATR): ν (cm^{-1}) = 1716 (C=O); MS (ESI): *m/z* (%): 411.2 (MNa^+ + 1, 17), 410.2 (MNa^+, 82), 388.2 (2), 251.1 (1), 250.1 (9), 228.1 (1); HRMS (ESI): *m/z* calcd. for $C_{23}H_{33}NO_4Na$: 410.2307 [MNa^+]; found: 410.2316; $[\alpha]_D^{20}$ = -57.9 (c = 0.11 g/100 mL in CH_2Cl_2).

NMR signals corresponding to the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.79-0.97 (m, 10H, 3 × CH_3, $(CH_3)_2C\underline{H}$), 1.04-1.18 (m, 5H, 1 × $H_{3'}$, 1 × $H_{4'}$, CH=CHC$\underline{H_3}$), 1.44-1.61 (m, 2H, 1 × $H_{6'}$, $H_{5'}$), 1.69-1.76 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.93-2.04 (m, 1H, 1 × $H_{6'}$), 2.14-2.23 (m, 1H, $H_{2'}$), 3.60-3.68 (m, 1H, H_4), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.68-4.78 (m, 1H, $H_{1'}$), 5.33-5.38 (m, 1H, H_3), 6.30 (d, *J* = 2.3 Hz, 1H, H_6), 6.95 (d, *J* = 7.3 Hz, 1H, H_2), 7.35 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.6 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 22.1 (CH_3) 23.7 ($C_{3'}$), 26.1 (C_4), 26.5 ($(CH_3)_2\underline{C}H$), 31.5 ($C_{5'}$), 34.3 ($C_{4'}$), 41.2 ($C_{6'}$), 47.3 ($C_{2'}$), 55.4 (OCH_3), 55.5 (OCH_3), 76.7 ($C_{1'}$), 95.5 (C_6), 98.1 (C_8), 114.5 (C_{4a}), 115.5 (C_3), 125.2 (C_2), 137.5 (C_{8a}), 152.5 (CO), 156.8 (C_7), 158.4 (C_5).

NMR signals corresponding to the minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.79-0.97 (m, 10H, 3 × CH_3, $(CH_3)_2C\underline{H}$), 1.04-1.18 (m, 5H, 1 × $H_{3'}$, 1 × $H_{4'}$, CH=CHC$\underline{H_3}$), 1.44-1.61 (m, 2H, 1 × $H_{6'}$, $H_{5'}$), 1.69-1.76 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.93-2.04 (m, 1H, 1 × $H_{6'}$), 2.14-2.23 (m, 1H, $H_{2'}$), 3.60-3.68 (m, 1H, H_4), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.68-4.78 (m, 1H, $H_{1'}$), 5.33-5.38 (m, 1H, H_3), 6.30 (d, *J* = 2.3 Hz, 1H, H_6), 6.93 (d, *J* = 7.3 Hz, 1H, H_2), 7.32 (d, *J* = 2.3 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.6 (CH_3), 20.8 (CH_3), 22.1 (CH_3), 22.2 (CH_3), 23.7 ($C_{3'}$), 26.1 (C_4), 26.7 ($(CH_3)_2\underline{C}H$), 31.5 ($C_{5'}$), 34.3 ($C_{4'}$), 41.4 ($C_{6'}$), 47.3 ($C_{2'}$), 55.4 (OCH_3), 55.5 (OCH_3), 76.5 ($C_{1'}$), 95.6 (C_6), 98.0 (C_8), 114.8 (C_{4a}), 115.8 (C_3), 125.3 (C_2), 137.6 (C_{8a}), 152.5 (CO), 156.8 (C_7), 158.4 (C_5).

*(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 5,7-dimethoxy-4-phenylquinoline-1(4H)-carboxylate (**16gc**)*



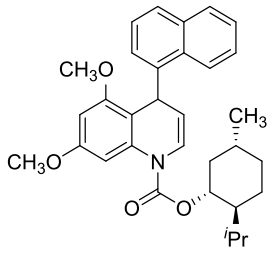
Prepared from (1*R*,2*S*,5*R*)-2-isoprpyl-5-methylcyclohexyl cinnamyl(3,5-dimethoxyphenyl)carbamate **11gc** (0.12 g, 0.26 mmol), *p*-TsOH (48.8 mg, 0.26 mmol), benzoquinone (27.7 mg, 0.26 mmol) and $PdCl_2(CH_3CN)_2$ (3.3 mg, 0.013 mmol) in dioxane (17.1 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **16gc** was obtained as a mixture of diastereoisomers in a 63:37 ratio and as an oil (89.4 mg, 78%): IR (ATR): ν = 1716 cm^{-1} (C=O); MS (ESI): *m/z* (%): 475.3 (MNa^+ + 1, 34), 474.3 (MNa^+, 100), 470.2 (4), 458.4 (2), 457.3 (8), 363.2 (5); HRMS (ESI): *m/z* calcd. for $C_{28}H_{37}NO_4Na$: 474.2620 [MNa^+]; found: 474.2621; $[\alpha]_D^{20}$ = -25.3 (c = 0.088 g/100 mL in CH_2Cl_2).

NMR signals corresponding to the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.72-0.98 (m, 10H, 3 × CH_3, $(CH_3)_2C\underline{H}$), 1.07-1.18 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.46-1.53 (m, 1H, 1 × $H_{6'}$), 1.53-1.60 (m, 1H, $H_{5'}$), 1.70-1.76 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.94-2.03 (m, 1H, 1 × $H_{6'}$), 2.18-2.25 (m, 1H, $H_{2'}$), 3.74 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.76-4.89 (m, 2H, $H_{1'}$, H_4), 5.50 (ddd, *J* = 11.1, 7.6, 6.3 Hz, 1H, H_3), 6.28 (d, *J* = 2.2 Hz, 1H, H_6), 7.09 (d, *J* = 7.6 Hz, 1H, H_2), 7.12-7.25

(m, 5H, Ph), 7.38 (d, *J* = 2.2 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.6 (CH_3), 20.8 (CH_3), 22.1 (CH_3), 23.7 ($C_{3'}$), 26.6 ((CH_3)$_2$CH), 31.5 ($C_{5'}$), 34.3 ($C_{4'}$), 37.3 (C_4), 41.2 ($C_{6'}$), 47.4 ($C_{2'}$), 55.4 (OCH_3), 55.6 (OCH_3), 77.0 ($C_{1'}$), 95.7 (C_6), 98.3 (C_8), 112.5 (C_{4a}), 113.8 (C_3), 125.6 (C_2), 126.2 ($C_{4''}$), 127.4 ($C_{2''}$, $C_{6''}$), 128.3 ($C_{3''}$, $C_{5''}$), 137.7 (C_{8a}), 145.0 ($C_{1''}$), 152.5 (CO), 157.1 (C_7), 158.9 (C_5).

NMR signals corresponding to the minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.72-0.98 (m, 10H, 3 × CH_3, (CH_3)$_2$CH), 1.07-1.18 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.46-1.53 (m, 1H, 1 × $H_{6'}$), 1.53-1.60 (m, 1H, $H_{5'}$), 1.70-1.76 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.94-2.03 (m, 1H, 1 × $H_{6'}$), 2.18-2.25 (m, 1H, $H_{2'}$), 3.73 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.76-4.89 (m, 2H, $H_{1'}$, H_4), 5.50 (ddd, *J* = 11.1, 7.6, 6.3 Hz, 1H, H_3), 6.28 (d, *J* = 2.2 Hz, 1H, H_6), 7.08 (d, *J* = 7.6 Hz, 1H, H_2), 7.12-7.25 (m, 5H, Ph), 7.38 (d, *J* = 2.2 Hz, 1H, H_8); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.5 (CH_3), 20.8 (CH_3), 22.1 (CH_3), 23.6 ($C_{3'}$), 26.6 ((CH_3)$_2$CH), 31.5 ($C_{5'}$), 34.3 ($C_{4'}$), 37.3 (C_4), 41.4 ($C_{6'}$), 47.4 ($C_{2'}$), 55.4 (OCH_3), 55.6 (OCH_3), 76.7 ($C_{1'}$), 96.0 (C_6), 98.2 (C_8), 113.0 (C_{4a}), 114.2 (C_3), 125.8 (C_2), 126.2 ($C_{4''}$), 127.5 ($C_{2''}$, $C_{6''}$), 128.3 ($C_{3''}$, $C_{5''}$), 137.7 (C_{8a}), 144.8 ($C_{1''}$), 152.4 (CO), 157.0 (C_7), 158.9 (C_5).

*(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 5,7-dimethoxy-4-(naphthalene-1-yl)quinoline-1(4H)-carboxylate (**16gl**)*



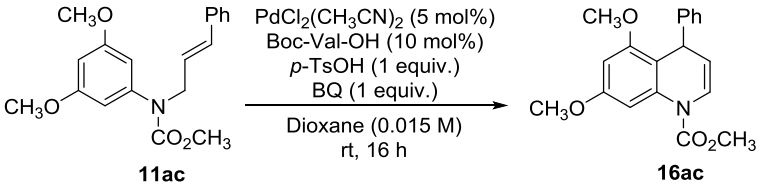
Prepared from methyl (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (3,5-dimethoxyphenyl)((*E*)-3-(naphthalene-1-yl)allyl)carbamate **11gl** (84.8 mg, 0.17 mmol), *p*-TsOH (32.2 mg, 0.17 mmol), benzoquinone (18.3 mg, 0.17 mmol) and $PdCl_2(CH_3CN)_2$ (2.2 mg, 0.0085 mmol) in dioxane (11.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **16gl** was obtained as a mixture of diastereoisomers in a 58:42 ratio and as a solid (66.5 mg, 79%): mp (CH_2Cl_2) 73-75 ºC; IR (ATR): ν (cm^{-1}) = 1713 (C=O); MS (ESI): *m/z* (%): 523.3 (MNa^+ + 1, 17), 522.3 (MNa^+, 58), 501.3 (MH^+ + 1, 9), 500.3 (MH^+, 28), 364.1 (2), 363.1 (19), 362.1 (100), 338.3 (6), 190.1 (2); HRMS (ESI): *m/z* calcd. for $C_{32}H_{38}NO_4$: 500.2801 [MH^+]; found: 500.2794; $[\alpha]_D^{20}$ = -87.0 (c = 0.071 g/100 mL in CH_2Cl_2).

NMR signals corresponding to the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.78-0.99 (m, 10H, 3 × CH_3, (CH_3)$_2$CH), 1.03-1.27 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.41-1.66 (m, 2H, 1 × $H_{6'}$, $H_{5'}$), 1.68-1.79 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.80-2.07 (m, 1H, 1 × $H_{6'}$), 2.17-2.25 (m, 1H, $H_{2'}$), 3.56 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.84 (qd, *J* = 10.7, 4.3 Hz, 1H, $H_{1'}$), 5.61-5.77 (m, 2H, H_3, H_4), 6.35 (d, *J* = 2.2 Hz, 1H, H_6), 6.93-7.11 (m, 2H, H_2, $H_{2''}$), 7.32 (t, *J* = 7.7 Hz, 1H, $H_{7''}$), 7.49-7.58 (m, 2H, H_8, $H_{3''}$), 7.62 (t, *J* = 7.7 Hz, 1H, $H_{6''}$), 7.70 (d, *J* = 8.1 Hz, 1H, $H_{4''}$), 7.90 (d, *J* = 7.9 Hz, 1H, $H_{8''}$); 8.39 (d, *J* = 8.1 Hz, 1H, $H_{5''}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.7 (CH_3),

20.8 (CH_3), 22.0 (CH_3), 23.7 ($C_{3'}$), 26.6 ((CH_3)$_2$CH), 31.5 ($C_{5''}$), 33.3 ($C_{4'}$), 34.3 (C_4), 41.1 ($C_{6'}$), 47.3 ($C_{2'}$), 55.5 (OCH_3), 55.6 (OCH_3), 76.7 ($C_{1'}$), 95.8 (C_6), 98.1 (C_8), 112.8 (C_{4a}), 113.4 (C_3), 123.5 ($C_{2''}$), 124.1 ($C_{8''}$), 125.3 (C_2), 125.9 ($C_{6''}$), 126.1 ($C_{3''}$, $C_{7''}$), 126.6 ($C_{4''}$), 128.9 ($C_{5''}$), 131.0 ($C_{8a''}$), 134.0 ($C_{4a''}$), 138.9 (C_{8a}), 141.3 ($C_{1''}$), 152.5 (CO), 157.2 (C_7), 159.1 (C_5).

NMR signals corresponding to the minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.78-0.99 (m, 10H, 3 × CH_3, (CH_3)$_2$CH), 1.03-1.27 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.41-1.66 (m, 2H, 1 × $H_{6'}$, $H_{5'}$), 1.68-1.79 (m, 2H, 1 × $H_{3'}$, 1 × $H_{4'}$), 1.80-2.07 (m, 1H, 1 × $H_{6'}$), 2.17-2.25 (m, 1H, $H_{2'}$), 3.56 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.84 (qd, *J* = 10.7, 4.3 Hz, 1H, $H_{1'}$), 5.61-5.77 (m, 2H, H_3, H_4), 6.35 (d, *J* = 2.2 Hz, 1H, H_6), 6.93-7.11 (m, 2H, H_2, $H_{2''}$), 7.32 (t, *J* = 7.7 Hz, 1H, $H_{7''}$), 7.49-7.58 (m, 2H, H_8, $H_{3''}$), 7.62 (t, *J* = 7.7 Hz, 1H, $H_{6''}$), 7.70 (d, *J* = 8.1 Hz, $H_{4''}$), 7.90 (d, *J* = 7.9 Hz, 1H, $H_{8''}$); 8.39 (d, *J* = 8.1 Hz, 1H, $H_{5''}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.5 (CH_3), 20.7 (CH_3), 22.1 (CH_3), 23.6 ($C_{3'}$), 26.4 ((CH_3)$_2$CH), 31.5 ($C_{5'}$), 33.2 ($C_{4'}$), 34.3 (C_4), 41.4 ($C_{6'}$), 47.3 ($C_{2'}$), 55.5 (OCH_3), 55.6 (OCH_3), 76.7 ($C_{1'}$), 96.0 (C_6), 98.1 (C_8), 111.6 (C_{4a}), 112.1 (C_3), 123.5 ($C_{2''}$), 124.2 ($C_{8''}$), 125.3 (C_2), 125.8 ($C_{6''}$), 126.1 ($C_{3''}$, $C_{7''}$), 126.5 ($C_{4''}$), 128.9 ($C_{5''}$), 131.0 ($C_{8a''}$), 134.0 ($C_{4a''}$), 138.9 (C_{8a}), 141.3 ($C_{1''}$), 152.6 (CO), 157.2 (C_7), 159.1 (C_5).

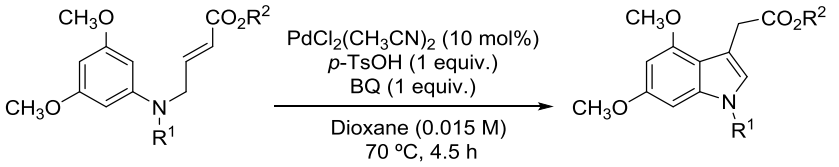
4.18. Use of Boc-Val-OH as ligand for the synthesis of 16ac in a 1 mmol scale



11ac **16ac**

To a solution of **11ac** (0.33 g, 1.0 mmol) in dioxane (68 mL), *p*-TsOH (0.19 g, 1.0 mmol), BQ (0.11 g, 1.0 mmol), Boc-Val-OH (22.1 mg, 0.10 mmol) and $PdCl_2(CH_3CN)_2$ (19.0 mg, 0.05 mmol) were added and the reaction was stirred at room temperature for 16 h. Afterwards, water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) affording **16ac** as a solid (0.28 g, 85%).

4.19. General procedure for the Pd(II)-catalyzed intramolecular alkenylation reaction of esters 12aa-12ba. Sythesis of 3-substituted indoles 17aa-17ba

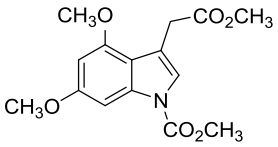


12aa-12ba

17aa, $R^1 = CO_2CH_3$, $R^2 = CH_3$
17ab, $R^1 = CO_2CH_3$, $R^2 = Et$
17ac, $R^1 = CO_2CH_3$, $R^2 = {}^n Bu$
17ad, $R^1 = CO_2CH_3$, $R^2 = {}^t Bu$
17ae, $R^1 = CO_2CH_3$, $R^2 = CH_2Ph$
17ba, $R^1 = CO_2{}^t Bu$, $R^2 = CH_3$

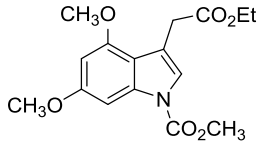
To a solution of the corresponding ester **12aa-12ba** (1 mmol) in dioxane (66.7 mL), *p*-TsOH (1 mmol), benzoquinone (1 mmol) and $PdCl_2(CH_3CN)_2$ (0.1 mmol) were added and the reaction mixture was stirred at 70 ºC for 4.5 h. Afterwards, water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt) affording the corresponding 4-substituted indoes **17aa-17ba.**

*Methyl 4,6-dimethoxy-3-(2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (**17aa**)*



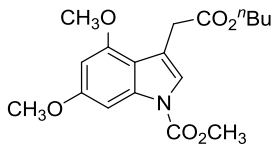
Prepared from methyl *(E)*-4-((3,5-dimethoxyphenyl) (methoxycarbonyl)amino)but-2-enoate **12aa** (90.7 mg, 0.29 mmol), *p*-TsOH (55.8 mg, 0.29 mmol), benzoquinone (31.7 mg, 0.29 mmol) and $PdCl_2(CH_3CN)_2$ (7.6 mg, 0.029 mmol) in dioxane (19.4 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **17aa** was obtained as a solid (61.1 mg, 68%): mp (CH_2Cl_2) 98-101 ºC; IR (ATR): ν (cm^{-1}) = 1728 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.70 (s, 3H, OCH_3), 3.80 (d, *J* = 0.9 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.30 (d, *J* = 2.0, 1H, H_5), 7.28 (s, 1H, H_7), 7.37 (br s, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 32.3 (CH_2), 51.9 ($CO_2\underline{C}H_3$), 53.6 ($CO_2\underline{C}H_3$), 55.2 (OCH_3), 55.7 (OCH_3), 91.6 (C_5), 94.7 (C_7), 113.7 (C_3), 114.1 (C_{3a}), 121.1 (C_2), 137.5 (C_{7a}), 151.4 (C_6), 154.3 (C_4), 159.3 ($N\underline{C}O_2CH_3$), 172.2 ($\underline{C}O_2CH_3$); MS (ESI): *m/z* (%): 309.1 (MH^+ + 1, 13), 308.1 (MH^+, 100), 307.1 (3), 306.1 (2), 248.1 (2); HRMS (ESI): *m/z* calcd. for $C_{15}H_{18}NO_6$: 308.1134 [MH^+]; found: 308.1136.

*Methyl 3-(2-ethoxy-2-oxoethyl)-4,6-dimethoxy-1H-indole-1-carboxylate (**17ab**)*



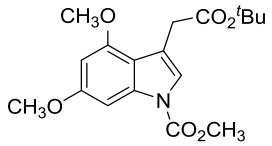
Prepared from ethyl *(E)*-4-((3,5-dimethoxyphenyl) (methoxycarbonyl)amino)but-2-enoate **12ab** (0.13 g, 0.39 mmol), *p*-TsOH (75.1 mg, 0.39 mmol), benzoquinone (42.7 mg, 0.39 mmol) and $PdCl_2(CH_3CN)_2$ (10.2 mg, 0.039 mmol) in dioxane (26.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **17ab** was obtained as a solid (86.4 mg, 68%): mp (CH_2Cl_2) 77-80 ºC; IR (ATR): ν (cm^{-1}) = 1731 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.25 (t, *J* = 7.1 Hz, 3H, CH_3), 3.78 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2), 6.30 (d, *J* = 1.9, 1H, H_5), 7.28 (br s, 1H, H_7), 7.37 (br s, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.3 (CH_3), 32.6 (CH_2), 53.6 ($CO_2\underline{C}H_3$), 55.2 (OCH_3), 55.7 (OCH_3), 60.6 (OCH_2), 91.5 (C_5), 94.6 (C_7), 113.8 (C_3), 114.3 (C_{3a}), 121.1 (C_2), 137.5 (C_{7a}), 151.5 (C_6), 154.3 (C_4), 159.3 ($\underline{C}O_2CH_3$), 171.7 ($\underline{C}O_2Et$); MS (ESI): *m/z* (%): 323.1 (MH^+ + 1, 13), 322.1 (MH^+, 100), 321.1 (3), 248.1 (1); HRMS (ESI): *m/z* calcd. for $C_{16}H_{20}NO_6$: 322.1291 [MH^+]; found: 322.1300.

*Methyl 3-(2-butoxy-2-oxoethyl)-4,6-dimethoxy-1H-indole-1-carboxylate (**17ac**)*



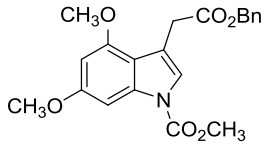
Prepared from butyl *(E)*-4-((3,5-dimethoxyphenyl) (methoxycarbonyl)amino)but-2-enoate **12ac** (0.11 g, 0.31 mmol), *p*-TsOH (58.6 mg, 0.31 mmol), benzoquinone (33.3 mg, 0.31 mmol) and $PdCl_2(CH_3CN)_2$ (8.0 mg, 0.031 mmol) in dioxane (20.5 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **17ac** was obtained as a solid (68.0 mg, 63%): mp (CH_2Cl_2) 79-80 ºC; IR (ATR): ν (cm^{-1}) = 1731 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.90 (t, *J* = 7.3 Hz, 3H, CH_3), 1.22-1.46 (m, 2H, $C\underline{H_2}CH_3$), 1.51-1.69 (m, 2H, $OCH_2\underline{CH_2}$), 3.79 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.17 (t, *J* = 6.7 Hz, 2H, OCH_2), 6.30 (d, *J* = 2.0, 1H, H_5), 7.29 (s, 1H, H_7), 7.38 (br s, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 13.7 (CH_3), 19.1 ($\underline{C}H_2CH_3$), 30.7 ($OCH_2\underline{C}H_2$), 32.6 (CH_2), 53.6 ($CO_2\underline{C}H_3$), 55.2 (OCH_3), 55.7 (OCH_3), 64.5 (OCH_2), 91.5 (C_5), 94.6 (C_7), 113.8 (C_3), 114.3 (C_{3a}), 121.1 (C_2), 137.5 (C_{7a}), 151.5 (C_6), 154.3 (C_4), 159.3 ($\underline{C}O_2CH_3$), 171.8 ($\underline{C}O_2{}^n$Bu); MS (ESI): *m/z* (%): 351.2 (MH^+ + 1, 15), 350.2 (MH^+, 100), 349.2 (5), 348.1 (5); HRMS (ESI): *m/z* calcd. for $C_{18}H_{24}NO_6$: 350.1604 [MH^+]; found: 350.1604.

*Methyl 3-(2-(tert-butoxy)-2-oxoethyl)- 4,6-dimethoxy-1H-indole-1-carboxylate (**17ad**)*



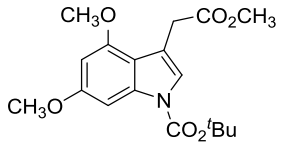
Prepared from *tert*-butyl *(E)*-4-((3,5-dimethoxyphenyl) (methoxycarbonyl)amino)but-2-enoate **12ad** (0.14 g, 0.40 mmol), *p*-TsOH (75.9 mg, 0.40 mmol), benzoquinone (43.2 mg, 0.40 mmol) and $PdCl_2(CH_3CN)_2$ (10.4 mg, 0.040 mmol) in dioxane (26.6 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **17ad** was obtained as an oil (75.3 mg, 54%): IR (ATR): ν (cm^{-1}) = 1735 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.45 (s, 9H, 3 × CH_3), 3.70 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.30 (d, *J* = 2.0, 1H, H_5), 7.27 (s, 1H, H_7), 7.37 (br s, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.3 (3 × CH_3), 33.6 (CH_2), 53.6 ($CO_2\underline{C}H_3$), 55.1 (OCH_3), 55.7 (OCH_3), 80.3 ($\underline{C}(CH_3)_3$), 91.5 (C_5), 94.6 (C_7), 113.9 (C_3), 114.8 (C_{3a}), 121.0 (C_2), 137.5 (C_{7a}), 151.5 (C_6), 154.3 (C_4), 159.2 ($\underline{C}O_2CH_3$), 171.0 ($\underline{C}O_2{}^t$Bu); MS (ESI): *m/z* (%): 351.2 (MH^+ + 1, 4), 350.2 (MH^+, 31), 295.1 (11), 294.1 (100), 248.1 (3); HRMS (ESI): *m/z* calcd. for $C_{18}H_{24}NO_6$: 350.1604 [MH^+]; found: 350.1608.

*Methyl 3-(2-(benzyloxy)-2-oxoethyl)- 4,6-dimethoxy-1H-indole-1-carboxylate (**17ae**)*



Prepared from benzyl *(E)*-4-((3,5-dimethoxyphenyl)-(methoxycarbonyl)amino)but-2-enoate **12ae** (0.10 g, 0.27 mmol), *p*-TsOH (51.2 mg, 0.27 mmol), benzoquinone (29.1 mg, 0.27 mmol) and $PdCl_2(CH_3CN)_2$ (7.0 mg, 0.027 mmol) in dioxane (17.9 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **17ae** was obtained as a solid (80.4 mg, 78%): mp (CH_2Cl_2) 136-138 ºC; IR (ATR): ν (cm^{-1}) = 1735 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.66 (s, 3H, OCH_3), 3.85 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 5.17 (s, 2H, $OC\underline{H}_2Ph$), 6.28 (d, *J* = 1.9 Hz, 1H, H_5), 7.24-7.45 (m, 7H, Ph, H_7, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 32.6 (CH_2), 53.6 ($CO_2\underline{C}H_3$), 55.0 (OCH_3), 55.7 (OCH_3), 66.4 (OCH_2), 91.5 (C_5), 94.7 (C_7), 113.8 (C_3), 114.1 (C_{3a}), 121.2 (C_2), 128.1 ($C_{4'}$), 128.3 ($C_{2'}$, $C_{6'}$), 128.5 ($C_{3'}$, $C_{5'}$), 136.2 ($C_{1'}$), 137.5 (C_{7a}), 151.5 (C_6), 154.3 (C_4), 159.3 ($\underline{C}O_2CH_3$), 171.5 ($\underline{C}O_2Bn$); MS (ESI): *m/z* (%): 407.1 (MNa^+ + 1, 14), 406.1 (MNa^+, 81), 385.1 (MH^+ + 1, 18), 384.1 (MH^+, 100), 383.1 (17), 356.1 (2); 338.1 (7), 293.1 (2); HRMS (ESI): *m/z* calcd. for $C_{21}H_{22}NO_6$: 384.1447 [MH^+]; found: 384.1452.

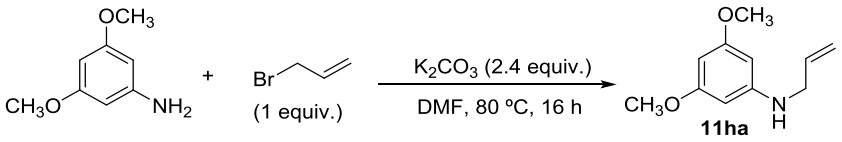
*tert-Butyl 4,6-dimethoxy-3-(2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (**17ba**)*



Prepared from methyl *(E)*-4-((*tert*-butoxycarbonyl)(3,5-dimethoxyphenyl)amino)but-2-enoate **12ba** (0.11 g, 0.33 mmol), *p*-TsOH (62.0 mg, 0.33 mmol), benzoquinone (38.8 mg, 0.33 mmol) and $PdCl_2(CH_3CN)_2$ (8.5 mg, 0.033 mmol) in dioxane (21.7 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1), **17ba** was obtained as a solid (46.4 mg, 41%): mp (CH_2Cl_2) 103-105 ºC; IR (ATR): ν (cm^{-1}) = 1756, 1720 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.64 (s, 9H, 3 × CH_3), 3.71 (s, 3H, OCH_3), 3.80 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.29 (d, *J* = 1.7, 1H, H_5), 7.26 (s, 1H, H_7), 7.35 (br s, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.2 (3 × CH_3), 32.4 (CH_2), 51.9 (CO_2CH_3), 55.2 (OCH_3), 55.7 (OCH_3), 83.3 ($\underline{C}(CH_3)_3$), 91.6 (C_5), 94.5 (C_7), 113.2 (C_3), 113.8 (C_{3a}), 121.7 (C_2), 137.4 (C_{7a}), 149.7 (C_6), 154.2 (C_4), 159.1 ($\underline{C}O_2{}^t$Bu), 172.4 ($\underline{C}O_2CH_3$); MS (ESI): *m/z* (%): 351.2 (MH^+ + 1, 14), 350.2 (MH^+, 100), 349.1 (2), 295.1 (7), 294.1 (72), 293.1 (3); HRMS (ESI): *m/z* calcd. for $C_{18}H_{24}NO_6$: 350.1604 [MH^+]; found: 350.1606.

4.20. Synthesis of methyl (2-allyl-3,5-dimethoxyphenyl)carbamate (13aa)

*4.20.1. Step 1: N-allylation. Synthesis of N-allyl-3,5-dimethoxyaniline (**11ha**)*[46]

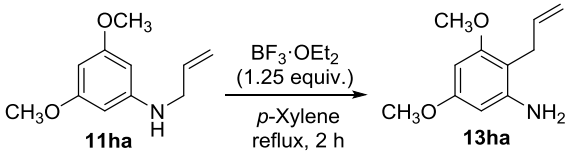


Over a solution of commercially available 3,5-diemthoxyailine (1.0 g, 6.7 mmol) in dry DMF (10 mL) were successively added, under argon atmosphere, K_2CO_3 (2.2 g, 16.1 mmol) and allyl bromide (0.58 mL, 6.7 mmol). The reaction was stirred overnight at 80 ºC and quenched with water (20 mL). The mixture was washed with water (3 × 20 mL) and the aqueous phase extracted with AcOEt (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) **11ha** was obtained as an oil (0.68 g, 52%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.69-3.80 (m, 8H, 2 x OCH_3, NCH_2), 3.88 (s, 1H, NH), 5.09-5.24 (m, 1H, 1 x CH=C$\underline{H_2}$), 5.25-5.41 (m, 1H, 1 x CH=C$\underline{H_2}$), 5.84 (d, *J* = 2.2 Hz, 2H, H_2, H_6), 5.87-6.05 (m, 2H, H_4,

[46] Yang, S.-C.; Chung, W.-H. *Tetrahedron Lett.* **1999**, *40*, 953.

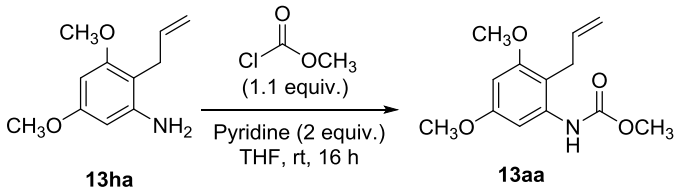
C<u>H</u>=CH$_2$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 46.6 (NCH$_2$), 55.1 (2 x OCH$_3$), 89.9 (C$_4$), 91.9 (C$_2$, C$_6$), 116.2 (CH=C<u>H</u>$_2$), 135.5 (C<u>H</u>=CH$_2$), 150.1 (C$_1$), 161.8 (C$_3$, C$_5$).

*4.20.2. Step 2: Claisen rearrangement. Synthesis of 2-allyl-3,5-dimethoxyaniline (**13ha**)*[47]



Over a solution of *N*-allyl-3,5-dimethoxyaniline **11ha** (0.49 g, 2.5 mmol) in dry *p*-xylene (10 mL), BF$_3$·OEt$_2$ (0.38 mL, 3.1 mmol) was added dropwise under argon atmosphere. The solution was stirred at reflux for 2 h and it was allowed to cool down to room temperature. Afterwards, a 10 % aqueous solution of NaOH (15 mL) was added and the mixture was extracted with AcOEt (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **13ha** as an oil (0.16 g, 33%): ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 3.33 (dt, *J* = 5.8, 1.7 Hz, 2H, C<u>H$_2$</u>CH=CH$_2$), 3.71 (br s, 2H, NH$_2$), 3.77 (s, 3H, OCH$_3$), 3.78 (s, 3H, OCH$_3$), 5.01-5.09 (m, 2H, CH=C<u>H$_2$</u>), 5.85-5.94 (m, 1H, C<u>H</u>=CH$_2$), 5.93 (d, *J* = 2.3 Hz, 1H, H$_4$), 6.01 (d, *J* = 2.3 Hz, 1H, H$_6$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 27.9 (<u>C</u>H$_2$CH=CH$_2$), 55.2 (OCH$_3$), 55.7 (OCH$_3$), 89.6 (C$_4$), 93.6 (C$_6$), 104.7 (C$_2$), 114.5 (CH=<u>C</u>H$_2$), 136.4 (<u>C</u>H=CH$_2$), 146.7 (C$_1$), 158.9 (C$_5$), 159.6 (C$_3$).

*4.20.3. Step 3: N-protection. Synthesis of methyl (2-allyl-3,5-dimethoxyphenyl)carbamate (**13aa**)*

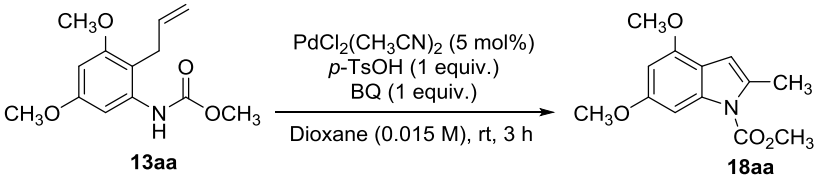


Over a solution of 2-allyl-3,5-dimethoxyaniline **13ha** (51.1 mg, 0.26 mmol) and pyridine (42.6 µL, 0.53 mmol) in dry THF (7 mL) under argon atmosphere, methyl chloroformate (22.5

[47] Ye, K.-Y.; Dai, L.-X.; You, S.-L. *Org. Biomol. Chem.* **2012**, *10*, 5932.

µL, 0.29 mmol) was added dropwise. The reaction was stirred for 16 h at room temperature and afterwards, the solvent was removed under reduced pressure. The crude reaction was dissolved in CH_2Cl_2 (15 mL) and washed with a 10% aqueous solution of HCl (2 × 15 mL) and with water (15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/AcOEt 8/2) afforded **13aa** as a solid (63.9 mg, 96%): mp (CH_2Cl_2) 83-84 ºC; IR (ATR): ν (cm^{-1}) = 3310 (N-H), 1695 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.36 (dt, *J* = 5.6, 1.6 Hz, 2H, $C\underline{H_2}CH=CH_2$), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.93-5.14 (m, 2H, $CH=C\underline{H_2}$), 5.83-5.97 (m, 1H, $C\underline{H}=CH_2$), 5.26 (d, *J* = 2.4 Hz, 1H, H_4), 6.69 (br s, 1H, H_6), 7.18 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 27.9 ($\underline{C}H_2CH=CH_2$), 52.3 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.8 (OCH_3), 95.0 (C_4), 97.8 (C_6), 109.2 (C_2), 115.2 ($CH=\underline{C}H_2$), 136.1 ($\underline{C}H=CH_2$), 137.9 (C_1), 154.3 (CO), 158.1 (C_5), 159.4 (C_3); MS (ESI): *m/z* (%): 275.1 (MNa^+ + 1, 11), 274.1 (MNa^+, 100), 252.1 (6); HRMS (ESI): *m/z* calcd. for $C_{13}H_{17}NO_4Na$: 274.1055 [MNa^+]; found: 274.1060.

4.21. Pd(II)-catalyzed intramolecular alkenylation of carbamate 13aa. Synthesis of methyl 4,6-dimethoxy-2-methyl-1*H*-indole-1-carboxylate (18aa)

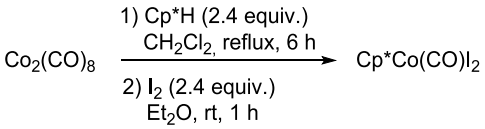


13aa **18aa**

Over a solution of methyl (2-allyl-3,5-dimethoxyphenyl)carbamate **13aa** (55.5 mg, 0.22 mmol) in dioxane (14.7 mL), *p*-TsOH (42.0 mg, 0.22 mmol), benzoquinone (23.9 mg, 0.22 mmol) and $PdCl_2(CH_3CN)_2$ (2.9 mg, 0.011 mmol) were added. The solution was stirred at room temperature for 3 h. Afterwards, water was added to quench the reaction and it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) affording **18aa** as a solid (42.7 mg, 78 %): mp (CH_2Cl_2) 88-90 ºC; IR (ATR): ν (cm^{-1}) = 1720 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.54 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.35 (d, *J* = 1.9 Hz, 1H, H_5), 6.36 (s, 1H, H_3), 7.36 (d, *J* = 1.9 Hz, 1H, H_7); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.8 (CH_3), 53.4 ($CO_2\underline{C}H_3$), 55.4 (OCH_3), 55.8 (OCH_3), 92.7 (C_7), 94.3 (C_5), 105.1 (C_3), 113.7 (C_{3a}), 134.4 (C_2), 138.0 (C_{7a}), 152.2 (CO), 152.9 (C_4), 158.2 (C_6); MS (ESI): *m/z* (%): 251.1 (MH^+ + 1, 11), 250.1 (MH^+, 100), 249.1 (18), 190.1 (4); HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NO_4$: 250.1079 [MH^+]; found: 250.1079.

