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PARA OPTAR AL GRADO DE DOCTOR

CON MENCIÓN "DOCTOR INTERNACIONAL"

Leioa, 2022

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NAZIOARTEKO BIKAINTASUN CAMPUSA
CAMPUS DE EXCELENCIA INTERNACIONAL

TESI ZUZENDARIAREN BAIMENA TESIA AURKEZTEKO	**AUTORIZACIÓN DEL/LA DIRECTORA/A DE TESIS PARA SU PRESENTACIÓN**

Zuzendariaren izen-abizenak /Nombre y apellidos de las directoras: **Esther Lete Expósito** y **Nuria Sotomayor Anduiza**

IFZ /NIF: 16026226X (EL); 16040929Q (NS)

Tesiaren izenburua / Título de la tesis: **Transition metal-catalyzed C(sp^2)-H acylation and olefination reactions for the functionalization of (Hetero)Arenes**

Doktorego programa / Programa de doctorado: **Química Sintética e Industrial**

Doktoregaiaren izen-abizenak / Nombre y apellidos del doctorando: **Carlos Santiago Álvarez**

Unibertsitateak horretarako jartzen duen tresnak emandako ANTZEKOTASUN TXOSTENA ikusita, baimena ematen dut goian aipatzen den tesia aurkez dadin, horretarako baldintza guztiak betetzen baititu.	Visto el INFORME DE SIMILITUD obtenido de la herramienta que a tal efecto pone a disposición la universidad, autorizo la presentación de la tesis doctoral arriba indicada, dado que reúne las condiciones necesarias para su defensa.

Tokia eta data / Lugar y fecha: Leioa, 21 de febrero de 2022

E. Lete

N. Sotomayor

Sin. / Fdo.: Tesiaren zuzendariak / Las directoras de la tesis

VOCAL 1º, VOCAL 2º, VOCAL 3º,

Fdo.: Fdo.: Fdo.:

Dr/a: _____Dr/a: _____Dr/a:_____

EL DOCTORANDO,

Fdo.: Carlos Santiago Álvarez

Me gustaría expresar mi mas sincera gratitud a las Dras. Esther Lete y Nuria Sotomayor por haberme dado la oportunidad de realizar mi Tesis Doctoral bajo su supervisión, así como la ayuda y dedicación recibida, sobre todo en momentos de incertidumbre, para la realización de la misma.

I am also very grateful to Prof. Manuel van Gemmeren for giving me the opportunity to join his researching group at Münster University to carry out my three-month stay, and the labmates I met there.

Del mismo modo, dar gracias al Gobierno Vasco por el contrato predoctoral como Personal Investigador en Formación en el marco de la subvención a Grupos Consolidados del Sistema Universitario Vasco, así como al Ministerio de Ciencia y Tecnología (proyectos CTQ2016-74881-P y PID2019-104148GB-I00), el Gobierno Vasco (Grupos IT1045-16) y la Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU) por la financiación recibida para la realización de este trabajo.

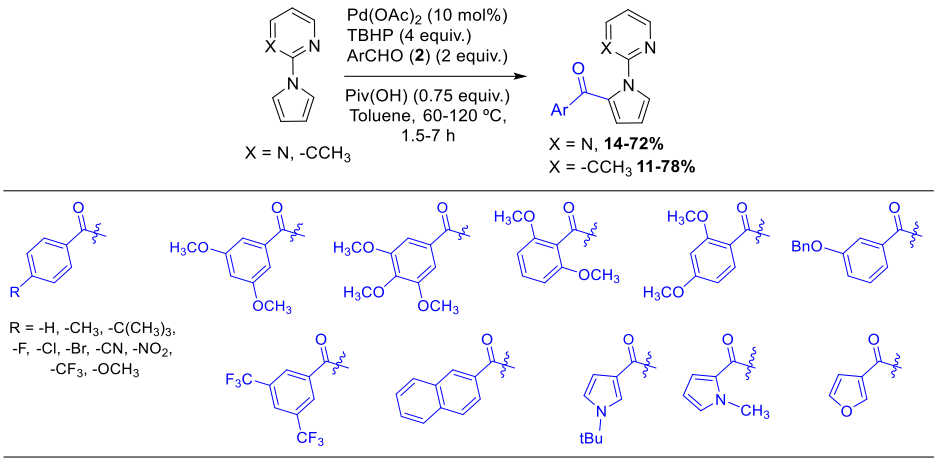
Gracias al Departamento de Orgánica e Inorgánica, en especial a mis compañeros de laboratorio por estos 4 años de ayuda, compañía y gratos momentos.

A mi familia y amigos, gracias por el apoyo.

Resumen

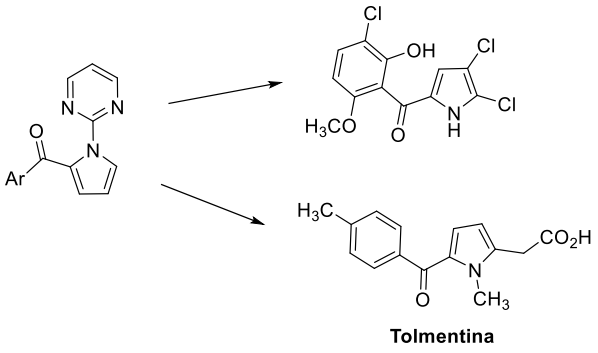
El trabajo de investigación que se recoge en la presente memoria se centra en el desarrollo de nuevos métodos de formación de enlaces carbono-carbono (acilación, aminocarbonilación y alquenilación) de anillos heteroaromáticos, tales como pirroles o tiofenos, mediante reacciones de activación C-H catalizadas por Pd(II) y Co(III).

Tras una breve introducción (capítulo 1) para poner en contexto este trabajo, se plantean los objetivos generales y específicos de esta tesis doctoral. En el segundo capítulo, se describe la metodología desarrollada para la acilación de pirroles en la posición C-2 catalizada por Pd(II) empleando aldehídos como fuente de radical acilo en presencia de TBHP como oxidante. La presencia de un aditivo moderadamente ácido, como el ácido piválico es crucial para aumentar la reactividad. El uso de 2-pirimidina como grupo director conduce a 2-acilpirroles con rendimientos moderados a buenos, aunque siempre se obtuvieron los correspondientes 2,5-diacilpirroles como subproductos. Esta reacción secundaria pudo evitarse usando 3-metil-2-piridina como grupo director, obteniendo selectivamente los pirroles monoacilados. La reacción se ha extendido a una serie de aldehídos aromáticos y heteroaromáticos, obteniendo los mejores resultados cuando se emplearon aldehídos aromáticos ricos en electrones (Esquema 1).



Esquema 1. Reacción de acilación de pirroles con aldehídos catalizada por Pd(II).

Para demostrar la utilidad sintética de esta metodología, se ha aplicado el procedimiento, por un lado, a la síntesis de un análogo del alcaloide pirrolomicínico Celastramicina y, por otro, a la síntesis de Tolmetina, un antiinflamatorio no esteroideo (Esquema 2).