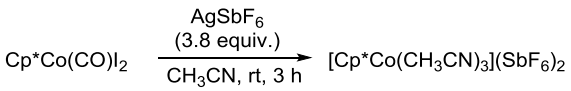
5. AMIDE-DIRECTED INTRAMOLECULAR Co(III)-CATALYZED C–H HYDROARYLATION OF ALKENES FOR THE SYNTHESIS OF DIHYDROBENZOFURANS WITH A QUATERNARY CENTER

5.1. Preparation of Cp*Co(CO)I_2 catalyst[9]



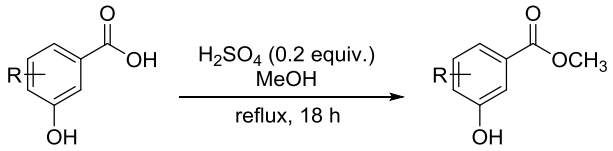
To a well-dried 100-mL-round-bottom flask were successively added $Co_2(CO)_8$ (1.1 g, 3.3 mmol), degassed and anhydrous CH_2Cl_2 (20 mL) and pentamethylcyclopentadiene (1.2 mL, 7.9 mmol) under argon atmosphere. The reaction mixture was heated at reflux for 6 h and then, it was allowed to cool down to room temperature. After removing the solvent *in vacuo*, the residue was dissolved in dry and degassed Et_2O (10 mL) and a solution of I_2 (1.0 g, 7.9 mmol) in dry and degassed Et_2O (10 mL) was added dropwise under argon atmosphere *via* a xyringe. The mixture was stirred for 1 h at room temperature and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/CH_2Cl_2, 10/0-2/8), affording the desired catalyst as a deep purple crystalline solid (1.7 g, 54% yield based on Co): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.24 (s, 15H, 5 × C<u>H</u>$_3$-Cp).

5.2. Preparation of [Cp*Co(CH_3CN)$_3$](SbF_6)$_2$ catalyst[10]



To a suspenssion of Cp*Co(CO)I_2 (0.28 g, 0.59 mmol) in dry CH_3CN (5 mL), a solution of $AgSbF_6$ (0.81 g, 2.2 mmol) in dry CH_3CN (6 mL) was added *via cannula* under argon atmosphere. Then, a solid precipitated immediately. After stirring the reaction mixture for 3 h at room temperature, the resulting suspenssion was filtered trough celite and washed with CH_3CN (3 × 20 mL). The filtrate was evaporated *in vacuo* to afford the desired catalyst as a pink-purple solid (0.25 g, 55%): ^{1}H NMR (300 MHz, CD_3CN): δ (ppm) = 1.41 (s, 15 H, 5 × C<u>H</u>$_3$-Cp), 1.99 (s, 9H, 3 × C<u>H</u>$_3$CN).

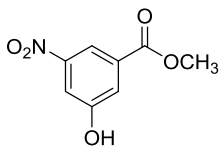
5.3. General procedure for the esterification of 3-hydroxybenzoic acids. Synthesis of methyl 3-hydroxybenzoates TB-TO



TB R^1 = 5-NO_2
TC R^1 = 5-Br
TE R^1 = 4-CH_3
TF R^1 = 4-OCH_3
TG R^1 = 4-F
TO R^1 = 5-OH

Over a solution of the corresponding 3-hydroxybenzoic acid (1 mmol) in dry methanol (5.4 mL), H_2SO_4 (0.2 mmol) was added and the mixture was heated at reflux under argon atmosphere for 18 h. The reaction mixture was allowed to cool down to room temperature, neutralized with a 2 M aqueous solution of NaOH and the volatiles were evaporated under reduced pressure. The residue was redisolved in AcOEt (20 mL) and in a saturated aqueous solution of $KHSO_4$ (10 mL), the phases were separated and the organic phase was washed with H_2O (2 × 15 mL) and brine (15 mL). The organic extract was dried (Na_2SO_4) and the solvent was evaporated *in vacuo*, obtaining the corresponding methyl 3-hydroxybenzoates **TB-TO** pure.

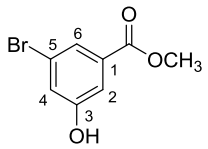
*Methyl 3-hydroxy-5-nitrobenzoate (**TB**)*[48]



Prepared from 3-hydroxy-5-nitrobenzoic acid (0.98 g, 5.4 mmol) and H_2SO_4 (0.06 mL, 1.1 mmol) in dry methanol (29.0 mL). After work-up, **TB** was obtained as a solid (0.97 g, 92%): ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ (ppm) = 3.92 (s, 3H, OCH_3), 7.69-7.74 (m, 1H, H_4), 7.78 (t, *J* = 2.2 Hz, 1H, H_2), 8.09-8.15 (m, 1H, H_6), 9.60 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $(CD_3)_2CO$): δ (ppm) = 52.1 (OCH_3), 113.9 (C_6), 114.8 (C_4), 121.9 (C_2), 132.6 (C_1), 149.1 (C_5), 158.3 (C_3), 164.4 (CO).

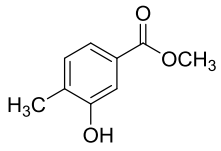
[48] Ghosh, K.; Rit, R.K.; Ramesh, E.; Sahoo, A.K. *Angew. Chem. Int. Ed.* **2016**, *55*, 7821.

*Methyl 3-bromo-5-hydroxybenzoate (**TC**)*[49,50a]



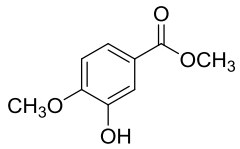
Prepared from 3-bromo-5-hydroxybenzoic acid (1.2 g, 5.6 mmol) and H_2SO_4 (0.06 mL, 1.1 mmol) in dry methanol (30.4 mL). After work-up, **TC** was obtained as a solid (1.1 g, 85%): ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ (ppm) = 3.88 (s, 3H, OCH_3), 7.25-7.29 (m, 1H, H_2), 7.43-7.47 (m, 1H, H_4), 7.58-7.61 (m, 1H, H_6), 9.14 (br s, 1H, OH); ^{13}C NMR (75.5 MHz, $(CD_3)_2CO$): δ (ppm) = 51.8 (OCH_3), 115.3 (C_2), 122.2 (C_5), 122.7 (C_6), 123.2 (C_4), 133.2 (C_1), 158.5 (C_3), 165.0 (CO).

*Methyl 3-hydroxy-4-methylbenzoate (**TE**)*[48,50b]



Prepared from 3-hydroxy-4-methylbenzoic acid (1.1 g, 7.2 mmol) and H_2SO_4 (0.08 mL, 1.4 mmol) in dry methanol (38.7 mL). After work-up, **TE** was obtained as a solid (1.1 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.32 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 6.27 (br s, 1H, OH), 7.16-7.23 (m, 1H, H_5), 7.53 (dd, *J* = 7.8, 1.5 Hz, 1H, H_6), 7.62 (d, *J* = 1.5 Hz, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.2 (CH_3), 52.3 (OCH_3), 115.9 (C_2), 121.8 (C_6), 128.7 (C_4), 130.5 (C_1), 131.0 (C_5), 154.2 (C_3), 167.7 (CO).

*Methyl 3-hydroxy-4-methoxybenzoate (**TF**)*[48,50c]

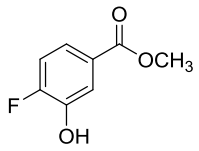


Prepared from 3-hydroxy-4-methoxybenzoic acid (1.3 g, 7.7 mmol) and H_2SO_4 (0.08 mL, 1.5 mmol) in dry methanol (41.5 mL). After work-up, **TF** was obtained as a solid (1.3 g, 91%):^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.86 (br s, 1H, OH), 6.87 (d, *J* = 8.6 Hz, 1H, H_5), 7.53-7.70 (m, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.0 ($CO_2\underline{C}H_3$), 56.0 (OCH_3), 109.9 (C_5), 115.7 (C_2), 122.8 (C_6), 123.3 (C_1), 145.3 (C_3), 150.5 (C_4), 166.9 (CO).

[49] Mukherjee, K.; Ramesh, E.; Ghosh, K.; Sahoo, A.K. *Asian J. Org. Chem.* **2018**, *7*, 1380.

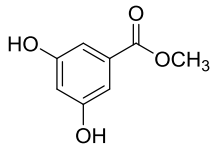
[50] a) Park, K.; Lee, B.M.; Hyun, K.H.; Han, T.; Lee, D.H.; Choi, H.H. *ACS Med. Chem. Lett.* **2015**, *6*, 296; b) Payne, R.J.; Bulloch, E.M.M.; Abell, A.D.; Abell, C. *Org. Biomol. Chem.* **2005**, *3*, 3629; c) Payne, R.J.; Toscano, M.D.; Bulloch, E.M.M.; Abell, A.D.; Abell, C. *Org. Biomol. Chem.* **2005**, *3*, 2271; d) Piao, Y.Z.; Kim, Y.J.; Kim, Y.A.; Lee, H.-S.; Hammock, B.D.; Lee, Y.T. *J. Agric. Food Chem.* **2009**, *57*, 10004.

*Methyl 4-fluoro-3-hydroxybenzoate (**TG**)*[48,50d]



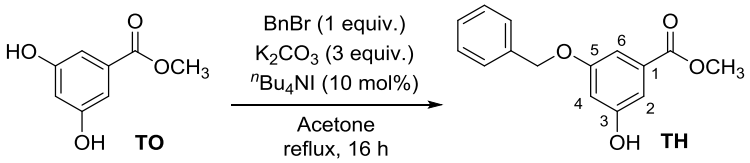
Prepared from 4-fluoro-3-hydroxybenzoic acid (0.96 g, 6.1 mmol) and H_2SO_4 (0.07 mL, 1.3 mmol) in dry methanol (33.2 mL). After work-up, **TG** was obtained as a solid (0.97 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.92 (s, 3H, OCH_3), 6.43 (br s, 1H, OH), 7.11 (dd, *J* = 10.1, 8.7 Hz, 1H, H_5), 7.56 (ddd, *J* = 8.7, 4.6, 2.0 Hz, H_6), 7.74 (dd, *J* = 8.4, 2.0 Hz, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.5 (OCH_3), 115.8 (d, *J* = 17.5 Hz, C_5), 119.1 (d, *J* = 4.5 Hz, C_2), 122.8 (d, *J* = 8.8 Hz, C_6), 126.7 (d, *J* = 3.8 Hz, C_1), 143.8 (d, *J* = 15.4 Hz, C_3), 154.4 (d, *J* = 248.0 Hz, C_4), 166.8 (CO).

*Methyl 3,5-dihydroxybenzoate (**TO**)*[48,51]



Prepared from 3,5-dihydroxybenzoic acid (3.1 g, 20.2 mmol) and H_2SO_4 (0.22 mL, 4.0 mmol) in dry methanol (108.9 mL). After work-up, **TO** was obtained as a solid (3.1 g, 91%): ^{1}H NMR (300 MHz, CD_3OD): δ (ppm) = 3.84 (s, 3H, OCH_3), 4.86 (br s, 2H, 2 × OH), 6.48 (t, 1H, *J* = 2.4 Hz, H_4), 6.92 (d, 2H, *J* = 2.4 Hz, H_2, H_6); ^{13}C NMR (75.5 MHz, CD_3OD): δ (ppm) = 52.5 (OCH_3), 108.2 (C_4), 108.8 (C_2, C_6), 133.0 (C_1), 159.7 (C_3, C_5), 168.7 (CO).

5.4. Synthesis of methyl 3-(benzyloxy)-5-hydroxybenzoate (TH)[48,52]

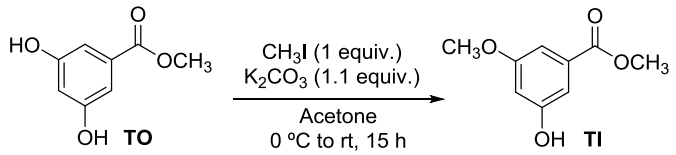


Over a suspension of methyl 3,5-dihydroxybenzoate **TO** (1.9 g, 11.0 mmol) and K_2CO_3 (4.6 g, 33.1 mmol) in acetone (34.0 mL), benzyl bromide (1.3 mL, 11.0 mmol) was added, followed by ^{n}Bu$_4$NI (0.41 g, 1.1 mmol). The reaction mixture has stirred at reflux for 16 h. Afterwards, it was allowed to cool down to room temperature, H_2O (40 mL) was added and the mixture was extracted with AcOEt (3 × 20 mL). The combined organic extracts were

[51] Röder, N.; Marszalek, T.; Limbach, D.; Pisula, W.; Detert, H. *ChemPhysChem* **2019**, *20*, 463.
[52] Mikami, S.; Kitamura, S.; Negoro, N.; Sasaki, S.; Suzuki, M.; Tsujihata, Y.; Miyazaki, T.; Ito, R.; Suzuki, N.; Miyazaki, J.; Santou, T.; Kanzaki, N.; Funami, M.; Tanaka, T.; Yasuma, T.; Momose, Y. *J. Med. Chem.* **2012**, *55*, 3756.

washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **TH** was obtained as a solid (0.83 g, 29%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.92 (s, 3H, OCH_3), 5.08 (s, 2H, $OC\underline{H_2}Ph$), 5.88 (br s, 1H, OH), 6.72 (t, *J* = 2.3 Hz, H_4), 7.21 (dd, *J* = 2.3, 1.3 Hz, H_2), 7.27 (dd, *J* = 2.3, 1.3 Hz, H_6), 7.29-7.47 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.4 (OCH_3), 70.3 ($O\underline{C}H_2Ph$), 107.5 (C_4), 108.1 (C_6), 109.6 (C_2), 127.6 ($C_{2'}$, $C_{6'}$), 128.2 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 132.0 (C_1), 136.4 ($C_{1'}$), 156.9 (C_3), 160.0 (C_5), 167.1 (CO).

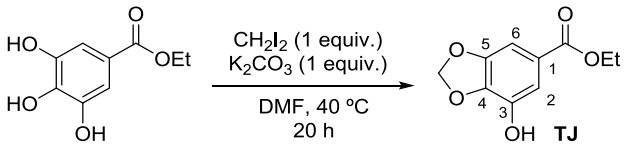
5.5. Synthesis of methyl 3-hydroxy-5-methoxybenzoate (TI)[48,53]



Over a suspension of methyl 3,5-dihydroxybenzoate **TO** (1.4 g, 8.2 mmol) and K_2CO_3 (1.3 g, 9.1 mmol) in dry acetone (41.2 mL), iodomethane (0.51 mL, 8.2 mmol) was added under argon atmosphere at 0 ºC. The reaction mixture was then allowed to warm up to room temperature and stirred for 15 h. Afterwards, H_2O (30 mL) was added and it was extracted with AcOEt (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1). That way, **TI** was obtained as a solid (0.53 g, 36%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.84 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.39 (br s, 1H, OH), 6.64 (t, 1H, *J* = 2.3 Hz, H_4), 7.15-7.20 (m, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.5 ($CO_2\underline{C}H_3$), 55.6 (OCH_3), 106.7 (C_4), 107.1 (C_6), 109.3 (C_2), 132.0 (C_1), 156.9 (C_3), 160.9(C_5), 167.1 (CO).

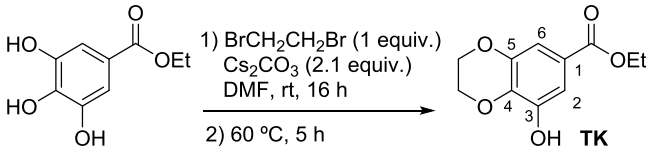
[53] Nawrat, C.C.; Palmer, L.I.; Blake, A.L.; Moody, C.J. *J. Org. Chem.* **2013**, *78*, 5587.

5.6. Synthesis of ethyl 7-hydroxybenzo[*d*][1,3]dioxole-5-carboxylate (TJ)[54]



Over a suspension of ethyl gallate (2.1 g, 10.4 mmol) and K_2CO_3 (1.4 g, 10.4 mmol) in dry DMF (23.2 mL), CH_2I_2 (0.84 mL, 10.4 mmol) was added under argon atmosphere and at 40 ºC. The reaction mixture was stirred at that same temperature for 20 h. The mixture was then diluted with H_2O (100 mL) and extracted with AcOEt (3 × 40 mL). The combined organic phases were washed with brine (40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **TJ** was obtained as a solid (0.55 g, 25%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.39 (t, *J* = 7.1 Hz, 3H, CH_3), 4.36 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 5.97 (br s, 1H, OH), 6.06 (s, 2H, OCH_2O), 7.16 (d, *J* = 1.5 Hz, H_6), 7.42 (d, *J* = 1.5 Hz, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.3 (CH_3), 61.3 (OCH_2), 102.3 (OCH_2O), 103.1 (C_6), 114.1 (C_2), 124.6 (C_1), 138.4 (C_4), 139.2 (C_5), 148.8 (C_3), 166.4 (CO).

5.7. Synthesis of ethyl 8-hydroxy-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (TK)[55]



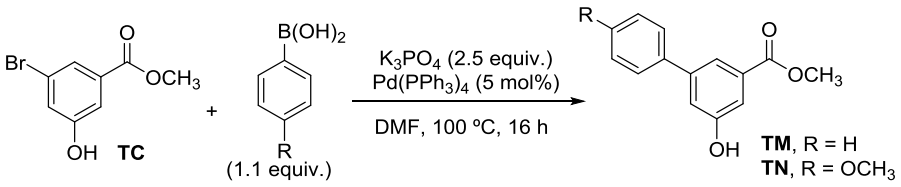
Over a suspension of ethyl gallate (2.5 g, 12.8 mmol) and Cs_2CO_3 (8.8 g, 26.9 mmol) in dry DMF (37.1), 1,2-dibromoethane (1.1 mL, 12.8 mmol) was added under argon atmosphere. The reaction mixture was stirred for 16 h at room temperature and at 60 ºC for 5 h. Afterwards, H_2O (50 mL) was added and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel,

[54] Takaoka, S.; Takaoka, N.; Minoshima, Y.; Huang, J.-M.; Kubo, M.; Harada, K.; Hioki, H.; Fukuyama, Y. *Tetrahedron* **2009**, *65*, 8354.

[55] Ehrhardt, C.; Irie, O.; Lorthiois, E.L.J.; Maibaum, J.K.; Ostermann, N.; Sellner, H.A.; Preparation of 3,4-substituted pyrrolidines for treatments of hypertension. WO 2006100036 A1, April 28, 2006.

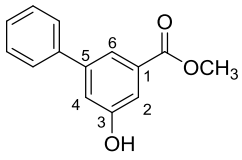
petroleum ether/AcOEt 6/4), **TK** was obtained as a solid (0.53 g, 20%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.36 (t, *J* = 7.1 Hz, 3H, CH_3), 4.19-4.46 (m, 6H, $OC\underline{H_2}CH_3$, $OC\underline{H_2}C\underline{H_2}O$), 5.83 (br s, 1H, OH), 7.20 (d, *J* = 1.8 Hz, H_6), 7.26 (d, *J* = 1.8 Hz, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.3 (CH_3), 61.0 ($O\underline{C}H_2CH_3$), 64.2 ($O\underline{C}H_2CH_2O$), 64.9 ($OCH_2\underline{C}H_2O$), 109.3 (C_2), 111.0 (C_6), 123.0 (C_1), 135.4 (C_4), 143.4 (C_5), 145.0 (C_3), 166.3 (CO).

5.8. General procedure for the Suzuki-Miyaura coupling of methyl 3-bromo-5-hydroxybenzoate (TC). Synthesis of methyl 3-hydroxybenzoates TM and TN



Over a solution of methyl 3-bromo-5-hydroxybenzoate **TC** (1 mmol) in dry and degassed DMF (2.0 mL), the corresponding boronic acid (1.1 mmol), K_3PO_4 (2.5 mmol) and $Pd(PPh_3)_4$ (0.05 mmol) were successively added under argon atmosphere. The reaction mixture was stirred at 100 ºC for 16 h. Afterwards, it was allowed to cool down to room temperature and quenched with a 2 M aqueous solution of HCl (20 mL). The mixture was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt), the corresponding methyl 3-hydroxybenzoates **TM** and **TN** were obtained.

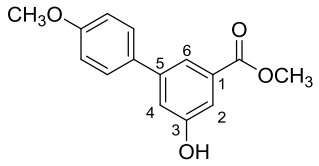
*Methyl 5-hydroxy-[1,1´-biphenyl]-3-carboxylate (**TM**)*[56]



Prepared from methyl 3-bromo-5-hydroxybenzoate **TC** (0.65 g, 2.8 mmol), $PhB(OH)_2$ (0.38 g, 3.1 mmol), K_3PO_4 (1.5 g, 7.0 mmol) and $Pd(PPh_3)_4$ (0.16 g, 0.14 mmol) in dry and degassed DMF (5.6 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 5/1), **TM** was obtained as a solid (0.48 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.97 (s, 3H, OCH_3), 6.55 (br s, 1H, OH), 7.33-7.49 (m, 4H, H_4, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.57-7.66 (m, 3H, H_2, $H_{2'}$, $H_{6'}$), 7.87 (t, *J* = 1.5 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.5 (OCH_3), 115.3 (C_2), 119.0 (C_4), 120.8 (C_6), 127.1 ($C_{2'}$, $C_{6'}$), 127.9 ($C_{4'}$), 128.9 ($C_{3'}$, $C_{5'}$), 131.6 (C_1), 139.8 (C_5), 143.2 ($C_{1'}$), 156.4 (C_3), 167.6 (CO).

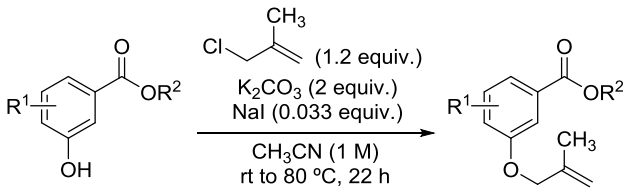
[56] Ye, B.; Cramer, N. *Synlett* **2015**, *26*, 1490.

*Methyl 5-hydroxy-4´-methoxy-[1,1´-biphenyl]-3-carboxylate (**TN**)*



Prepared from methyl 3-bromo-5-hydroxybenzoate **TC** (1.1 g, 4.6 mmol), 4[(OCH_3)C_6H_4]$B(OH)_2$ (0.76 g, 5.0 mmol), K_3PO_4 (2.4 g, 11.4 mmol) and $Pd(PPh_3)_4$ (0.26 g, 0.23 mmol) in dry and degassed DMF (9.2 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 75/25), **TN** was obtained as a solid (0.87 g, 74%): mp (CH_2Cl_2) 132-134 ºC; IR (ATR): ν (cm^{-1}) = 3378 (O-H), 1718 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.88 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 5.35 (br s, 1H, OH), 6.94-7.05 (m, 2H, $H_{3'}$, $H_{5'}$), 7.25-7.27 (m, 1H, H_4), 7.49 (dd, *J* = 2.4, 1.4 Hz, 1H, H_2), 7.52-7.60 (m, 2H, $H_{2'}$, $H_{6'}$), 7.85 (t, *J* = 1.4 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.5 (OCH_3), 55.4 (OCH_3), 114.3 ($C_{3'}$, $C_{5'}$), 114.7 (C_2), 118.5 (C_4), 120.3 (C_6), 128.2 ($C_{2'}$, $C_{6'}$), 131.6 (C_1), 132.3 (C_5), 142.7 ($C_{1'}$), 156.4 (C_3), 159.5 ($C_{4'}$), 167.6 (CO); MS (ESI): *m/z* (%): 258.1 ($M\text{-}H^-$ + 1, 12), 257.1 ($M\text{-}H^-$, 100), 242.1 (2). 193.2 (1); HRMS (ESI): *m/z* calcd. for $C_{15}H_{13}O_4$: 257.0814 [$M\text{-}H^-$]; found: 257.0818.

5.9. General procedure for the alkylation of 3-hydroxybenzoates TA-TN. Synthesis of 3-((2-methylallyl)oxy)benzoates UAA-UAN

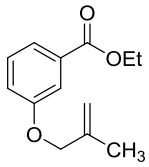


TA-TN

UAA, R^1 = H, R^2 = Et
UAB, R^1 = 5-NO_2, R^2 = CH_3
UAC, R^1 = 5-Br, R^2 = CH_3
UAD, R^1 = 4,5-$(OCH_3)_2$, R^2 = CH_3
UAE, R^1 = 4-CH_3, R^2 = CH_3
UAF, R^1 = 4-OCH_3, R^2 = CH_3
UAG, R^1 = 4-F, R^2 = CH_3
UAH, R^1 = 5-OBn, R^2 = CH_3
UAI, R^1 = 5-OCH_3, R^2 = CH_3
UAJ, R^1 = 4,5-OCH_2O, R^2 = Et
UAK, R^1 = 4,5-OCH_2CH_2O, R^2 = Et
UAM, R^1 = 5-Ph, R^2 = CH_3
UAN, R^1 = 5-[4$(OCH_3)C_6H_4$], R^2 = CH_3

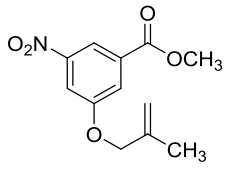
Over a suspension of the corresponding 3-hydroxybezoate **TA-TN** (1 mmol) and K_2CO_3 (2 mmol) in dry CH_3CN (1 mL), 3-chloro-2-methylprop-1-ene (1.2 mmol) was added under argon atmosphere. The mixture was stirred at room temperature for 30 minutes and NaI (0.033 mmol) was added. After that, the reaction was placed in an oil bath preheated to 80 ºC and it was stirred at that temperature for 3 h. Afterwards, additional 3-chloro-2-methylprop-1-ene (1.2 mmol) and CH_3CN (1 mL) were added and the reaction mixture was further stirred at 80 ºC for 19 h. After that time, It was diluted with AcOEt (10 mL) and H_2O (10 mL) and the phases were separated. The aqueous phase was extracted with AcOEt (2 × 15 mL), the combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*, affording the corresponding 3-((2-methylallyl)oxy)benzoates **UAA-UAN** without further purification or after purification by flash column chromatography (silica gel, petroleum ether/AcOEt).

*Ethyl 3-((2-methylallyl)oxy)benzoate (**UAA**)*[57]



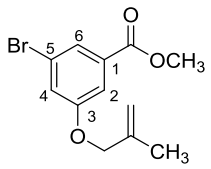
Prepared from commercially available ethyl 3-hydroxybenzoate **TA** (0.66 g, 4.0 mmol), K_2CO_3 (1.1 g, 8.0 mmol), 3-chloro-2-methylprop-1-ene (0.47 mL, 4.8 mmol) and NaI (19.9 mg, 0.13 mmol) in dry CH_3CN (4 mL). After work-up, **UAA** was obtained as an oil without further purification (0.72 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.39 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H_3}$), 1.84 (s, 3H, $C(C\underline{H_3})C=CH_2$), 4.37 (q, *J* = 7.2 Hz, $OC\underline{H_2}CH_3$), 4.48 (s, 2H, $OC\underline{H_2}C(CH_3)=CH_2$), 5.00 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 5.11 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 7.11 (dd, *J* = 7.9, 2.6 Hz, 1H, H_4), 7.33 (t, *J* = 7.9 Hz, 1H, H_5), 7.56-7.70 (m, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.3 ($OCH_2\underline{C}H_3$), 19.4 (CH_3), 61.0 ($O\underline{C}H_2CH_3$), 71.8 ($O\underline{C}H_2C(CH_3)=CH_2$), 112.9 ($C(CH_3)=\underline{C}H_2$), 115.1 ($C_2$), 119.8 ($C_4$), 122.0 ($C_6$), 129.3 ($C_5$), 131.7 ($C_1$), 140.5 ($\underline{C}(CH_3)=CH_2$), 158.7 ($C_3$), 166.4 (CO).

*Methyl 3-((2-methylallyl)oxy)-5-nitrobenzoate (**UAB**)*[48]



Prepared from methyl 3-hydroxy-5-nitrobenzoate **TB** (0.71 g, 3.6 mmol), K_2CO_3 (1.0 g, 7.2 mmol), 3-chloro-2-methylprop-1-ene (0.43 mL, 4.3 mmol) and NaI (17.9 mg, 0.12 mmol) in dry CH_3CN (3.6 mL). After work-up and purification by flash column chromatography (petroleum ether/AcOEt 19/1), **UAB** was obtained as a solid (0.70 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.86 (s, 3H, $C(C\underline{H_3})=CH_2$), 3.99 (s, 3H, OCH_3), 4.58 (s, 2H, $OC\underline{H_2}C(CH_3)=CH_2$), 5.07 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 5.15 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 7.91 (dd, *J* = 2.6, 1.4 Hz, 1H, H_4), 7.94 (t, *J* = 2.6 Hz, 1H, H_2), 8.45 (dd, *J* = 1.4, 2.6 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.3 ($C(\underline{C}H_3)=CH_2$), 52.8 (OCH_3), 72.7 ($O\underline{C}H_2C(CH_3)=CH_2$), 113.7 ($C(CH_3)=\underline{C}H_2$), 114.0 ($C_6$), 116.7 ($C_4$), 121.9 ($C_2$), 132.6 ($C_1$), 139.3 ($\underline{C}(CH_3)=CH_2$), 149.1 ($C_5$), 159.3 ($C_3$), 164.9 (CO).

*Methyl 3-bromo-5-((2-methylallyl)oxy)benzoate (**UAC**)*[49]

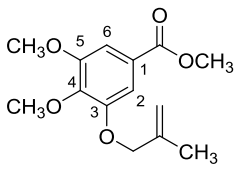


Prepared from methyl 3-bromo-5-hydroxybenzoate **TC** (0.71 g, 3.1 mmol), K_2CO_3 (0.85 g, 6.2 mmol), 3-chloro-2-methylprop-1-ene (0.36 mL, 3.7 mmol) and NaI (17.3 mg, 0.10 mmol) in dry CH_3CN (3.1 mL). After work-up, **UAC** was obtained as an oil without further purification (0.82 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.73 (s, 3H, $C(C\underline{H_3})=CH_2$), 3.82 (s, 3H, OCH_3), 4.36 (s, 2H, $OC\underline{H_2}C(CH_3)=CH_2$), 4.92 (br s, 1H, 1 ×

[57] Davis, T.A.; Hyster, T.K.; Rovis, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 14181

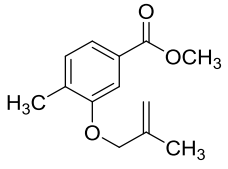
C(CH_3)=C$\underline{H_2}$), 5.00 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 7.16 (dd, *J* = 2.5, 1.8 Hz, 1H, H_2), 7.41 (t, *J* = 2.5, 1.3 Hz, H_4), 7.64-7.67 (m, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.3 (C($\underline{C}H_3$)=CH_2), 52.4 (OCH_3), 72.1 (O$\underline{C}H_2$C(CH_3)=CH_2), 113.3 (C(CH_3)=$\underline{C}H_2$), 114.4 (C_2), 122.6 (C_5), 122.8 (C_6), 125.0 (C_4), 132.7 (C_1), 139.9 ($\underline{C}$(CH_3)=CH_2), 159.3 (C_3), 165.6 (CO).

*Methyl 3,4-dimethoxy-5-((2-methylallyl)oxy)benzoate (**UAD**)*[48]



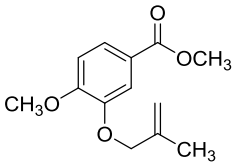
Prepared from commercially available methyl 3-hydroxy-4,5-dimethoxybenzoate **TD** (0.47 g, 2.2 mmol), K_2CO_3 (0.61 g, 4.4 mmol), 3-chloro-2-methylprop-1-ene (0.26 mL, 2.6 mmol) and NaI (10.9 mg, 0.07 mmol) in dry CH_3CN (2.2 mL). After work-up, **UAD** was obtained as a solid without further purification (0.54 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.85 (s, 3H, C($C\underline{H_3}$)=CH_2), 3.90 (s, 3H, O$C\underline{H_3}$), 3.90 (s, 3H, O$C\underline{H_3}$), 3.92 (s, 3H, O$C\underline{H_3}$), 4.52 (s, 2H, O$C\underline{H_2}$C(CH_3)=CH_2), 5.00 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.13 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 7.29 (s, 2H, H_6, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 52.2 (OCH_3), 56.2 (OCH_3), 60.9 (OCH_3), 72.7 (O$\underline{C}H_2$C(CH_3)=CH_2), 106.8 (C_6), 108.6 (C_2), 112.9 (C(CH_3)=$\underline{C}H_2$), 125.0 (C_1), 140.4 ($\underline{C}$(CH_3)=CH_2), 142.6 (C_4), 152.0, 153.1 (C_3, C_5), 166.7 (CO).

*Methyl 4-methyl-3-((2-methylallyl)oxy)benzoate (**UAE**)*[48]



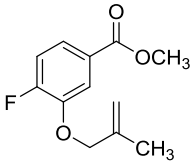
Prepared from methyl 3-hydroxy-4-methylbenzoate **TE** (0.66 g, 4.0 mmol), K_2CO_3 (1.1 g, 7.9 mmol), 3-chloro-2-methylprop-1-ene (0.47 mL, 4.8 mmol) and NaI (19.6 mg, 0.13 mmol) in dry CH_3CN (4 mL). After work-up, **UAE** was obtained as an oil without further purification (0.83 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.78 (s, 3H, C($C\underline{H_3}$)=CH_2), 2.23 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.41 (s, 2H, O$C\underline{H_2}$C(CH_3)=CH_2), 4.92 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.06 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 7.11 (d, *J* = 7.7 Hz, 1H, H_5), 7.39 (d, *J* = 1.4 Hz, H_2), 7.48 (dd, *J* = 7.7, 1.4 Hz, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.6 (CH_3), 19.5 (C($\underline{C}H_3$)=CH_2), 52.0 (OCH_3), 71.6 (O$\underline{C}H_2$C(CH_3)=CH_2), 111.7 (C_2), 112.4 (C(CH_3)=$\underline{C}H_2$), 122.0 (C_6), 128.8 (C_4), 130.5 (C_5), 132.8 (C_1), 140.7 ($\underline{C}$(CH_3)=CH_2), 156.6 (C_3), 167.2 (CO).

*Methyl 4-methoxy-3-((2-methylallyl)oxy)benzoate (**UAF**)*[48]



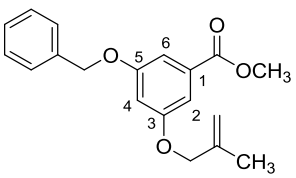
Prepared from methyl 3-hydroxy-4-methoxybenzoate **TF** (0.71 g, 3.9 mmol), K_2CO_3 (1.1 g, 7.7 mmol), 3-chloro-2-methylprop-1-ene (0.46 mL, 4.7 mmol) and NaI (19.2 mg, 0.13 mmol) in dry CH_3CN (3.9 mL). After work-up, **UAF** was obtained as an oil without further purification (0.87 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.86 (s, 3H, C(C$\underline{H_3}$)=CH_2), 3.89 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.57 (s, 2H, OC$\underline{H_2}$C(CH_3)=CH_2), 5.02 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.14 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.90 (d, *J* = 8.5 Hz, 1H, H_5), 7.56 (d, *J* = 2.0 Hz, H_2), 7.68 (dd, *J* = 8.5, 2.0 Hz, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 52.0 (OCH_3), 56.0 (OCH_3), 72.6 (O$\underline{C}H_2$C(CH_3)=CH_2), 110.6 (C_5), 113.1 (C(CH_3)=$\underline{C}H_2$), 114.2 (C_2), 122.5 (C_1), 123.8 (C_6), 140.3 ($\underline{C}$(CH_3)=CH_2), 147.7 (C_4), 153.5 (C_3), 166.9 (CO).

*Methyl 4-fluoro-3-((2-methylallyl)oxy)benzoate (**UAG**)*[48]



Prepared from methyl 4-fluoro-3-hydroxybenzoate **TG** (0.87 g, 4.3 mmol), K_2CO_3 (1.2 g, 8.7 mmol), 3-chloro-2-methylprop-1-ene (0.51 mL, 5.2 mmol) and NaI (21.5 mg, 0.14 mmol) in dry CH_3CN (4.3 mL). After work-up, **UAG** was obtained as an oil without further purification (0.87 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.84 (s, 3H, C(C$\underline{H_3}$)=CH_2), 3.88 (s, 3H, OCH_3), 4.53 (s, 2H, OC$\underline{H_2}$C(CH_3)=CH_2), 5.00 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.13 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 7.05-7.13 (m, 1H, H_5), 7.57-7.67 (m, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.2 (C($\underline{C}H_3$)=CH_2), 52.2 (OCH_3), 72.9 (O$\underline{C}H_2$C(CH_3)=CH_2), 113.5 (C(CH_3)=$\underline{C}H_2$), 116.0 (d, *J* = 19.3 Hz, C_5), 116.2 (d, *J* = 3.2 Hz, C_2), 123.2 (d, *J* = 8.0 Hz, C_6), 126.5 (d, *J* = 3.5 Hz, C_1), 139.9 ($\underline{C}$(CH_3)=CH_2), 146.6 (d, *J* = 11.0 Hz, C_3), 155.8 (d, *J* = 254.2 Hz, C_4), 166.1 (d, *J* = 1.1 Hz, CO).