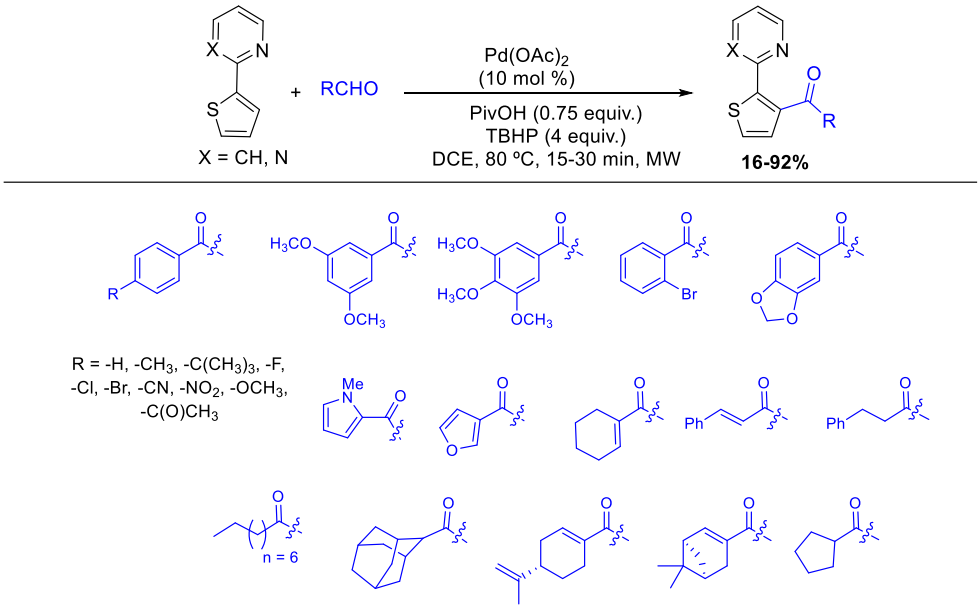


Esquema 2. Síntesis del análogo de Celestramicina y Tolmenina.

Además, se ha evaluado la actividad leishmanicida, así como la citotoxicidad, de algunos 2-acylpirroles sintetizados frente a *L. donovani* y *L. amazonensis*, responsables de las dos

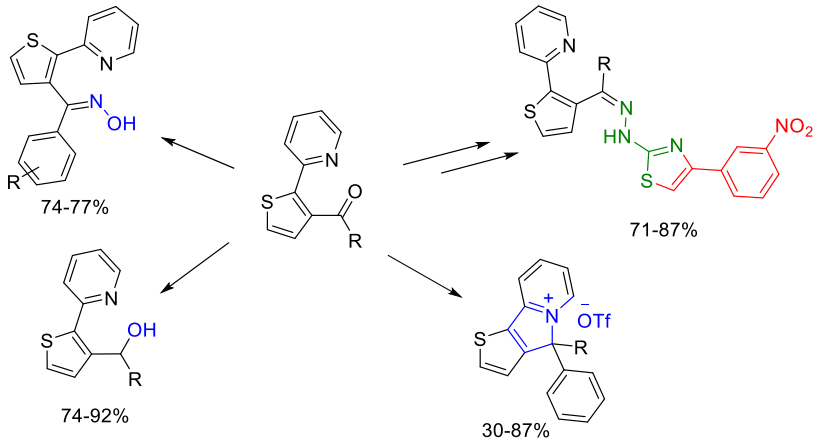
formas clínicas principales de esta enfermedad tropical desatendida, la leishmaniasis cutánea y visceral, respectivamente. Los ensayos biológicos *in vitro* con promastigotes de *L. amazonensis*, realizados por la Dr. M. A. Dea de la Universidad CEU Cardenal Herrera (Valencia), revelaron que varios acilpirroles presentaban una actividad antileishmanicida comparable e incluso seis veces mayor que el fármaco de referencia, Miltefosina. Asimismo, se ha observado que la mayoría de los compuestos mostraron baja citotoxicidad, CC_{50} > 100 µg/mL en células J774, dosis más alta probada, presentando, por tanto, menor toxicidad que Miltefosina. Esta es una característica importante, ya que la toxicidad de los fármacos es una de las principales limitaciones de la quimioterapia actual para la leishmaniasis.

En el segundo apartado del capítulo, se ha estudiado la reacción de acilación de tiofenos en la posición C3 con aldehídos, catalizada por Pd(II) y asistida por irradiación por microondas. El control de la regisoelectividad se ha logrado mediante grupos orto-directores 2-piridinilo y 2-pirimidilo en C-2 del tiofeno. De esta forma, se ha logrado acceder con buenos rendimientos a una serie de (ciclo)alquil / aril tienil cetonas en condiciones suaves y en tiempos de reacción cortos (15 a 30 min), en comparación con las condiciones térmicas estándar (Esquema 3). Esta metodología se ha extendido a la acilación de otros heterociclos como el pirrol, el benzotiofeno o el furano.



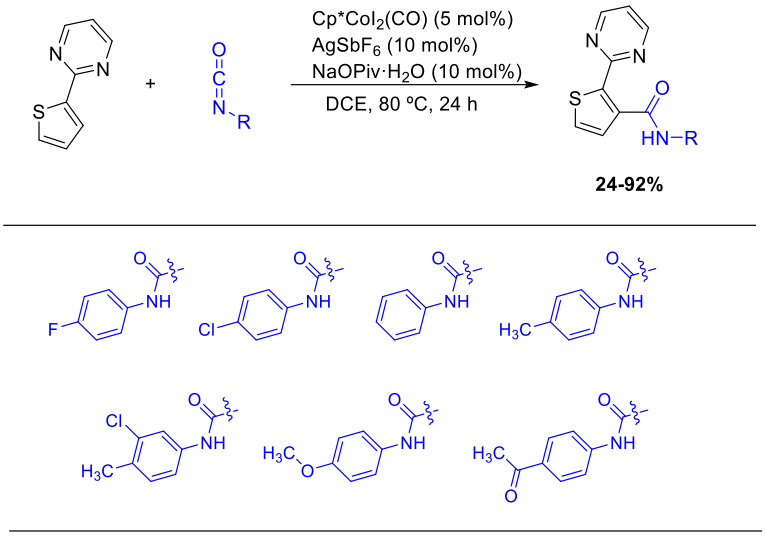
Esquema 3. Reacción de acilación de tiofenos con aldehídos catalizada por Pd(II).

Dada la versatilidad del grupo carbonilo, se ha llevado a cabo varias diversificaciones de dicho grupo para demostrar la utilidad de nuestra metodología, entre las que se encuentran: reducción del grupo carbonilo, síntesis de oximas, síntesis de 4-(3-nitrofenil)tiazol-2-ilhidrazonas (A través de la síntesis de (*Z*)-tiosemicarbazonas y reacción de Hantzsch), y por último una ciclación en la cual el grupo director está implicado y que forma parte de la estructura final (Esquema 4).



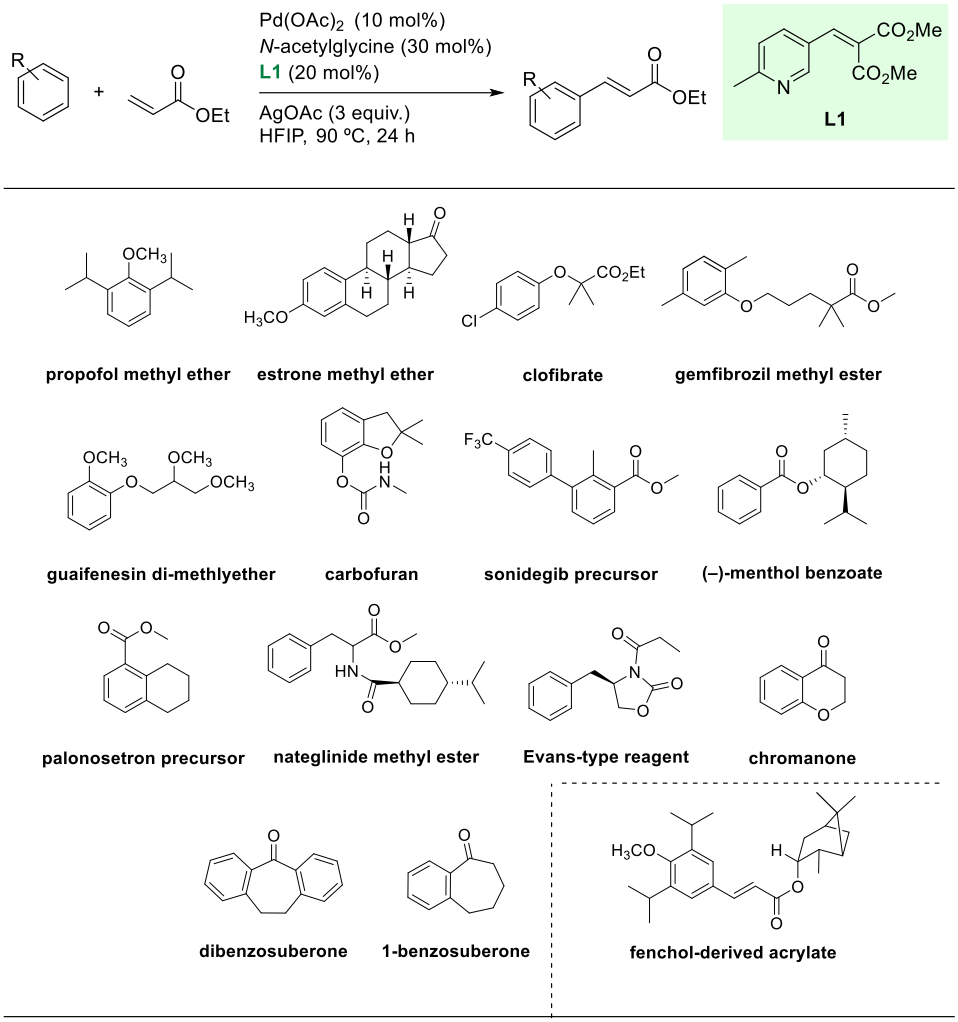
Esquema 4. Diversificaciones de 3-acyl tiofenos.

Dado que el cobalto es un metal de transición más abundante, barato y menos tóxico que el paladio y otros metales nobles, se decidió estudiar el empleo de catalizadores de Cp*Co(III) para realizar la acilación de compuestos heteroaromáticos. Así, en el tercer capítulo de la tesis, se describen, en primer lugar, los ensayos de acilación de tiofenos con aldehídos catalizada por Cp*Co(III). Sin embargo, empleando condiciones análogas a las descritas en el capítulo 2 para las reacciones catalizadas por Pd(II), únicamente se obtuvieron los aciltiofenos con rendimientos bajos. Por otra parte, se ha explorado la adición nucleófila de enlaces C-H de tiofenos a isocianatos catalizada por Co(III), usando el grupo pirimidilo para controlar la regioselectividad de la reacción. Tras la optimización de las condiciones de reacción, se extendió la metodología a varios isocianatos aromáticos (Esquema 5).



Esquema 5. Síntesis de thiofenil-3-carboxamidas.

Finalmente, en el cuarto capítulo, se describe el trabajo realizado en mi estancia predoctoral en la Universidad de Münster en Alemania, bajo la supervisión del Prof. Manuel Antonio van Gemmeren. En dicho trabajo se amplió el estudio que realizaron en 2018 sobre olefinación C-H no dirigida catalizada por Pd(II) en presencia de dos ligandos complementarios, al concepto de funcionalización en etapa tardía. Así, se utilizaron las condiciones de reacción optimizadas sobre moléculas complejas y con bioactividad, construyendo una pequeña librearía de compuestos tal y como se muestra en el Esquema 6. Por último, se explican los ensayos de extender la metodología utilizada a acrilatos propargilicos para la síntesis, tras una reacción click con azidas, de triazoles 1,4-bisustituidos, los cuales son conocidos por ser estructuras privilegiadas en química médica.



Esquema 6. Olefinación en etapa-tardía de arenos catalizada por Pd(II).

Summary

The research work collected in this thesis is focused on the development of new methodologies of carbon-carbond bond formation (acylation, aminocarbonylation and olefination) of heteroaromatic rings, such as pyrroles or thiophenes *via* C-H activation reactions catalyzed by Pd(II) and Co(III).

In the first chapter, and to give context to this thesis, the experience of our researching group in the Palladium and Cobalt catalyzed reactions is described.

The second chapter is focused, on the one hand, on the development of a methodology of Pd(II)-catalyzed acylation of pyrroles. The optimized reaction conditions have been applied to the synthesis of Celastramycin analogue and Tolmentin. As a secondary objective, anti-leishmanicidal activity against visceral (*L. donovani*) and cutaneous (*L. amazonensis*) leishmaniasis and cytotoxicity of some of the synthesized 2-acylpyrroles have been evaluated through biological assays carried out by Dr. M. A. Dea from University CEU Cardenal Herrera (Valencia). On the other hand, Pd(II)-catalyzed C-3 acylation of thiophenes with aldehydes *via* C(sp^2)-H activation has been developed. To show the synthetic applicability, selected ketones were subjected to further diversifications, including an intramolecular reaction, which involves the directing group.

In the third chapter, the attempts to expand the methodology has been designed in the second chapter about C-H acylation of pyrroles, to Co(III) catalysis, is described. Furthermore, the nucleophilic addition of thiophene C-H bond to isocyanates catalyzed by Co(III) has been explored.

Finally, in the fourth chapter, the research realized in my predoctoral three-month stay in Prof. Manuel Antonio van Gemmeren´s research group at the Organic Chemistry Institute of the University of Münster is explained, which was focused on the use of dual-ligand-based palladium catalysts for the late-stage olefination of bioactive arenes.

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COBALT(III)-CATALYZED C-H ACYLATION AND AMINOARBONYLATION OF HETEROAROMATICS

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EXPERIMENTAL SECTION

Abbreviations, acronyms and symbols

abs	Absorption	**DBN**	1,5-Diazabicyclo[4.3.0]non-5-ene
aq.	Aqueous	**DCE**	Dichloroethane
ATR	Attenuated Total Reflection	**DCM**	Dichloromethane
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)	**DCP**	Dicumyl peroxide
Boc	*tert*-Butyloxycarbonyl	**DDQ**	2,3-Dichloro-5,6-dicyano-p-benzoquinone
bpy	Bypyridine	**DEPT**	Distorsionless Enhancement by Polarization Transfer
BQ	1,4-Benzoquinone	**DFT**	Density-functional theory
c	Concentration	**DG**	Directing group
CC_{50}	Cytotoxic Concentration	**DHODH**	Dihydroorotate dehydrogenase
CCD	Charge-coupled device	**DHR**	Dehydrogenative Heck reaction
CCE	Constant current electrolysis	**DME**	Dimethoxyethane
CL	Cutaneous Leishmaniasis	**DMF**	*N*,*N*-Dimethylformamide
CMD	Concerted metalation-deprotonation	**DMSO**	Dimethylsulfoxide
[Co]	Cobalt source	**dppp**	1,3-Bis(diphenylphosphino)propane
COD	1,5-Cyclooctadiene	***dr***	Diastereomeric ratio
COSY	COrrelated SpectroscopY	**Ed(s).**	Editor(s)
Cp*	Cyclopentadienyl	***ee***	Enantiomeric excess
CSA	Camphorsulfonic acid	**EI**	Electron ionization
CuAAc	Copper(I)-catalyzed azide-alkyne cycloaddition	**em**	Emision
Comp.	Compound		
δ	Chemical shift		
dba	Dibenzylideneacetone		