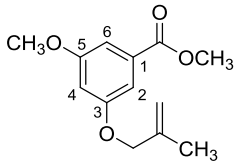
*Methyl 3-(benzyloxy)-5-((2-methylallyl)oxy)benzoate (**UAH**)*[48]



Prepared from methyl 3-(benzyloxy)-5-hydroxybenzoate **TH** (0.30 g, 1.2 mmol), K_2CO_3 (0.32 g, 2.3 mmol), 3-chloro-2-methylprop-1-ene (0.14 mL, 1.4 mmol) and NaI (5.8 mg, 0.04 mmol) in dry CH_3CN (1.2 mL). After work-up, **UAH** was obtained as an oil without further purification (0.35 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.85 (s, 3H, C(C$\underline{H_3}$)=CH_2), 3.93 (s, 3H, OCH_3), 4.47 (s, 2H, OC$\underline{H_2}$C(CH_3)=CH_2), 5.02 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.10 (s, 2H, OC$\underline{H_2}$Ph), 5.12 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.78 (t, *J* = 2.4 Hz, H_4), 7.22-7.49 (m, 7H, H_6, H_2,

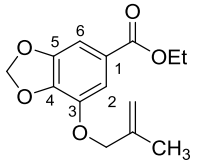
Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C(<u>C</u>H_3)=CH_2), 52.3 (OCH_3), 70.3 (O<u>C</u>H_2Ph), 72.0 (O<u>C</u>H_2C(CH_3)=CH_2), 107.2 (C_4), 108.1, 108.5 (C_6, C_2), 113.0 (C(CH_3)=<u>C</u>H_2), 127.6 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 132.0 (C_1), 136.5 ($C_{1'}$), 140.5 (<u>C</u>(CH_3)=CH_2), 159.7, 159.8 (C_3, C_5), 166.8 (CO).

*Methyl 3-methoxy-5-((2-methylallyl)oxy)benzoate (**UAI**)*[48]



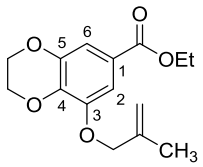
Prepared from methyl 3-hydroxy-5-methoxybenzoate **TI** (92.6 mg, 0.51 mmol), K_2CO_3 (0.14 g, 1.0 mmol), 3-chloro-2-methylprop-1-ene (59.7 µL, 0.61 mmol) and NaI (2.5 mg, 0.017 mmol) in dry CH_3CN (0.5 mL). After work-up, **UAI** was obtained as an oil without further purification (0.11 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.84 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 3.82 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.45 (s, 2H, OC<u>H</u>$_2$C(CH_3)=CH_2), 5.00 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 5.11 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 6.68 (t, *J* = 2.4 Hz, H_4), 7.16-7.24 (m, 2H, H_6, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C(<u>C</u>H_3)=CH_2), 52.2 (OCH_3), 55.5 (OCH_3), 71.9 (O<u>C</u>H_2C(CH_3)=CH_2), 106.4 (C_4), 107.2 (C_6), 108.1 (C_2), 112.9 (C(CH_3)=<u>C</u>H_2), 132.0 (C_1), 140.5 (<u>C</u>(CH_3)=CH_2), 159.8, 160.6 (C_3, C_5), 166.8 (CO).

*Ethyl 7-((2-methylallyl)oxy)benzo[d][1,3]dioxole-5-carboxylate (**UAJ**)*



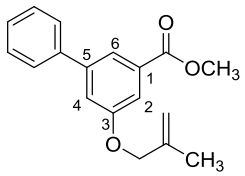
Prepared from ethyl 7-hydroxybenzo[*d*][1,3]dioxole-5-carboxylate **TJ** (0.41 g, 2.0 mmol), K_2CO_3 (0.54 g, 3.9 mmol), 3-chloro-2-methylprop-1-ene (0.23 mL, 2.4 mmol) and NaI (9.7 mg, 0.06 mmol) in dry CH_3CN (2.0 mL). After work-up, **UAJ** was obtained as an oil without further purification (0.52 g, quant.): IR (ATR): ν (cm^{-1}) = 1713 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.38 (t, *J* = 7.1 Hz, 3H, OCH_2C<u>H</u>$_3$), 1.85 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 4.34 (q, *J* = 7.1 Hz, 2H, OC<u>H</u>$_2$$CH_3$), 4.58 (s, 2H, OC<u>H</u>$_2$C(CH_3)=CH_2), 5.01 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 5.12 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 6.05 (s, 2H, OCH_2O), 7.20 (d, *J* = 1.5 Hz, 1H, H_6), 7.34 (d, *J* = 1.5 Hz, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.3 (OCH_2<u>C</u>H_3), 19.4 (C(<u>C</u>H_3)=CH_2), 61.0 (O<u>C</u>$H_2$$CH_3$), 73.2 (O<u>C</u>$H_2$C($CH_3$)=$CH_2$), 102.2 ($OCH_2O$), 103.8 ($C_6$), 112.0 ($C_2$), 113.4 (C($CH_3$)=<u>C</u>$H_2$), 124.7 ($C_1$), 139.7 (<u>C</u>($CH_3$)=$CH_2$), 140.3 ($C_4$), 142.2 ($C_5$), 148.8 ($C_3$), 165.9 (CO); MS (ESI): *m/z* (%): 266.1 (MH^+ + 1, 4), 265.1 (MH^+, 27), 264.1 (4), 219.1 (33), 193.1 (21), 191.1 (8), 165.1 (6), 163.1 (9), 151.1 (7); HRMS (ESI): *m/z* calcd. for $C_{14}H_{17}O_5$: 265.1076 [MH^+]; found: 265.1068.

*Ethyl 8-((2-methylallyl)oxy)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylate (**UAK**)*



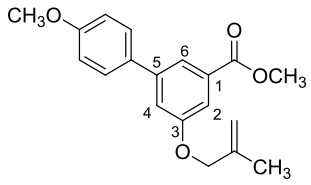
Prepared from ethyl 8-hydroxy-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate **TK** (0.45 g, 2.2 mmol), K_2CO_3 (0.60 g, 4.3 mmol), 3-chloro-2-methylprop-1-ene (0.25 mL, 2.6 mmol) and NaI (10.7 mg, 0.07 mmol) in dry CH_3CN (2.2 mL). After work-up, **UAK** was obtained as a solid without further purification (0.53 g, 88%): mp (CH_2Cl_2) 82-84 ºC; IR (ATR): ν (cm^{-1}) = 1706 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.28 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 1.76 (s, 3H, $C(C\underline{H_3})=CH_2$), 4.09-4.35 (m, 6H, $OC\underline{H_2}C\underline{H_2}O$, $OC\underline{H_2}CH_3$), 4.45 (s, 2H, $OC\underline{H_2}C(CH_3)=CH_2$), 4.92 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 5.04 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 7.12 (d, *J* = 1.9 Hz, 1H, H_6), 7.17 (d, *J* = 1.9 Hz, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.3 ($OCH_2\underline{C}H_3$), 19.4 ($C(\underline{C}H_3)=CH_2$), 60.8 ($O\underline{C}H_2CH_3$), 64.0 ($O\underline{C}H_2CH_2O$), 64.7 ($OCH_2\underline{C}H_2O$), 72.8 ($O\underline{C}H_2C(CH_3)=CH_2$), 107.2 ($C_2$), 112.2 ($C_6$), 113.2 ($C(CH_3)=\underline{C}H_2$), 122.3 ($C_1$), 137.8 ($C_4$), 140.3 ($\underline{C}(CH_3)=CH_2$), 143.6 ($C_5$), 147.7 ($C_3$), 166.1 (CO); MS (ESI): *m/z* (%): 302.1 (MNa^+ + 1, 12), 301.1 (MNa^+, 100), 279.1 (MH^+, 18), 233.1 (8), 207.1 (11), 165.1 (3); HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}O_5$: 279.1232 [MH^+]; found: 279.1225.

*Methyl 5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxylate (**UAM**)*



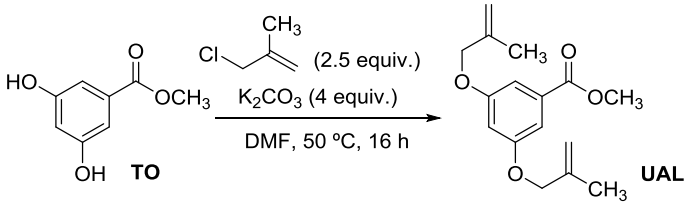
Prepared from methyl 5-hydroxy-[1,1´-biphenyl]-3-carboxylate **TM** (0.38 g, 1.7 mmol), K_2CO_3 (0.46 g, 3.3 mmol), 3-chloro-2-methylprop-1-ene (0.19 mL, 2.0 mmol) and NaI (8.2 mg, 0.05 mmol) in dry CH_3CN (1.7 mL). After work-up, **UAM** was obtained as an oil without further purification (0.44 g, 94%): IR (ATR): ν (cm^{-1}) = 1720 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.89 (s, 3H, $C(C\underline{H_3})=CH_2$), 3.97 (s, 3H, OCH_3), 4.56 (s, 2H, $OC\underline{H_2}C(CH_3)=CH_2$), 5.06 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 5.18 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 7.35-7.52 (m, 4H, H_4, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.57-7.69 (m, 3H, H_2, $H_{2'}$, $H_{6'}$), 7.92 (t, *J* = 1.5 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 ($C(\underline{C}H_3)=CH_2$), 52.3 (OCH_3), 72.1 ($O\underline{C}H_2C(CH_3)=CH_2$), 113.1 ($C(CH_3)=\underline{C}H_2$), 113.8 ($C_2$), 118.9 ($C_4$), 121.1 ($C_6$), 127.2 ($C_{2'}$, $C_{6'}$), 127.9 ($C_{4'}$), 128.9 ($C_{3'}$, $C_{5'}$), 131.8 (C_1), 140.0 (C_5), 140.5 ($\underline{C}(CH_3)=CH_2$), 142.8 ($C_{1'}$), 159.1 (C_3), 166.9 (CO); MS (ESI): *m/z* (%): 305.1 (MNa^+, 13), 284.1 (MH^+ + 1, 9), 283.1 (MH^+, 64), 282.1 (33), 252.1 (18), 251.1 (100); HRMS (ESI): *m/z* calcd. for $C_{18}H_{19}O_3$: 283.1334 [MH^+]; found: 283.1321.

*Methyl 4´-methoxy-5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxylate (**UAN**)*



Prepared from methyl 5-hydroxy-4´-methoxy-[1,1´-biphenyl]-3-carboxylate **TN** (0.73 g, 2.8 mmol), K_2CO_3 (0.78 g, 5.7 mmol), 3-chloro-2-methylprop-1-ene (0.33 mL, 3.4 mmol) and NaI (14.0 mg, 0.093 mmol) in dry CH_3CN (2.8 mL). After work-up, **UAN** was obtained as an oil without further purification (0.83 g, 93%): IR (ATR): ν (cm^{-1}) = 1718 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.89 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 3.86 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.54 (s, 2H, OC<u>H</u>$_2$C(CH_3)=CH_2), 5.05 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 5.17 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 7.00 (d, *J* = 8.4 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.34 (s, 1H, H_4), 7.52-7.66 (m, 3H, H_2, $H_{2'}$, $H_{6'}$), 7.88 (s, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.5 (C(<u>C</u>H_3)=CH_2), 52.2 (OCH_3), 55.3 (OCH_3), 72.0 (O<u>C</u>H_2C(CH_3)=CH_2), 113.0 (C(CH_3)=<u>C</u>H_2), 113.1 (C_2), 114.3 ($C_{3'}$, $C_{5'}$), 118.4 (C_4), 120.6 (C_6), 128.2 ($C_{2'}$, $C_{6'}$), 131.7 (C_1), 132.5 (C_5), 140.6 (<u>C</u>(CH_3)=CH_2), 142.4 ($C_{1'}$), 159.1, 159.6 (C_3, $C_{4'}$), 167.0 (CO); MS (ESI): *m/z* (%): 336.1 (MNa^+ + 1, 18), 335.1 (MNa^+, 100), 332.1 (15), 314.1 (MH^+ + 1, 6), 313.1 (MH^+, 40), 312.1 (43), 282.1 (6), 281.1 (39), 196.6 (4); HRMS (ESI): *m/z* calcd. for $C_{19}H_{20}O_4Na$: 335.1259 [MNa^+]; found: 335.1255.

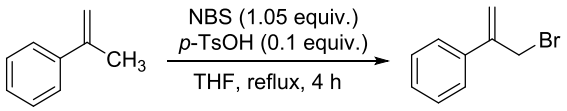
5.10. Dialkylation of methyl 3,5-dihydroxybenzoate (TO). Synthesis of methyl 3,5-bis((2-methylallyl)oxy)benzoate (UAL)[48]



Over a suspension of methyl 3,5-dihydroxybenzoate **TO** (1.0 g, 5.9 mmol) and K_2CO_3 (3.3 g, 23.8 mmol) in dry DMF (15 mL), 3-chloro-2-methylprop-1-ene (1.5 mL, 14.9 mmol) was added under argon atmosphere. The reaction mixture was stirred at 50 ºC for 16 h and afterwards, water (10 mL) and AcOEt (20 mL) were added. After the first extraction, phases were separated and the organic phase was washed with H_2O (3 × 10 mL) and with brine (15 mL). The organic extract was dried (Na_2SO_4) and volatiles were evaporated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 18/1), **UAL** was obtained as an oil (1.4 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.84 (s, 6H, 2 × C(C<u>H</u>$_3$)=CH_2), 3.91 (s, 3H, OCH_3), 4.46 (s, 4H, 2 × OC<u>H</u>$_2$C(CH_3)=CH_2), 5.01 (br s, 2H,

C(CH_3)=C$\underline{H_2}$), 5.11 (br s, 2H, C(CH_3)=C$\underline{H_2}$), 6.72 (t, *J* = 2.3 Hz, 1H, H_4), 7.21 (d, *J* = 2.3 Hz, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (2 × C($\underline{C}H_3$)=CH_2), 52.2 (OCH_3), 72.0 (2 × O$\underline{C}H_2$C(CH_3)=CH_2), 107.1 (C_4), 108.2 (C_2, C_6), 113.0 (2 × C(CH_3)=$\underline{C}H_2$), 131.9 (C_1), 140.5 (2 × $\underline{C}$(CH_3)=CH_2), 159.7 (C_3, C_5), 166.8 (CO).

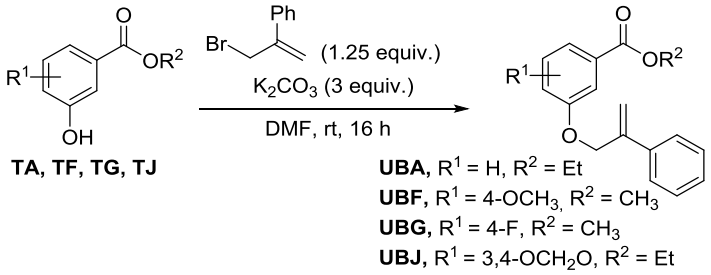
5.11. Synthesis of (3-bromoprop-1-en-2-yl)benzene[58]



Over a solution of α-methylstyrene (0.7 mL, 5.4 mmol) in dry THF (16.2 mL), *p*-TsOH (0.10 g, 0.54 mmol) and NBS (1.0 g, 5.7 mmol) were subsequently added under argon atmosphere. The mixture was then heated at reflux for 4 h and it was allowed to cool down to room temperature. The reaction mixture was diluted with petroleum ether (80 mL) and washed with H_2O (3 × 40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. That way, crude (3-bromoprop-1-en-2-yl)benzene was obtained as an oil and it was used in the next step without further purification (0.99 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.40 (s, 2H, CH_2Br), 5.50 (br s, 1H, 1 × C(Ph)=C$\underline{H_2}$), 5.57 (br s, 1H, 1 × C(Ph)=C$\underline{H_2}$), 7.31-7.57 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 34.3 (CH_2Br), 117.3 (C(Ph)=$\underline{C}H_2$), 126.2 (C_2, C_6), 128.2 (C_4), 128.7 (C_3, C_5), 137.7 (C_1), 144.4 ($\underline{C}$(Ph)=CH_2).

[58] Tripathi, C.B.; Mukherjee, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 8450.

5.12. General procedure for the alkylation of 3-hydroxybenzoates TA, TF, TG and TJ. Synthesis of 3-((2-phenylallyl)oxy)benzoates UBA-UBJ

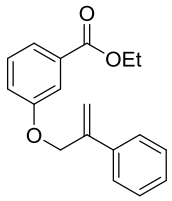


TA, TF, TG, TJ

UBA, R^1 = H, R^2 = Et
UBF, R^1 = 4-OCH_3, R^2 = CH_3
UBG, R^1 = 4-F, R^2 = CH_3
UBJ, R^1 = 3,4-OCH_2O, R^2 = Et

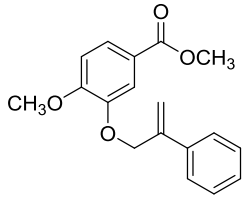
Over a solution of the corresponding 3-hydroxybenzoate **TA-TJ** (1 mmol) in dry DMF (15 mL), K_2CO_3 (3 mmol) was added under argon atmosphere. Afterwards, a solution of (3-bromoprop-1-en-2-yl)benzene (1.25 mmol) in dry DMF (5 mL) was added *via cannula*. The reaction mixture was stirred at room temperature for 16 h and H_2O (15 mL) was added. The mixture was extracted with AcOEt (20 mL) and the organic extract was washed with H_2O (3 × 15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt), the corresponding 3-((2-phenylallyl)oxy)benzoates **UBA-UBJ** were obtained.

*Ethyl 3-((2-phenylallyl)oxy)benzoate (**UBA**)*



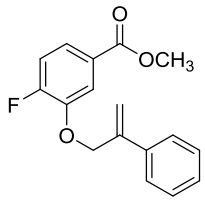
Prepared from commercially available ethyl 3-hydroxybenzoate **TA** (0.56 g, 3.4 mmol), K_2CO_3 (1.4 g, 10.1 mmol) and (3-bromoprop-1-en-2-yl)benzene (0.83 g, 4.2 mmol). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 18/1), **UBA** was obtained as an oil (0.75 g, 79%): IR (ATR): ν (cm^{-1}) = 1712 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.42 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 4.40 (q, *J* = 7.1 Hz, $OC\underline{H_2}CH_3$), 4.97 (s, 2H, $OC\underline{H_2}C(Ph)=CH_2$), 5.51 (br s, 1H, 1 × $C(Ph)=C\underline{H_2}$), 5.66 (br s, 1H, 1 × $C(Ph)=C\underline{H_2}$), 7.14-7.20 (m, 1H, H_4), 7.31-7.45 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{5'}$, H_5) 7.48-7.55 (m, 2H, $H_{2'}$, $H_{6'}$), 7.66-7.74 (m, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.4 ($OCH_2\underline{C}H_3$), 61.1 ($O\underline{C}H_2CH_3$), 70.0 ($O\underline{C}H_2C(Ph)=CH_2$), 115.2 ($C(Ph)=\underline{C}H_2$), 115.3 ($C_2$), 120.1 ($C_4$), 122.3 ($C_6$), 126.1 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 129.4 (C_5), 131.9 (C_1), 138.3 ($C_{1'}$), 142.8 ($\underline{C}(Ph)=CH_2$), 158.6 (C_3), 166.5 (CO); MS (ESI): *m/z* (%): 305.1 (MNa^+, 9), 284.1 (MH^+ + 1, 16), 283.1 (MH^+, 100), 255.1 (27), 237.1 (33), 211.1 (14), 205.1 (37), 177.1 (22), 161.1 (11), 117.1 (10); HRMS (ESI): *m/z* calcd. for $C_{18}H_{19}O_3$: 283.1334 [MH^+]; found: 283.1327.

*Methyl 4-methoxy-3-((2-phenylallyl)oxy)benzoate (**UBF**)*



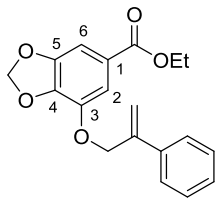
Prepared from methyl 3-hydroxy-4-methoxybenzoate **TF** (0.32 g, 1.8 mmol), K_2CO_3 (0.73 g, 5.3 mmol) and (3-bromoprop-1-en-2-yl)benzene (0.44 g, 2.2 mmol). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **UBF** was obtained as a solid (0.41 g, 77%): mp (CH_2Cl_2) 66-67 ºC; IR (ATR): ν (cm^{-1}) = 1708 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.02 (s, 2H, $OCH_2C(Ph)=CH_2$), 5.53 (br s, 1H, 1 × $C(Ph)=CH_2$), 5.63 (br s, 1H, 1 × $C(Ph)=CH_2$), 6.92 (d, *J* = 8.5 Hz, 1H, H_5), 7.30-7.43 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.49-7.55 (m, 2H, $H_{2'}$, $H_{6'}$), 7.64 (d, *J* = 2.0 Hz, H_2), 7.72 (dd, *J* = 8.4, 2.0 Hz, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.0 (OCH_3), 56.0 (OCH_3), 70.9 ($OCH_2C(Ph)=CH_2$), 110.8 (C_5), 114.8 ($C(Ph)=CH_2$), 114.9 (C_2), 122.6 (C_1), 124.2 (C_6), 126.2 ($C_{2'}$, $C_{6'}$), 128.0 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 138.4 ($C_{1'}$), 142.7 ($C(Ph)=CH_2$), 147.6 (C_4), 153.8 (C_3), 166.8 (CO).

*Methyl 4-fluoro-3-((2-phenylallyl)oxy)benzoate (**UBG**)*



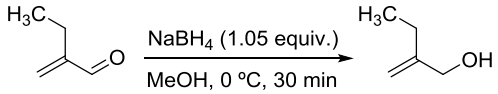
Prepared from methyl 4-fluoro-3-hydroxybenzoate **TG** (0.59 g, 3.5 mmol), K_2CO_3 (1.4 g, 10.4 mmol) and (3-bromoprop-1-en-2-yl)benzene (0.86 g, 4.3 mmol). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 18/1), **UBG** was obtained as an oil (0.74 g, 74%): IR (ATR): ν (cm^{-1}) = 1717 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.93 (s, 3H, OCH_3), 5.03 (s, 2H, $OCH_2C(Ph)=CH_2$), 5.55 (br s, 1H, 1 × $C(Ph)=CH_2$), 5.66 (br s, 1H, 1 × $C(Ph)=CH_2$), 7.15 (dd, *J* = 10.6, 8.5 Hz, 1H, H_5), 7.31-7.44 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$) 7.48-7.55 (m, 2H, $H_{2'}$, $H_{6'}$), 7.69 (ddd, *J* = 8.5, 4.5, 2.0 Hz, 1H, H_6), 7.76 (dd, *J* = 8.5, 2.0 Hz, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 52.3 (OCH_3), 71.2 ($OCH_2C(Ph)=CH_2$), 115.4 ($C(Ph)=CH_2$), 116.2 (d, *J* = 19.3 Hz, C_5), 116.8 (d, *J* = 3.2 Hz, C_2), 123.6 (d, *J* = 8.0 Hz, C_6), 126.1 ($C_{2'}$, $C_{6'}$), 126.6 (d, *J* = 3.5 Hz, C_1), 128.2 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 138.1 ($C_{1'}$), 142.4 ($C(Ph)=CH_2$), 146.5 (d, *J* = 11.1 Hz, C_3), 156.0 (d, *J* = 254.7 Hz, C_4), 166.1 (CO); MS (ESI): *m/z* (%): 309.1 (MNa^+, 18), 288.1 (MH^+ + 1, 10), 287.1 (MH^+, 52), 255.1 (48), 209.1 (33), 205.1 (18), 163.1 (8), 150.1 (9), 149.1 (100), 117.1 (29); HRMS (ESI): *m/z* calcd. for $C_{17}H_{16}FO_3$: 287.1083 [MH^+]; found: 287.1077.

*Ethyl 7-((2-phenylallyl)oxy)benzo[d][1,3]dioxole-5-carboxylate (**UBJ**)*



Prepared from ethyl 7-hydroxybenzo[*d*][1,3]dioxole-5-carboxylate **TJ** (0.31 g, 1.5 mmol), K_2CO_3 (0.61 g, 4.4 mmol) and (3-bromoprop-1-en-2-yl)benzene (0.36 g, 1.8 mmol). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2), **UBJ** was obtained as a solid (0.43 g, 90%): mp (CH_2Cl_2) 40-43 ºC; IR (ATR): ν = 1704 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.39 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 4.36 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 5.06 (s, 2H, $OC\underline{H_2}C(Ph)=CH_2$), 5.52 (br s, 1H, 1 × $C(Ph)=C\underline{H_2}$), 5.64 (br s, 1H, 1 × $C(Ph)=C\underline{H_2}$), 6.01 (s, 2H, OCH_2O), 7.25 (d, *J* = 1.4 Hz, 1H, H_6), 7.27-7.42 (m, 4H, H_2, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.47-7.56 (m, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.4 ($OCH_2\underline{C}H_3$), 61.0 ($O\underline{C}H_2CH_3$), 71.3 ($O\underline{C}H_2C(Ph)=CH_2$), 102.2 ($OCH_2O$), 104.0 ($C_6$), 112.5 ($C_2$), 115.3 ($C(Ph)=\underline{C}H_2$), 124.7 ($C_1$), 126.1 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 138.2 ($C_{1'}$), 139.9 (C_4), 142.0 (C_5), 142.8 ($\underline{C}(Ph)=CH_2$), 149.0 (C_3), 165.8 (CO); MS (ESI): *m/z* (%): 350.1 (MNa^+ + 1, 14), 349.1 (MNa^+, 100), 328.1 (MH^+ + 1, 8), 327.1 (MH^+, 49), 282.1 (9), 281.1 (63), 255.1 (10), 250.1 (6), 249.1 (60), 221.0 (6), 177.1 (6); HRMS (ESI): *m/z* calcd. for $C_{19}H_{18}O_5Na$: 349.1052 [MNa^+]; found: 349.1049.

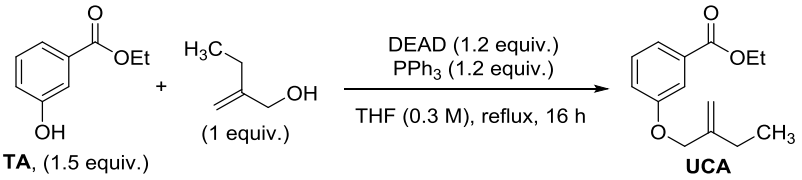
5.13. Synthesis of 2-methylenebutan-1-ol[59]



Over a solution of commercially available 2-methylenebutanal (2.0 mL, 20.4 mmol) in dry MeOH (10.2 mL), $NaBH_4$ (0.81 g, 21.4 mmol) was added portionwise at 0 ºC and under argon atmosphere. The reaction mixture was stirred at that same temperature for 30 minutes and afterwards, a saturated aqueous solution of NH_4Cl (10 mL) was added to quench the reaction. The mixture was diluted with water (20 mL) and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and carefully concentrated under reduced pressure. After purification by flash column chromatography (silica gel, pentane/Et_2O 6/4), 2-methylenebutan-1-ol was obtained as an oil (0.87 g, 49%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.04 (t, *J* = 7.1 Hz, 3H, CH_3), 2.05 (q, *J* = 7.1 Hz, 2H, $C\underline{H_2}CH_3$), 2.56 (br s, 1H, OH), 4.04 (s, 2H, OCH_2), 4.77-4.90 (m, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 4.93-5.04 (m, 1H, 1 × $C(CH_3)=C\underline{H_2}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 12.1 (CH_3), 25.6 ($\underline{C}H_2CH_3$), 65.6 (CH_2OH), 107.8 ($C(Et)=\underline{C}H_2$), 150.6 ($\underline{C}(Et)=CH_2$).

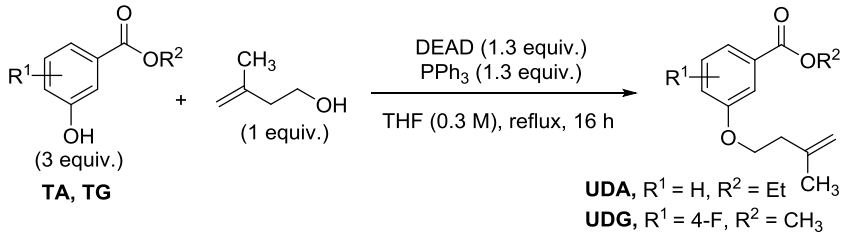
[59] Liu, X.; Zhang, W.; Wang, Y.; Zhang, Z.-X.; Jiao, L.; Liu, Q. *J. Am. Chem. Soc.* **2018**, *140*, 6873.

5.14. Mitsunobu reaction for the alkylation of ethyl 3-hydroxybenzoate (TA). Synthesis of ethyl 3-(2-methylenebutoxy)benzoate (UCA)



Over a solution of ethyl 3-hydroxybenzoate **TA** (1.8 g, 10.7 mmol), 2-methylenebutan-1-ol (0.62 g, 7.1 mmol) and PPh_3 (2.2 g, 8.6 mmol) in dry THF (23.8 mL), DIAD (1.7 mL, 8.6 mmol) was added under argon atmosphere. The mixture was stirred at reflux for 16 h and the volatiles were evaporated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 19/1), **UCA** was obtained as an oil (1.1 g, 63%): IR (ATR): ν (cm^{-1}) = 1718 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.12 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$), 1.40 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.18 (t, *J* = 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 4.38 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 4.52 (s, 2H, $OCH_2C(Et)=CH_2$), 5.02 (br s, 1H, 1 × C(Et)=C$\underline{H_2}$), 5.15 (br s, 1H, 1 × C(Et)=C$\underline{H_2}$), 7.12 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H, H_4), 7.33 (t, *J* = 7.9 Hz, 1H, H_5), 7.58-7.74 (m, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 12.0 ($CH_2\underline{C}H_3$), 14.3 ($OCH_2\underline{C}H_3$), 25.9 ($\underline{C}H_2CH_3$), 61.0 ($O\underline{C}H_2CH_3$), 71.0 ($O\underline{C}H_2C(Et)=CH_2$), 111.1 (C(Et)=$\underline{C}H_2$), 115.1 ($C_2$), 119.9 ($C_4$), 122.0 ($C_6$), 129.3 ($C_5$), 131.8 ($C_1$), 146.1 ($\underline{C}(Et)=CH_2$), 158.8 ($C_3$), 166.4 (CO); MS (ESI): *m/z* (%): 235.1 (MH^+, 6), 207.1 (3), 205.1 (4), 200.2 (2), 191.1 (1), 163.1 (3), 135.1 (1), 121.1 (2); HRMS (ESI): *m/z* calcd. for $C_{14}H_{19}O_3$: 235.1334 [MH^+]; found: 235.1335.

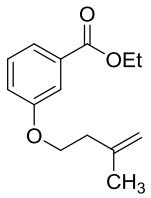
5.15. General procedure for the Mitsunobu reaction of 3-hydroxybenzoates TA and TG. Synthesis of 3-((3-methylbut-3-en-1-yl)oxy)benzoates UDA-UDG



Over a solution of the corresponding 3-hydroxybenzoate **TA** and **TG** (3 mmol), 3-methyl-3-buten-1-ol (1 mmol) and PPh_3 (1.3 mmol) in dry THF (3.3 mL), DEAD (40% wt. in toluene)

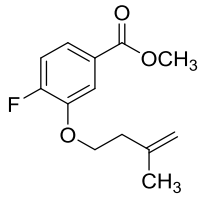
(1.3 mmol) was added under argon atmosphere. The solution was stirred at reflux for 16 h and afterwards, it was allowed to cool down to room temperature and volatiles were evaporated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt, 18/1), the corresponding 3-((3-methylbut-3-en-1-yl)oxy)benzoates **UDA-UDG** were obtained.

*Ethyl 3-((3-methylbut-3-en-1-yl)oxy)benzoate (**UDA**)*[57]



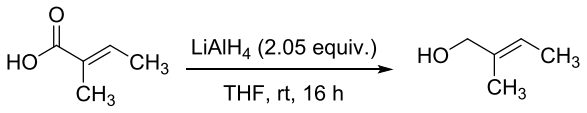
Prepared from commercially available ethyl 3-hydroxybenzoate **TA** (2.0 g, 11.9 mmol), 3-methyl-3-buten-1-ol (0.4 mL, 4.0 mmol), PPh_3 (1.4 mmol, 5.1 mmol) and DEAD (40% wt. in toluene) (2.2 g, 5.1 mmol) in dry THF (13.2 mL). After purification by flash column chromatography, **UDA** was obtained as an oil (0.82 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.39 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 1.81 (s, 3H, CH_3), 2.51 (t, *J* = 6.8 Hz, 2H, $C\underline{H_2}C(CH_3)=CH_2$), 4.11 (t, *J* = 6.8 Hz, 2H, $OC\underline{H_2}CH_2C(CH_3)=CH_2$), 4.37 (q, *J* = 7.1 Hz, $OC\underline{H_2}CH_3$), 4.82 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 4.86 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 7.09 (ddd, *J* = 7.9, 2.6, 1.5 Hz, 1H, H_4), 7.32 (t, *J* = 7.9 Hz, 1H, H_5), 7.58 (dd, *J* = 2.6, 1.5 Hz, 1H, H_2), 7.64 (dt, *J* = 7.9, 1.5 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 14.3 ($OCH_2\underline{C}H_3$), 22.8 (CH_3), 37.1 ($\underline{C}H_2C(CH_3)=CH_2$), 61.0 ($O\underline{C}H_2CH_3$), 66.6 ($O\underline{C}H_2CH_2C(CH_3)=CH_2$), 112.1 ($C(CH_3)=\underline{C}H_2$), 114.8 ($C_2$), 119.8 ($C_4$), 121.9 ($C_6$), 129.3 ($C_5$), 131.8 ($C_1$), 142.0 ($\underline{C}(CH_3)=CH_2$), 158.8 ($C_3$), 166.5 (CO).

*Ethyl 4-fluoro-3-((3-methylbut-3-en-1-yl)oxy)benzoate (**UDG**)*



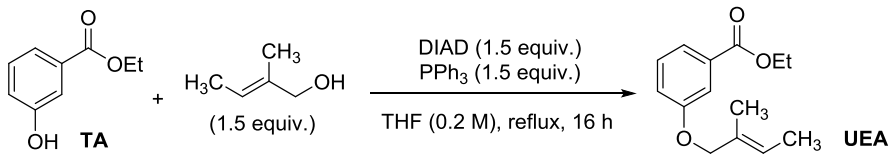
Prepared from methyl 4-fluoro-3-hydroxybenzoate **TG** (1.2 g, 7.1 mmol), 3-methyl-3-buten-1-ol (0.24 mL, 2.4 mmol), PPh_3 (0.80 mmol, 3.1 mmol) and DEAD (40% wt. in toluene) (1.3 g, 3.1 mmol) in dry THF (7.8 mL). After purification by flash column chromatography, **UDG** was obtained as an oil (0.41 g, 73%): IR (ATR): ν (cm^{-1}) = 1724 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.83 (s, 3H, CH_3), 2.56 (t, *J* = 6.9 Hz, 2H, $C\underline{H_2}C(CH_3)=CH_2$), 3.91 (s, 3H, OCH_3), 4.20 (t, *J* = 6.9 Hz, 2H, $OC\underline{H_2}CH_2C(CH_3)=CH_2$), 4.83 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 4.87 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 7.11 (dd, *J* = 10.7, 8.4 Hz, 1H, H_5), 7.60-7.79 (m, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.8 (CH_3), 37.0 ($\underline{C}H_2C(CH_3)=CH_2$), 52.2 ($OCH_3$), 68.0 ($O\underline{C}H_2CH_2C(CH_3)=CH_2$), 112.4 ($C(CH_3)=\underline{C}H_2$), 115.9 (d, *J* = 3.4 Hz, C_2), 116.0 (d, *J* = 19.2 Hz, C_5), 123.1 (d, *J* = 8.0 Hz, C_6), 126.5 (d, *J* = 3.2 Hz, C_1), 141.7 ($\underline{C}(CH_3)=CH_2$), 146.9 (d, *J* = 11.2 Hz, C_3), 155.8 (d, *J* = 254.1 Hz, C_4), 166.2 (CO).

5.16. Synthesis of *(E)*-2-methylbut-2-en-1-ol[60]



A solution of tiglic acid (1.5, 15.2 mmol) in dry THF (20 mL) was added dropwise *via cannula* to a suspension of $LiAlH_4$ (1.2 g, 31.2 mmol) in dry THF (40 mL) under argon atmosphere. The reaction mixture was stirred at room temperature for 16 h. Afterwards, the mixture was cooled down to 0 ºC, quenched with a saturated aqueous solution of NH_4Cl, filtered through Celite® and washed with AcOEt (30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. That way, *(E)*-2-methybut-2-en-1-ol was obtained as an oil and used in the next step without further purification (0.77 g, 59%); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.62 (d, *J* = 7.0 Hz, 3H, C(CH_3)=CHC$\underline{H_3}$), 1.64-1.67 (m, 4H, OH, C($C\underline{H_3}$)=C$\underline{H}$CH_3), 3.99 (s, 2H, C$\underline{H_2}$OH), 5.49 (qq, 1H, *J* = 7.0, 1.0 Hz, C(CH_3)=C$\underline{H}$CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 13.1 (C(CH_3)=C$\underline{H}$CH_3), 13.4 (C($\underline{C}H_3$)=CHCH_3), 69.1 ($\underline{C}H_2$OH), 120.7 (C(CH_3)=$\underline{C}$HCH_3), 135.5 ($\underline{C}$(CH_3)=CHCH_3).

5.17. Mitsunobu reaction for the alkylation of ethyl 3-hydroxybenzoate (TA). Synthesis of ethyl *(E)*-3-((2-methylbut-2-en-1-yl)oxy)benzoate (UEA)[57]

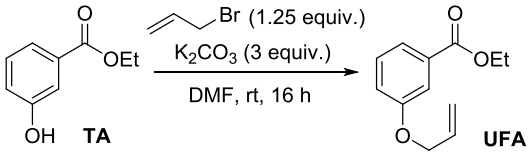


Over a solution of ethyl 3-hydroxybenzoate **TA** (0.73 g, 4.4 mmol), *(E)*-2-methylbut-2-en-1-ol (0.57 g, 6.6 mmol) and PPh_3 (1.7 g, 6.6 mmol) in dry THF (22.1 mL), DIAD (1.3 mL, 6.6 mmol) was added dropwise under argon atmosphere. The solution was stirred at reflux for 16 h and afterwards, it was allowed to cool down to room temperature and volatiles were evaporated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 20/1) ethyl *(E)*-3-((2-methylbut-2-en-1-yl)oxy)benzoate **UEA** was obtained as an oil (0.55 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.40 (t, *J* = 7.1 Hz, 3H, OCH_2C$\underline{H_3}$), 1.65-1.71 (m, 3H, C(CH_3)=CHC$\underline{H_3}$), 1.75 (s, 3H, C($C\underline{H_3}$)=CHCH_3), 4.38 (q, *J* = 7.1 Hz,

[60] Venning, A.R.O.; Kwiatkowski, M.R.; Roque Peña, J.E.; Lainhart, B.C.; Guruparan, A.A.; Alexanian, E.J. *J. Am. Chem. Soc.* **2017**, *139*, 11595.

2H, OC<u>H</u>$_2$CH$_3$), 4.43 (s, 2H, OC<u>H</u>$_2$C(CH$_3$)=CH$_2$), 5.60-5.76 (m, 1H, C(CH$_3$)=C<u>H</u>CH$_3$), 7.11 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H, H$_4$), 7.33 (t, *J* = 7.9 Hz, 1H, H$_5$), 7.56-7.59 (m, 2H, H$_2$, H$_6$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 13.2 (CH$_3$), 13.6 (CH$_3$), 14.3 (CH$_3$), 61.0 (O<u>C</u>H$_2$CH$_3$), 74.2 (O<u>C</u>H$_2$C(CH$_3$)=CH$_2$), 115.2 (C$_2$), 119.9 (C$_4$), 121.9 (C$_6$), 123.7 (C(CH$_3$)=<u>C</u>HCH$_3$), 129.2 (C$_5$), 130.4 (C$_1$), 131.7 (<u>C</u>(CH$_3$)=CHCH$_3$), 158.9 (C$_3$), 166.5 (CO).

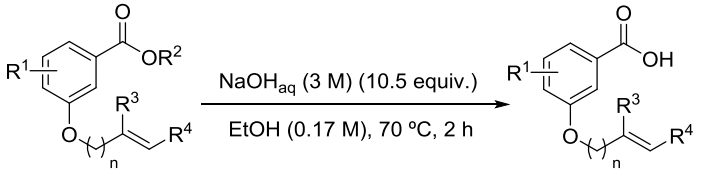
5.18. Alkylation of ethyl 3-hydroxybenzoate (TA). Synthesis of ethyl 3-(allyloxy)benzoate (UFA)[61]



Over a solution commercially available ethyl 3-hydroxybenzoate **TA** (0.5 g, 3.0 mmol) in dry DMF (10 mL), K$_2$CO$_3$ (1.2 g, 9.0 mmol) and allyl bromide (0.33 mL, 3.8 mmol) were successively added under argon atmosphere. The reaction mixture was stirred at room temperature for 16 h and afterwards, water was added. The mixture was extracted with AcOEt (20 mL) and the organic phase was washed with H$_2$O (5 × 15 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated *in vacuo*. After drying the obtained residue under high vacuum, **UFA** was obtained as an oil without further purification (0.52 g, 83%): ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 1.39 (t, *J* = 7.1 Hz, 3H, OCH$_2$C<u>H</u>$_3$), 4.38 (q, *J* = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 4.58 (dt, *J* = 5.3, 1.5 Hz, 2H, OC<u>H</u>$_2$CH=CH$_2$), 5.30 (dq, *J* = 10.5, 1.5 Hz, 1H, 1 × CH=C<u>H</u>$_2$), 5.44 (dq, *J* = 17.3, 1.5 Hz, 1H, 1 × CH=C<u>H</u>$_2$), 6.06 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 1H, C<u>H</u>=CH$_2$), 7.11 (ddd, *J* = 7.9, 2.7, 1.5 Hz, 1H, H$_4$), 7.33 (t, *J* = 7.9 Hz, 1H, H$_5$), 7.59 (dd, *J* = 2.7, 1.5 Hz, 1H, H$_2$), 7.65 (dd, *J* = 7.9, 1.5 Hz, 1H, H$_6$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 14.3 (OCH$_2$<u>C</u>H$_3$), 61.0 (O<u>C</u>H$_2$CH$_3$), 68.9 (O<u>C</u>H$_2$CH=CH$_2$), 115.0 (C$_2$), 117.8 (CH=<u>C</u>H$_2$), 119.9 (C$_4$), 122.1 (C$_6$), 129.3 (C$_5$), 131.8 (C$_1$), 132.9 (<u>C</u>H=CH$_2$), 158.5 (C$_3$), 166.4 (CO).

[61] Betschart, C.; Lerchner, A.; Machauer, R.; Rueeger, H.; Tintelnot-Blomley, M.; Veenstra, S.J. Preparation of macrocyclic lactones for treatment of β-amyloid related disease. WO 2006074950 A1, January 13, 2006.

5.19. General procedure for the hydrolysis of esters UAA-UFA. Synthesis of carboxylic acids VAA-VFA



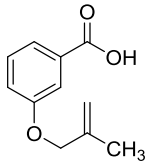
UAA-UFA

R^2 = CH_3, Et

VAA, R^1 = H, R^3 = CH_3, R^4 = H, n = 1
VAB, R^1 = 5-NO_2, R^3 = CH_3, R^4 = H, n = 1
VAC, R^1 = 5-Br, R^3= CH_3, R^4 = H, n = 1
VAD, R^1 = 4,5-$(OCH_3)_2$, R^3 = CH_3, R^4 = H, n = 1
VAE, R^1 = 4-CH_3, R^3 = CH_3, R^4 = H, n = 1
VAF, R^1 = 4-OCH_3, R^3 = CH_3, R^4 = H, n = 1
VAG, R^1 = 4-F, R^3 = CH_3, R^4 = H, n = 1
VAH, R^1 = 5-OBn, R^3 = CH_3, R^4 = H, n = 1
VAI, R^1 = 5-OCH_3, R^3 = CH_3, R^4 = H, n = 1
VAJ, R^1 = 4,5-OCH_2O, R^3 = CH_3, R^4 = H, n = 1
VAK, R^1 = 4,5-OCH_2CH_2O, R^3 = CH_3, R^4 = H, n = 1
VAL, R^1 = 5-$OCH_2C(CH_3)=CH_2$, R^3 = CH_3, R^4 = H, n = 1
VAM, R^1 = 5-Ph, R^3 = CH_3, R^4 = H, n = 1
VAN, R^1 = 5-[4$(OCH_3)C_6H_4$], R^3 = CH_3, R^4 = H, n = 1
VBA, R^1 = H, R^3 = Ph, R^4 = H, n = 1
VBF, R^1 = 4-OCH_3, R^3 = Ph, R^4 = H, n = 1
VBG, R^1 = 4-F, R^3 = Ph, R^4 = H, n = 1
VBJ, R^1 = 4,5-OCH_2O, R^3 = Ph, R^4 = H, n = 1
VCA, R^1 = H, R^3 = Et, R^4 = H, n = 1
VDA, R^1 = H, R^3 = CH_3, R^4 = H, n = 2
VDG, R^1 = 4-F, R^3 = CH_3, R^4 = H, n = 2
VEA, R^1 = H, R^3 = CH_3, R^4 = CH_3, n = 1
VFA, R^1 = H, R^3 = H, R^4 = H, n = 1

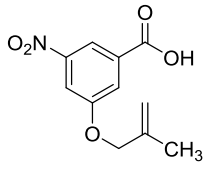
Over a solution of the corresponding ester **UAA-UFA** (1 mmol) in EtOH (5.9 mL), a 3 M aqueous solution of NaOH (10.5 mmol) was added and the mixture was stirred at 70 ºC for 2 h. Then, it was allowed to cool down to room temperature and a 1 M aqueous solution of HCl was added while stirring until a white solid precipitated (pH = 1-2). Afterwards, AcOEt (15 mL) was added to dissolve the formed precipitate and the phases were separated. The organic extract was washed with H_2O (2 × 15 mL) and brine (15 mL), and dried (Na_2SO_4). The volatiles were evaporated *in vacuo,* obtaining the corresponding carboxylic acids **VAA-VFA** without further purification.

*3-((2-Methylallyl)oxy)benzoic acid (**VAA**)[48,57]*



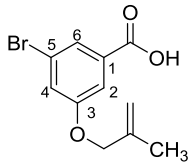
Prepared from ethyl 3-((2-methylallyl)oxy)benzoate **UAA** (0.62 g, 2.8 mmol) and a 3 M aqueous solution of NaOH (9.8 mL, 29.5 mmol) in EtOH (16.5 mL). After work up, **VAA** was obtained as a solid (0.50 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.85 (s, 3H, C($\underline{C}H_3$)=CH_2), 4.50 (s, 2H, O$\underline{C}H_2$C(CH_3)=CH_2), 5.02 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 5.13 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 7.19 (dd, *J* = 8.0, 2.8 Hz, 1H, H_4), 7.38 (dd, *J* = 8.0, 8.0 Hz, 1H, H_5), 7.62-7.68 (m, 1H, H_2), 7.73 (d, *J* = 8.0 Hz, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 71.9 (O$\underline{C}H_2$C(CH_3)=CH_2), 113.0 (C(CH_3)=$\underline{C}H_2$), 115.5 (C_2), 121.1 (C_4), 122.8 (C_6), 129.5 (C_5), 130.5 (C_1), 140.4 ($\underline{C}$(CH_3)=CH_2), 158.7 (C_3), 172.3 (CO).

*3-((2-methylallyl)oxy)-5-nitrobenzoic acid (**VAB**)[48]*



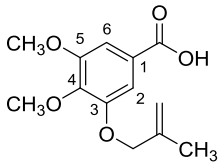
Prepared from methyl 3-((2-methylallyl)oxy)-5-nitrobenzoate **UAB** (0.60 g, 2.4 mmol) and a 3 M aqueous solution of NaOH (8.4 mL, 25.1 mmol) in EtOH (14.1 mL). After work up, **VAB** was obtained as a solid (0.48 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.88 (s, 3H, C($\underline{C}H_3$)=CH_2), 4.60 (s, 2H, O$\underline{C}H_2$C(CH_3)=CH_2), 5.09 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 5.17 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 7.94-7.98 (m, 1H, H_4), 7.97-8.02 (m, 1H, H_2), 8.51 (s, 1H, H_6), 11.69 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.3 (C($\underline{C}H_3$)=CH_2), 72.7 (O$\underline{C}H_2$C(CH_3)=CH_2), 114.1 (C(CH_3)=$\underline{C}H_2$), 114.6 (C_6), 117.2 (C_4), 122.3 (C_2), 131.6 (C_1), 139.2 ($\underline{C}$(CH_3)=CH_2), 149.2 (C_5), 159.4 (C_3), 170.2 (CO).

*3-Bromo-5-((2-methylallyl)oxy)benzoic acid (**VAC**)[49]*



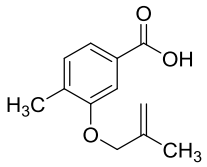
Prepared from methyl 3-bromo-5-((2-methylallyl)oxy)benzoate **UAC** (0.55 g, 1.9 mmol) and a 3 M aqueous solution of NaOH (6.7 mL, 20.2 mmol) in EtOH (11.3 mL). After work up, **VAC** was obtained as a solid (0.46 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.86 (s, 3H, C($\underline{C}H_3$)=CH_2), 4.50 (s, 2H, O$\underline{C}H_2$C(CH_3)=CH_2), 5.05 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 5.13 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 7.31-7.33 (m, 1H, H_2), 7.58 (t, *J* = 2.4, 1.5 Hz, H_4), 7.85 (t, *J* = 1.5 Hz, 1H, H_6), 10.80 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.3 (C($\underline{C}H_3$)=CH_2), 72.2 (O$\underline{C}H_2$C(CH_3)=CH_2), 113.5 (C(CH_3)=$\underline{C}H_2$), 114.9 (C_2), 122.8 (C_5), 123.9 (C_6), 125.6 (C_4), 131.7 (C_1), 139.8 ($\underline{C}$(CH_3)=CH_2), 159.4 (C_3), 171.0 (CO).

*3,4-Dimethoxy-5-((2-methylallyl)oxy)benzoic acid (**VAD**)[48]*



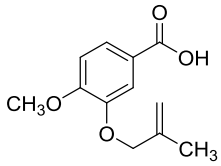
Prepared from methyl 3,4-dimehoxy-5-((2-methylallyl)oxy)benzoate **UAD** (0.45 g, 1.7 mmol) and a 3 M aqueous solution of NaOH (5.9 mL, 17.8 mmol) in EtOH (10.0 mL). After work up, **VAD** was obtained as a solid (0.41 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.86 (s, 3H, C($\underline{C}H_3$)=CH_2), 3.92 (s, 3H, O$\underline{C}H_3$), 3.96 (s, 3H, O$\underline{C}H_3$), 4.55 (s, 2H, O$\underline{C}H_2$C(CH_3)=CH_2), 5.02 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 5.14 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 7.38 (s, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 52.2 (OCH_3), 60.9 (OCH_3), 72.8 (O$\underline{C}H_2$C(CH_3)=CH_2), 107.4 (C_6), 109.3 (C_2), 113.0 (C(CH_3)=$\underline{C}H_2$), 124.1 (C_1), 140.3 ($\underline{C}$(CH_3)=CH_2), 143.5 (C_4), 152.0, 153.1 (C_3, C_5), 172.0 (CO).

*4-Methyl-3-((2-methylallyl)oxy)benzoic acid (**VAE**)[48]*



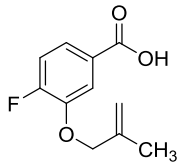
Prepared from methyl 4-methyl-3-((2-methylallyl)oxy)benzoate **UAE** (0.62 g, 2.8 mmol) and a 3 M aqueous solution of NaOH (9.8 mL, 29.4 mmol) in EtOH (16.5 mL). After work up, **VAE** was obtained as a solid (0.56 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.89 (s, 3H, C($\underline{C}H_3$)=CH_2), 2.35 (s, 3H, CH_3), 4.53 (s, 2H, O$\underline{C}H_2$C(CH_3)=CH_2), 5.04 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 5.17 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 7.16-7.30 (m, 1H, H_5), 7.55 (d, *J* = 1.4 Hz, H_2), 7.67 (dd, *J* = 7.7, 1.4 Hz, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.7 (CH_3), 19.5 (C($\underline{C}H_3$)=CH_2), 71.6 (O$\underline{C}H_2$C(CH_3)=CH_2), 112.1 (C_2), 112.5 (C(CH_3)=$\underline{C}H_2$), 122.8 (C_6), 127.9 (C_4), 130.6 (C_5), 133.9 (C_1), 140.6 ($\underline{C}$(CH_3)=CH_2), 156.7 (C_3), 172.2 (CO).

*4-Methoxy-3-((2-methylallyl)oxy)benzoic acid (**VAF**)[48]*



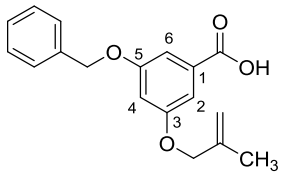
Prepared from methyl 4-methoxy-3-((2-methylallyl)oxy)benzoate **UAF** (0.78 g, 3.3 mmol) and a 3 M aqueous solution of NaOH (11.6 mL, 34.7 mmol) in EtOH (19.4 mL). After work up, **VAF** was obtained as a solid (0.67 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.87 (s, 3H, C($\underline{C}H_3$)=CH_2), 3.97 (s, 3H, OCH_3), 4.59 (s, 2H, O$\underline{C}H_2$C(CH_3)=CH_2), 5.04 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 5.15 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 6.94 (d, *J* = 8.5 Hz, 1H, H_5), 7.62 (d, *J* = 2.0 Hz, H_2), 7.79 (dd, *J* = 8.5, 2.0 Hz, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 56.1 (OCH_3), 72.6 (O$\underline{C}H_2$C(CH_3)=CH_2), 110.7 (C_5), 113.2 (C(CH_3)=$\underline{C}H_2$), 114.5 (C_2), 121.6 (C_1), 124.7 (C_6), 140.3 ($\underline{C}$(CH_3)=CH_2), 147.8 (C_4), 154.2 (C_3), 172.1 (CO)

*4-Fluoro-3-((2-methylallyl)oxy)benzoic acid (**VAG**)48*[48]



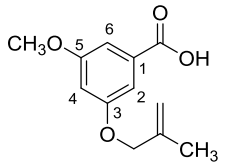
Prepared from methyl 4-fluoro-3-((2-methylallyl)oxy)benzoate **UAG** (0.69 g, 3.1 mmol) and a 3 M aqueous solution of NaOH (10.8 mL, 32.4 mmol) in EtOH (18.2 mL). After work up, **VAG** was obtained as a solid (0.59 g, 91%): ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ (ppm) = 1.86 (s, 3H, $C(C\underline{H_3})=CH_2$), 4.67 (s, 2H, $OC\underline{H_2}C(CH_3)=CH_2$), 5.03 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 5.16 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 7.28 (dd, *J* = 11.0, 8.4 Hz, 1H, H_5), 7.69 (ddd, *J* = 8.4, 4.5, 2.0 Hz, 1H, H_6), 7.75 (dd, *J* = 8.4, 2.0 Hz, 1H, H_2), 10.64 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $(CD_3)_2CO$): δ (ppm) = 18.5 ($C(\underline{C}H_3)=CH_2$), 72.4 ($O\underline{C}H_2C(CH_3)=CH_2$), 112.4 ($C(CH_3)=\underline{C}H_2$), 116.0 (d, *J* = 19.4 Hz, C_5), 116.3 (d, *J* = 3.1 Hz, C_2), 123.3 (d, *J* = 8.0 Hz, C_6), 127.2 (d, *J* = 3.1 Hz, C_1), 140.6 ($\underline{C}(CH_3)=CH_2$), 146.6 (d, *J* = 11.0 Hz, C_3), 155.5 (C_4, *J* = 251.8 Hz, C_4), 165.8 (CO).

*3-(Benzyloxy)-5-((2-methylallyl)oxy)benzoic acid (**VAH**)*[48]



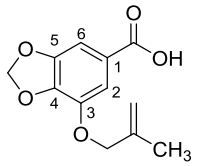
Prepared from methyl 3-(benzyloxy)-5-((2-methylallyl)-oxy)benzoate **UAH** (0.18 g, 0.57 mmol) and a 3 M aqueous solution of NaOH (2.0 mL, 6.0 mmol) in EtOH (3.4 mL). After work up, **VAH** was obtained as a solid (0.15 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.86 (s, 3H, $C(C\underline{H_3})=CH_2$), 4.49 (s, 2H, $OC\underline{H_2}C(CH_3)=CH_2$), 5.03 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 5.12 (s, 3H, $OC\underline{H_2}Ph$, 1 × $C(CH_3)=C\underline{H_2}$), 6.83 (t, *J* = 2.4 Hz, H_4), 7.27-7.55 (m, 7H, H_2, H_6, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (CH_3), 70.4 ($O\underline{C}H_2Ph$), 72.0 ($O\underline{C}H_2C(CH_3)=CH_2$), 108.2 ($C_4$), 108.6, 109.0 ($C_2$, C_6), 113.1 ($C(CH_3)=\underline{C}H_2$), 127.6 ($C_{2'}$, $C_{6'}$), 128.2 ($C_{4'}$), 128.7 ($C_{3'}$, $C_{5'}$), 131.0 (C_1), 136.5 ($C_{1'}$), 140.4 ($\underline{C}(CH_3)=CH_2$), 159.8, 159.9 (C_3, C_5), 171.5 (CO).

*3-Methoxy-5-((2-methylallyl)oxy)benzoic acid (**VAI**)*[48]



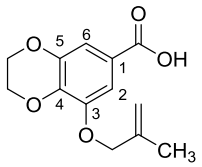
Prepared from methyl 3-methoxy-5-((2-methylallyl)oxy)benzoate **UAI** (0.34 g, 1.4 mmol) and a 3 M aqueous solution of NaOH (5.0 mL, 14.9 mmol) in EtOH (8.4 mL). After work up, **VAI** was obtained as a solid (0.29 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.76 (s, 3H, $C(C\underline{H_3})=CH_2$), 3.76 (s, 3H, OCH_3), 4.39 (s, 2H, $OC\underline{H_2}C(CH_3)=CH_2$), 4.93 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 5.03 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 6.65 (t, *J* = 2.3 Hz, H_4), 7.12-7.27 (m, 2H, H_2, H_6), 10.64 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 ($C(\underline{C}H_3)=CH_2$), 55.6 (OCH_3), 72.0 ($O\underline{C}H_2C(CH_3)=CH_2$), 107.4 ($C_4$), 107.8 ($C_6$), 108.6 ($C_2$), 113.1 ($C(CH_3)=\underline{C}H_2$), 131.1 ($C_1$), 140.4 ($\underline{C}(CH_3)=CH_2$), 159.8 ($C_3$), 160.7 ($C_5$), 172.0 (CO).

*7-((2-Methylallyl)oxy)benzo[d][1,3]dioxole-5-carboxylic acid (**VAJ**)*



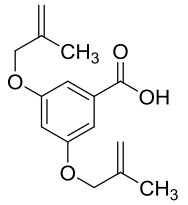
Prepared from ethyl 7-((2-methylallyl)oxy)benzo[*d*][1,3]dioxole-5-carboxylate **UAJ** (0.45 g, 1.7 mmol) and a 3 M aqueous solution of NaOH (6.0 mL, 17.9 mmol) in EtOH (10 mL). After work up, **VAJ** was obtained as a solid (0.37 g, 92%): mp (CH_2Cl_2) 136-138 ºC; IR (ATR): ν (cm^{-1}) = 2970 (O-H), 1687 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.86 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 4.60 (s, 2H, OC<u>H</u>$_2$C(CH_3)=CH_2), 5.03 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 5.14 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 6.09 (s, 2H, OCH_2O), 7.28 (d, *J* = 1.5 Hz, 1H, H_6), 7.41 (d, *J* = 1.5 Hz, H_2), 10.85 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.3 (C(<u>C</u>H_3)=CH_2), 73.2 (O<u>C</u>H_2C(CH_3)=CH_2), 102.4 (OCH_2O), 104.4 (C_6), 112.7 (C_2), 113.5 (C(CH_3)=<u>C</u>H_2), 123.3 (C_1), 140.2 (<u>C</u>(CH_3)=CH_2), 140.7 (C_4), 142.3 (C_5), 148.9 (C_3), 171.6 (CO); MS (ESI): *m/z* (%): 259.1 (MNa^+, 3), 238.1 (MH^+ + 1, 4), 237.1 (MH^+, 26), 219.1 (7), 193.1 (2); HRMS (ESI): *m/z* calcd. for $C_{12}H_{13}O_5$: 237.0763 [MH^+]; found: 237.0761.

*8-((2-Methylallyl)oxy)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid (**VAK**)[48]*



Prepared from ethyl 8-((2-methylallyl)oxy)-2,3-dihydrobenzo[*b*][1,4]-dioxine-6-carboxylate **UAK** (0.40 g, 1.4 mmol) and a 3 M aqueous solution of NaOH (5.1 mL, 15.2 mmol) in EtOH (8.5 mL). After work up, **VAK** was obtained as a solid (0.34 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.87 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 4.28-4.35 (m, 2H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 4.38-4.44 (m, 2H, OCH_2C<u>H</u>$_2$O), 4.57 (s, 2H, OC<u>H</u>$_2$C(CH_3)=CH_2), 5.04 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 5.15 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 7.28 (d, *J* = 2.1 Hz, 1H, H_6), 7.37 (d, *J* = 2.1 Hz, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C(<u>C</u>H_3)=CH_2), 64.0 (O<u>C</u>H_2CH_2O), 64.8 (OCH_2<u>C</u>H_2O), 72.9 (O<u>C</u>H_2C(CH_3)=CH_2), 107.7 (C_2), 113.1 (C_6), 113.3 (C(CH_3)=<u>C</u>H_2), 120.9 (C_1), 138.7 (C_4), 140.2 (<u>C</u>(CH_3)=CH_2), 143.7 (C_5), 147.8 (C_3), 171.3 (CO).

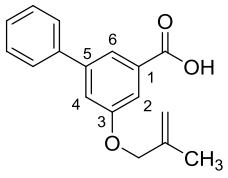
*3,5-Bis((2-methylallyl)oxy)benzoic acid (**VAL**)[48]*



Prepared from methyl 3,5-bis((2-methylallyl)oxy)benzoate **UAL** (0.92 g, 3.3 mmol) and a 3 M aqueous solution of NaOH (11.6 mL, 34.8 mmol) in EtOH (19.5 mL). After work up, **VAL** was obtained as a solid (0.78 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.86 (s, 6H, 2 × C(C<u>H</u>$_3$)=CH_2), 4.49 (s, 4H, 2 × OC<u>H</u>$_2$C(CH_3)=CH_2), 5.03 (br s, 2H, C(CH_3)=C<u>H</u>$_2$), 5.13 (br s, 2H, C(CH_3)=C<u>H</u>$_2$), 6.78 (t, *J* = 2.3 Hz, 1H, H_4), 7.30 (d, *J* = 2.3 Hz, 1H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (2 × C(<u>C</u>H_3)=CH_2), 72.0 (2 × O<u>C</u>H_2C(CH_3)=CH_2), 108.1

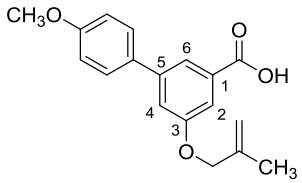
(C_4), 108.7 (C_2, C_6), 113.1 (2 × C(CH_3)=$\underline{C}H_2$), 131.0 (C_1), 140.4 (2 × $\underline{C}$(CH_3)=CH_2), 159.8 (C_3, C_5), 172.0 (CO).

*5-((2-Methylallyl)oxy)-[1,1´-biphenyl]-3-carboxylic acid (**VAM**)*



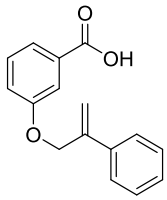
Prepared from methyl 5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxylate **UAM** (0.32 g, 1.1 mmol) and a 3 M aqueous solution of NaOH (4.0 mL, 12.0 mmol) in EtOH (6.7 mL). After work up V**AM** was obtained as a solid (0.29 g, 93%): mp (CH_2Cl_2) 176-179 ºC; IR (ATR): ν (cm^{-1}) = 2855 (O-H), 1687 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.79 (s, 3H, C($C\underline{H}_3$)=CH_2), 4.47 (s, 2H, O$C\underline{H}_2$C(CH_3)=CH_2), 4.96 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 5.07 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 7.24-7.43 (m, 4H, H_4, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.50-7.59 (m, 3H, H_2, $H_{2'}$, $H_{6'}$), 7.84-7.92 (m, 1H, H_6), 10.11 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 72.1 (O$\underline{C}H_2$C(CH_3)=CH_2), 113.2 (C(CH_3)=$\underline{C}H_2$), 114.2 (C_2), 119.8 (C_4), 121.7 (C_6), 127.2 ($C_{2'}$, $C_{6'}$), 128.0 ($C_{4'}$), 128.9 ($C_{3'}$, $C_{5'}$), 130.9 (C_1), 139.9 (C_5), 140.4 ($\underline{C}$(CH_3)=CH_2), 143.0 ($C_{1'}$), 159.2 (C_3), 172.1 (CO); MS (ESI): *m/z* (%): 291.1 (MNa^+, 30), 270.1 (MH^+ + 1, 3), 269.1 (MH^+, 12), 222.1 (9); HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}O_3$: 269.1178 [MH^+]; found: 269.1178.

*4´-Methoxy-5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxylic acid (**VAN**)*



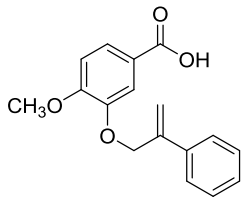
Prepared from methyl 4´-methoxy-5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxylate **UAN** (0.48 g, 1.5 mmol), and a 3 M aqueous solution of NaOH (5.4 mL, 16.2 mmol) in EtOH (9.1 mL). After work up, **VAN** was obtained as a solid (0.41 g, 90%): mp (CH_2Cl_2) 145-147 ºC; IR (ATR): ν (cm^{-1}) = 2889 (O-H), 1686 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.90 (s, 3H, C($C\underline{H}_3$)=CH_2), 3.89 (s, 3H, OCH_3), 4.57 (s, 2H, O$C\underline{H}_2$C(CH_3)=CH_2), 5.07 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 5.18 (br s, 1H, 1 × C(CH_3)=C$\underline{H}_2$), 6.96-7.09 (d, *J* = 8.4 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.36-7.46 (m, 1H, H_4), 7.54-7.65 (m, 3H, H_2, $H_{2'}$, $H_{6'}$), 7.93-8.00 (m, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.5 (C($\underline{C}H_3$)=CH_2), 55.4 (OCH_3), 72.1 (O$\underline{C}H_2$C(CH_3)=CH_2), 113.2 (C(CH_3)=$\underline{C}H_2$), 113.5 (C_2), 114.4 ($C_{3'}$, $C_{5'}$), 119.4 (C_4), 121.3 (C_6), 128.2 ($C_{2'}$, $C_{6'}$), 130.9 (C_1), 132.3 (C_5), 140.5 ($\underline{C}$(CH_3)=CH_2), 142.5 ($C_{1'}$), 159.2, 159.7 (C_3, $C_{4'}$), 172.2 (CO); MS (ESI): *m/z* (%): 322.1 (MNa^+ + 1, 4), 321.1 (MNa^+, 55), 301.1 (MH^+ + 2, 25), 300.1 (MH^+ + 1, 8), 299.1 (MH^+, 63), 298.1 (5), 255.1 (14), 149.0 (6); HRMS (ESI): *m/z* calcd. for $C_{18}H_{19}O_4$: 299.1283 [MH^+]; found: 299.1281.

*3-((2-Phenylallyl)oxy)benzoic acid (**VBA**)*



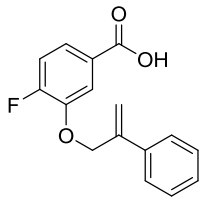
Prepared from ethyl 3-((2-phenylallyl)oxy)benzoate **UBA** (0.72 g, 2.5 mmol) and a 3 M aqueous solution of NaOH (8.9 mL, 26.7 mmol) in EtOH (14.9 mL). After work up, **VBA** was obtained as a solid (0.59 g, 92%): mp (CH_2Cl_2) 97-99 ºC; IR (ATR): ν (cm^{-1}) =2818 (O-H), 1676 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.00 (s, 2H, OC$\underline{H_2}$C(Ph)=CH_2), 5.54 (br s, 1H, 1 × C(Ph)=C$\underline{H_2}$), 5.68 (br s, 1H, 1 × C(Ph)=C$\underline{H_2}$), 7.22-7.30 (m, 1H, H_4), 7.32-7.48 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{5'}$, H_5) 7.50-7.58 (m, 2H, $H_{2'}$, $H_{6'}$), 7.71-7.85 (m, 2H, H_2, H_6), 11.39 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 70.1 (O$\underline{C}$H$_2$C(Ph)=CH_2), 115.2 (C(Ph)=$\underline{C}$H$_2$), 115.7 (C_2), 121.4 (C_4), 123.1 (C_6), 126.1 ($C_{2'}$, $C_{6'}$), 128.2 ($C_{4'}$), 128.6 ($C_{2'}$, $C_{6'}$), 129.6 (C_5), 130.7 (C_1), 138.2 ($C_{1'}$), 142.7 ($\underline{C}$(Ph)=CH_2), 158.7 (C_3), 172.3 (CO); MS (ESI): *m/z* (%): 254.1 ($M\text{-}H^-$ + 1, 13), 253.1 ($M\text{-}H^-$, 100), 210.1 (6), 209.1 (46), 207.1 (5), 136.0 (8), 92.0 (7); HRMS (ESI): *m/z* calcd. for $C_{16}H_{13}O_3$: 253.0865 [$M\text{-}H^-$]; found: 253.0871.

*4-Methoxy-3-((2-phenylallyl)oxy)benzoic acid (**VBF**)*



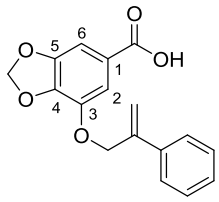
Prepared from methyl 4-methoxy-3-((2-phenylallyl)oxy)benzoate **UBF** (0.29 g, 0.97 mmol) and a 3 M aqueous solution of NaOH (3.4 mL, 1.0 mmol) in EtOH (5.7 mL). After work up, **VBF** was obtained as a solid (0.25 g, 90%): mp (CH_2Cl_2) 66-67 ºC; IR (ATR): ν (cm^{-1}) = 2939 (O-H), 1676 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.84 (s, 3H, OCH_3), 4.94 (s, 2H, OC$\underline{H_2}$C(Ph)=CH_2), 5.42 (br s, 1H, 1 × C(Ph)=C$\underline{H_2}$), 5.53 (br s, 1H, 1 × C(Ph)=C$\underline{H_2}$), 6.85 (d, *J* = 8.5 Hz, 1H, H_5), 7.20-7.33 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.38-7.48 (m, 2H, $H_{2'}$, $H_{6'}$), 7.59 (d, *J* = 1.8 Hz, 1H, H_2), 7.71 (dd, *J* = 8.4, 1.8 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 56.1 (OCH_3), 70.9 (O$\underline{C}$H$_2$C(Ph)=CH_2), 110.9 (C_5), 115.0 (C_2), 115.2 (C(Ph)=$\underline{C}$H$_2$), 121.6 (C_1), 125.1 (C_6), 126.2 ($C_{2'}$, $C_{6'}$), 128.0 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 138.4 ($C_{1'}$), 142.6 ($\underline{C}$(Ph)=CH_2), 147.7 (C_4), 154.5 (C_3), 171.8 (CO); MS (ESI): *m/z* (%): 308.1 (MNa^+ + 1, 14), 307.1 (MNa^+, 100), 286.1 (MH^+ + 1, 11), 285.1 (MH^+, 81), 268.1 (14), 267.1 (99), 255.1 (19), 237.1 (23), 207.1 (31), 151.0 (22), 117.1 (11); HRMS (ESI): *m/z* calcd. for $C_{17}H_{16}O_4Na$: 307.0946 [MNa^+]; found: 307.0946.

*4-Fluoro-3-((2-phenylallyl)oxy)benzoic acid (**VBG**)*



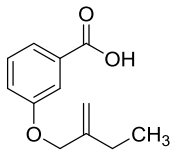
Prepared from methyl 4-fluoro-3-((2-phenylallyl)oxy)benzoate **UBG** (0.48 g, 1.7 mmol) and a 3 M aqueous solution of NaOH (5.9 mL, 17.7 mmol) in EtOH (9.9 mL). After work up, **VBG** was obtained as a solid (0.43 g, 93%): mp (CH_2Cl_2) 133-135 ºC; IR (ATR): ν (cm^{-1}) = 2941 (O-H), 1681 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.06 (s, 2H, OC<u>H$_2$</u>C(Ph)=CH$_2$), 5.55 (br s, 1H, 1 × C(Ph)=C<u>H$_2$</u>), 5.67 (br s, 1H, 1 × C(Ph)=C<u>H$_2$</u>), 7.19 (dd, *J* = 10.5, 8.4 Hz, 1H, H$_5$), 7.33-7.45 (m, 3H, H$_{3'}$, H$_{4'}$, H$_{5'}$) 7.49-7.56 (m, 2H, H$_{2'}$, H$_{6'}$), 7.74-7.85 (m, 2H, H$_2$, H$_6$), 9.39 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 71.2 (O<u>C</u>H$_2$C(Ph)=CH$_2$), 115.5 (C(Ph)=<u>C</u>H$_2$), 116.4 (d, *J* = 19.5 Hz, C$_5$), 117.3 (d, *J* = 3.3 Hz, C$_2$), 124.5 (d, *J* = 8.2 Hz, C$_6$), 125.6 (d, *J* = 3.2 Hz, C$_1$), 126.1 (C$_{2'}$, C$_{6'}$), 128.2 (C$_{4'}$), 128.6 (C$_{3'}$, C$_{5'}$), 138.0 (C$_{1'}$), 142.3 (<u>C</u>(Ph)=CH$_2$), 146.6 (d, *J* = 11.1 Hz, C$_3$), 156.6 (d, *J* = 256.1 Hz, C$_4$), 171.2 (CO).

*7-((2-Phenylallyl)oxy)benzo[d][1,3]dioxole-5-carboxylic acid (**VBJ**)*



Prepared from ethyl 7-((2-phenylallyl)oxy)benzo[*d*][1,3]dioxole-5-carboxylate **UBJ** (0.24 g, 0.7 mmol) and a 3 M aqueous solution of NaOH (2.6 mL, 7.8 mmol) in EtOH (4.4 mL). After work up, **VBJ** was obtained as a solid (0.21 g, 95%): mp (CH_2Cl_2) 169-172 ºC; IR (ATR): ν (cm^{-1}) = 2897 (O-H), 1680 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.07 (s, 2H, OC<u>H$_2$</u>C(Ph)=CH$_2$), 5.51 (br s, 1H, 1 × C(Ph)=C<u>H$_2$</u>), 5.64 (br s, 1H, 1 × C(Ph)=C<u>H$_2$</u>), 6.09 (s, 2H, OCH_2O), 7.27-7.30 (m, 3H, H$_6$, H$_2$, OH), 7.33-7.53 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 71.4 (O<u>C</u>H$_2$C(Ph)=CH$_2$), 102.4 (OCH_2O), 104.7 (C$_6$), 113.3 (C$_2$), 115.4 (C(Ph)=<u>C</u>H$_2$), 123.3 (C$_1$), 126.1 (C$_{2'}$, C$_{6'}$), 128.1 (C$_{4'}$), 128.5 (C$_{3'}$, C$_{5'}$), 138.1 (C$_{1'}$), 140.9 (C$_4$), 142.1 (C$_5$), 142.6 (<u>C</u>(Ph)=CH$_2$), 149.0 (C$_3$), 170.7 (CO); MS (ESI): *m/z* (%): 298.1 (M-H$^-$ + 1, 14), 297.1 (M-H$^-$, 100), 253.1 (19), 225.1 (6), 180.0 (6), 136.0 (6); HRMS (ESI): *m/z* calcd. for $C_{17}H_{13}O_5$: 297.0763 [M-H$^-$]; found: 297.0761.