equiv.	Equivalent	**LED**	Light Emitting Diode
ESI	ElectroSpray Ionization	**Lit.**	Literature
EWG	Electron Withdrawing Group	**LSF**	Late-stage functionalization
ESR	Electro Spin Resonance	**M**	Metal
FDA	Food and Drug Administration	**M^+**	Molecular Ion (MS)
		MCL	Mucocutaneous Leishmaniasis
F+	*N*-fluoro-2,4,6-trimethylpyridinium triflate	**Moc**	Fluoren-9-ylmethoxy carbonyl
		m.p.	Melting point
FBS	Foetal bovine serum	**MPAA**	Mono Protected Amino-Acid
FID	Flame ionization detector	**MS**	Molecular Sieves; Mass Spectrometry
GC	Gas chromatography		
HetAr	Heteroaryl	**MW**	MicroWave
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol	**m/z**	Mass to charge ratio
		N/A	No Activity
hMAO	Human monoamine oxidase	**NCS**	*N*-Chlorosuccinimide
HMBC	Heteronuclear Multiple Bond Correlation	**NMA**	N-Methylaniline
		NMR	Nuclear Magnetic Resonance
HPLC	High Performance Liquid Chromatography	**nOe**	Nuclear Overhausser Effect
		NOESY	Nuclear Overhausser Effect Enhancement SpectroscopY
HRMS	High Resolution Mass Spectrometry		
		NSAID	NonSteroidal Anti-Inflammatory Drugs
HSQC	Heteronuclear Single Quantum Coherence		
		[Ox]	Oxidant
IC_{50}	Half maximal inhibitory concentration	**p.**	Page
		[Pd]	Palladium source
IR	Infrared	**phen**	1,10-Phenanthroline
J	Coupling Constant	**PKDL**	Post-kala-azar dermal leishmaniasis
KIE	Kinetic Isotope Effect		
L	Ligand		

PMP	1,2,2,6,6-pentamethylpiperidine
PQ	Phenanthrene-9,10-quinone
ppy	2-Phenyl pyridine
Prod.	Product
PT	Perturbation Theory
PS	Polystyrene
Py	Pyridine
Pyr	Pyrimidine
QTOF	Quadrupole time-of-flight mass spectrometer
Quant.	Quantitative
rt	Room temperature
RVC	Reticulated vitreous carbon
SD	Standard deviation
SDS	Sodium Dodecyl Sulfate
SI	Selectivity Index
T	Temperature
t	Time
TBHP	*tert*-Butyl hydroperoxide
TBPB	*tert*-Butyl peroxybenzoate
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TFBen	Benzene-1,3,5-triyl triformate
TFE	2,2,2-trifluoroethanol
THF	Tetrahydrofurane
TIPS	Triisopropylsilyl
TML	Thin layer chromatography
TMS	Trimethylsilyl
UPLC	Ultra Performance Liquid Chromatography
UV	Ultraviolet
VL	Visceral Leishmaniasis
vs.	Versus
X-Phos	Dicyclohexyl[2′,4′,6′-tris(propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane

I

Group precedents and aims of the thesis

1.1. GROUP PRECEDENTS

Transition-metal direct C-H functionalization/activation, i.e. transformation of non-activated C-H bonds into C-C or C-X bonds, has emerged as an efficient, atom-economical, and environmentally friendly synthetic tool for the preparation of complex multifunctional molecules, being a good alternative to traditional cross-coupling chemistry. This transformation, though attractive in its simplicity, represents a significant challenge in chemical synthesis, largely due to the difficulties associated with the chemoselective activation of relatively inert C-H bonds. The wide presence of C-H bonds in organic molecules makes them attractive starting materials for the preparation of complex compounds. The procedure allows the introduction of complexity and diversity on a core molecule.

Palladium (II) catalysis has been widely used in C-H activation and functionalization of $C(sp^2)$-H bonds of arenes or heteroarenes or even simple alkenes.[1] In many cases, C-H activation requires the use of a convenient directing group to control the regioselectivity and enhance reactivity.[2] However, to obtain the target compounds it is necessary to use easily removable directing groups,[3] or, alternatively, directing groups that could be easily functionalized. Besides, ligands, such as pyridines, picolinamides or monoprotected aminoacids (MPPAs) that coordinate to the metal center and deliver the catalyst to the targeted C-H bond, can be used as an alternative to strategies based on directing groups.[4]

During the last years, our group has investigated in the dehydrogenative Heck reaction (DHR), also known as Fujiwara-Moritani reaction.[5] The procedure has been mainly used for

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[1] a) Lei, A.; Shi, W.; Liu, W.; Zhang, H.; He, C. *Oxidative Cross-Coupling Reactions*, Wiley, Weinheim, 2017; b) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild metal-catalyzed C–H activation: examples and concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900- 2936.

[2] Sambiagio, C.; Schonbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A comprehensive overview of directing groups applied in metal-catalysed C–H functionalisation chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603- 6743.

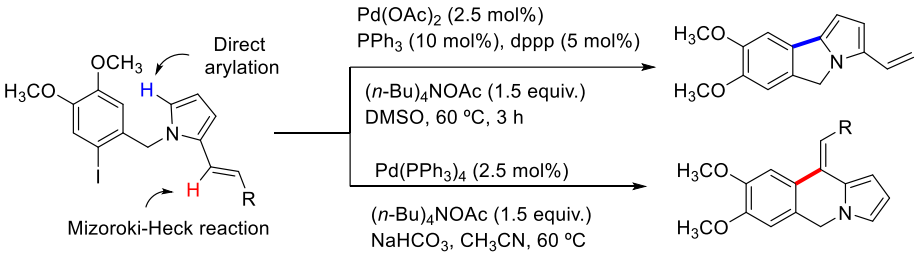
[3] Rej, S.; Chatani, N. Rhodium-Catalyzed $C(sp^2)$- or $C(sp^3)$−H Bond Functionalization Assisted by Removable Directing Groups. *Angew. Chem. Int. Ed*. **2019**, *58*, 8304-8329.

[4] Engle, K. M. The mechanism of palladium(II)-mediated C–H cleavage with mono-*N*-protected amino acid (MPAA) ligands: origins of rate acceleration**.** *Pure. Appl. Chem*. **2016**, *88*, 119.

[5] a) Larhed, M. Ed., *Science of Synthesis. Cross Coupling and Heck-Type Reactions 3. Metal-Catalyzed Heck-Type Reactions and C-H Couplings via C-H Activation*; Georg Thieme Verlag: Stuttgart, 2013; b) Le Bras, J.; Muzart, J. .Intermolecular Dehydrogenative Heck Reactions. *Chem. Rev.* **2011**, *111*,

alkenylation of electron-rich heteroarenes (e.g. indole and pyrrole), and there were few examples described with electron-deficient heteroarenes such as pyridines and quinolones.[6] The intramolecular variant for the synthesis of carbocyclic and heterocyclic frameworks was underexplored, and the selectivity *exo/endo* was an important issue that had to be addressed. In fact, the *endo*-trig cyclizations are rare and have been reported mainly when the *exo* processes are blocked.[7]

Before the study of Fujiwara-Moritani reaction, our group studied the competitive intramolecular Mizoroki-Heck and direct arylation reactions of 2-alkenyl-substituted *N*-(o-iodobenzyl)pyrroles with different substitution patterns on alkene to obtain pyrroloisoquinolines or isoindoles. The chemioselectivity of the reaction could be successfully modified depending the catalytic system used (Scheme 1.1).[8]



Scheme 1.1. Mizoroki-Heck reaction *vs* direct arylation reaction.

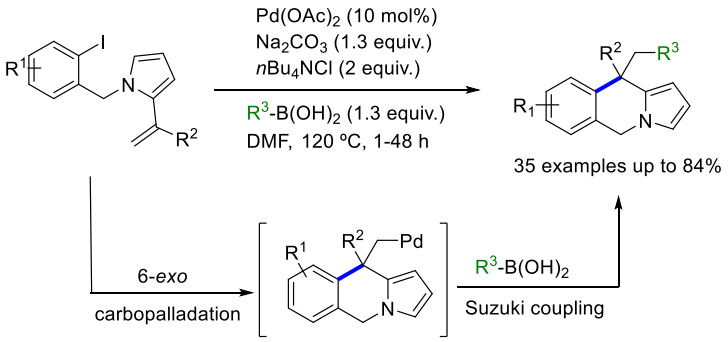
1170-1214; c) Zhou, L.; Lu, W. Towards Ideal Synthesis:Alkenylation of Aryl CH Bonds by a Fujiwara–Moritani Reaction. *Chem. Eur. J.* **2014**, *20*, 634-642.

[6] Quinolones: a) Li, M.; Li, L.; Ge, H. Direct C-3-Alkenylation of Quinolones *via* Palladium-Catalyzed C-H Functionalization. *Adv. Synth. Catal.* **2010**, *352*, 2445-2449; Piridones: b) Yua, Y.-Y.; Georg, G. I. Biomimetic Aerobic C-H Olefination of Cyclic Enaminones at Room Temperature: Development toward the Synthesis of 1,3,5-Trisubstituted Benzenes. *Adv. Synth. Catal.* **2014**, *356*, 1359-1369.

[7] Selected examples: a) Neumann, J. J.; Rakshit, S.; Dröe, T.; Würtz, S.; Glorius, F. Exploring the Oxidative Cyclization of Substituted *N*-Aryl Enamines: Pd-Catalyzed Formation of Indoles from Anilines. *Chem. Eur. J.* **2011**, *17*, 7298-7303; b) Kandukuri, S. R.; Schiffner, J. A.; Oestreich, M. Aerobic Palladium(II)-Catalyzed 5-*endo-trig* Cyclization: An Entry into the Diastereoselective C-2 Alkenylation of Indoles with Tri- and Tetrasubstituted Double Bonds. *Angew. Chem. Int. Ed.* **2012**, *51*, 1265-1269.

[8] Lage, S.; Martínez-Estíbaliz, U.; Sotomayor, N.; Lete, E. Intramolecular Palladium-Catalyzed Direct Arylation *vs.* Heck Reactions: Synthesis of Pyrroloisoquinolines and Isoindoles. *Adv. Synth. Catal.* **2009**, *351*, 2460-2468.

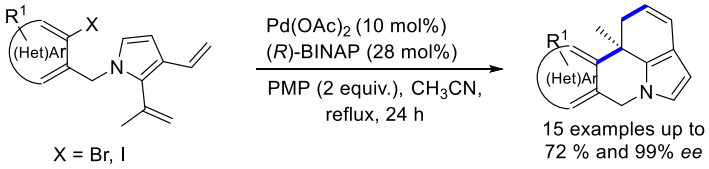
We have also carried out carbopalladation/Suzuki cascade reaction,[9] where a series of pyrrolo[1,2-*b*]isoquinolines could be generated from *N*-(2-iodobenzyl)-2-(alkenyl)-1*H*-pyrroles after a cyclization through 6-*exo* carbopalladation process, which generates a quaternary center at C-10 position. The resulting σ-alkylpalladium intermediate could be trapped with an arylboronic acid, leading the corresponding C-10 disubstituted pyrrolo[1,2-*b*]isoquinolines (Scheme 1.2).



Scheme 1.2. Carbopalladation-Suzuki cascade.

In the same way, our group could access to C-11b-(*R*) substituted lycorane analogues *via* a catalytic asymmetric Heck-Heck 6-*exo*/6-*endo* cascade reaction where (*R*)-BINAP was used as chiral ligand (Scheme 1.3).[10] The use of PMP (1,2,2,6,6-Pentamethylpiperidine) as base and CH_3CN as solvent was crucial to avoid hydride transfer.

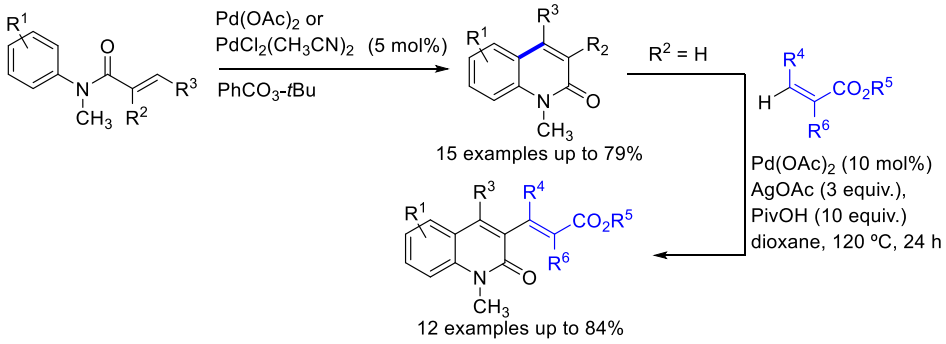
[9] Barbolla, I.; Sotomayor, N.; Lete, E. Carbopalladation/Suzuki Coupling Cascade for the Generation of Quaternary Centers: Access to Pyrrolo[1,2-*b*]isoquinolines. *J. Org. Chem.* **2019**, *84*, 10183-10196.
[10] Coya, E.; Sotomayor, N.; Lete, E. Enantioselective Palladium-Catalyzed Heck–Heck Cascade Reactions: Ready Access to the Tetracyclic Core of Lycorane Alkaloids. *Adv. Synth. Catal.* **2015**, *357*, 3206-3214.



Scheme 1.3. Intramolecular 6-*exo*/6-*endo* Mizoroki–Heck cascade reaction.

Regarding Fujiwara-Moritani reaction, our group has been able to perform both 6-*exo*- and 6-*endo*-trig dehydrogenative Heck reactions by substrate design and selecting the adequate catalyst, oxidant, and experimental conditions.

Thus, the intramolecular selective 6-*endo*-trig C–H alkenylation of *N*-alkyl substituted *N*-phenylacrylamides led to 4-substituted quinolin-2[1*H*]-ones, which have been further functionalized at C-3 position of the quinolone core through a second intermolecular C-H alkenylation reaction (Scheme 1.4).[11] The procedure has also been extended to the synthesis of functionalized coumarines.[12]

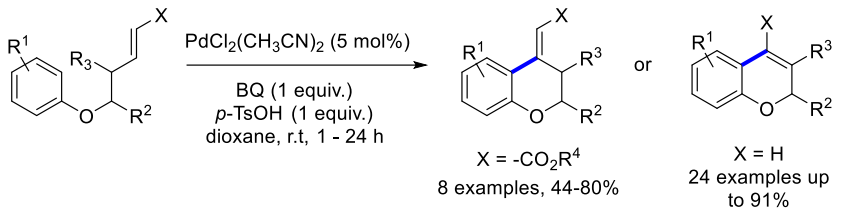


Scheme 1.4. Intramolecular/intermolecular Heck-Heck reaction.

[11] Ortiz-de-Elguea, V.; Sotomayor, N.; Lete, E. Two Consecutive Palladium(II)-Promoted C-H Alkenylation Reactions for the Synthesis of 3-Alkenylquinolones**.** *Adv. Synth. Catal.* **2015**, *357*, 463-473.

[12] Ortiz-de-Elguea, V.; Carral-Menoyo, A.; Simón-Vidal, L.; Martinez-Nunes, M.; Barbolla, I.; Lete, M. G.; Sotomayor, N.; Lete, E. Pd(II)-Catalyzed Fujiwara-Moritani Reactions for the Synthesis and Functionalization of Substituted Coumarins. *ACS Omega* **2021**, *6*, 29483-29494.