*3-(2-Methylenebutoxy)benzoic acid (**VCA**)[62]*

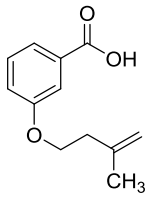


Prepared from ethyl 3-(2-methylenebutoxy)benzoate **UCA** (0.72 g, 3.1 mmol) and a 3 M aqueous solution of NaOH (10.7 mL, 32.2 mmol) in EtOH (18.0 mL). After work up, **VCA** was obtained as a solid (0.60 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.15 (t, *J* = 7.5 Hz, 3H, CH$_2$C<u>H$_3$</u>), 2.21 (q,

[62] Ye, B.; Donets, P.A.; Cramer, N. *Angew. Chem. Int. Ed*. **2014**, *53*, 507.

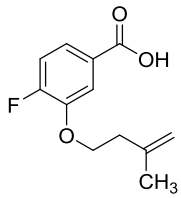
J = 7.5 Hz, 2H, C<u>H</u>$_2$CH$_3$), 4.56 (s, 2H, OC<u>H</u>$_2$C(Et)=CH$_2$), 5.05 (br s, 1H, 1 × C(Et)=C<u>H</u>$_2$), 5.18 (br s, 1H, 1 × C(Et)=C<u>H</u>$_2$), 7.21 (ddd, *J* = 7.9, 2.4, 1.0 Hz, 1H, H$_4$), 7.40 (t, *J* = 7.9 Hz, 1H, H$_5$), 7.67 (dd, *J* = 2.4, 1.1 Hz, 1H, H$_2$), 7.75 (dt, *J* = 7.9, 1.1 Hz, H$_6$), 11.74 (br s, 1H, CO$_2$H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 12.0 (CH$_2$<u>C</u>H$_3$), 25.9 (<u>C</u>H$_2$CH$_3$), 71.1 (O<u>C</u>H$_2$C(Et)=CH$_2$), 111.3 (C(Et)=<u>C</u>H$_2$), 115.5 (C$_2$), 121.1 (C$_4$), 122.8 (C$_6$), 129.5 (C$_5$), 130.5 (C$_1$), 146.0 (<u>C</u>(Et)=CH$_2$), 158.8 (C$_3$), 172.1 (CO).

*3-((3-Methylbut-3-en-1-yl)oxy)benzoic acid (**VDA**)[57]*



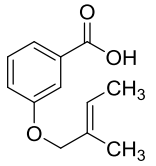
Prepared from ethyl 3-((3-methylbut-3-en-1-yl)oxy)benzoate **UDA** (0.66 g, 2.8 mmol) and a 3 M aqueous solution of NaOH (9.8 mL, 29.4 mmol) in EtOH (16.5 mL) at 80 ºC. After work up, **VDA** was obtained as a solid (0.53 g, 92%): ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 1.85 (s, 3H, C(C<u>H</u>$_3$)=CH$_2$), 2.56 (t, *J* = 6.8 Hz, 2H, C<u>H</u>$_2$C(CH$_3$)=CH$_2$), 4.17 (t, *J* = 6.8 Hz, 2H, OC<u>H</u>$_2$CH$_2$C(CH$_3$)=CH$_2$), 4.85 (br s, 1H, 1 × C(CH$_3$)=C<u>H</u>$_2$), 4,89 (br s, 1H, 1 × C(CH$_3$)=C<u>H</u>$_2$), 7.18 (dd, *J* = 8.2, 1.9 Hz,1H, H$_4$), 7.40 (t, *J* = 7.9 Hz, 1H, H$_5$), 7.66 (br s, 1H, H$_2$), 7.74 (d, *J* = 7.9 Hz, 1H, H$_6$), 11.27 (br s, 1H, CO$_2$H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 22.8 (C(<u>C</u>H$_3$)=CH$_2$), 37.1 (<u>C</u>H$_2$C(CH$_3$)=CH$_2$), 66.7 (O<u>C</u>H$_2$CH$_2$C(CH$_3$)=CH$_2$), 112.2 (C(CH$_3$)=<u>C</u>H$_2$), 115.1 (C$_2$), 121.0 (C$_4$), 122.7 (C$_6$), 129.5 (C$_5$), 130.5 (C$_1$), 142.0 (<u>C</u>(CH$_3$)=CH$_2$), 158.9 (C$_3$), 172.0 (CO).

*4-Fluoro-3-((3-methylbut-3-en-1-yl)oxy)benzoic acid (**VDG**)*



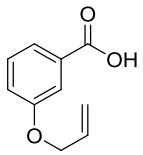
Prepared from methyl 4-fluoro-3-((3-methylbut-3-en-1-yl)oxy)benzoate **UDG** (0.21 g, 0.87 mmol) and a 3 M aqueous solution of NaOH (3.1 mL, 9.2 mmol) in EtOH (5.1 mL). After work up, **VDG** was obtained as a solid (0.15 g, 75%): mp (CH$_2$Cl$_2$) 128-130 ºC; IR (ATR): ν (cm^{-1}) = 2973 (O-H), 1681 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 1.86 (s, 3H, C(C<u>H</u>$_3$)=CH$_2$), 2.59 (t, *J* = 6.8 Hz, 2H, C<u>H</u>$_2$C(CH$_3$)=CH$_2$), 4.23 (t, *J* = 6.8 Hz, 2H, OC<u>H</u>$_2$CH$_2$C(CH$_3$)=CH$_2$), 4.85 (br s, 1H, 1 × C(CH$_3$)=C<u>H</u>$_2$), 4,90 (br s, 1H, 1 × C(CH$_3$)=C<u>H</u>$_2$), 7.12-7.21 (m, 1H, H$_5$), 7.70-7.78 (m, 2H, H$_2$, H$_6$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 22.8 (C(<u>C</u>H$_3$)=CH$_2$), 37.0 (<u>C</u>H$_2$C(CH$_3$)=CH$_2$), 68.1 (O<u>C</u>H$_2$CH$_2$C(CH$_3$)=CH$_2$), 112.5 (C(CH$_3$)=<u>C</u>H$_2$), 116.2 (d, *J* = 19.5 Hz, C$_5$), 116.3 (d, *J* = 3.5 Hz, C$_2$), 124.1 (d, *J* = 8.2 Hz, C$_6$), 125.6 (d, *J* = 3.3 Hz, C$_1$), 141.7 (<u>C</u>(CH$_3$)=CH$_2$), 147.1 (d, *J* = 11.2 Hz, C$_3$), 156.4 (d, *J* = 255.6 Hz, C$_4$), 171.1 (CO).

*(E)-3-((2-Methylbut-2-en-1-yl)oxy)benzoic acid (**VEA**)*[48,57]



Prepared from ethyl *(E)*-3-((2-methylbut-2-en-1-yl)oxy)benzoate **UEA** (0.31 g, 1.3 mmol) and a 3 M aqueous solution of NaOH (4.7 mL, 14.0 mmol) in EtOH (7.8 mL). After work up, **VEA** was obtained as a solid (0.27 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.71 (d, *J* = 6.6 Hz, 3H, $C(CH_3)=CHC\underline{H_3}$), 1.78 (s, 3H, $C(C\underline{H_3})=CHCH_3$), 4.47 (s, 2H, $OC\underline{H_2}C(CH_3)=CH_2$), 5.69 (q, *J* = 6.6 Hz, 1H, $C(CH_3)=C\underline{H}CH_3$), 7.14-7.25 (m, 1H, H_4), 7.39 (t, *J* = 7.9 Hz, 1H, H_5), 7.67 (br s, 1H, H_2) 7.74 (d, *J* = 7.9 Hz, 1H, H_6), 9.58 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 13.3 (CH_3), 13.6 (CH_3), 73.2 ($O\underline{C}H_2C(CH_3)=CH_2$), 115.6 ($C_2$), 121.2 ($C_4$), 122.6 ($C_6$), 123.9 ($C(CH_3)=\underline{C}HCH_3$), 129.5 ($C_5$), 130.5 ($C_1$), 131.3 ($\underline{C}(CH_3)=CHCH_3$), 159.0 ($C_3$), 172.1 (CO).

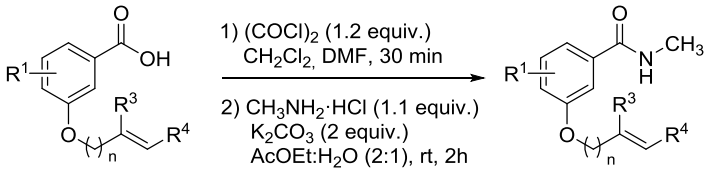
*3-(Allyloxy)benzoic acid (**VFA**)*[48,63]



Prepared from ethyl 3-(allyloxy)benzoate **UFA** (0.35 g, 1.7 mmol) and a 3 M aqueous solution of NaOH (5.9 mL, 1.8 mmol) in EtOH (9.9 mL). After work up, **VFA** was obtained as a solid (0.30 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.63 (d, *J* = 4.9 Hz, 2H, $OC\underline{H_2}CH=CH_2$), 5.35 (d, *J* = 10.5 Hz, 1H, 1 × $CH=C\underline{H_2}$), 5.47 (d, *J* = 17.2 Hz, 1H, 1 × $CH=C\underline{H_2}$), 6.10 (ddt, *J* = 17.2, 10.5, 4.9 Hz, 1H, $C\underline{H}=CH_2$), 7.21 (d, *J* = 8.0 Hz, 1H, H_4), 7.40 (t, *J* = 8.0 Hz, 1H, H_5), 7.68 (br s, 1H, H_2), 7.76 (d, *J* = 8.0 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 69.0 ($O\underline{C}H_2CH=CH_2$), 115.4 (C_2), 118.0 ($CH=\underline{C}H_2$), 121.2 (C_4), 122.9 (C_6), 129.6 (C_5), 130.6 (C_1), 132.8 ($\underline{C}H=CH_2$), 158.6 (C_3), 172.4 (CO).

[63] Wen, J.; Chennamadhavuni, D.; Morel, S.R.; Hadden, M.K. *ACS Med. Chem. Lett.* **2019**, *10*, 1290.

5.20. General procedure for the amidation of carboxylic acids VAA-VFA. Synthesis of amides 19aa-19fa



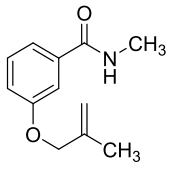
VAA-VFA

19aa, R^1 = H, R^3 = CH_3, R^4 = H, n = 1
19ab, R^1 = 5-NO_2, R^3 = CH_3, R^4 = H, n = 1
19ac, R^1 = 5-Br, R^3 = CH_3, R^4 = H, n = 1
19ad, R^1 = 4,5-$(OCH_3)_2$, R^3 = CH_3, R^4 = H, n = 1
19ae, R^1 = 4-CH_3, R^3 = CH_3, R^4 = H, n = 1
19af, R^1 = 4-OCH_3, R^3 = CH_3, R^4 = H, n = 1
19ag, R^1 = 4-F, R^3 = CH_3, R^4 = H, n = 1
19ah, R^1 = 5-OBn, R^3 = CH_3, R^4 = H, n = 1
19ai, R^1 = 5-OCH_3, R^3 = CH_3, R^4 = H, n = 1
19aj, R^1 = 4,5-OCH_2O, R^3 = CH_3, R^4 = H, n = 1
19ak, R^1 = 4,5-OCH_2CH_2O, R^3 = CH_3, R^4 = H, n = 1
19al, R^1 = 5-$OCH_2C(CH_3)=CH_2$, R^3 = CH_3, R^4 = H, n = 1
19am, R^1 = 5-Ph, R^3 = CH_3, R^4 = H, n = 1
19an, R^1 = 5-[4$(OCH_3)C_6H_4$], R^3 = CH_3, R^4 = H, n = 1
19ba, R^1 = H, R^3 = Ph, R^4 = H, n = 1
19bf, R^1 = 4-OCH_3, R^3 = Ph, R^4 = H, n = 1
19bg, R^1 = 4-F, R^3 = Ph, R^4 = H, n = 1
19bj, R^1 = 4,5-OCH_2O, R^3 = Ph, R^4 = H, n = 1
19ca, R^1 = H, R^3 = Et, R^4 = H, n = 1
19da, R^1 = H, R^3 = CH_3, R^4 = H, n = 2
19dg, R^1 = 4-F, R^3 = CH_3, R^4 = H, n = 2
19ea, R^1 = H, R^3 = CH_3, R^4 = CH_3, n = 1
19fa, R^1 = H, R^3 = H, R^4 = H, n = 1

Over a solution of the corresponding carboxylic acid **VAA-VFA** (1 mmol) in dry CH_2Cl_2 (5 mL), one drop of DMF was added under argon atmosphere, followed by dropwise addition of oxalyl chloride (1.2 mmol). The mixture was stirred for 30 min at room temperature and the volatiles were evaporated *in vacuo*. The residue was redissolved in AcOEt (3.3 mL) and then, CH_3NH_2·HCl (1.1 mmol), K_2CO_3 (2 mmol) and H_2O (1.7 mL) were subsequently added. The solution was stirred for 2 h and afterwards, the phases were separated. The aqueous phase was extracted with AcOEt (15 mL) and the combined organic extracts were washed with H_2O (15 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The

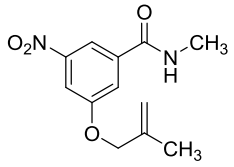
corresponding amides **19aa-19fa** were obtained without further purification or after purification by flash column chromatography (silica gel, petroleum ether/AcOEt).

*N-Methyl-3-((2-methylallyl)oxy)benzamide (**19aa**)*[57]



Prepared from 3-((2-methylallyl)oxy)benzoic acid **VAA** (0.22 g, 1.1 mmol) and oxalyl chloride (0.12 mL, 1.4 mmol) in dry CH_2Cl_2 (5.7 mL); followed by CH_3NH_2·HCl (84.2 mg, 1.2 mmol) and K_2CO_3 (0.31 g, 2.3 mmol) in AcOEt (3.8 mL) and H_2O (1.9 mL). After work-up, **19aa** was obtained as a solid without further purification (0.22 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.82 (s, 3H, C(C<u>H</u>$_3$)=CH$_2$), 2.99 (d, *J* = 4.8 Hz, 3H, NCH$_3$), 4.45 (s, 2H, OC<u>H</u>$_2$C(CH$_3$)=CH$_2$), 4.99 (br s, 1H, 1 × C(CH$_3$)=C<u>H</u>$_2$), 5.09 (br s, 1H, 1 × C(CH$_3$)=C<u>H</u>$_2$), 6.49 (br s, 1H, NH), 7.00-7.07 (m, 1H, H$_4$), 7.27-7.32 (m, 2H, H$_5$, H$_6$), 7.36-7.40 (m, 1H, H$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C(<u>C</u>H$_3$)=CH$_2$), 26.9 (NCH$_3$), 71.8 (O<u>C</u>H$_2$C(CH$_3$)=CH$_2$), 112.9 (C(CH$_3$)=<u>C</u>H$_2$), 113.3 (C$_2$), 118.2 (C$_4$), 118.8 (C$_6$), 129.5 (C$_5$), 136.0 (C$_1$), 140.5 (<u>C</u>(CH$_3$)=CH$_2$), 159.0 (C$_3$), 168.2 (CO).

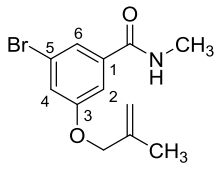
*N-Methyl-3-((2-methylallyl)oxy)-5-nitrobenzamide (**19ab**)*[64]



Prepared from 3-((2-methylallyl)oxy)-5-nitrobenzoic acid **VAB** (0.28 g, 1.2 mmol) and oxalyl chloride (0.12 mL, 1.4 mmol) in dry CH_2Cl_2 (5.8 mL); followed by CH_3NH_2·HCl (86.7 mg, 1.3 mmol) and K_2CO_3 (0.32 g, 2.3 mmol) in AcOEt (4.0 mL) and H_2O (2.0 mL). After work-up, **19ab** was obtained as a solid without further purification (0.27 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.76 (s, 3H, C(C<u>H</u>$_3$)=CH$_2$), 2.97 (d, *J* = 4.8 Hz, 3H, NCH$_3$), 4.47 (s, 2H, OC<u>H</u>$_2$C(CH$_3$)=CH$_2$), 4.97 (br s, 1H, 1 × C(CH$_3$)=C<u>H</u>$_2$), 5.04 (br s, 1H, 1 × C(CH$_3$)=C<u>H</u>$_2$), 6.52 (br s, 1H, NH), 7.66 (dd, *J* = 2.2, 1.5 Hz, 1H, H$_2$), 7.77 (t, *J* = 2.2 Hz, 1H, H$_4$), 8.02-8.08 (m, 1H, H$_6$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.3 (C(<u>C</u>H$_3$)=CH$_2$), 27.1 (NCH$_3$), 72.6 (O<u>C</u>H$_2$C(CH$_3$)=CH$_2$), 112.2 (C(CH$_3$)=<u>C</u>H$_2$), 113.5 (C$_4$), 113.9 (C$_6$), 120.3 (C$_2$), 137.0 (C$_1$), 139.4 (<u>C</u>(CH$_3$)=CH$_2$), 149.0 (C$_5$), 159.5 (C$_3$), 165.8 (CO).

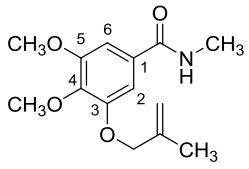
[64] Rit, R.K.; Ghosh, K.; Mandal, R.; Sahoo, A.K. *J. Org. Chem.* **2016**, *81*, 8552.

*3-Bromo-N-methyl-5-((2-methylallyl)oxy)benzamide (**19ac**)*



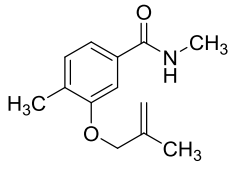
Prepared from 3-bromo-5-((2-methylallyl)oxy)benzoic acid **VAC** (0.30 g, 1.1 mmol) and oxalyl chloride (0.11 mL, 1.3 mmol) in dry CH_2Cl_2 (5.5 mL); followed by CH_3NH_2·HCl (81.2 mg, 1.2 mmol) and K_2CO_3 (0.30 g, 2.2 mmol) in AcOEt (3.7 mL) and H_2O (1.9 mL). After work-up, **19ac** was obtained as a solid without further purification (0.26 g, 84%): mp (CH_2Cl_2) 61-64 ºC; IR (ATR): ν (cm^{-1}) = 3310 (N-H), 1637 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.73 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 2.91 (d, *J* = 4.8 Hz, 3H, NCH_3), 4.35 (s, 2H, OC<u>H</u>$_2$C(CH_3)=CH_2), 4.92 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 5.00 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 6.41 (br s, 1H, NH), 7.09 (dd, *J* = 2.3, 1.7 Hz, 1H, H_2), 7.20 (t, *J* = 2.3, 1.7 Hz, 1H, H_4), 7.35 (t, *J* = 1.7 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.3 (C(<u>C</u>H$_3$)=CH_2), 27.0 (NCH_3), 72.1 (O<u>C</u>H$_2$C(CH_3)=CH_2), 112.5 (C_2), 113.3 (C(CH_3)=<u>C</u>H$_2$), 121.0 (C_6), 122.1 (C_4), 122.8 (C_5), 137.4 (C_1), 139.9 (<u>C</u>(CH_3)=CH_2), 159.6 (C_3), 166.8 (CO); MS (ESI): *m/z* (%): 306.0 (MNa^+, 100), 286.0 (MH^+ + 2, 35), 285.0 (MH^+ + 1, 4), 284.0 (MH^+, 36), 148.1 (2); HRMS (ESI): *m/z* calcd. for $C_{12}H_{15}BrNO_2$: 284.0286 [MH^+]; found: 284.0287.

*3,4-Dimethoxy-N-methyl-5-((2-methylallyl)oxy)benzamide (**19ad**)[64]*



Prepared from 3,4-dimethoxy-5-((2-methylallyl)oxy)benzoic acid **VAD** (0.27 g, 1.1 mmol) and oxalyl chloride (0.11 mL, 1.3 mmol) in dry CH_2Cl_2 (5.3 mL); followed by CH_3NH_2·HCl (79.3 mg, 1.2 mmol) and K_2CO_3 (0.29 g, 2.1 mmol) in AcOEt (3.6 mL) and H_2O (1.8 mL). After work-up, **19ad** was obtained as an oil without further purification (0.27 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.84 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 2.99 (d, *J* = 4.8 Hz, 3H, NCH_3), 3.88 (s, 3H, OC<u>H</u>$_3$), 3.90 (s, 3H, OC<u>H</u>$_3$), 4.50 (s, 2H, OC<u>H</u>$_2$C(CH_3)=CH_2), 5.00 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 5.11 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 6.30 (br s, 1H, NH), 6.99 (d, *J* = 1.9 Hz, H_6), 7.01 (d, *J* = 1.9 Hz, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C(<u>C</u>H$_3$)=CH_2), 26.9 (NCH_3), 56.3 (OCH_3), 60.9 (OCH_3), 72.9 (O<u>C</u>H$_2$C(CH_3)=CH_2), 104.4 (C_6), 106.1 (C_2), 112.9 (C(CH_3)=<u>C</u>H$_2$), 130.0 (C_1), 140.5 (<u>C</u>(CH_3)=CH_2), 141.2 (C_4), 152.3, 153.3 (C_3, C_5), 168.0 (CO).

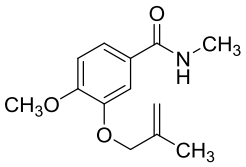
*N,4-Dimethyl-3-((2-methylallyl)oxy)benzamide (**19ae**)[64]*



Prepared from 4-methyl-3-((2-methylallyl)oxy)benzoic acid **VAE** (0.35 g, 1.7 mmol) and oxalyl chloride (0.17 mL, 2.0 mmol) in dry CH_2Cl_2 (8.4 mL); followed by CH_3NH_2·HCl (0.12 mg, 1.8 mmol) and K_2CO_3 (0.46 g, 3.4 mmol) in AcOEt (5.7 mL) and H_2O (2.9 mL). After

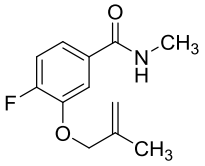
work-up, **19ae** was obtained as a solid without further purification (0.33 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.86 (s, 3H, C($\underline{CH_3}$)=CH_2), 2.30 (s, 3H, CH_3), 3.01 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.50 (s, 2H, O$\underline{CH_2}$C(CH_3)=CH_2), 5.01 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.14 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.21 (br s, 1H, NH), 7.16 (s, 2H, H_2, H_5) 7.35 (s, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 16.4 (CH_3), 19.4 (C($\underline{C}H_3$)=CH_2), 26.8 (NCH_3), 71.6 (O$\underline{C}H_2$C(CH_3)=CH_2), 110.2 (C_2), 112.3 (C(CH_3)=$\underline{C}H_2$), 118.0 (C_6), 130.4 (C_5), 130.8 (C_4), 133.4 (C_1), 140.8 ($\underline{C}$(CH_3)=CH_2), 157.0 (C_3), 168.2 (CO)

*4-Methoxy-N-methyl-3-((2-methylallyl)oxy)benzamide (**19af**)*[49,64]



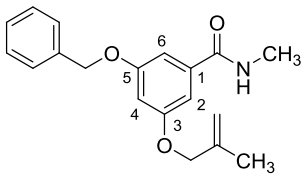
Prepared from 4-methoxy-3-((2-methylallyl)oxy)benzoic acid **VAF** (0.33 g, 1.5 mmol) and oxalyl chloride (0.15 mL, 1.8 mmol) in dry CH_2Cl_2 (7.5 mL); followed by CH_3NH_2·HCl (0.11 mg, 1.6 mmol) and K_2CO_3 (0.41 g, 3.0 mmol) in AcOEt (5.1 mL) and H_2O (2.5 mL). After work-up, **19af** was obtained as a solid without further purification (0.31 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.84 (s, 3H, C($\underline{CH_3}$)=CH_2), 2.99 (d, *J* = 4.8 Hz, 3H, NCH_3), 3.91 (s, 3H, OCH_3), 4.55 (s, 2H, O$\underline{CH_2}$C(CH_3)=CH_2), 5.00 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.12 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.19 (br s, 1H, NH), 6.87 (d, *J* = 8.4 Hz, 1H, H_5), 7.29 (dd, *J* = 8.4, 2.0 Hz, H_6), 7.42 (d, *J* = 2.0 Hz, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 26.8 (NCH_3), 56.0 (OCH_3), 72.6 (O$\underline{C}H_2$C(CH_3)=CH_2), 110.8 (C_5), 112.7 (C(CH_3)=$\underline{C}H_2$), 113.0 (C_2), 119.6 (C_6), 127.2 (C_1), 140.4 ($\underline{C}$(CH_3)=CH_2), 148.1 (C_4), 152.1 (C_3), 167.8 (CO)

*4-Fluoro-N-methyl-3-((2-methylallyl)oxy)benzamide (**19ag**)*[64]



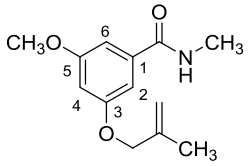
Prepared from 4-fluoro-3-((2-methylallyl)oxy)benzoic acid **VAG** (0.32 g, 1.5 mmol) and oxalyl chloride (0.15 mL, 1.8 mmol) in dry CH_2Cl_2 (7.6 mL); followed by CH_3NH_2·HCl (0.11 mg, 1.7 mmol) and K_2CO_3 (0.42 g, 3.0 mmol) in AcOEt (5.2 mL) and H_2O (2.6 mL). After work-up, **19ag** was obtained as a solid without further purification (0.30 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.76 (s, 3H, C($\underline{CH_3}$)=CH_2), 2.92 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.47 (s, 2H, O$\underline{CH_2}$C(CH_3)=CH_2), 4.94 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.05 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.13 (br s, 1H, NH), 7.01 (dd, *J* = 10.6, 8.4 Hz, 1H, H_5), 7.15 (ddd, *J* = 8.4, 4.2, 2.1 Hz, 1H, H_6), 7.42 (dd, *J* = 8.1, 2.1 Hz, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.3 (C($\underline{C}H_3$)=CH_2), 26.9 (NCH_3), 72.9 (O$\underline{C}H_2$C(CH_3)=CH_2), 113.5 (C(CH_3)=$\underline{C}H_2$), 114.7 (d, *J* = 2.8 Hz, C_2), 116.0 (d, *J* = 19.4 Hz, C_5), 119.1 (d, *J* = 7.7 Hz, C_6), 131.1 (d, *J* = 3.6 Hz, C_1), 140.0 ($\underline{C}$(CH_3)=CH_2), 146.9 (d, *J* = 10.8 Hz, C_3), 154.6 (d, *J* = 251.9 Hz, C_4), 167.2 (CO).

*3-(Benzyloxy)-N-methyl-5-((2-methylallyl)oxy)benzamide (**19ah**)*



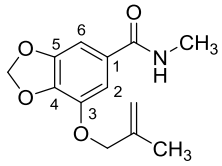
Prepared from 3-(benzyloxy)-5-((2-methylallyl)oxy)benzoic acid **VAH** (0.14 g, 0.46 mmol) and oxalyl chloride (47.2 µL, 0.56 mmol) in dry CH_2Cl_2 (2.3 mL); followed by CH_3NH_2·HCl (34.5 mg, 0.51 mmol) and K_2CO_3 (0.13 g, 0.93 mmol) in AcOEt (1.6 mL) and H_2O (0.79 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **19ah** was obtained as a solid (0.14 g, 96%): mp (CH_2Cl_2) 92-93 ºC; IR (ATR): ν (cm^{-1}) = 3243 (N-H), 1631 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.83 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 2.98 (d, *J* = 4.8 Hz, 3H, NCH_3), 4.43 (s, 2H, OC<u>H</u>$_2$C(CH_3)=CH_2), 4.88-5.21 (m, 4H, C(CH_3)=C<u>H</u>$_2$, C<u>H</u>$_2$Ph), 6.26 (br s, 1H, NH), 6.68 (t, *J* = 2.1 Hz, 1H, H_4), 6.94 (s, 1H, H_6), 7.00 (s, 1H, H_2), 7.29-7.47 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C(<u>C</u>H$_3$)=CH_2), 26.9 (NCH_3), 70.3 (O<u>C</u>H$_2$Ph), 72.0 (O<u>C</u>H$_2$C(CH_3)=CH_2), 105.0 (C_4), 105.8, 106.1 (C_2, C_6), 113.0 (C(CH_3)=<u>C</u>H$_2$), 127.6 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 136.5 (C_1), 136.8 ($C_{1'}$), 140.5 (<u>C</u>(CH_3)=CH_2), 160.0 (C_3, C_5), 168.0 (CO); MS (ESI): *m/z* (%): 335.1 (MNa^+ + 1, 17), 334.1 (MNa^+, 100), 313.2 (MH^+ + 1, 9), 312.2 (MH^+, 55), 91.1 (2); HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}NO_3$: 312.1600 [MH^+]; found: 312.1596.

*3-Methoxy-N-methyl-5-((2-methylallyl)oxy)benzamide (**19ai**)*[64]



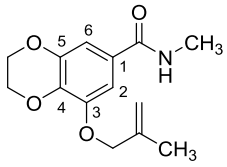
Prepared from 3-methoxy-5-((2-methylallyl)oxy)benzoic acid **VAI** (0.29 g, 1.3 mmol) and oxalyl chloride (0.13 mL, 1.6 mmol) in dry CH_2Cl_2 (6.6 mL); followed by CH_3NH_2·HCl (98.4 mg, 1.5 mmol) and K_2CO_3 (0.37 g, 2.6 mmol) in AcOEt (4.5 mL) and H_2O (2.3 mL). After work-up, **19ai** was obtained as a solid without further purification (0.28 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.83 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 3.00 (d, *J* = 4.9 Hz, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 4.45 (s, 2H, OC<u>H</u>$_2$C(CH_3)=CH_2), 5.01 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 5.10 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 6.19 (br s, 1H, NH), 6.60 (t, *J* = 2.3 Hz, H_4), 6.88-6.93 (m, 2H, H_6, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C(<u>C</u>H$_3$)=CH_2), 26.8 (NCH_3), 55.5 (OCH_3), 71.9 (O<u>C</u>H$_2$C(CH_3)=CH_2), 104.2 (C_4), 105.0, 105.7 (C_2, C_6), 112.9 (C(CH_3)=<u>C</u>H$_2$), 136.8 (C_1), 140.5 (<u>C</u>(CH_3)=CH_2), 160.0 (C_3), 160.8 (C_5), 168.2 (CO).

*N-Methyl-7-((2-methylallyl)oxy)benzo[d][1,3]dioxole-5-carboxamide (**19aj**)*



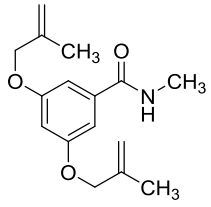
Prepared from 7-((2-methylallyl)oxy)benzo[*d*][1,3]dioxole-5-carboxylic acid **VAJ** (0.31 g, 1.3 mmol) and oxalyl chloride (0.13 mL, 1.6 mmol) in dry CH_2Cl_2 (6.5 mL); followed by $CH_3NH_2{\cdot}HCl$ (97.2 mg, 1.4 mmol) and K_2CO_3 (0.36 g, 2.6 mmol) in AcOEt (4.5 mL) and H_2O (2.2 mL). After work-up, **19aj** was obtained as a solid without further purification (0.29 g, 90%): mp (CH_2Cl_2) 99-101 ºC; IR (ATR) (cm^{-1}): ν = 3350 (N-H), 1605 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.84 (s, 3H, C($\underline{CH_3}$)=CH_2), 2.99 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.58 (s, 2H, O$\underline{CH_2}$C(CH_3)=CH_2), 5.00 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.11 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.04 (s, 2H, OCH_2O), 6.07 (br s, 1H, NH), 6.89 (d, *J* = 1.5 Hz, 1H, H_6), 7.09 (d, *J* = 1.5 Hz, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.3 (C($\underline{C}H_3$)=CH_2), 26.9 (NCH_3), 73.3 (O$\underline{C}H_2$C(CH_3)=CH_2), 100.9 (OCH_2O), 102.0 (C_6), 109.7 (C_2), 113.3 (C(CH_3)=$\underline{C}H_2$), 129.1 (C_1), 138.3 ($\underline{C}$(CH_3)=CH_2), 140.3 (C_4), 142.5 (C_5), 149.0 (C_3), 167.4 (CO); MS (ESI): *m/z* (%): 272.1 (MNa^+, 100), 251.1 (MH^+ + 1, 3), 250.1 (MH^+, 27), 193.1 (3); HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NO_4$: 250.1079 [MH^+]; found: 250.1077.

*N-Methyl-8-((2-methylallyl)oxy)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide (**19ak**)[64]*



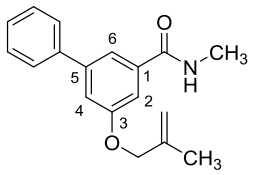
Prepared from 8-((2-methylallyl)oxy)-2,3-dihydrobenzo[*b*][1,4] dioxine-6-carboxylic acid **VAK** (0.29 g, 1.2 mmol) and oxalyl chloride (0.12 mL, 1.4 mmol) in dry CH_2Cl_2 (5.8 mL); followed by $CH_3NH_2{\cdot}HCl$ (86.8 mg, 1.3 mmol) and K_2CO_3 (0.32 g, 2.3 mmol) in AcOEt (4.0 mL) and H_2O (2.0 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 5/5), **19ak** was obtained as a solid (0.28 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.84 (s, 3H, C($\underline{CH_3}$)=CH_2), 2.98 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.24-4.32 (m, 2H, O$\underline{CH_2}CH_2O$), 4.32-4.39 (m, 2H, $OCH_2\underline{CH_2}O$), 4.54 (s, 2H, O$\underline{CH_2}$C(CH_3)=CH_2), 5.01 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.12 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.12 (br s, 1H, NH), 6.88 (d, *J* = 2.0 Hz, 1H, H_6), 7.04 (d, *J* = 2.0 Hz, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 26.9 (NCH_3), 64.1 (O$\underline{C}H_2CH_2O$), 64.6 ($OCH_2\underline{C}H_2O$), 72.8 (O$\underline{C}H_2$C(CH_3)=CH_2), 105.4 (C_2), 108.6 (C_6), 113.1 (C(CH_3)=$\underline{C}H_2$), 126.6 (C_1), 136.4 ($\underline{C}$(CH_3)=CH_2), 140.3 (C_4), 143.7 (C_5), 148.1 (C_3), 167.6 (CO).

*N-Methyl-3,5-bis((2-methylallyl)oxy)benzamide (**19al**)*



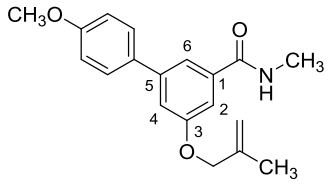
Prepared from 3,5-bis((2-methylallyl)oxy)benzoic acid **VAL** (0.31 g, 1.2 mmol) and oxalyl chloride (0.12 mL, 1.4 mmol) in dry CH_2Cl_2 (6.0 mL); followed by $CH_3NH_2{\cdot}HCl$ (88.4 mg, 1.3 mmol) and K_2CO_3 (0.33 g, 2.4 mmol) in AcOEt (4.1 mL) and H_2O (2.1 mL). After work-up, **19al** was obtained as a solid without further purification (0.30 g, 91%): mp (CH_2Cl_2) 79-82 ºC; IR (ATR): ν (cm^{-1}) = 3250 (N-H), 1595 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.80 (s, 6H, 2 × C($C\underline{H_3}$)=CH_2), 2.96 (d, *J* = 4.8 Hz, 3H, NCH_3), 4.40 (s, 4H, 2 × O$C\underline{H_2}$C(CH_3)=CH_2), 4.97 (br s, 2H, C(CH_3)=C$\underline{H_2}$), 5.07 (br s, 2H, C(CH_3)=C$\underline{H_2}$), 6.58-6.62 (m, 2H, NH, H_4), 6.93 (d, *J* = 2.3 Hz, 2H, H_2, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (2 × C($\underline{C}H_3$)=CH_2), 26.9 (NCH_3), 71.9 (2 × O$\underline{C}H_2$C(CH_3)=CH_2), 104.9 (C_4), 105.8 (C_2, C_6), 112.9 (2 × C(CH_3)=$\underline{C}H_2$), 136.7 (C_1), 140.5 (2 × $\underline{C}$(CH_3)=CH_2), 159.9 (C_3, C_5), 168.1 (CO); MS (ESI): *m/z* (%): 298.1 (MNa^+, 48), 277.2 (MH^+ + 1, 13), 276.2 (MH^+, 100), 245.1 (4), 219.1 (10); HRMS (ESI): *m/z* calcd. for $C_{16}H_{22}NO_3$: 276.1600 [MH^+]; found: 276.1601.