On the other hand, 6-*exo*-trig cyclizations of aryl homoallyl ethers provided direct access to highly and diversely substituted 2*H*-chromenes when terminal alkene is used and chromanes when an electron-withdrawing group is inserted on the alkene (Scheme 1.5).[13]

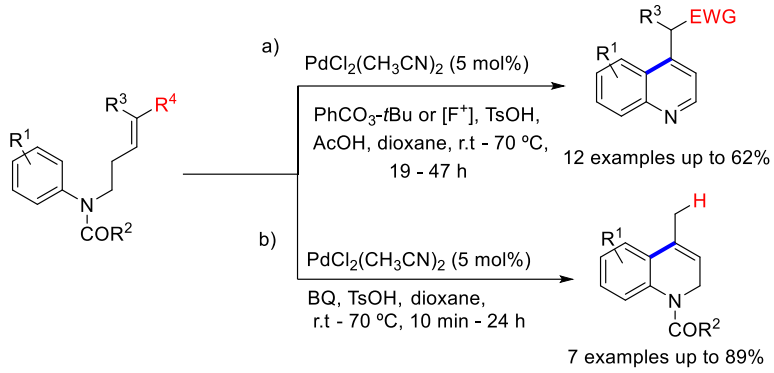


Scheme 1.5. Synthesis of chromanes and 2*H*-chromenes through intramolecular Fujiwara-Moritani reaction.

In a similar way, our group could access to 4-substituted quinolines and 4-substituted dihydroquinolines through *via* intramolecular palladium(II)-catalyzed C–H alkenylation. The insertion of electron-withdrawing groups on alkene provided quinolone core after the removal of *N*-protecting group (Scheme 1.6a). Instead, when terminal alkene is used, the corresponding dihydroquinolines were obtained (Scheme 1.6b).[14]

[13] Carral-Menoyo, A.; Misol, A.; Gómez-Redondo, M.; Sotomayor, N.; Lete, E. Palladium(II)-Catalyzed Intramolecular C–H Alkenylation for the Synthesis of Chromanes. *J. Org. Chem.* **2019**, *84*, 2048-2060.

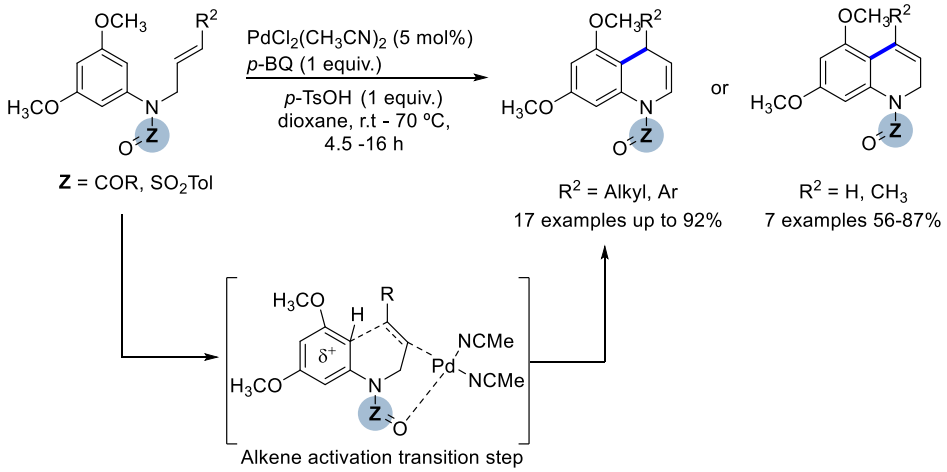
[14] Carral-Menoyo, A.; Ortiz-de Elguea, V.; Martínez-Nunes, M.; Sotomayor, N; Lete, E. Palladium-Catalyzed Dehydrogenative Coupling: An Efficient Synthetic Strategy for the Construction of the Quinoline Core. *Mar. Drugs* **2017**, *15*, 276.



Scheme 1.6. Synthesis of (dihydro)quinolones through intramolecular Fujiwara-Moritani reaction.

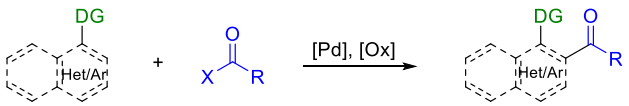
We have also recently demonstrated that the 6-*endo* process is also favored in intramolecular Pd(II)-catalyzed C-H alkenylation reaction of substituted *N*-allylanilines to give 4-substituted 1,4-dihydroquinolines. The introduction of a carbamate group on the nitrogen atom is determinant for the control of the regioselectivity. A DFT study of the mechanistic pathway has shown that the initial palladation would proceed *via* prior activation of the alkene, being coordination of the carbamate to the palladium center crucial to favor the *endo* attack (Scheme 1.7).[15] DFT calculation about the β-elimination of of the H atom clarified that the regioslectivity of this step is not dictated by the relative stability of the adducts, but because of the kinetic of the step itself.

[15] Carral-Menoyo, A.; Sotorríos, L.; Ortiz-de-Elguea, V.; Diaz-Andrés, A.; Sotomayor, N.; Gómez-Bengo, E.; Lete, E. 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. *J. Org. Chem.* **2020**, *85*, 2486-2503.



Scheme 1.7. Intramolecular Pd(II)-catalyzed C-H alkenylation.

On the other hand, the Pd(II)-catalyzed acylation of (hetero)arenes *via* radical formation promoted by an oxidant has recently emerged as catalytic alternative to classical acylation methods, reducing the production of toxic metal waste (Scheme 1.8). Many directing groups, specially *N* containing directing groups such as pyridine, pyridimidine, arylazo, and acyl radical sources as aldehydes, oxoacids, toluene derivatives and alcohols, are used for this purpose.[16] However, further development is required to face mainly selectivity problems, in order to be applied in the synthesis of complex molecules. The ins and outs of this Pd(II)-catalyzed C-H functionalization will be extensively discussed in chapter II.



Scheme 1.8. General scheme of Pd(III)-catalyzed (hetero)arene acylation.

[16] Wu, S. F. Acylation of (Hetero)Arenes through C-H Activation with Aroyl Surrogates. *Chem. Eur. J.* **2015**, *21*, 12252- 12265.

Besides, the use of cheaper, more abundant and less toxic first row transition metals to replace palladium or rhodium complexes has started to attract significant attention.[17] In this context, environmentally benign cobalt complexes show a huge potential for applications in homogeneous catalysis.[18] The reduced electronegativity of cobalt as compared to rhodium (1.88 vs. 2.28 in Pauling scale) results in more nucleophilic organometallic cobalt complexes, allowing new reactivities and improved selectivities.