*N-Methyl-5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxamide (**19am**)*



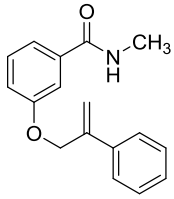
Prepared from 5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxylic acid **VAM** (0.20 g, 0.76 mmol) and oxalyl chloride (77.1 µL, 0.91 mmol) in dry CH_2Cl_2 (3.8 mL); followed by $CH_3NH_2{\cdot}HCl$ (56.4 mg, 0.83 mmol) and K_2CO_3 (0.21 g, 1.5 mmol) in AcOEt (2.3 mL) and H_2O (1.3 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **19am** was obtained as a solid (0.20 g, 94%): mp (CH_2Cl_2) 99-101 ºC; IR (ATR): ν (cm^{-1}) = 3246 (N-H), 1631 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.84 (s, 3H, C($C\underline{H_3}$)=CH_2), 2.99 (d, *J* = 4.8 Hz, 3H, NCH_3), 4.49 (s, 2H, O$C\underline{H_2}$C(CH_3)=CH_2), 5.02 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.12 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.77 (br s, 1H, NH), 7.24-7.27 (m, 1H, H_2), 7.31-7.46 (m, 4H, H_4, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.51-7.61 (m, 3H, H_6, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 26.9 (NCH_3), 71.9 (O$\underline{C}H_2$C(CH_3)=CH_2), 112.0 (C_2), 113.0 (C(CH_3)=$\underline{C}H_2$), 116.9 (C_4), 118.1 (C_6), 127.1 ($C_{2'}$, $C_{6'}$), 127.8 ($C_{4'}$), 128.8 ($C_{3'}$, $C_{5'}$), 136.5 (C_1), 140.2 (C_5), 140.5 ($\underline{C}$(CH_3)=CH_2), 142.9 ($C_{1'}$), 159.3 (C_3), 168.3 (CO); MS (ESI): *m/z* (%): 305.1 (MNa^+ + 1, 14), 304.1 (MNa^+, 97), 283.2 (MH^+ + 1, 13), 282.2 (MH^+, 85), 225.1 (3); HRMS (ESI): *m/z* calcd. for $C_{18}H_{20}NO_2$: 282.1494 [MH^+]; found: 282.1485.

*4´-Methoxy-N-methyl-5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxamide (**19an**)*



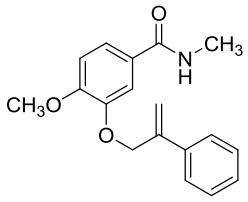
Prepared from 4´-methoxy-5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxylic acid **VAN** (0.30 g, 1.0 mmol) and oxalyl chloride (0.10 mL, 1.2 mmol) in dry CH_2Cl_2 (6.0 mL); followed by CH_3NH_2·HCl (74.7 mg, 1.1 mmol) and K_2CO_3 (0.28 g, 2.0 mmol) in AcOEt (4.0 mL) and H_2O (2.0 mL). After work-up, **19an** was obtained as a solid without further purification (0.30 g, 94%): mp (CH_2Cl_2) 120-122 ºC; IR (ATR): ν (cm^{-1}) = 3247 (N-H), 1644 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.85 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 3.01 (d, *J* = 4.8 Hz, 3H, NCH_3), 3.84 (s, 3H, OCH_3), 4.50 (s, 2H, OC<u>H</u>$_2$C(CH_3)=CH_2), 5.02 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 5.13 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 6.53 (br s, 1H, NH), 6.96 (d, *J* = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.22 (s, 1H, H_2), 7.29 (s, 1H, H_4), 7.47-7.57 (m, 3H, H_6, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C(<u>C</u>H_3)=CH_2), 26.9 (NCH_3), 55.4 (OCH_3), 71.9 (O<u>C</u>H_2C(CH_3)=CH_2), 111.3 (C_2), 113.0 (C(CH_3)=<u>C</u>H_2), 114.3 ($C_{3'}$, $C_{5'}$), 116.5 (C_4), 117.6 (C_6), 128.2 ($C_{2'}$, $C_{6'}$), 132.7 (C_1), 136.5 (C_5), 140.6 (<u>C</u>(CH_3)=CH_2), 142.5 ($C_{1'}$), 159.3, 159.5 (C_3, $C_{4'}$), 168.3 (CO); MS (ESI): *m/z* (%): 335.1 (MNa^+ + 1, 3), 334.1 (MNa^+, 19), 313.2 (MH^+ + 1, 15), 312.2 (MH^+, 100), 255.1 (3); HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}NO_3$: 312.1600 [MH^+]; found: 312.1601.

*N-Methyl-3-((2-phenylallyl)oxy)benzamide (**19ba**)*[57]



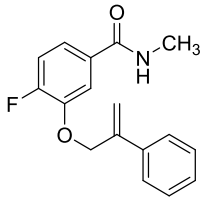
Prepared from 3-((2-phenylallyl)oxy)benzoic acid **VBA** (0.31 g, 1.2 mmol) and oxalyl chloride (0.12 mL, 1.5 mmol) in dry CH_2Cl_2 (6.1 mL); followed by CH_3NH_2·HCl (90.6 mg, 1.3 mmol) and K_2CO_3 (0.34 g, 2.4 mmol) in AcOEt (4.1 mL) and H_2O (2.1 mL). After work-up, **19ba** was obtained as a solid without further purification (0.31 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.95 (d, *J* = 4.8 Hz, 3H, NCH_3), 4.90 (s, 2H, OC<u>H</u>$_2$C(Ph)=CH_2), 5.46 (br s, 1H, 1 × C(Ph)=C<u>H</u>$_2$), 5.61 (br s, 1H, 1 × C(Ph)=C<u>H</u>$_2$), 6.87 (br s, 1H, NH), 7.01-7.11 (m, 1H, H_4), 7.24-7.41 (m, 5H, Ph), 7.42-7.53 (m, 3H, H_2, H_5, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 25.9 (NCH_3), 69.9 (O<u>C</u>H_2C(Ph)=CH_2), 113.4 (C_2), 115.1 (C(Ph)=<u>C</u>H_2), 118.3 (C_4), 119.3 (C_6), 126.0 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 129.6 (C_5), 136.1 (C_1), 138.2 ($C_{1'}$), 142.8 (<u>C</u>(Ph)=CH_2), 158.8 (C_3), 168.2 (CO).

*4-Methoxy-N-methyl-3-((2-phenylallyl)oxy)benzamide (**19bf**)*



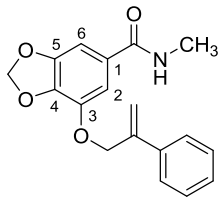
Prepared from 4-methoxy-3-((2-phenylallyl)oxy)benzoic acid **VBF** (0.18 g, 0.62 mmol) and oxalyl chloride (62.6 µL, 0.74 mmol) in dry CH_2Cl_2 (2.9 mL); followed by CH_3NH_2·HCl (45.8 mg, 0.68 mmol) and K_2CO_3 (0.17 g, 1.2 mmol) in AcOEt (2.0 mL) and H_2O (1.0 mL). After work-up, **19bf** was obtained as a solid without further purification (0.16 g, 88%): mp (CH_2Cl_2) 114-117 ºC; IR (ATR): ν (cm^{-1}) = 3282 (N-H), 1627 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.89 (d, *J* = 4.8 Hz, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 4.91 (s, 2H, $OC\underline{H_2}C(Ph)=CH_2$), 5.40 (br s, 1H, 1 × $C(Ph)=C\underline{H_2}$), 5.51 (br s, 1H, 1 × $C(Ph)=C\underline{H_2}$), 6.03 (br s, 1H, NH), 6.79 (d, *J* = 8.4 Hz, 1H, H_5), 7.16-7.46 (m, 7H, H_2, H_6, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.8 (NCH_3), 56.1 (OCH_3), 70.9 ($O\underline{C}H_2C(Ph)=CH_2$), 111.0 ($C_5$), 113.4 ($C_2$), 115.0 ($C(Ph)=\underline{C}H_2$), 120.2 ($C_6$), 126.1 ($C_{2'}$, $C_{6'}$), 127.2 (C_1), 128.0 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 138.4 ($C_{1'}$), 142.7 ($\underline{C}(Ph)=CH_2$), 147.9 (C_4), 152.5 (C_3), 167.7 (CO); MS (ESI): *m/z* (%): 321.1 (MNa^+ + 1, 8), 320.1 (MNa^+, 54), 299.1 (MH^+ + 1, 15), 298.1 (MH^+, 100), 241.1 (8), 220.1 (8); HRMS (ESI): *m/z* calcd. for $C_{18}H_{20}NO_3$: 298.1443 [MH^+]; found: 298.1450.

*4-Fluoro-N-methyl-3-((2-phenylallyl)oxy)benzamide (**19bg**)*



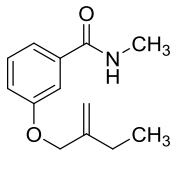
Prepared from 4-fluoro-3-((2-phenylallyl)oxy)benzoic acid **VBG** (0.27 g, 1.0 mmol) and oxalyl chloride (0.10 mL, 1.2 mmol) in dry CH_2Cl_2 (5.0 mL); followed by CH_3NH_2·HCl (74.8 mg, 1.1 mmol) and K_2CO_3 (0.28 g, 2.0 mmol) in AcOEt (3.4 mL) and H_2O (1.7 mL). After work-up, **19bg** was obtained as a solid without further purification (0.27 g, 95%): mp (CH_2Cl_2) 92-94 ºC; IR (ATR): ν (cm^{-1}) = 3310 (N-H), 1634 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.00 (d, *J* = 4.9 Hz, 3H, NCH_3), 5.02 (s, 2H, $OC\underline{H_2}C(Ph)=CH_2$), 5.52 (br s, 1H, 1 × $C(Ph)=C\underline{H_2}$), 5.64 (br s, 1H, 1 × $C(Ph)=C\underline{H_2}$), 6.15 (br s, 1H, NH), 7.11 (dd, *J* = 10.6, 8.4 Hz, 1H, H_5), 7.23-7.43 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$) 7.46-7.57 (m, 3H, H_2, H_6, $H_{4'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.9 (NCH_3), 71.2 ($O\underline{C}H_2C(Ph)=CH_2$), 115.2 (d, *J* = 2.8 Hz, C_2), 115.5 ($C(Ph)=\underline{C}H_2$), 116.1 (d, *J* = 19.3 Hz, C_5), 119.7 (d, *J* = 7.8 Hz, C_6), 126.1 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 131.1 (d, *J* = 3.7 Hz, C_1), 138.1 ($C_{1'}$), 142.4 ($\underline{C}(Ph)=CH_2$), 146.7 (d, *J* = 11.2 Hz, C_3), 154.9 (d, *J* = 252.3 Hz, C_4), 167.2 (CO); MS (ESI): *m/z* (%): 309.1 (MNa^+ + 1, 15), 308.1 (MNa^+, 100), 287.1 (MH^+ + 1, 3), 286.1 (MH^+, 21), 208.1 (6); HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}FNO_2$: 286.1243 [MH^+]; found: 286.1238.

*N-Methyl-7-((2-phenylallyl)oxy)benzo[d][1,3]dioxole-5-carboxamide (**19bj**)*



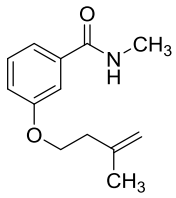
Prepared from 7-((2-phenylallyl)oxy)benzo[*d*][1,3]dioxole-5-carboxylic acid **VBJ** (0.15 g, 0.51 mmol) and oxalyl chloride (51.9 µL, 0.61 mmol) in dry CH_2Cl_2 (2.5 mL); followed by $CH_3NH_2{\cdot}HCl$ (38.0 mg, 0.56 mmol) and K_2CO_3 (0.14 g, 1.0 mmol) in AcOEt (1.7 mL) and H_2O (0.87 mL). After work-up, **19bj** was obtained as a solid without further purification (0.15 g, 92%): mp (CH_2Cl_2) 118-121 ºC; IR (ATR): ν (cm^{-1}) = 3293 (N-H), 1619 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.96 (d, *J* = 4.7 Hz, 3H, NCH_3), 5.03 (s, 2H, $OC\underline{H_2}C(Ph)=CH_2$), 5.47 (br s, 1H, 1 × $C(Ph)=C\underline{H_2}$), 5.61 (br s, 1H, 1 × $C(Ph)=C\underline{H_2}$), 6.00 (s, 2H, OCH_2O), 6.29 (br s, 1H, NH), 6.93 (s, 1H, H_6), 7.10 (s, 1H, H_2), 7.26-7.41 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.43-7.52 (m, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.9 (NCH_3), 71.4 ($O\underline{C}H_2C(Ph)=CH_2$), 101.4 ($OCH_2O$), 102.0 ($C_6$), 110.2 ($C_2$), 115.3 ($C(Ph)=\underline{C}H_2$), 126.1 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 129.1 (C_1), 138.1 ($C_{1'}$), 138.5 (C_4), 142.1 (C_5), 142.7 ($\underline{C}(Ph)=CH_2$), 149.1 (C_3), 167.5 (CO); MS (ESI): *m/z* (%): 335.1 (MNa^+ + 1, 9), 334.1 (MNa^+, 64), 313.1 (MH^+ + 1, 14), 312.1 (MH^+, 100), 255.1 (6), 234.1 (12); HRMS (ESI): *m/z* calcd. for $C_{18}H_{18}NO_4$: 312.1236 [MH^+]; found: 312.1239.

*N-Methyl-3-(2-methylenebutoxy)benzamide (**19ca**)*



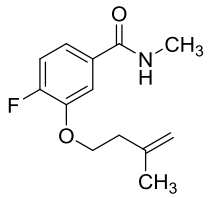
Prepared from 3-(2-methylenebutoxy)benzoic acid **VCA** (0.54 g, 2.6 mmol) and oxalyl chloride (0.26 mL, 3.1 mmol) in dry CH_2Cl_2 (12.4 mL); followed by $CH_3NH_2{\cdot}HCl$ (0.19 mg, 2.9 mmol) and K_2CO_3 (0.72 g, 5.2 mmol) in AcOEt (8.4 mL) and H_2O (4.2 mL). After work-up, **19ca** was obtained as an oil without further purification (0.51 g, 90%): IR (ATR): ν (cm^{-1}) = 3317 (N-H), 1637 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.02 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H_3}$), 2.07 (q, *J* = 7.4 Hz, 2H, $C\underline{H_2}CH_3$), 2.91 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.41 (s, 2H, $OC\underline{H_2}C(Et)=CH_2$), 4.91 (br s, 1H, 1 × $C(Et)=C\underline{H_2}$), 5.04 (br s, 1H, 1 × $C(Et)=C\underline{H_2}$), 6.35 (br s, 1H, NH), 6.86-7.04 (m, 1H, H_4), 7.17-7.23 (m, 2H, H_5, H_6), 7.29-7.32 (m, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 11.9 ($CH_2\underline{C}H_3$), 25.8 ($\underline{C}H_2CH_3$), 26.8 (NCH_3), 70.9 ($O\underline{C}H_2C(Et)=CH_2$), 110.9 ($C(Et)=\underline{C}H_2$), 113.3 ($C_2$), 118.1 ($C_4$), 119.1 ($C_6$), 129.4 ($C_5$), 135.9 ($C_1$), 146.1 ($\underline{C}(Et)=CH_2$), 158.9 ($C_3$), 168.4 (CO); MS (ESI): *m/z* (%): 243.1 (MNa^+ + 1, 7), 242.1 (MNa^+, 78), 221.1 (MH^+ + 1, 10), 220.1 (MH^+, 100), 163.1 (5), 152.1 (7), 121.1 (5), 107.0 (5); HRMS (ESI): *m/z* calcd. for $C_{13}H_{18}NO_2$: 220.1338 [MH^+]; found: 220.1337.

*N-Methyl-3-((3-methylbut-3-en-1-yl)oxy)benzamide (**19da**)*[57]



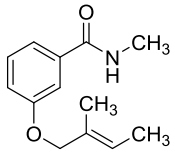
Prepared from 3-((3-methylbut-3-en-1-yl)oxy)benzoic acid **VDA** (0.41 g, 2.0 mmol) and oxalyl chloride (0.20 mL, 2.4 mmol) in dry CH_2Cl_2 (9.9 mL); followed by CH_3NH_2·HCl (0.15 g, 2.2 mmol) and K_2CO_3 (0.55 g, 4.0 mmol) in AcOEt (6.7 mL) and H_2O (3.4 mL). After work-up, **19da** was obtained as a solid without further purification (0.41 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.79 (s, 3H, C(C$\underline{H_3}$)=CH_2), 2.49 (t, *J* = 6.7 Hz, 2H, C$\underline{H_2}$C(CH_3)=CH_2), 2.98 (d, *J* = 4.8 Hz, 3H, NCH_3), 4.09 (t, *J* = 6.7 Hz, 2H, OC$\underline{H_2}$$CH_2$C($CH_3$)=$CH_2$), 4.79 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 4.84 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.56 (br s, 1H, NH), 6.97-7.07 (m, 1H, H_4), 725-7.32 (m, 2H, H_5, H_6), 7.33-7.39 (m, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.8 (C($\underline{C}H_3$)=CH_2), 26.8 (NCH_3), 37.1 ($\underline{C}H_2$C(CH_3)=CH_2), 66.6 (O$\underline{C}H_2$$CH_2$C($CH_3$)=$CH_2$), 112.1 (C($CH_3$)=$\underline{C}H_2$), 112.9 ($C_2$), 118.0 ($C_4$), 118.7 ($C_6$), 129.5 ($C_5$), 136.1 ($C_1$), 142.0 ($\underline{C}$($CH_3$)=$CH_2$), 159.1 ($C_3$), 168.2 (CO).

*4-Fluoro-N-methyl-3-((3-methylbut-3-en-1-yl)oxy)benzamide (**19dg**)*



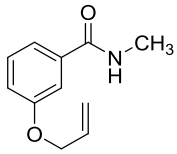
Prepared from 4-fluoro-3-((3-methylbut-3-en-1-yl)oxy)benzoic acid **VDG** (0.14 g, 0.63 mmol) and oxalyl chloride (63.5 µL, 0.75 mmol) in dry CH_2Cl_2 (3.1 mL); followed by CH_3NH_2·HCl (46.4 mg, 0.69 mmol) and K_2CO_3 (0.17 g, 1.3 mmol) in AcOEt (2.1 mL) and H_2O (1.1 mL). After work-up and purification by flash column chromatography (silica gel, petroleum ether/AcOEt 5/5), **19dg** was obtained as a solid (0.11 g, 77%): mp (CH_2Cl_2) 61-64 ºC; IR (ATR): ν (cm^{-1}) = 3389 (N-H), 1637 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.81 (s, 3H, C(C$\underline{H_3}$)=CH_2), 2.54 (t, *J* = 6.7 Hz, 2H, C$\underline{H_2}$C(CH_3)=CH_2), 2.99 (d, *J* = 4.7 Hz, 3H, NCH_3), 4.17 (t, *J* = 6.7 Hz, 2H, OC$\underline{H_2}$$CH_2$C($CH_3$)=$CH_2$), 4.80 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 4.86 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.42 (br s, 1H, NH), 7.00-7.15 (m, 1H, H_5), 7.20-7.30 (m, 1H, H_2), 7.45-7.57 (m, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.8 (C($\underline{C}H_3$)=CH_2), 26.9 (NCH_3), 37.0 ($\underline{C}H_2$C(CH_3)=CH_2), 68.0 (O$\underline{C}H_2$$CH_2$C($CH_3$)=$CH_2$), 112.3 (C($CH_3$)=$\underline{C}H_2$), 114.9 (d, *J* = 2.9 Hz, C_2), 115.9 (d, *J* = 19.3 Hz, C_5), 119.1 (d, *J* = 7.7 Hz, C_6), 131.1 (d, *J* = 3.7 Hz, C_1), 141.7 ($\underline{C}$(CH_3)=CH_2), 147.2 (d, *J* = 11.0 Hz, C_3), 154.6 (d, *J* = 251.6 Hz, C_4), 167.3 (CO); MS (ESI): *m/z* (%): 261.1 (MNa^+ + 1, 2), 260.1 (MNa^+, 100), 239.1 (MH^+ + 1, 5), 238.1 (MH^+, 46), 170.1 (16); HRMS (ESI): *m/z* calcd. for $C_{13}H_{17}FNO_2$: 238.1243 [MH^+]; found: 238.1239.

*(E)-N-Methyl-3-((2-methylbut-2-en-1-yl)oxy)benzamide (**19ea**)*[57]



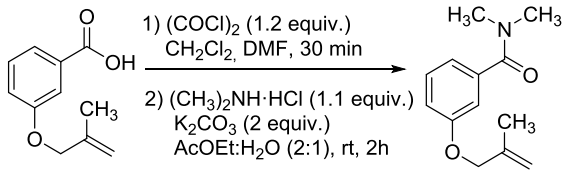
Prepared from *(E)*-3-((2-methylbut-2-en-1-yl)oxy)benzoic acid **VEA** (0.23 g, 1.1 mmol) and oxalyl chloride (0.11 mL, 1.3 mmol) in dry CH_2Cl_2 (5.5 mL); followed by $CH_3NH_2{\cdot}HCl$ (82.0 mg, 1.2 mmol) and K_2CO_3 (0.31 g, 2.2 mmol) in AcOEt (3.8 mL) and H_2O (1.9 mL). After work-up, **19ea** was obtained as a solid without further purification (0.20 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.66 (d, *J* = 6.7 Hz, 3H, C(CH_3)=CHC$\underline{H_3}$), 1.72 (s, 3H, C($C\underline{H_3}$)=CHCH_3), 2.97 (d, *J* = 4.8 Hz, 3H, NCH_3), 4.39 (s, 2H, O$C\underline{H_2}$C(CH_3)=CHCH_3), 5.51-5.69 (m, 1H, C(CH_3)=C$\underline{H}CH_3$), 6.60 (br s, 1H, NH), 6.93-7.07 (m, 1H, H_4), 7.22-7.32 (m, 2H, H_5, H_6), 7.35-7.40 (m, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 13.2 (CH_3), 13.6 (CH_3), 26.8 (NCH_3), 74.2 (O$\underline{C}H_2$C(CH_3)=CHCH_3), 113.3 (C_2), 118.2 (C_4), 118.7 (C_6), 123.6 (C(CH_3)=$\underline{C}HCH_3$), 129.4 (C_5), 131.4 ($\underline{C}$(CH_3)=CHCH_3), 136.0 (C_1), 159.2 (C_3), 168.2 (CO).

*3-(Allyloxy)-N-methylbenzamide (**19fa**)*



Prepared from 3-(allyloxy)benzoic acid **VFA** (0.22 g, 1.2 mmol) and oxalyl chloride (0.12 mL, 1.5 mmol) in dry CH_2Cl_2 (5.8 mL); followed by $CH_3NH_2{\cdot}HCl$ (90.3 mg, 1.3 mmol) and K_2CO_3 (0.34 g, 2.4 mmol) in AcOEt (3.9 mL) and H_2O (2.0 mL). After work-up, **19fa** was obtained as a solid without further purification (0.20 g, 85%): mp (CH_2Cl_2) 68-69 ºC; IR (ATR): ν (cm^{-1}) = 3342 (N-H), 1633 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.87 (d, *J* = 4.8 Hz, 3H, NCH_3), 4.44 (d, *J* = 5.2 Hz, 2H, O$C\underline{H_2}$CH=CH_2), 5.13-5.23 (m, 1H, 1 × CH=C$\underline{H_2}$), 5.25-5.35 (m, 1H, 1 × CH=C$\underline{H_2}$), 5.93 (ddt, *J* = 15.8, 10.5, 5.2 Hz, 1H, C$\underline{H}$=CH_2), 6.71 (br s, 1H, NH), 6.93 (d, *J* = 7.8 Hz, 1H, H_4), 7.14-7.34 (m, 3H, H_2, H_5, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 25.8 (NCH_3), 67.8 (O$\underline{C}H_2$CH=CH_2), 112.1 (C_2), 116.8 (CH=$\underline{C}H_2$), 117.2 (C_4), 118.0 (C_6), 128.5 (C_5), 131.9 ($\underline{C}$H=CH_2), 135.0 (C_1), 157.7 (C_3), 167.2 (CO); MS (ESI): *m/z* (%): 215.1 (MNa^+ + 1, 3), 214.1 (MNa^+, 46), 193.1 (MH^+ + 1, 8), 192.1 (MH^+, 100), 107.0 (10); HRMS (ESI): *m/z* calcd. for $C_{11}H_{14}NO_2$: 192.1025 [MH^+]; found: 192.1027.

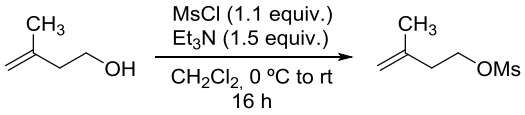
5.21. Synthesis of *N,N*-dimethyl-3-((2-methylallyl)oxy)benzamide (20aa)[57]



VAA **20aa**

Over a solution of 3-((2-methylallyl)oxy)benzoic acid **VAA** (0.15 g, 0.79 mmol) in dry CH_2Cl_2 (4.0 mL), one drop of DMF was added under argon atmosphere, followed by dropwise addition of oxalyl chloride (80.2 µL, 0.95 mmol). The mixture was stirred for 30 min at room temperature and the volatiles were evaporated *in vacuo*. The residue was redissolved in AcOEt (2.7 mL) and then, $(CH_3)_2NH{\cdot}HCl$ (70.8 mg, 0.87 mmol), K_2CO_3 (0.22 g, 1.6 mmol) and H_2O (1.3 mL) were subsequently added. The solution was stirred for 2 h and afterwards, the phases were separated. The aqueous phase was extracted with AcOEt (15 mL) and the combined organic extracts were washed with H_2O (15 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Amide **20aa** was obtained as a solid without further purification (0.17 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.83 (s, 3H, C($\underline{CH_3}$)=CH_2), 2.98 (s, 3H, NCH_3), 3.11 (s, 3H, NCH_3), 4.45 (s, 2H, O$\underline{CH_2}$C(CH_3)=CH_2), 5.00 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.10 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.93-7.04 (m, 3H, H_4, H_5, H_6), 7.25-7.36 (m, 1H, H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 35.3 (NCH_3), 39.5 (NCH_3), 71.8 (O$\underline{C}H_2$C(CH_3)=CH_2), 112.8 (C(CH_3)=$\underline{C}H_2$), 113.3 (C_2), 116.2 (C_4), 119.3 (C_6), 129.4 (C_5), 137.6 (C_1), 140.6 ($\underline{C}$(CH_3)=CH_2), 158.7 (C_3), 171.3 (CO).

5.22. Synthesis of 3-methylbut-3-en-1-yl methanesulfonate[65]

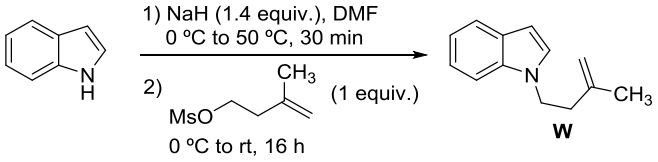


A solution of 3-methyl-3-buten-1-ol (3.0 mL, 29.7 mmol) and Et_3N (6.2 mL, 44.6 mmol) in dry CH_2Cl_2 (21.2 mL) was cooled to 0ºC under argon atmosphere and over it, a solution of methanesulfonyl chloride (2.5 mL, 32.7 mmol) in dry CH_2Cl_2 (1.8 mL) was added dropwise *via cannula*. The mixture was stirred at 0ºC for 2h, then allowed to warm up to room

[65] Brodney, M.A.; Cole, M.L.; Freemont, J.A.; Kyi, S.; Junk, P.C.; Padwa, A.; Riches, A.G.; Ryan, J.H. *Tetrahedron Lett.* **2007**, *48*, 1939.

temperatre and stirred for 16 h. Afterwards, H_2O (30 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic extracts were washed with H_2O (2 x 20 mL) and brine (15 mL), then dried and concentrated to give 3-methylbut-3-en-1-yl methanesulfonate as an oil (4.9 g, cuant.). This compound was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.77 (s, 3H, C($C\underline{H_3}$)=CH_2), 2.45 (t, *J* = 6.9 Hz, 2H, $OCH_2C\underline{H_2}C(CH_3)=CH_2$), 3.00 (s, 3H, SO_2CH_3), 4.32 (t, *J* = 6.9 Hz, 2H, $OC\underline{H_2}CH_2C(CH_3)=CH_2$), 4.78 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 4.87 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.19 (C($\underline{C}H_3$)=CH_2), 36.9 (SO_2CH_3), 37.1 ($OCH_2\underline{C}H_2C(CH_3)=CH_2$), 68.2 ($O\underline{C}H_2CH_2C(CH_3)=CH_2$), 113.0 (C($CH_3$)=$\underline{C}H_2$), 140.3 ($\underline{C}(CH_3)=CH_2$).

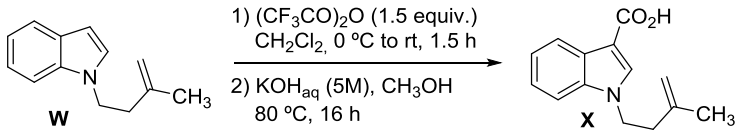
5.23. *N*-Alkylation of indole. Synthesis of 1-(3-methylbut-3-en-1-yl)-1*H*-indole (W)[66]



Over a suspension of NaH (0.57 g, 14.3 mmol) in dry DMF (25.6 mL), indole (1.2 g, 10.2 mmol) was added portionwise under argon atmosphere at 0 ºC. The mixture was stirred at 50 ºC for 30 minutes and afterwards, it was cooled down to 0 ºC and 3-methylbut-3-en-1-yl methanesulfonate (1.7 g, 10.2 mmol) was added slowly. The reaction mixture was stirred at room temperature for 16 h, quenched with H_2O (15 mL) and extracted with hexane (4 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 18/1), **W** was obtained as an oil (0.85 g, 36%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.93 (s, 3H, C($C\underline{H_3}$)=CH_2), 2.54-2.77 (m, 2H, $C\underline{H_2}C(CH_3)=CH_2$), 4.28-4.49 (m, 2H, $NC\underline{H_2}CH_2C(CH_3)=CH_2$), 4.88 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 4,98 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 6.66 (dd, *J* = 3.1, 0.9 Hz, 1H, H_3), 7.23 (d, *J* = 3.1 Hz, 1H, H_2), 7.28 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, H_5), 7.39 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, H_6), 7.48-7.55 (m, 1H, H_7), 7.77-7.85 (m, 1H, H_4); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.8 (C($\underline{C}H_3$)=CH_2), 38.3 ($NCH_2\underline{C}H_2C(CH_3)=CH_2$), 45.2 ($N\underline{C}H_2CH_2C(CH_3)=CH_2$), 101.3 ($C_3$), 109.5 ($C_7$), 112.7 (C($CH_3$)=$\underline{C}H_2$), 119.5 ($C_5$), 121.3 ($C_4$), 121.6 ($C_6$), 127.9 ($C_2$), 128.9 ($C_{3a}$), 136.1 ($C_{7a}$), 142.5 ($\underline{C}(CH_3)=CH_2$).

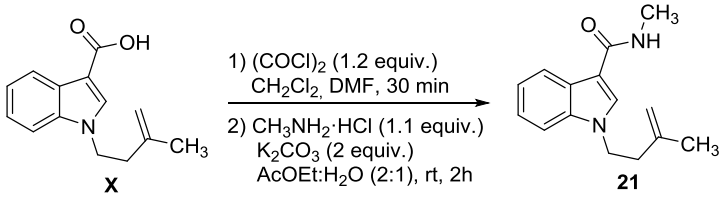
[66] Fernández, D.F.; Gulías, M.; Mascareñas, J.L.; López, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 9541.

5.24. Synthesis of 1-(3-methylbut-3-en-1-yl)-1*H*-indole-3-carboxylic acid (X)[66]



Over a solution of 1-(3-methylbut-3-en-1-yl)-1*H*-indole **W** (0.75 g, 4.1 mmol) in dry CH_2Cl_2 (5.5 mL), trifluoroacetic anhydride (0.86 mL, 6.2 mmol) was added at 0 ºC under argon atmosphere. The reaction mixture was stirred at rt for 1.5 h and after that time, the volatiles were evaporated *in vacuo*. The obtained residue was dissolved in CH_3OH (4.1 mL) and in a 5 M aqueous solution of KOH (4.1 mL, 20.6 mmol). The mixture was stirred at 80 ºC for 16 h and allowed to cool down to room temperature. Afterwards, a 10% aqueous solution of HCl was added until the solution reached pH 1-2 and it was extracted with AcOEt (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 4/6), **X** was obtained as an solid (0.71 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.82 (s, 3H, C(C<u>H</u>$_3$)=CH_2), 2.61 (t, *J* = 7.4 Hz, 2H, C<u>H</u>$_2$C(CH_3)=CH_2), 4.31 (t, *J* = 7.4 Hz, 2H, NC<u>H</u>$_2$$CH_2$C($CH_3$)=$CH_2$), 4.72 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 4.87 (br s, 1H, 1 × C(CH_3)=C<u>H</u>$_2$), 7.30-7.38 (m, 2H, H_5, H_6), 7.39-7.47 (m, 1H, H_7), 7.94 (s, 1H, H_2), 8.24-8.33 (m, 1H, H_4); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.5 (C(<u>C</u>H$_3$)=CH_2), 37.7 (NC<u>H</u>$_2$$CH_2$C($CH_3$)=$CH_2$), 45.6 (N<u>C</u>H$_2$$CH_2$ C(CH_3)=CH_2), 106.4 (C_3), 110.1 (C_7), 113.2 (C(CH_3)=<u>C</u>H$_2$), 122.0 (C_5), 122.2 (C_6), 122.9 (C_4), 127.1 (C_{3a}), 135.6 (C_2), 136.6 (C_{7a}), 141.4 (<u>C</u>(CH_3)=CH_2), 171.1 (CO).

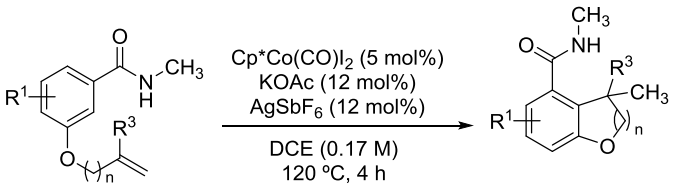
5.25. Synthesis of *N*-methyl-1-(3-methylbut-3-en-1-yl)-1*H*-indole-3-carboxamide (21)[57]



Over a solution of 1-(3-methylbut-3-en-1-yl)-1*H*-indole-3-carboxylic acid **X** (0.19 g, 0.81 mmol) in dry CH_2Cl_2 (4.1 mL), one drop of DMF was added under argon atmosphere, followed by dropwise addition of oxalyl chloride (82.3 µL, 0.97 mmol). The mixture was stirred for 30 min at room temperature and the volatiles were evaporated *in vacuo*. The residue was redissolved in AcOEt (2.8 mL) and then, CH_3NH_2·HCl (60.2 mg, 0.89 mmol),

K_2CO_3 (0.25 g, 1.8 mmol) and H_2O (1.4 mL) were subsequently added. The solution was stirred for 2 h and afterwards, the phases were separated. The aqueous phase was extracted with AcOEt (15 mL) and the combined organic extracts were washed with H_2O (15 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 4/6 to 0/10), amide **21** was obtained as a solid (0.12 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.79 (s, 3H, $C(C\underline{H_3})=CH_2$), 2.55 (t, *J* = 7.4 Hz, 2H, $NCH_2C\underline{H_2}C(CH_3)=CH_2$), 3.06 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.25 (t, *J* = 7.4 Hz, 2H, $NC\underline{H_2}CH_2C(CH_3)=CH_2$), 4.70 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 4.84 (br s, 1H, 1 × $C(CH_3)=C\underline{H_2}$), 6.00 (br s, 1H, NH), 7.23-7.33 (m, 2H, H_5, H_6), 7.37-7.44 (m, 1H, H_7), 7.71 (s, 1H, H_2), 7.92-7.98 (m, 1H, H_4); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 22.5 ($C(\underline{C}H_3)=CH_2$), 26.3 (NCH_3), 37.9 ($NCH_2\underline{C}H_2C(CH_3)=CH_2$), 45.4 ($N\underline{C}H_2CH_2C(CH_3)=CH_2$), 110.1 ($C_7$), 111.1 ($C_3$), 113.0 ($C(CH_3)=\underline{C}H_2$), 120.2 ($C_5$), 121.3 ($C_6$), 122.4 ($C_4$), 125.4 ($C_{3a}$), 131.2 ($C_2$), 136.4 ($C_{7a}$), 141.6 ($\underline{C}(CH_3)=CH_2$), 166.0 (CO).

5.26. General procedure for the Co(III)-catalyzed intramolecular C-H alkylation of amides 19aa-19dg and 21. Synthesis of dihydrobenzofurans 22aa-22ca, chromanes 23da-23dg and pyrroloindole 24

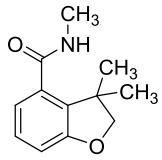


19aa-19dg

22aa, R^1 = H, R^3 = CH_3, n = 1
22ab, R^1 = 5-NO_2, R^3 = CH_3, n = 1
22ac, R^1 = 5-Br, R^3 = CH_3, n = 1
22ad, R^1 = 4,5-$(OCH_3)_2$, R^3 = CH_3, n = 1
22af, R^1 = 4-OCH_3, R^3 = CH_3, n = 1
22ag, R^1 = 4-F, R^3 = CH_3, n = 1
22ah, R^1 = 5-OBn, R^3 = CH_3, n = 1
22ai, R^1 = 5-OCH_3, R^3 = CH_3, n = 1
22aj, R^1 = 4,5-OCH_2O, R^3 = CH_3, n = 1
22ak, R^1 = 4,5-OCH_2CH_2O, R^3 = CH_3, n = 1
22al, R^1 = 5-$OCH_2C(CH_3)=CH_2$, R^3 = CH_3, n = 1
22am, R^1 = 5-Ph, R^3 = CH_3, n = 1
22an, R^1 = 5-[4$(OCH_3)C_6H_4$], R^3 = CH_3, n = 1
22ba, R^1 = H, R^3 = Ph, n = 1
22bf, R^1 = 4-OCH_3, R^3 = Ph, n = 1
22bg, R^1 = 4-F, R^3 = Ph, n = 1
22bj, R^1 = 4,5-OCH_2O, R^3 = Ph, n = 1
22ca, R^1 = H, R^3 = Et, n = 1
23da, R^1 = H, R^3 = CH_3, n = 2
23dg, R^1 = 4-F, R^3 = CH_3, n = 2

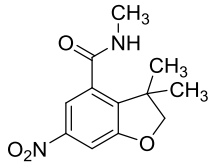
The corresponding amides **19aa-19dg** and **21** (1 equiv.), $AgSbF_6$ (0.12 equiv.), KOAc (0.12 equiv.) and Cp*Co(CO)I_2 (0.05 equiv.) were successively weighed in a 20-mL vial (23 × 72 mm). Then, DCE (0.17 M) was added and the mixture was stirred at room temperature for 3 minutes before placing the reaction vessel in an oil bath preheated to 120 ºC. The reaction mixture was stirred at that temperature for 4 h and afterwards, it was diluted with AcOEt (20 mL). The volatiles were evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt) to afford the corresponding benzofurans **22aa-22ca**, chromanes **23da-23dg** and pyrroloindole **24**.

*N,3,3-Trimethyl-2,3-dihydrobenzofuran-4-carboxamide (**22aa**)[57,64]*



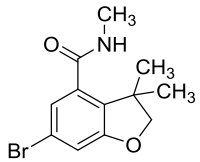
Prepared from *N*-methyl-3-((2-methylallyl)oxy)benzamide **19aa** (62.7 mg, 0.31 mmol), $AgSbF_6$ (12.6 mg, 0.037 mmol), KOAc (3.6 mg, 0.037 mmol) and $Cp^*Co(CO)I_2$ (7.3 mg, 0.015 mmol) in DCE (1.8 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **22aa** was obtained as a solid (57.0 mg, 91%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.43 (s, 6H, 2 × CH_3), 2.95 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.17 (s, 2H, 2 × H_2), 6.04 (br s, 1H, NH), 6.79-6.86 (m, 2H, H_5, H_7), 7.10 (t, *J* = 7.8, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 25.9 (2 × CH_3), 26.6 (NCH_3), 42.9 (C_3), 85.3 (C_2), 111.7 (C_7), 112.0 (C_5), 128.2 (C_6), 133.6 (C_{3a}), 133.8 (C_4), 160.3 (C_{7a}), 169.6 (CO).

*N,3,3-Trimethyl-6-nitro-2,3-dihydrobenzofuran-4-carboxamide (**22ab**)[64]*



Prepared from *N*-methyl-3-((2-methylallyl)oxy)-5-nitrobenzamide **19ab** (62.5 mg, 0.25 mmol), $AgSbF_6$ (10.3 mg, 0.030 mmol), KOAc (2.9 mg, 0.030 mmol) and $Cp^*Co(CO)I_2$ (5.9 mg, 0.012 mmol) in DCE (1.5 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **22ab** was obtained as a solid (56.9 mg, 91%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.44 (s, 6H, 2 × CH_3), 2.98 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.28 (s, 2H, 2 × H_2), 6.37 (br s, 1H, NH), 7.55 (d, *J* = 2.0 Hz, 1H, H_7), 7.71 (d, *J* = 2.0 Hz, 1H, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 25.5 (2 × CH_3), 26.8 (NCH_3), 43.2 (C_3), 86.2 (C_2), 106.5 (C_7), 114.8 (C_5), 133.8 (C_4), 141.6 (C_{3a}), 147.9 (C_6), 161.2 (C_{7a}), 167.3 (CO).

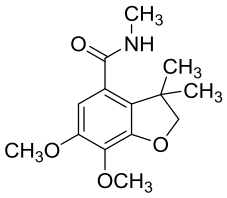
*6-Bromo-N,3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (**22ac**)*



Prepared from 3-bromo-*N*-methyl-5-((2-methylallyl)oxy)benzamide **19ac** (68.2 mg, 0.22 mmol), $AgSbF_6$ (9.0 mg, 0.027 mmol), KOAc (2.6 mg, 0.027 mmol) and $Cp^*Co(CO)I_2$ (5.2 mg, 0.011 mmol) in DCE (1.3 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **22ac** was obtained as a solid (60.6 mg, 84%): mp (CH_2Cl_2) 138-139 ºC; IR (ATR): ν (cm^{-1}) = 3228 (N-H), 1627 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.41 (s, 6H, 2 × CH_3), 2.95 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.19 (s, 2H, 2 × H_2), 6.11 (br s, 1H, NH), 6.93-7.02 (m, 2H, H_7, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 25.8 (2 × CH_3), 26.7 (NCH_3), 42.7 (C_3), 85.8 (C_2), 115.1 (C_7), 120.9 (C_6), 121.8 (C_5), 133.3 (C_{3a}), 134.6 (C_4), 161.3 (C_{7a}), 168.1 (CO); MS (ESI): *m/z* (%): 306.0 (MNa^+, 14), 286.0 (MH^+ + 2, 99), 285.0

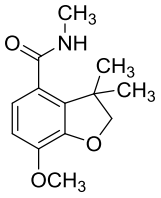
(MH^+ + 1, 10), 284.0 (MH^+, 100); HRMS (ESI): *m/z* calcd. for $C_{12}H_{15}BrNO_2$: 284.0286 [MH^+]; found: 284.0294.

*6,7-Dimethoxy-N,3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (**22ad**)*[64]



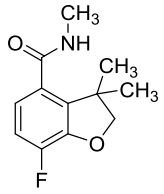
Prepared from 3,4-dimethoxy-*N*-methyl-5-((2-methylallyl)oxy)-benzamide **19ad** (65.2 mg, 0.25 mmol), $AgSbF_6$ (10.1 mg, 0.029 mmol), KOAc (2.9 mg, 0.029 mmol) and Cp*Co(CO)I_2 (5.8 mg, 0.012 mmol) in DCE (1.4 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **22ad** was obtained as a solid (57.0 mg, 87%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.39 (s, 6H, 2 × CH_3), 2.92 (d, *J* = 4.9 Hz, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.18 (s, 2H, 2 × H_2), 6.11 (br s, 1H, NH), 6.38 (s, 1H, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 25.9 (2 × CH_3), 26.6 (NCH_3), 42.9 (C_3), 56.4 (OCH_3), 60.6 (OCH_3), 86.3 (C_2), 103.6 (C_5), 127.1 (C_{3a}), 128.7 (C_4), 134.9 (C_7), 151.7, 152.2 (C_6, C_{7a}), 169.4 (CO).

*7-Methoxy-N,3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (**22af**)*[64]



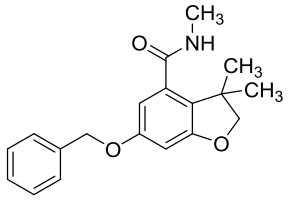
Prepared from 4-methoxy-*N*-methyl-3-((2-methylallyl)oxy)benzamide **19af** (65.8 mg, 0.28 mmol), $AgSbF_6$ (11.5 mg, 0.034 mmol), KOAc (3.3 mg, 0.034 mmol) and Cp*Co(CO)I_2 (6.7 mg, 0.014 mmol) in DCE (1.6 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 5/5), **22af** was obtained as a solid (41.2 mg, 63%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.37 (s, 6H, 2 × CH_3), 2.86 (d, *J* = 4.9 Hz, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 4.15 (s, 2H, 2 × H_2), 5.94 (br s, 1H, NH), 6.60 (d, *J* = 8.3 Hz, 1H, H_6), 6.78 (d, *J* = 8.3 Hz, 1H, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 25.8 (2 × CH_3), 26.7 (NCH_3), 43.7 (C_3), 55.9 (OCH_3), 86.0 (C_2), 110.3 (C_6), 120.2 (C_5), 126.0 (C_4), 135.3 (C_{3a}), 146.2 (C_{7a}), 148.4 (C_7), 169.4 (CO).

*7-Fluoro-N,3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (**22ag**)*[64]



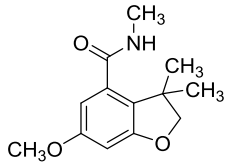
Prepared from 4-fluoro-*N*-methyl-3-((2-methylallyl)oxy)benzamide **19ag** (67.8 mg, 0.30 mmol), $AgSbF_6$ (12.5 mg, 0.036 mmol), KOAc (3.6 mg, 0.036 mmol) and Cp*Co(CO)I_2 (7.2 mg, 0.015 mmol) in DCE (1.8 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **22ag** was obtained as a solid (62.9 mg, 93%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.43 (s, 6H, 2 × CH_3), 2.92 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.25 (s, 2H, 2 × H_2), 6.13 (br s, 1H, NH), 6.78 (dd, *J* = 8.4, 4.3 Hz, 1H, H_5), 6.86 (dd, *J* = 9.9, 8.4 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 25.7 (2 × CH_3), 26.6 (NCH_3), 43.8 (d, *J* = 1.8 Hz, C_3), 86.5 (C_2), 115.1 (d, *J* = 17.3 Hz, C_6), 119.8 (d, *J* = 5.9 Hz, C_5), 129.4 (d, *J* = 3.6 Hz, C_4), 137.9 (d, *J* = 3.2 Hz, C_{3a}), 146.9 (d, *J* = 16.5 Hz, C_{7a}), 148.6 (d, *J* = 255.9 Hz, C_7), 168.9 (CO).

*6-(Benzyloxy)-N,3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (**22ah**)*



Prepared from 3-(benzyloxy)-*N*-methyl-5-((2-methylallyl)oxy)-benzamide **19ah** (68.2 mg, 0.22 mmol), $AgSbF_6$ (9.0 mg, 0.027 mmol), KOAc (2.6 mg, 0.027 mmol) and Cp*Co(CO)I_2 (5.2 mg, 0.011 mmol) in DCE (1.3 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **22ah** was obtained as a solid (62.1 mg, 91%): mp (CH_2Cl_2) 102-104 ºC; IR (ATR): ν (cm^{-1}) = 3307 (N-H), 1612 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.42 (s, 6H, 2 × CH_3), 2.93 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.18 (s, 2H, 2 × H_2), 4.99 (s, 2H, O$\underline{C}H_2$Ph), 6.15 (br s, 1H, NH), 6.49 (s, 2H, H_5, H_7), 7.27-7.46 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.2 (2 × CH_3), 26.6 (NCH_3), 42.4 (C_3), 70.4 (O$\underline{C}H_2$Ph), 86.0 (C_2), 98.8 (C_5), 106.0 (C_7), 126.3 (C_{3a}), 127.5 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 133.7 (C_4), 136.6 ($C_{1'}$), 159.1 (C_6), 161.6 (C_{7a}), 169.4 (CO); MS (ESI): *m/z* (%): 335.1 (MNa^+ + 1, 17), 334.1 (MNa^+, 100), 313.2 (MH^+ + 1, 6), 312.2 (MH^+, 36); HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}NO_3$: 312.1600 [MH^+]; found: 312.1590.

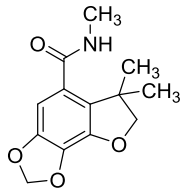
*6-Methoxy-N,3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (**22ai**)*[64]



Prepared from 3-methoxy-*N*-methyl-5-((2-methylallyl)oxy)-benzamide **19ai** (68.2 mg, 0.29 mmol), $AgSbF_6$ (12.0 mg, 0.035 mmol), KOAc (3.4 mg, 0.035 mmol) and Cp*Co(CO)I_2 (6.9 mg, 0.014 mmol) in DCE (1.7 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 5/5), **22ai** was

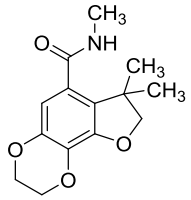
obtained as a solid (55.4 mg, 81%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.38 (s, 6H, 2 × CH_3), 2.92 (d, *J* = 4.9 Hz, 3H, NCH_3), 3.73 (s, 3H, OCH_3), 4.16 (s, 2H, 2 × H_2), 6.09 (br s, 1H, NH), 6.36 (d, *J* = 2.3 Hz, 1H, H_7), 6.39 (d, *J* = 2.3 Hz, 1H, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.1 (2 × CH_3), 26.5 (NCH_3), 42.4 (C_3), 55.6 (OCH_3), 86.0 (C_2), 97.9 (C_5), 104.9 (C_7), 125.9 (C_{3a}), 133.6 (C_4), 160.0 (C_6), 161.6 (C_{7a}), 169.4 (CO).

*N,6,6-Trimethyl-6,7-dihydro-[1,3]dioxolo[4,5-g]benzofuran-5-carboxamide (**22aj**)*



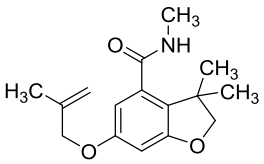
Prepared from *N*-methyl-7-((2-methylallyl)oxy)benzo[*d*][1,3]dioxole-5-carboxamide **19aj** (64.2 mg, 0.26 mmol), $AgSbF_6$ (10.6 mg, 0.031 mmol), KOAc (3.0 mg, 0.031 mmol) and Cp*Co(CO)I_2 (6.1 mg, 0.013 mmol) in DCE (1.5 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **22aj** was obtained as a solid (60.5 mg, 94%): mp (CH_2Cl_2) 176-177 ºC; IR (ATR): ν (cm^{-1}) = 3307 (N-H), 1649 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.42 (s, 6H, 2 × CH_3), 2.94 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.24 (s, 2H, 2 × H_2), 5.96 (br s, 3H, NH, OCH_2O), 6.41 (s, 1H, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 25.7 (2 × CH_3), 26.7 (NCH_3), 43.2 (C_3), 87.1 (C_2), 100.1 (OCH_2O), 101.9 (C_5), 126.0 (C_{3a}), 131.3 (C_4), 131.7 (C_7), 142.5 (C_6), 148.5 (C_{7a}), 169.1 (CO); MS (ESI): *m/z* (%): 273.1 (MNa^+ + 1, 10), 272.1 (MNa^+, 100), 251.1 (MH^+ + 1, 5), 250.1 (MH^+, 51), 193.1 (11); HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}NO_4$: 250.1079 [MH^+]; found: 250.1077.

*N,7,7-Trimethyl-2,3,7,8-tetrahydro-[1,4]dioxino[2,3-g]benzofuran-6-carboxamide (**22ak**)*[64]



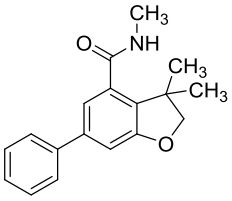
Prepared from *N*-methyl-8-((2-methylallyl)oxy)-2,3-dihydrobenzo[*b*]-[1,4]dioxine-6-carboxamide **19ak** (71.5 mg, 0.27 mmol), $AgSbF_6$ (11.2 mg, 0.033 mmol), KOAc (3.2 mg, 0.033 mmol) and Cp*Co(CO)I_2 (6.5 mg, 0.014 mmol) in DCE (1.6 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 5/5), **22ak** was obtained as a solid (41.4 mg, 58%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.42 (s, 6H, 2 × CH_3), 2.93 (d, *J* = 4.7 Hz, 3H, NCH_3), 4.15-4.34 (m, 6H, OCH_2CH_2O, 2 × H_2), 5.93 (br s, 1H, NH), 6.44 (s, 1H, H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.0 (2 × CH_3), 26.6 (NCH_3), 43.3 (C_3), 64.4 ($O\underline{C}H_2CH_2O$), 64.6 ($OCH_2\underline{C}H_2O$), 86.9 (C_2), 108.2 (C_5), 124.9 (C_{3a}), 127.9 (C_4), 130.8 (C_7), 143.2 (C_6), 148.3 (C_{7a}), 169.0 (CO).

*N,3,3-Trimethyl-6-((2-methylallyl)oxy)-2,3-dihydrobenzofuran-4-carboxamide (**22al**)*



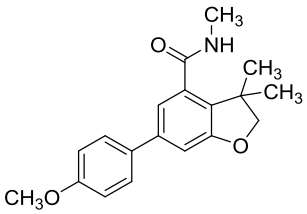
Prepared from *N*-methyl 3,5-bis((2-methylallyl)oxy)benzamide **19al** (61.0 mg, 0.22 mmol), $AgSbF_6$ (9.1 mg, 0.027 mmol), KOAc (2.6 mg, 0.027 mmol) and Cp*Co(CO)I_2 (5.3 mg, 0.011 mmol) in DCE (1.3 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **22al** was obtained as an oil (40.8 mg, 67%): IR (ATR): ν (cm^{-1}) = 3300 (N-H), 1648 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.33 (s, 6H, 2 × CH_3), 1.72 (s, 3H, C(C$\underline{H_3}$)=CH_2), 2.87 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.10 (s, 2H, 2 × H_2), 4.29 (s, 2H, OC$\underline{H_2}$C(CH_3)=CH_2), 4.90 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 4.98 (br s, 1H, 1 × C(CH_3)=C$\underline{H_2}$), 5.88 (br s, 1H, NH), 6.35 (s, 2H, H_5, H_7); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 19.4 (C($\underline{C}H_3$)=CH_2), 26.2 (2 × CH_3), 26.6 (NCH_3), 42.4 (C_3), 72.1 (O$\underline{C}H_2$C(CH_3)=CH_2), 86.0 (C_2), 98.7 (C_5), 105.9 (C_7), 112.9 (C(CH_3)=$\underline{C}H_2$), 126.1 (C_{3a}), 133.6 (C_4), 140.6 ($\underline{C}$(CH_3)=CH_2), 159.2 (C_6), 161.6 (C_{7a}), 169.4 (CO); MS (ESI): *m/z* (%): 298.1 (MNa^+, 40), 277.2 (MH^+ + 1, 13), 276.2 (MH^+, 100), 245.1 (4), 219.1 (19); HRMS (ESI): *m/z* calcd. for $C_{16}H_{22}NO_3$: 276.1600 [MH^+]; found: 276.1605.

*N,3,3-Trimethyl-6-phenyl-2,3-dihydrobenzofuran-4-carboxamide (**22am**)*



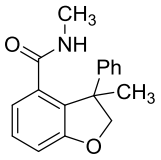
Prepared from *N*-methyl-5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxamide **19am** (64.4 mg, 0.23 mmol), $AgSbF_6$ (9.4 mg, 0.028 mmol), KOAc (2.7 mg, 0.028 mmol) and Cp*Co(CO)I_2 (5.5 mg, 0.011 mmol) in DCE (1.4 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **22am** was obtained as a solid (62.0 mg, 96%): mp (CH_2Cl_2) 128-130 ºC; IR (ATR): ν (cm^{-1}) = 3246 (N-H), 1631 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.48 (s, 6H, 2 × CH_3), 2.96 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.23 (s, 2H, 2 × H_2), 6.03 (br s, 1H, NH), 7.06 (s, 1H, H_7), 7.08 (s, 1H, H_5), 7.30-7.49 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.49-7.57 (m, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.0 (2 × CH_3), 26.6 (NCH_3), 42.8 (C_3), 85.6 (C_2), 110.3 (C_7), 118.2 (C_5), 127.0 ($C_{2'}$, $C_{6'}$), 127.6 ($C_{4'}$), 128.8 ($C_{3'}$, $C_{5'}$), 132.9 (C_{3a}), 133.8 (C_4), 140.3 (C_6), 141.9 ($C_{1'}$), 161.0 (C_{7a}), 169.6 (CO); MS (ESI): *m/z* (%): 305.1 (MNa^+ + 1, 15), 304.1 (MNa^+, 100), 283.2 (MH^+ + 1, 9), 282.1 (MH^+, 58), 225.1 (2); HRMS (ESI): *m/z* calcd. for $C_{18}H_{20}NO_2$: 282.1494 [MH^+]; found: 282.1492.

*6-(4-Methoxyphenyl)-N,3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (**22an**)*



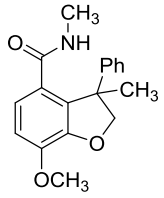
Prepared from 4´-methoxy-*N*-methyl-5-((2-methylallyl)oxy)-[1,1´-biphenyl]-3-carboxamide **19an** (73.1 mg, 0.23 mmol), $AgSbF_6$ (9.7 mg, 0.028 mmol), KOAc (2.8 mg, 0.028 mmol) and Cp*Co(CO)I_2 (5.6 mg, 0.012 mmol) in DCE (1.4 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3), **22an** was obtained as a solid (64.4 mg, 88%): mp (CH_2Cl_2) 120-123 ºC; IR (ATR): ν (cm^{-1}) = 3349 (N-H), 1637 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.47 (s, 6H, 2 × CH_3), 2.97 (d, *J* = 4.8 Hz, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 4.22 (s, 2H, 2 × H_2), 6.09 (br s, 1H, NH), 6.94 (d, *J* = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.00-7.05 (m, 2H, H_5, H_7), 7.45 (d, *J* = 8.7 Hz, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.0 (2 × CH_3), 26.6 (NCH_3), 42.8 (C_3), 55.3 (OCH_3), 85.6 (C_2), 109.8 (C_7), 114.2 ($C_{3'}$, $C_{5'}$), 117.7 (C_5), 128.1 ($C_{2'}$, $C_{6'}$), 132.3 (C_{3a}), 132.8 (C_4), 133.8 ($C_{1'}$), 141.5 (C_6), 159.4, 161.0 ($C_{4'}$, C_{7a}), 169.7 (CO); MS (ESI): *m/z* (%): 335.1 (MNa^+ + 1, 3), 334.1 (MNa^+, 21), 313.2 (MH^+ + 1, 16), 312.2 (MH^+, 100), 255.1 (3); HRMS (ESI): *m/z* calcd. for $C_{19}H_{22}NO_3$: 312.1600 [MH^+]; found: 312.1603.

*N,3-Dimethyl-3-phenyl-2,3-dihydrobenzofuran-4-carboxamide (**22ba**)*[57]



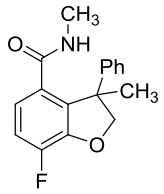
Prepared from *N*-methyl-3-((2-phenylallyl)oxy)benzamide **19ba** (70.0 mg, 0.26 mmol), $AgSbF_6$ (10.8 mg, 0.031 mmol), KOAc (3.1 mg, 0.031 mmol) and Cp*Co(CO)I_2 (6.2 mg, 0.013 mmol) in DCE (1.5 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **22ba** was obtained as a solid (53.1 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.88 (s, 3H, CH_3), 2.49 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.45 (s, *J* = 8.6 Hz, 1H, 1 × H_2), 4.54 (s, *J* = 8.6 Hz, 1H, 1 × H_2), 5.11 (br s, 1H, NH), 6.97 (d, *J* = 7.8 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.19-7.37 (m, 6H, H_5, H_6, H_7, $H_{3'}$, $H_{4'}$, $H_{5'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 24.1 (CH_3), 26.1 (NCH_3), 50.0 (C_3), 87.2 (C_2), 111.8 (C_7), 120.4 (C_5), 126.4 ($C_{2'}$, $C_{6'}$), 126.8 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 129.1 (C_6), 132.8 (C_{3a}), 133.9 (C_4), 145.9 ($C_{1'}$), 160.4 (C_{7a}), 168.6 (CO).

*7-Methoxy-N,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-4-carboxamide (**22bf**)*



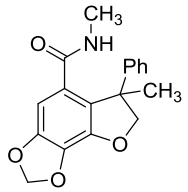
Prepared from 4-methoxy-*N*-methyl-3-((2-phenylallyl)oxy)benzamide **19bf** (72.6 mg, 0.24 mmol), $AgSbF_6$ (10.1 mg, 0.029 mmol), KOAc (2.9 mg, 0.029 mmol) and Cp*Co(CO)I_2 (5.8 mg, 0.012 mmol) in DCE (1.4 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 4/6), **22bf** was obtained as a solid (31.7 mg, 44%): mp (CH_2Cl_2) 124-125 ºC; IR (ATR): ν (cm^{-1}) = 3310 (N-H), 1648 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.90 (s, 3H, CH_3), 2.50 (d, *J* = 4.9 Hz, 3H, NCH_3), 3.96 (s, 3H, OCH_3), 4.52 (d, *J* = 8.7 Hz, 1H, 1 × H_2), 4.60 (d, *J* = 8.7 Hz, 1H, 1 × H_2), 5.04 (br s , 1H, NH), 6.84 (d, *J* = 8.4 Hz, 1H, H_6), 7.07 (d, *J* = 8.4 Hz, 1H, H_5), 7.21-7.42 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 23.9 (CH_3), 26.2 (NCH_3), 50.8 (C_3), 56.0 (OCH_3), 87.8 (C_2), 111.2 (C_6), 122.0 (C_5), 126.0 (C_4), 126.3 ($C_{2'}$, $C_{6'}$), 126.9 ($C_{4'}$), 128.7 ($C_{3'}$, $C_{5'}$), 133.9 (C_{3a}), 145.8 ($C_{1'}$), 146.4 (C_{7a}), 148.6 (C_7), 168.3 (CO); MS (ESI): *m/z* (%): 321.1 (MNa^+ + 1, 6), 320.1 (MNa^+, 43), 299.1 (MH^+ + 1, 15), 298.1 (MH^+, 100), 220.1 (6); HRMS (ESI): *m/z* calcd. for $C_{18}H_{20}NO_3$: 298.1443 [MH^+]; found: 298.1445.

*7-Fluoro-N,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-4-carboxamide (**22bg**)*



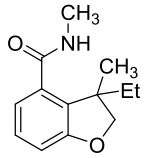
Prepared from 4-fluoro-*N*-methyl-3-((2-phenylallyl)oxy)benzamide **19bg** (73.3 mg, 0.26 mmol), $AgSbF_6$ (10.6 mg, 0.031 mmol), KOAc (3.0 mg, 0.031 mmol) and Cp*Co(CO)I_2 (6.1 mg, 0.013 mmol) in DCE (1.5 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **22bg** was obtained as a solid (63.2 mg, 86%): mp (CH_2Cl_2) 156-158 ºC; IR (ATR): ν (cm^{-1}) = 3339 (N-H), 1652 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.91 (s, 3H, CH_3), 2.49 (d, *J* = 4.8 Hz, 3H, NCH_3), 4.56 (d, *J* = 8.7 Hz, 1H, 1 × H_2), 4.64 (d, *J* = 8.7 Hz, 1H, 1 × H_2), 5.08 (br s, 1H, NH), 6.96 (dd, *J* = 4.4, 8.4 Hz, H_5), 7.00-7.05 (m, 1H, H_6), 7.19-7.44 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 23.9 (CH_3), 26.2 (NCH_3), 50.9 (C_3), 88.4 (C_2), 116.0 (d, *J* = 17.2 Hz, C_6), 121.4 (d, *J* = 6.0 Hz, C_5), 126.4 ($C_{2'}$, $C_{6'}$), 127.0 ($C_{4'}$), 128.7 ($C_{3'}$, $C_{5'}$), 129.6 (d, *J* = 3.7 Hz, C_4), 136.7 (d, *J* = 2.8 Hz, C_{3a}), 145.0 ($C_{1'}$), 147.1 (d, *J* = 11.1 Hz, C_{7a}), 148.8 (d, *J* = 250.1 Hz, C_7), 167.7 (CO); MS (ESI): *m/z* (%): 310.1 (MNa^+ + 2, 1), 309.1 (MNa^++ 1, 16), 308.1 (MNa^+, 100), 287.1 (MH^+ + 1, 4), 286.1 (MH^+, 27), 208.1 (5); HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}FNO_2$: 286.1243 [MH^+]; found: 286.1242.

*N,6-Dimethyl-6-phenyl-6,7-dihydro-[1,3]dioxolo[4,5-g]benzofuran-5-carboxamide (**22bj**)*



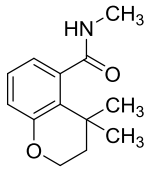
Prepared from *N*-methyl-7-((2-phenylallyl)oxy)benzo[*d*][1,3]dioxole-5-carboxamide **19bj** (71.4 mg, 0.23 mmol), $AgSbF_6$ (9.5 mg, 0.028 mmol), KOAc (2.7 mg, 0.028 mmol) and $Cp^*Co(CO)I_2$ (5.5 mg, 0.011mmol) in DCE (1.4 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **22bj** was obtained as a solid (54.9 mg, 77%): mp (CH_2Cl_2) 158-160 ºC; IR (ATR): ν (cm^{-1}) = 3285 (N-H), 1640 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.87 (s, 3H, CH_3), 2.47 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.50 (d, *J* = 8.6 Hz, 1H, 1 × H_2), 4.59 (d, *J* = 8.6 Hz, 1H, 1 × H_2), 5.07 (br s , 1H, NH), 6.02 (br s, 1H, 1 × OCH_2O), 6.04 (br s, 1H, 1 × OCH_2O), 6.58 (s, 1H, H_5), 7.16-7.46 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 23.9 (CH_3), 26.2 (NCH_3), 50.2 (C_3), 88.8 (C_2), 101.7 (OCH_2O), 102.2 (C_5), 126.3 ($C_{2'}$, $C_{6'}$), 126.6 (C_{3a}), 126.9 ($C_{4'}$), 128.7 ($C_{3'}$, $C_{5'}$), 130.2 (C_4), 131.9 (C_7), 142.6 (C_6), 145.7 ($C_{1'}$), 149.2 (C_{7a}), 168.0 (CO); MS (ESI): *m/z* (%): 335.1 (MNa^+ + 1, 7), 334.1 (MNa^+, 50), 313.1 (MH^+ + 1, 15), 312.1 (MH^+, 100), 234.1 (7); HRMS (ESI): *m/z* calcd. for $C_{18}H_{18}NO_4$: 312.1236 [MH^+]; found: 312.1242.

*3-Ethyl-N,3-dimethyl-2,3-dihydrobenzofuran-4-carboxamide (**22ca**)*[57,64]



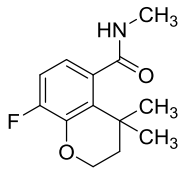
Prepared from *N*-methyl-3-(2-methylenebutoxy)benzamide **19ca** (60.0 mg, 0.27 mmol), $AgSbF_6$ (11.3 mg, 0.033 mmol), KOAc (3.2 mg, 0.033 mmol) and $Cp^*Co(CO)I_2$ (6.5 mg, 0.014 mmol) in DCE (1.6 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **22ca** was obtained as an oil (47.9 mg, 80%): IR (ATR): ν (cm^{-1}) = 3317 (N-H), 1637 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.79 (t, *J* = 7.5 Hz, 3H, $CH_2\underline{CH_3}$), 1.40 (s, 3H, CH_3), 1.74 (dq, *J* = 14.7, 7.5 Hz, 1H, 1 × $\underline{CH_2}CH_3$), 1.87-2.04 (m, 1H, 1 × $\underline{CH_2}CH_3$), 2.93 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.09 (d, *J* = 8.5 Hz, 1H, 1 × H_2), 4.34 (d, *J* = 8.5 Hz, 1H, 1 × H_2), 6.03 (br s, 1H, NH), 6.79-6.83 (m, 2H, H_5, H_7), 7.10 (t, *J* = 7.8 Hz, 1H, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 9.2 ($CH_2\underline{C}H_3$), 24.6 (CH_3), 26.6 (NCH_3), 31.5 ($\underline{C}H_2CH_3$), 46.9 (C_3), 82.3 (C_2), 111.5 (C_7), 119.0 (C_5), 128.2 (C_6), 132.4 (C_{3a}), 134.0 (C_4), 160.8 (C_{7a}), 169.7 (CO); MS (ESI): *m/z* (%): 243.1 (MNa^+ + 1, 1), 242.1 (MNa^+, 12), 221.1 (MH^+ + 1, 10), 220.1 (MH^+, 100), 163.1 (3), 152.1 (2), 121.1 (2), 107.0 (2); HRMS (ESI): *m/z* calcd. for $C_{13}H_{18}NO_2$: 220.1338 [MH^+]; found: 220.1336.

*N,4,4-Trimethylchroman-5-carboxamide (**23da**)*[57,64]



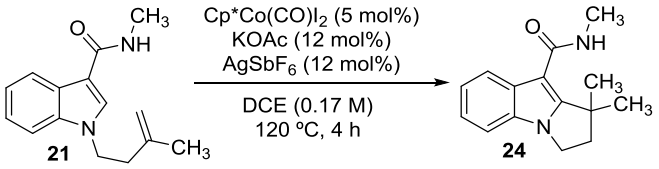
Prepared from *N*-methyl-3-((3-methylbut-3-en-1-yl)oxy)benzamide **19da** (61.5 mg, 0.28 mmol), $AgSbF_6$ (11.6 mg, 0.034 mmol), KOAc (3.3 mg, 0.034 mmol) and $Cp^*Co(CO)I_2$ (6.7 mg, 0.014 mmol) in DCE (1.5 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **23da** was obtained as a solid (38.0 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.45 (s, 6H, 2 × CH_3), 1.71-1.85 (m, 2H, 2 × H_3), 2.94 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.18-4.33 (m, 2H, 2 × H_2), 5.91 (br s, 1H, NH), 6.74 (dd, *J* = 7.3, 1.4 Hz, 1H, H_8), 6.82 (dd, *J* = 8.2, 1.4 Hz, 1H, H_6), 7.10 (dd, *J* = 8.2, 7.3 Hz, 1H, H_7); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.8 (NCH_3), 29.3 (2 × CH_3), 31.6 (C_4), 39.5 (C_3), 62.5 (C_2), 118.9 (C_8), 120.2 (C_6), 127.0 (C_7), 128.3 (C_5), 138.1 (C_{4a}), 154.1 (C_{8a}), 172.9 (CO).

*8-Fluoro-N,4,4-trimethylchroman-5-carboxamide (**23dg**)*



Prepared from 4-fluoro-*N*-methyl-3-((3-methylbut-3-en-1-yl)oxy)benzamide **19dg** (68.5 mg, 0.29 mmol), $AgSbF_6$ (11.9 mg, 0.035 mmol), KOAc (3.4 mg, 0.035 mmol) and $Cp^*Co(CO)I_2$ (6.9 mg, 0.014 mmol) in DCE (1.7 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3) **23dg** was obtained as a solid (53.2 mg, 78%): mp (CH_2Cl_2) 179-181 ºC; IR (ATR): ν (cm^{-1}) = 3300 (N-H), 1627 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.43 (s, 6H, 2 × CH_3), 1.72-1.85 (m, 2H, 2 × H_3), 2.90 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.23-4.35 (m, 2H, 2 × H_2), 6.06 (br s, 1H, NH), 6.65 (dd, *J* = 8.3, 5.3 Hz, 1H, H_6), 7.10 (dd, *J* = 10.2, 8.3 Hz, 1H, H_7); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.8 (NCH_3), 29.0 (2 × CH_3), 31.7 (d, *J* = 2.2 Hz, C_4), 39.0 (C_3), 62.8 (C_2), 113.0 (d, *J* = 18.6 Hz, C_7), 119.2 (d, *J* = 7.8 Hz, C_6), 131.2 (C_{4a}), 133.4 (d, *J* = 4.0 Hz, C_5), 142.7 (d, *J* = 10.1 Hz, C_{8a}), 152.5 (d, *J* = 247.3 Hz, C_8), 172.1 (CO); MS (ESI): *m/z* (%): 261.1 (MNa^+ + 1, 8), 260.1 (MNa^+, 83), 239.1 (MH^+ + 1, 10), 238.1 (MH^+, 100), 170.1 (5); HRMS (ESI): *m/z* calcd. for $C_{13}H_{17}FNO_2$: 238.1243 [MH^+]; found: 238.1237.

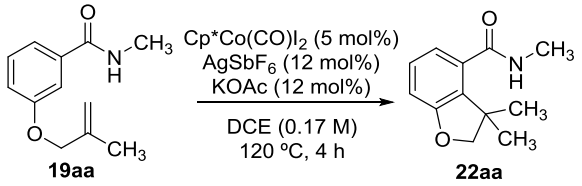
*N,1,1-Trimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide (**24**)*[57]



Prepared from *N*-methyl-1-(3-methylbut-3-en-1-yl)-1*H*-indole-3-carboxamide **21** (68.4 mg, 0.28 mmol), $AgSbF_6$ (11.6 mg, 0.034 mmol), KOAc (3.3 mg, 0.034 mmol) and $Cp^*Co(CO)I_2$ (6.7 mg, 0.014 mmol) in DCE (1.7 mL). After purification by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4), **24** was obtained as a solid (64.3 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.62 (s, 6H, 2 × CH_3), 2.46 (t, *J* = 7.0 Hz, 2H, 2 × $H_{3'}$), 3.06 (d, *J* = 4.9 Hz, 3H, NCH_3), 4.09 (t, *J* = 7.0 Hz, 2H, 2 × $H_{2'}$), 5.96 (br s, 1H, NH), 7.14-7.33 (m, 3H, H_5, H_6, H_7), 7.60-7.74 (m, 1H, H_4); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.3 (NCH_3), 26.5 (2 × CH_3), 40.5 ($C_{4'}$), 42.7 ($C_{3'}$), 44.1 ($C_{2'}$), 102.4 (C_7), 110.3 (C_3), 119.0 (C_5), 120.9, 121.3 (C_4, C_6), 129.4 (C_{3a}), 131.7 (C_{7a}), 156.5 (C_2), 166.1 (CO).