In contrast to Pd(II) catalysis, high-valent cobalt catalysis for this type of C-H activation reactions has been exploited only recently.[18,19] A significant breakthrough in this chemistry has been the discovery of the Cp*Co(III) complexes that have shown a wide reactivity for directed C-H bond functionalization reactions, mainly through electrophilic base-assisted mechanisms such as CMD, and using different directing groups.[20] These nucleophilic (hetero)aryl-Co(III) complexes have been reacted with electrophiles, such as imines, but also with unsaturated carbon-carbon bonds. For example, reaction with alkynes forms alkenylated products, through a redox-neutral pathway that does not require an external oxidant.[21] Cobalt-catalyzed DHRs have also been described by reaction of (hetero)aryl-Co(III) complexes with activated alkenes,[22] but also the intermediate obtained after migratory insertion could be driven to protodemetalation to afford alkylated products.[23] Allylic alcohol derivatives[30] have

[17] Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C–H Activation. *Chem. Rev*. **2019,** *119*, 2192-2452.
[18] a) Planas, O.; Chirila, P. G.; Whiteoak, C. J.; Ribas, X. In *Advances in Organometallic Chemistry*, P. Pérez, Ed.; Vol 69, pp. 209-282, Academic Press, San Diego, USA, 2018; b) Planas, O.; Whiteoak, C. J.; Ribas, X. In *Non-Noble Metal Catalysis: Molecular Approaches and Reactions*, R. J. M. K. Gebbink, M.-E. Moret, Eds.; pp. 297-328, Wiley-VCH, Weinheim, Germany, 2019.
[19] a) Moselage, M.; Li, J.; Ackermann, L. Cobalt-Catalyzed C–H Activation. *ACS Catalysis* **2016**, *6*, 498-525; b) Ujwaldev, S. M.; Harry, N. A.; Divakar, M. A.; Anilkumar, G. Cobalt-catalyzed C–H activation: recent progress in heterocyclic chemistry. *Catal. Sci. Technol*, **2018**, *8*, 5983-6018.
[20] a) Yoshino, T.; Matsunaga, S. (Pentamethylcyclopentadienyl)cobalt(III)-Catalyzed C–H Bond Functionalization: From Discovery to Unique Reactivity and Selectivity**.** *Adv. Synth. Catal*. **2017**, *359*, 1245-1262; b) Yoshino, T.; Matsunaga, S. In *Advances in Organometallic Chemistry*, Pérez, P. Ed.; Vol 68, p. 197, Academic Press, San Diego, USA, 2017.; c) Ghorai, J.; Ambarasan, P. Developments in Cp*Co^{III}-Catalyzed C−H Bond Functionalizations. *Asian. J. Org. Chem*. **2019**, *8*, 430-455.
[21] Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. Pyrroloindolone Synthesis *via* a Cp*Co^{III}-Catalyzed Redox-Neutral Directed C–H Alkenylation/Annulation Sequence. *J. Am. Chem. Soc*. **2014**, *136*, 5424-5431.
[22] Sk, M. R.; Bera, S. S.; Maji, M. D. Cp*Co(III)-Catalyzed C−H Alkenylation of Aromatic Ketones with Alkenes. *Adv. Synth Catal*. **2019**, *361*, 585- 590.
[23] Li, J.; Zhang, Z.; Ma, W.; Tang, M.; Wang, D.; Zou, L.-H. Mild Cobalt(III)-Catalyzed C–H Hydroarylation of Conjugated C=C/C=O Bonds. *Adv. Synth. Catal*. **2017**, *359*, 1717-1724.

been used in related allylation reactions through β-elimination of the corresponding leaving groups. An alternative to the use of these Cp*Co(III) is the use of Co(II) precatalysts that are oxidized *in situ* to Co(III) by an external oxidant, initiating the catalytic cycle. In this case, the C-H activation event is generally assisted by the use of bidentate directing groups, such as 8-aminoquinoline.[24] Using this type of directing group it has been possible to react unbiased alkenes driving the selectivity of the β-elimination step and resulting in an allylic selective DHR.[25] Besides, nucleophiles can also coordinate the electrophilic Co(III) center, following a reductive elimination for the formation of C-N or C-O or C-C bonds,[26] although these types of reactions are still underdeveloped. Formation of heterocycles has been achieved by reactions with alkynes or alkenes.[24,27] However, cyclization reactions onto an alkene or alkyne tethered to the (hetero)aromatic ring in an intramolecular fashion are almost not developed, in contrast with the Pd(II) catalyzed reactions. A recent example is the synthesis of benzofurans through a Cp*Co(III) catalyzed 5-*exo*-dig intramolecular hydroarylation of aryl propargyl ethers bearing an amide directing group on the aromatic ring.[28] Alternatively, the alkyne has been also tethered to the directing group, which also participates in the cyclization reaction, obtaining isoquinoline alkaloids.[29]

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[24] Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed, Aminoquinoline-Directed C(sp^2)-H Bond Alkenylation by Alkynes**.** *Angew. Chem. Int. Ed*. **2014**, *53*, 10209-10376.

[25] a) Maity, S.; Kancherla, R.; Dhawa, U.; Hoque, E.; Pimparkar, S.; Maiti, D. Switch to Allylic Selectivity in Cobalt-Catalyzed Dehydrogenative Heck Reactions with Unbiased Aliphatic Olefins. *ACS Catal*. **2016**, *6*, 5493-5499; b) Maity, S.; Dolui, P.; Kancherla, R.; Maiti, D. Introducing unactivated acyclic internal aliphatic olefins into a cobalt catalyzed allylic selective dehydrogenative Heck reaction. *Chem. Sci*. **2017**, *8*, 5181-5185.

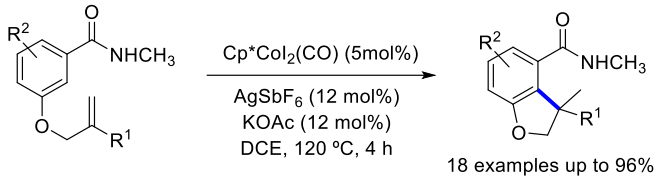
[26] a) C-N: Bera, S. S.; Sk, M. R.; Maji, M. S. Weakly Coordinating, Ketone-Directed (η^5-Pentamethylcyclopentadienyl)cobalt(III)- and (η^5-Pentamethylcyclopentadienyl)rhodium(III)-Catalyzed C−H Amidation of Arenes: A Route to Acridone Alkaloids. *Chem. Eur. J*. **2019**, *25*, 1806-1811; b) C-O: Ueno, R.; Natsui, S.; Chatani, N. Cobalt(II)-Catalyzed Acyloxylation of C–H Bonds in Aromatic Amides with Carboxylic Acids. *Org. Lett*. **2018**, *20*, 1062-1065; c) C-C: Bu, Q.; Gonka, E.; Kicinski, K.; Ackerman, L. Cobalt-Catalyzed Hiyama-Type C−H Activation with Arylsiloxanes: Versatile Access to Highly *ortho*-Decorated Biaryls**.** *Chem. Eur. J*. **2019**, *25*, 2213-2216.

[27] Martínez, A. M.; Rodriguez, N.; Gómez-Arrayás, R.; Carretero, J. C. Cobalt-Catalyzed ortho-C−H functionalization/alkyne annulation of benzylamine derivatives: Access to dihydroisoquinolines**.** *Chem. Eur. J*. **2017**, *23*, 11669-11676.

[28] Bera, S. S.; Debbarama, S.; Jana, S.; Maiji, M. S. Cobalt(III)-Catalyzed Construction of Benzofurans, Benzofuranones and One-Pot Orthogonal C−H Functionalizations to Access Polysubstituted Benzofurans. *Adv. Synth. Catal*. **2018**, *360*, 2204-2210.

[29] Lerchen, A.; Knecht T.; Koy, M.; Daniliuc, C. G.; Glorius, F. A General Cp^*Co^{III}-Catalyzed Intramolecular C−H Activation Approach for the Efficient Total Syntheses of Aromathecin, Protoberberine, and Tylophora Alkaloids. *Chem. Eur. J*. **2017**, *23*, 12149-12152.

In this context, our group published last year the first example of Cp*Co(III)-catalyzed intramolecular hydroarylation of allyl aryl ethers where an amide was used as directing group, for the synthesis of 3,3-disubstituted dihydrobenzofurans (Scheme 1.9).[30] The reaction was completely regioselective for the formation of cuaternary center and the methodology was also extended to the formation of six-membered rings and to *N*-homoallylindoles.