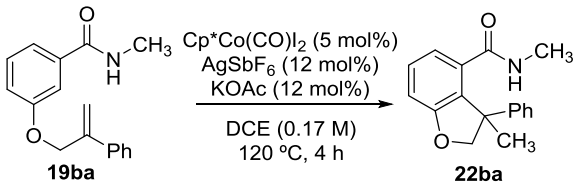
5.27. Cp*Co(III)-catalyzed synthesis of 22aa and 22ba in a 1 mmol scale

*5.27.1. Synthesis of **22aa** in a 1 mmol scale*



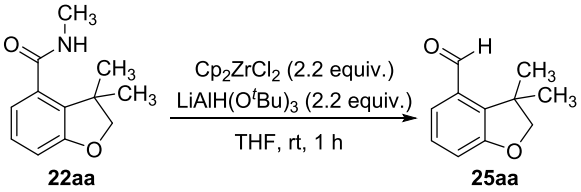
Amide **19aa** (0.21 g, 1.0 mmol), $AgSbF_6$ (42.2 mg, 0.12 mmol), KOAc (12.1 mg, 0.12 mmol) and $Cp^*Co(CO)I_2$ (24.4 mg, 0.05 mmol) were successively weighed in a 50-mL vial (25 × 150 mm). Then, DCE (6 mL) was added and the mixture was stirred at room temperature for 3 minutes before placing the reaction vessel in an oil bath preheated to 120 ºC. The reaction mixture was stirred at that temperature for 4 h and afterwards, it was diluted with AcOEt (20 mL). The volatiles were evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4) to afford **22aa** as a solid (0.20 mg, 93%).

*5.27.1. Synthesis of **22ba** in a 1 mmol scale*



Amide **19ba** (0.27 g, 1.0 mmol), $AgSbF_6$ (41.2 mg, 0.12 mmol), KOAc (11.8 mg, 0.12 mmol) and Cp*Co(CO)I_2 (23.4 mg, 0.05 mmol) were successively weighed in a 50-mL vial (25 × 150 mm). Then, DCE (5.9 mL) was added and the mixture was stirred at room temperature for 3 minutes before placing the reaction vessel in an oil bath preheated to 120 ºC. The reaction mixture was stirred at that temperature for 4 h and afterwards, it was diluted with AcOEt (20 mL). The volatiles were evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4) to afford **22ba** as a solid (0.17 mg, 65%).

5.28. Removal of the directing group. Synthesis of 3,3-dimethyl-2,3-dihydrobenzofuran-4-carbaldehyde (25aa)[67] by reduction of amide 22aa *via* an *in situ* formed Schwartz reagent.

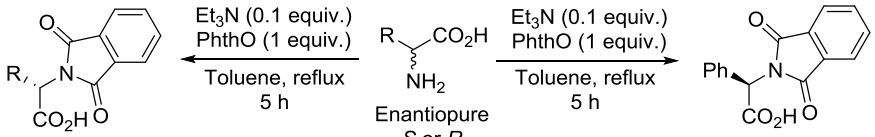


To a solution of *N*,3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide **22aa** (51.8 mg, 0.25 mmol) and Cp_2ZrCl_2 (0.16 g, 5.6 mmol) in dry THF (3 mL), a solution of LiAlH(O^tBu)$_3$ (1 M in THF) (0.56 mL, 5.6 mmol) was rapidly added under argon atmosphere. The reaction mixture was stirred at room temperature for 1 h and it was quenched by addition of H_2O (10 mL). A 0.5 M aqueous solution of HCl was added to adjust pH below 7 and the mixture was extracted with AcOEt (2 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. After purification by flash column

[67] Guan, Z.; Chen, S.; Huang, Y.; Yao, H. *Org. Lett.* **2019**, *21*, 3959.

chromatography (silica gel, petroleum ether/AcOEt 18/1), **25aa** was obtained as a solid (31.7 mg, 71%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.45 (s, 6H, 2 × CH_3), 4.19 (s, 2H, 2 × H_2), 6.95 (dd, *J* = 7.8, 1.1 Hz, 1H, H_7), 7.23 (d, *J* = 7.8 Hz, 1H, H_6), 7.31 (dd, *J* = 7.8, 1.2 Hz, 1H, H_5), 10.1 (s, 1H, C(O)H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 27.0 (2 × CH_3), 43.3 (C_3), 85.3 (C_2), 115.6 (C_7), 124.7 (C_5), 128.6 (C_6), 133.4 (C_4), 136.7 (C_{3a}), 160.8 (C_{7a}), 191.4 (CO).

5.29. General procedure for the synthesis of chiral carboxylic acids CCA1-CCA4

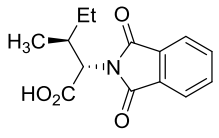


CCA1, R = *sec*-Bu
CCA2, R = ^{t}Bu
CCA3, R = Bn

CCA4

Over a solution of the corresponding enantiomerically pure and commercially available amino acid (1 mmol) in dry toluene (15 ml), phthalic anhydride (1 mmol) and Et_3N (0.1 equiv.) were subsequently added under argon atmosphere. The reaction was heated at relux for 5 h and afterwards, it was allowed to cool down to room temperature. Then, the solvent was removed under vacuum and the residue redissolved in CH_2Cl_2 (30 mL). The organic phase was washed with a 1M aqueous solution of HCl (2 × 15 mL) and with brine (15 mL), after which the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded the corresponding chiral carboxylic acids **CCA1-CCA4**.

*(2S,3S)-2-(1,3-Dioxoisoindolin-2-yl)-3-methylpentanoic acid (**CCA1**)*[68]

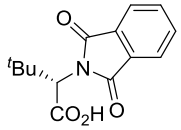


Prepared from L-*iso*-leucine (1.3 g, 10 mmol), phthalic anhydride (1.5 g, 10 mmol) and Et_3N (0.14 mL, 1.0 mmol) in dry toluene. After work-up and purification by flash column chromatography, **CCA1** was obtained as a solid (1.9 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.87 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H_3}$), 0.91-1.11 (m, 1H, 1 × $C\underline{H_2}CH_3$), 1.14 (d, *J* = 6.7 Hz, 3H, $CHC\underline{H_3}$), 1.46-1.61 (m, 1H, 1 × $C\underline{H_2}CH_3$), 2.48-2.63 (m, 1H, $C\underline{H}CH_3$), 4.72 (d, *J* = 8.4 Hz, 1H, $C\underline{H}^{sec}$Bu), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H, H_4, H_5), 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H, H_3, H_6), 10.3 (br s, 1H, CO_2H);

[68] Vincent, A.; Deschamps, D.; Martzel, T.; Lohier, J.-F.; Richards, C.J.; Gaumont, A.-C.; Perrio, S. *J. Org. Chem.* **2016**, *81*, 3961.

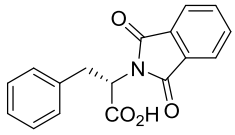
^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 10.9 ($CH_2\underline{C}H_3$), 16.8 ($CH\underline{C}H_3$), 25.9 ($\underline{C}H_2CH_3$), 34.4 ($\underline{C}HCH_3$), 57.0 ($\underline{C}H^{sec}Bu$), 123.7 (C_3, C_6), 131.6 (C_{2a}, C_{6a}), 134.3 (C_4, C_5), 167.8 (C_2O, C_7O), 174.5 ($\underline{C}O_2H$); $[\alpha]_D^{20}$ = -88.4 (c = 0.098 g/100 mL in CH_2Cl_2).

*(S)-2-(1,3-Dioxoisoindolin-2-yl)-3,3-dimethylbutanoic acid (**CCA2**)*[69]



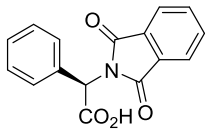
Prepared from L-*tert*-leucine (1.3 g, 10 mmol), phthalic anhydride (1.5 g, 10 mmol) and Et_3N (0.14 mL, 1.0 mmol) in dry toluene. After work-up and purification by flash column chromatography, **CCA2** was obtained as a solid (1.4 g, 54%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.20 (s, 9H, $C(CH_3)_3$), 4.75 (s, 1H, $C\underline{H}^tBu$), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H, H_4, H_5), 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H, H_3, H_6), 9.95 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 28.0 ($C(\underline{C}H_3)_3$), 35.7 ($\underline{C}(CH_3)_3$), 59.9 ($\underline{C}H^tBu$), 123.7 (C_3, C_6), 131.6 (C_{2a}, C_{6a}), 134.3 (C_4, C_5), 168.0 (C_2O, C_7O), 173.7 ($\underline{C}O_2H$); $[\alpha]_D^{20}$ = -98.5 (c = 0.13 g/100 mL in CH_2Cl_2).

*(S)-2-(1,3-Dioxoisoindolin-2-yl)-3-phenylpropanoic acid (**CCA3**)*[70]



Prepared from L-phenylalanine (1.7 g, 10 mmol), phthalic anhydride (1.5 g, 10 mmol) and Et_3N (0.14 mL, 1.0 mmol) in dry toluene. After work-up and purification by flash column chromatography, **CCA3** was obtained as a solid (2.1 g, 72%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.62 (d, *J* = 8.7 Hz, 2H, $C\underline{H}_2Ph$), 5.25 (dd, *J* = 8.7, 7.7 Hz, 1H, $C\underline{H}Bn$), 7.12-7.26 (m, 5H, Ph), 7.69 (dd, *J* = 5.5, 3.0 Hz, 2H, H_4, H_5), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H, H_3, H_6), 8.32 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 34.4 ($\underline{C}H_2Ph$), 53.1 ($\underline{C}HBn$), 123.6 (C_3, C_6), 127.0 ($C_{4'}$), 128.6 ($C_{2'}$, $C_{6'}$), 128.8 ($C_{3'}$, $C_{5'}$), 131.5 (C_{2a}, C_{6a}), 134.2 (C_4, C_5), 136.4 ($C_{1'}$), 167.4 (C_2O, C_7O), 174.7 (CO_2H); $[\alpha]_D^{20}$ = -252.5 (c = 0.12 g/100 mL in CH_2Cl_2).

*(R)-2-(1,3-Dioxoisoindolin-2-yl)-2-phenylacetic acid (**CCA4**)*[71]

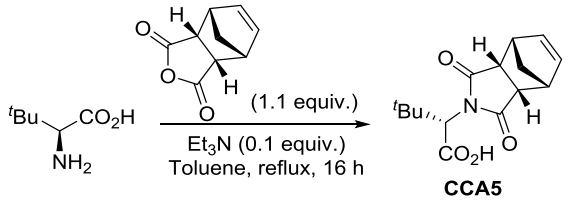


Prepared from D-phenylglycine (1.5 g, 10 mmol), phthalic anhydride (1.5 g, 10 mmol) and Et_3N (0.14 mL, 1.0 mmol) in dry toluene. After work-up and purification by flash column chromatography, **CCA4** was obtained as a solid (2.2 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) =

[69] Tsutsui, H.; Abe, T.; Nakamura, S.; Anada, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2005**, *53*, 1366.
[70] Surur, A.S.; Bock, C.; Beirow, K.; Wurm, K.; Schulig, L.; Kindermann, M.K.; Siegmund, W.; Bednarski, P.J.; Link, A. *Org. Biomol. Chem.* **2019**, *17*, 4512.
[71] Muller, G.W. (Celgene Corp., USA). Cyclic amides. US 5698579 A, Dec 16, 1997.

6.12 (s, 1H, C<u>H</u>Ph), 7.31-7.42 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$), 7.56-7.66 (m, 2H, $H_{3'}$, $H_{5'}$), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H, H_4, H_5), 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H, H_3, H_6), 10.33 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, ($CDCl_3$): δ (ppm) = 55.6 (<u>C</u>HPh), 123.8 (C_3, C_6), 128.6 ($C_{2'}$, $C_{6'}$), 128.8 ($C_{4'}$), 129.8 ($C_{3'}$, $C_{5'}$), 131.7 (C_{2a}, C_{6a}), 133.8 ($C_{1'}$), 134.3 (C_4, C_5), 167.1 (C_2O, C_7O), 173.7 (CO_2H); $[\alpha]_D^{20}$ = -71.8 (c = 0.10 g/100 mL in CH_2Cl_2).

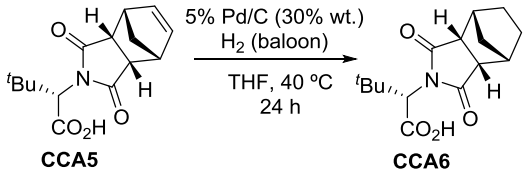
5.30. Synthesis of *(S)-N-*(*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximido)-*tert*-leucine (BHTL) (CCA5)[72]



Over a solution of *endo-cis*-5-norbornene-2,3-dicarboxylic anhydride (0.83 g, 5.0 mmol) and L-*tert*-leucine (0.60 g, 4.6 mmol) in dry toluene (15 mL), Et_3N (63.8 µL, 0.46 mmol) was added under argon atmosphere. The reaction was stirred at reflux for 16 h. After that time, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with a 0.1 M aqueous solution of HCl (2 × 15 mL), dried (Na_2SO_4) and concentrated at reduced pressure. Purification by flash column chromatography (silica gel, petroleum ether/AcOEt, 7/3), afforded **CCA5** as a solid (0.95 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.02 (s, 9H, $C(CH_3)_3$), 1.54 (d, *J* = 8.8, 1H, 1 × CH_2), 1.72 (dt, *J* = 8.8, 1.5, 1H, 1 × CH_2), 3.29-3.36 (m, 2H, H_3, H_6), 3.37-3.42 (m, 2H, H_{2a}, H_{6a}), 4.32 (s, 1H, C<u>H</u>^{t}Bu), 6.07-6.14 (m, 2H, C<u>H</u>=C<u>H</u>), 10.19 (br s, 1H, CO_2<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 27.8 (C(<u>C</u>H_3)$_3$), 35.4 (<u>C</u>(CH_3)$_3$), 45.0, 45.3 (C_3, C_6), 45.8, 46.1 (C_{2a}, C_{6a}), 52.5 (CH_2), 60.3 (<u>C</u>H^{t}Bu), 134.6 (<u>C</u>H=CH), 135.3 (CH=<u>C</u>H), 172.2 (<u>C</u>O_2H), 177.4, 177.5 (C_2O, C_7O); $[\alpha]_D^{20}$ = -67.7 (c = 0.10 g/100 mL in CH_2Cl_2).

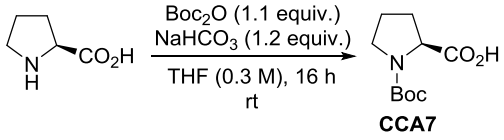
[72] Adly, F.G.; Gardiner, M.G.; Ghanem, A. *Chem. Eur. J.* **2016**, *22*, 3447.

5.31. Reduction of *(S)*-BHTL (CCA5). Synthesis of *(S)*-2-((3a*R*,4*R*,7*S*,7a*S*)-1,3-dioxooctahydro-2*H*-4,7-methanoisoindol-2-yl)-3,3-dimethylbutanoic acid (H_2-BHTL) (CCA6)[73]



Over a solution of *(S)*-BHTL **CCA5** (0.5 g, 1.8 mmol) in dry THF (15 mL), Pd-C (5%) (0.15 g, 30% wt.) was added under argon atmosphere. The reaction flask was evacuated and refilled with H_2 three times and afterwards, the mixture was allowed to stir at 40 ºC for 24 h under 1 atm of H_2 (balloon). Then, the mixture was cooled down to room temperature and filtered through a pad of Celite®. The filtrate was concentrated in vacuo and purified by flash column chromatography (silica gel, petroleum ether/AcOEt 7/3) to obtain **CCA6** as a solid (0.38 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.07 (s, 9H, $C(CH_3)_3$), 1.24-1.67 (m, 6H, CH_2, 2 × H_4, 2 × H_5), 2.73 (br s, 2H, H_3, H_6), 3.08-3.20 (m, 2H, H_{2a}, H_{6a}), 4.46 (s, 1H, C<u>H</u>^{t}Bu), 10.44 (br s, 1H, CO_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 24.7 (C_4, C_5), 28.0 ($C(\underline{C}H_3)_3$), 35.4 ($\underline{C}(CH_3)_3$), 39.3, 39.5 (C_3, C_6), 42.7 (C_{2a}, C_{6a}), 48.9 (CH_2), 60.1 (<u>C</u>H^{t}Bu), 172.5 (CO_2H), 178.2, 178.7 (C_2O, C_7O); $[\alpha]_D^{20}$ = -108.4 (c = 0.12 g/100 mL in CH_2Cl_2).

5.32. Synthesis of *N*-(*tert*-butoxycarbonyl)-L-proline (L-Boc-Pro-OH) (CCA7)[74]

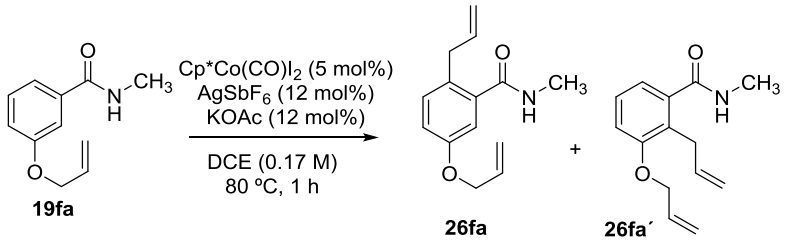


Over a solution of commercially available L-proline (1.0 g, 8.7 mmol) in dry THF (29 mL) $NaHCO_3$ (0.88 g, 10.4 mmol) and Boc_2O (2.1 g, 9.6 mmol) were subsequently added under argon atmosphere. The reaction was stirred at room temperature for 16 h and then, it was poured into water (100 mL). The resulting mixture was acidified to pH 2-3 with a 1 M aqueous solution of HCl and extracted with AcOEt (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dired (Na_2SO_4) and concentrated at reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum

[73] Fukagawa, S.; Kato, Y.; Tanaka, R.; Kojima, M.; Yoshino, T.; Matsunaga, S. *Angew. Chem. Int. Ed.* **2019**, *58*, 1153.
[74] Roane, J.; Wippich, J.; Ramgren, S.D.; Krische, M.J. *Org. Lett.* **2017**, *19*, 6634.

ether/AcOEt 8/2), affording **CCA7** as a solid and as a mixture of rotamers in a 60:40 ratio (1.2 g, 66%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.44 (s, 9H, $C(CH_3)_3$, minor rotamer), 1.50 (s, 9H, $C(CH_3)_3$, major rotamer), 1.83-2.42 (m, 4H, 2 × H_3 , 2 × H_4, both rotamers), 3.30-3.64 (m, 2H, 2 × H_5, both rotamers), 4.22-4.32 (m, 1H, 1 × H_2, minor rotamer), 4.33-4.42 (m, 1H, 1 × H_2, major rotamer), 9.04 (br s, 1H, CO_2H, both rotamers); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 23.7 (C_4, minor rotamer), 24.3 (C_4, major rotamer), 28.3 ($C(\underline{C}H_3)_3$, minor rotamer), 28.4 ($C(\underline{C}H_3)_3$, major rotamer), 28.8 (C_3, minor rotamer), 30.8 (C_3, major rotamer), 46.3 (C_5, minor rotamer), 46.9 (C_5, major rotamer), 59.0 (C_2, minor rotamer), 59.1 (C_2, major rotamer), 80.4 ($\underline{C}(CH_3)_3$, major rotamer), 81.2 ($\underline{C}(CH_3)_3$, minor rotamer), 153.9 (CO, major rotamer), 156.2 (CO, minor rotamer), 175.6 (CO_2H, major rotamer), 178.9 (CO_2H, minor rotamer); $[\alpha]_D^{20}$ = -144.9 (c = 0.13 g/100 mL in CH_2Cl_2).

5.33. Intermolecular allylation of 3-(allyloxy)-*N*-methylbenzamide (19fa). Synthesis of 2-allyl-5-(allyloxy)-*N*-methylbenzamide (26fa) and 2-allyl-3-(allyloxy)-*N*-methylbenzamide (26fa´)



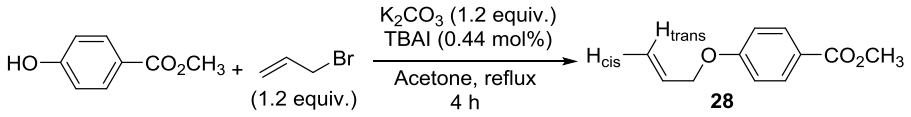
3-(Allyloxy)-*N*-methylbenzamide **19fa** (52.5 mg, 0.27 mmol), $AgSbF_6$ (11.3 mg, 0.033 mmol), KOAc (3.2 mg, 0.033 mmol) and Cp*Co(CO)I_2 (6.5 mg, 0.014 mmol) were successively weighed in a 20-mL vial (23 × 72 mm). Then, DCE (0.17 M) was added and the mixture was stirred at room temperature for 3 minutes before placing the reaction vessel in an oil bath preheated to 80 ºC. The reaction mixture was stirred at that temperature for 1 h and afterwards, it was diluted with AcOEt (20 mL). The volatiles were evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 6/4) to afford the corresponding allylated product as an oil (9.4 mg, 15%) and as a mixture of regioisomers **26fa** and **26fa´** (60:40): IR (ATR): ν (cm^{-1}) = 3289 (N-H), 1637 (C=O); MS (ESI): *m/z* (%): 254.1 (MNa^+, 33), 233.1 (MH^+ + 1, 12), 232.1 (MH^+, 100), 201.1 (2), 191.1 (2); HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}NO_2$: 232.1338 [MH^+]; found: 232.1342.

NMR signals corresponding to the major regioisomer 26fa: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.88 (d, *J* = 4.9 Hz, 3H, NCH_3), 3.36-3.41 (m, 2H, $C\underline{H_2}CH=CH_2$), 4.45 (dt, *J* = 5.2, 1.4

Hz, 2H, OC$\underline{H_2}$CH=CH$_2$), 4.83-5.02 (m, 2H, CH=C$\underline{H_2}$), 5.16-5.24 (m, 1H, 1 × OCH$_2$CH=C$\underline{H_2}$), 5.28-5.39 (m, 1H, 1 × OCH=C$\underline{H_2}$), 5.78 (br s, 1H, NH), 5.85-6.05 (m, 2H, OCH$_2$C$\underline{H}$=CH$_2$, CH$_2$C$\underline{H}$=CH$_2$), 6.80-6.87 (m, 1H, H$_4$), 6.89 (d, *J* = 2.7 Hz, 1H, H$_6$), 7.06 (d, *J* = 8.4 Hz, 1H, H$_3$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 26.6 (NCH$_3$), 36.8 (C$\underline{H_2}$CH=CH$_2$), 69.0 (OC$\underline{H_2}$CH=CH$_2$), 113.5 (C$_6$), 115.7 (CH=C$\underline{H_2}$), 116.6 (C$_3$, C$_4$), 117.8 (OCH$_2$CH=C$\underline{H_2}$), 129.3 (C$_2$), 131.6 (OCH$_2$C$\underline{H}$=CH$_2$), 137.5 (C$_1$), 138.2 (CH$_2$C$\underline{H}$=CH$_2$), 156.9 (C$_5$), 170.3 (CO).

NMR signals corresponding to the minor regioisomer 26fa´: ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 2.88 (d, *J* = 4.9 Hz, 3H, NCH$_3$), 3.48 (d, *J* = 6.1 Hz, 2H, C$\underline{H_2}$CH=CH$_2$), 4.48 (dt, *J* = 5.2, 1.6 Hz, 2H, OC$\underline{H_2}$CH=CH$_2$), 4.83-5.02 (m, 2H, CH=C$\underline{H_2}$), 5.16-5.24 (m, 1H, 1 × OCH$_2$CH=C$\underline{H_2}$), 5.28-5.39 (m, 1H, 1 × OCH=C$\underline{H_2}$), 5.78 (br s, 1H, NH), 5.85-6.05 (m, 2H, OCH$_2$C$\underline{H}$=CH$_2$, CH$_2$C$\underline{H}$=CH$_2$), 6.80-6.87 (m, 1H, H$_4$), 6.91-6.97 (m, 1H, H$_6$), 7.12 (t, *J* = 7.9 Hz, 1H, H$_5$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 26.5 (NCH$_3$), 31.5 (C$\underline{H_2}$CH=CH$_2$), 69.1 (OC$\underline{H_2}$CH=CH$_2$), 113.2 (C$_4$), 114.8 (CH=C$\underline{H_2}$), 117.1 (OCH$_2$CH=C$\underline{H_2}$), 119.7 (C$_6$), 125.9 (C$_2$), 127.4 (C$_5$), 133.0 (CH$_2$C$\underline{H}$=CH$_2$), 137.6 (OCH$_2$C$\underline{H}$=CH$_2$), 138.4 (C$_1$), 156.6 (C$_3$), 170.4 (CO).

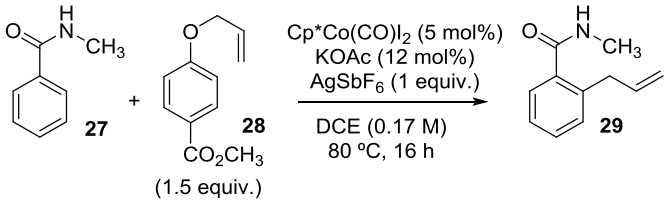
5.34. Synthesis of methyl 4-(allyloxy)benzoate (28)[75]



Over a mixture of methyl 4-hydroxybenzoate (0.76 g, 5.0 mmol), K$_2$CO$_3$ (0.83 g, 6.0 mmol) and TBAI (0.81 g, 2.2 mmol) in dry acetone (25 mL), allyl bromide (0.52 mL, 6.0 mmol) was added uder argon atmosphere. The reaction mixture was heated at reflux for 4 h and after that time, it was allowed to cool down to room temperature. Water (20 mL) and CH$_2$Cl$_2$ (20 mL) were added and the phases were separated. The aqueous layer was further extracted with CH$_2$Cl$_2$ (3 × 15 mL). Afterwards, the combined organic extracts were washed with brine (15 ml), dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **28** as an oil (0.86 g, 89%): ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) = 3.87 (s, 3H, CO$_2$CH$_3$), 4.56 (dt, *J* = 5.3, 1.5 Hz, 2H, OC$\underline{H_2}$CH=CH$_2$), 5.29 (dq, *J* = 10.5, 1.5 Hz, 1H, H$_{cis}$), 5.41 (dq, *J* = 17.3, 1.5 Hz, H$_{trans}$), 6.03 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 1H, OCH$_2$C$\underline{H}$=CH$_2$), 6.88-6.94 (m, 2H, H$_2$, H$_6$), 7.94-8.00 (m, 2H, H$_3$, H$_5$); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ (ppm) = 51.9 (CO$_2$C$\underline{H_3}$), 68.8 (OC$\underline{H_2}$CH=CH$_2$), 114.3 (C$_2$, C$_6$), 118.1 (OCH$_2$CH=C$\underline{H_2}$), 122.6 (C$_1$), 131.8 (C$_3$, C$_5$), 132.6 (OCH$_2$C$\underline{H}$=CH$_2$), 162.3 (C$_4$), 166.9 (CO).

[75] Gill, D.M.; Male, L.; Jones, A.M. *Eur. J. Org. Chem.* **2019**, 7568.

5.35. Cp*Co(III)-catalyzed intermolecular allylation of *N*-methylbenzamide (27) using 28 as allylating agent. Synthesis of 2-allyl-*N*-methylbenzamide (29)[76]

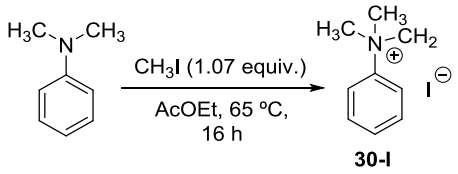


N-Methylbenzamide **27** (35.5 mg, 0.26 mmol), methyl 4-(allyloxy)benzoate **28** (75.7 mg, 0.39 mmol), $AgSbF_6$ (90.3 mg, 0.26 mmol), KOAc (3.1 mg, 0.032 mmol) and $Cp^*Co(CO)I_2$ (6.3 mg, 0.013 mmol) were successively weighed in a 16-mL vial (20 × 70 mm). Then, DCE (1.5 mL) was added and the mixture was stirred at room temperature for 3 minutes before placing the reaction vessel in a heating block preheated to 80 ºC. The reaction mixture was stirred at that temperature for 16 h and afterwards, it was diluted with AcOEt (20 mL). The volatiles were evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt 8/2-6/4) to afford the corresponding allylated product **29** as a solid (30.5 mg, 66%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.96 (d, *J* = 4.9 Hz, 3H, NCH_3), 3.55 (d, *J* = 6.3 Hz, 2H, $C\underline{H_2}CH=CH_2$), 4.93-5.15 (m, 2H, $CH_2CH=C\underline{H_2}$), 5.88-6.11 (m, 2H, NH, $CH_2C\underline{H}=CH_2$), 7.20-7.41 (m, 4H, H_3, H_4, H_5, H_6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 26.6 (NCH_3), 37.6 ($\underline{C}H_2CH=CH_2$), 115.9 ($CH_2CH=C\underline{H_2}$), 126.3 (C_3), 127.2 (C_6), 130.0 (C_5), 130.4 ,(C_4) 136.6 (C_1), 137.5, 137.7 ($CH_2\underline{C}H=CH_2$, C_2), 170.6 (CO).

[76] Gensch, T.; Vásquez-Céspedes, S.; Yu, D.-G.; Glorius, F. *Org. Lett.* **2015**, *17*, 3714.

6. Ru(II) CATALYSIS FOR THE *ORTHO*-MONO-METHYLATION OF 2-PHENYLPYRIDINE UTILIZING BENCH-STABLE AMMONIUM SALTS

6.1. Synthesis of phenyltrimethylammonium iodide (30-I)[77]

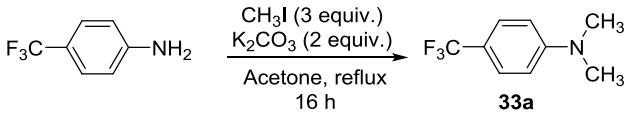


30-I

Over a solution of *N,N*-dimethylaniline (3.0 mL, 23.7 mmol) in AcOEt (20 mL), iodomethane was added dropwise (1.6 mL, 25.3 mmol) and the reaction mixture was allowed to stir at 65 ºC for 16 h. After that time, the remaining solvent was removed at reduced pressure and the resulting residue was dried in a vacuum oven at 60 ºC for 24 h. That way, **30-I** was obtained as a solid without further purification (6.2 g, quant.): ^{1}H NMR (300 MHz, D_2O): δ (ppm) = 3.58 (s, 9H, 3 × CH_3), 7.50-7.61 (m, 3H, H_2, H_4, H_6), 7.76 (d, *J* = 8.2 Hz, 2H, H_3, H_5).

6.2. Synthesis of *N,N,N*-trimethyl-4-(trifluoromethyl)benzenaminium iodide (33)

*6.2.1. Step 1: N-Dialkylation of 4-(trifluoromethyl)aniline. Synthesis of N,N-dimethyl-4-(trifluoromethyl)aniline (**33a**)[78]*



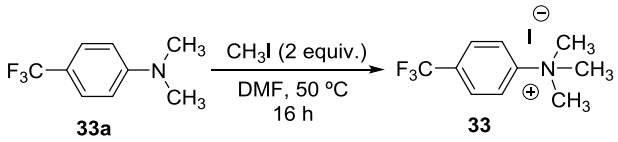
33a

Over a solution of commercially available 4-(trifluoromethyl)aniline (0.75 mL, 6.0 mmol) in acetone (20 mL), K_2CO_3 (1.7 g, 12.0 mmol) and iodomethane (1.1 mL, 18 mmol) were subsequently added and the reaction mixture was heated at reflux for 16 h. After that time, it was allowed to cool down to room temperature, diluted with Et_2O (30 mL) and washed with water (30 mL), a saturated aquous solution of $NaHCO_3$ (30 mL) and brine (30 mL). The combined organic fractions were then dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chormatogrphy (silica gel, petroleum ether/AcOEt 9/1) to afford **33a** as an

[77] Chen, Q.; Gao, F.; Tang, H.; Yao, M.; Zhao, Q.; Shi, Y.; Dang, Y.; Cao, C. *ACS Catal.* **2019**, *9*, 3730.
[78] Ratnikov, M.O.; Doyle, M.P. *J. Am. Chem. Soc.* **2013**, *135*, 1549.

oil (0.72 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.02 (s, 6H, 2 × CH_3), 6.71 (d, *J* = 8.7 Hz, 2H, H_2, H_6), 7.47 (d, *J* = 8.7 Hz, 2H, H_3, H_5).

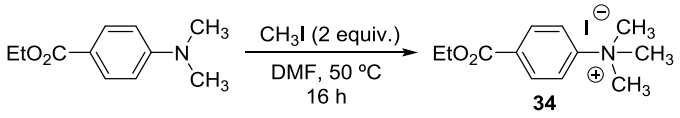
*6.2.2. Step 2: Overmethylation of **33a**. Synthesis of N,N,N*-trimethyl-4-(trifluoromethyl)-benzenaminium iodide *(**33**)*[79]



33a **33**

Over a solution of **33a** (0.5 g, 2.6 mmol) in DMF (2 mL), iodomethane was added (0.33 mL, 5.3 mmol). The mixture was stirred at 50 ºC for 16 h and the resulting precipitate was collected by filtration, washed with Et_2O (3 × 20 mL) and diried under vacuum to obtain **33** as a solid without further purification (0.76 g, 88%): ^{1}H NMR (300 MHz, DMSO-*d*6): δ (ppm) = 3.61 (s, 9H, 3 × CH_3), 7.48-7.56 (m, 2H, H_2, H_6), 8.02-8.08 (m, 2H, H_3, H_5).

6.3. Synthesis of 4-(ethoxycarbonyl)-*N,N,N*-trimethylbenzenaminium iodide (34)[79]

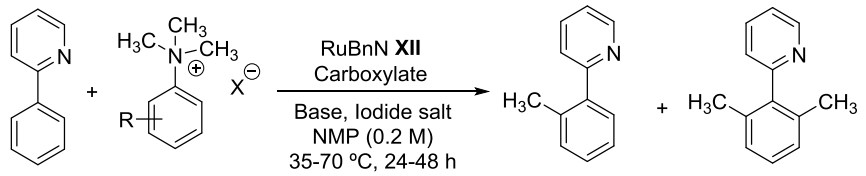


34

Over a solution of commercially available ethyl 4-(dimethylamino)benzoate (1.0 g, 5.2 mmol) in DMF (5 mL), iodomethane was added (0.64 mL, 10.4 mmol). The mixture was stirred at 50 ºC for 16 h and the resulting precipitate was collected by filtration, washed with Et_2O (3 × 20 mL) and diried under vacuum to obtain **34** as a solid without further purification (1.5 g, 88%): ^{1}H NMR (300 MHz, DMSO-*d*6): δ (ppm) = 1.34 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H_3}$), 3.67 (s, 9H, 3 × CH_3), 4.37 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H_2}CH_3$), 8.16 (s, 4H, H_2, H_3, H_4, H_6).

[79] Dai, W.-C.; Wang, Z.-X. *Chem. Asian J.* **2017**, *12*, 3005.

6.4. General procedure for the optimization of the reaction conditions for the *ortho*-mono-methylation of 2-phenylpyridine using 30, 33 and 34 as the methylating agents



30-Cl, R = H, X = Cl
30-Br, R = H, X = Br
30-I, R = H, X = I
33, R = CF_3, X = I
34, R = CO_2Et, X = I

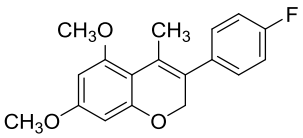
31 **32**

All the reactions were carried out in a 0.1 mmol scale regarding 2-phenylpyridine. The amount of the rest of the reagents depends on the experiment carried out in each case.

Inside a glovebox, the corresponding base, carboxylate, iodide salt and aryltrimethylammonium salt (**30, 33, 34**) were successively weighed into a vial. Catalyst RuBnN **XII** and 2-phenylpyridine (14.3 µL, 0.10 mmol) were then added, followed by a stock solution of hexadecane in NMP (3.3 mM, 0.5 mL) as internal standard. Afterwards, the reaction vessel was sealed, taken out from the glovebox, and placed in a heating block preheated to the indicated temperature. The solution was stirred at that temperature for the corresponding time. The resulting mixture was diluted with Et_2O and filtered though a small pad of silica gel. The resulting sample was analized *via* GC-FID.

7. CRYSTAL DATA FOR 3-(4-FLUOROPHENYL)-5,7-DIMETHOXY-4-METHYL-2*H*-CHROMENE (4am)

The structure of **4am** was unambiguously confirmed by single-crystal X-ray analysis. **4am** was recrystallized from dichloromethane. CCDC 1872267 contains the supplementary crystallographic data for this structure.



Crystal Data for 4am [$C_{18}H_{17}FO_3$ (*M* =300.32 g/mol)]: monoclinic, space group $P2_1/n$ (no. 14), *a* =3.9525(2) Å, *b* = 14.6990(8) Å, *c* = 24.6043(14) Å, *β* = 94.082(5)°, *V* = 1425.83(13) Å^3, *Z* = 4, *T* =149.99(10) K, μ(CuKα) = 0.853 mm^{-1}, *Dcalc* = 1.399 g/cm^3, 10886 reflections measured (7.01° ≤ 2Θ ≤137.99°), 2649 unique (R_{int} = 0.0709, R_{sigma} = 0.0561) which were used in all calculations. The final R_1 was 0.0688 (I > 2σ(I)) and wR_2 was 0.1820 (all data).

An ORTEP plot of compound **4am** with thermal ellipsoids at the 50% probability level with the atomic nomenclature used is shown in Figure 7.1.

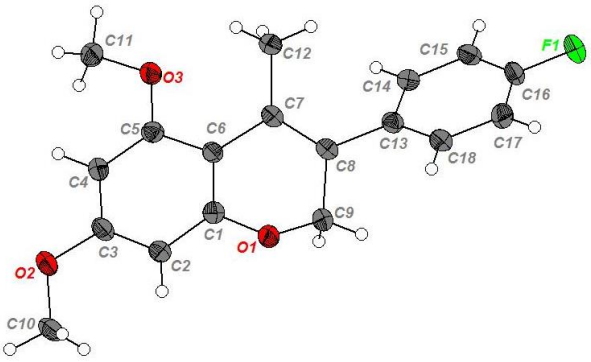


Figure 7.1. *ORTEP plot of compound* ***4am*** *with thermal ellipsoids at the 50% probability level with the atomic nomenclature used*