Scheme 1.9. Co(III)-catalyzed intramolecular hydroarylation of allyl aryl ethers.

1.2. GENERAL AIMS OF THE THESIS

The general goal of this thesis is the development of effective and selective methodologies for C-C bond formation *via* transition metal-catalyzed C-H functionalization reactions to provide access to biologically relevant structures containing heterocyclic frameworks. Thus, C(sp^2)-H activation strategies will be developed using Pd(II) catalysts, in which the group had already experience, but also studying approaches based on Co(III) catalysis.

1.2.1. Palladium (II)-Catalyzed Acylation of five-membered heteroaromatic rings

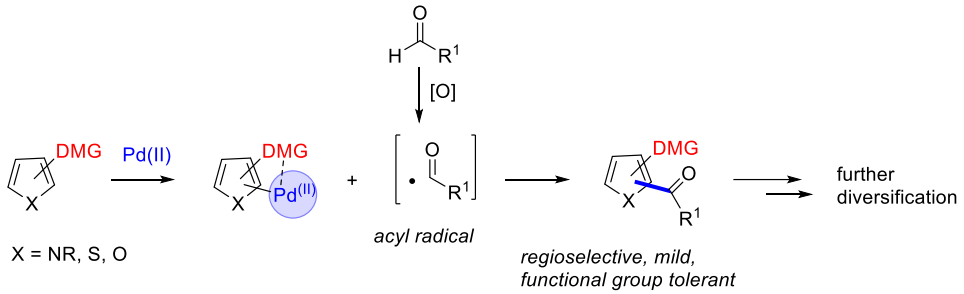
The first objective will be the development of a Pd(II)-catalyzed acylation of five-membered heteroaromatic rings, such as pyrroles and thiophenes. The Palladium(II) C-H acylation of pyrroles has been scarcely studied, one reason could be the competitive 2,5-diacylation reaction. Therefore, the first part of this work will be the design of selective C-2 acylation of pyrrole ring with aldehydes using different directing groups to control the selectivity of the process (Scheme 1.10.). In addition, to show the applicability of the reaction, selected ketones

[30] Carral-Menoyo, A.; Sotomayor, N.; Lete, E.; Amide-Directed Intramolecular Co(III)-Catalyzed C-H Hydroarylation of Alkenes for the Synthesis of Dihydrobenzofurans with a quaternary center *J. Org. Chem.* **2020**, *85*, 10261-10270.

will be used as intermediates in the synthesis of interesting acyl pyrroles.

The second objective will be focused on the selective C-3 acylation of the thiophene ring using a directing group, which will be introduced at C-2 position. The use of MW irradiation as an alternative to thermal conditions will be studied, in order to avoid long reaction times at high temperatures. Furthermore, to show the synthetic interest of acylthiophenes obtained, selected examples will be further derivatized.

Finally, as a secondary objective, the biological activity of some of the obtained ketones as anti-leishmanial agents will be evaluated.[31]

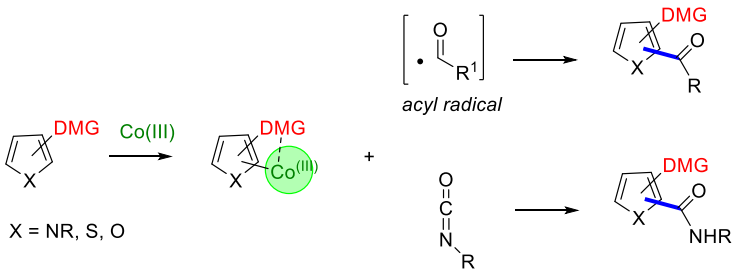


Scheme 1.10. Selective Pd(II)-catalyzed acylation of five-membered heteroaromatic rings.

1.2.2. Cobalt(III)-catalyzed C-H acylation and aminoarbonylation of heteroaromatics

In conection with the previous described objectives, in the second part of the work we decided to study the possibility of developing a Co(III)-catalyzed variant for the acylation reaction, replacing the more toxic and expensive Palladium. Besides, the use of Co(III) catalysis in aminocarbonylation reaction of heteroarenes will be also studied. (Scheme 1.11.).

[31] Anti-leishmanial assays were carried out by Dr. M. A. Dea, from CEU Cardenal Herrera (Valencia).



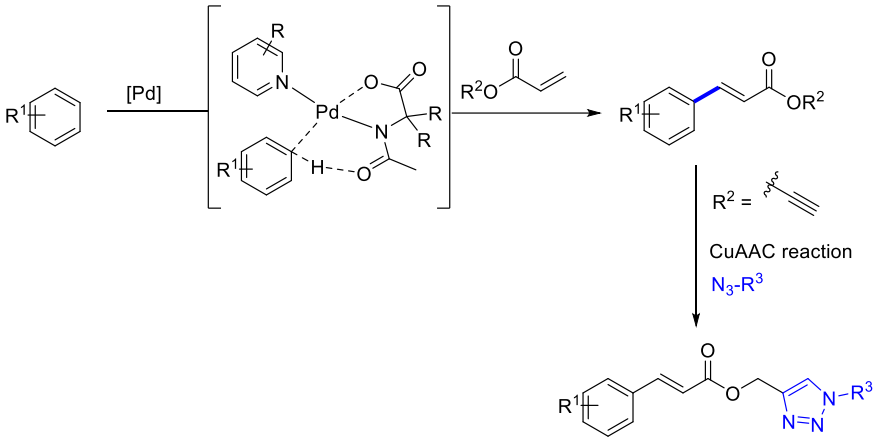
Scheme 1.11. Cobalt(III)-catalyzed acylation and aminocarbonylation of five-membered hetroaromatic rings.

1.2.3. Dual Ligand-Enabled Late-Stage Fujiwara-Moritani reaction

This chapter will be focused on the research carried out over the course of my three-months pre-doctoral stay in Prof. Manuel Antonio van Gemmeren´s research group at the Organic Chemistry Institute of the University of Münster.

Van Gemmeren´s group performed, in 2018, Palladium(II)-catalyzed nondirected C-H olefination in the presence of two complementary ligands.[32] Thus during this stay, I extended their study to the late-stage functionalization of complex bioactive arenes and acrylates *via* nondirected Fujiwara-Moritani reaction using the dual-ligand-based approach (Scheme 1.12). To complete this research, I explored the Fujiwara-Moritani reaction with propargylic acrylates and the subsequent CuAAc-reaction with corresponding substituted azides, so as to build, after a simple click reaction, 1,4-disubstituted triazoles which are appealing scaffolds in medicinal chemistry.

[32] Chen, H.; Wedi, P.; Meyer, T.; Tavakoli, G.; van Gemmeren, M. Dual Ligand-Enabled Nondirected C−H Olefination of Arenes. *Angew. Chem. Int. Ed.* **2018**, *57*, 2497-2501



Scheme 1.12. General objectives of my Ph.D three-month stay.

II

Palladium (II)-catalyzed acylation of five-membered heteroaromatic rings

2.1. INTRODUCTION

2.1.1. Acylation of arenes

2.1.2. Acylation of heteroarenes

2.2. OBJECTIVES

2.3. RESULTS AND DISCUSSION

2.3.1. Selective Palladium (II) catalyzed C-2 acylation of pyrroles with aldehydes

2.3.1.1. Synthesis of Celastramycin analogue **7** and Tolmentin **9**

2.3.1.2. Evaluation of biological activity of 2-acylpyrroles as anti-leishmanial agents

2.3.2. MW assisted Pd(II)-catalyzed acylation of thiophenes

2.3.2.1. Diversification of 3-acylthiophenes

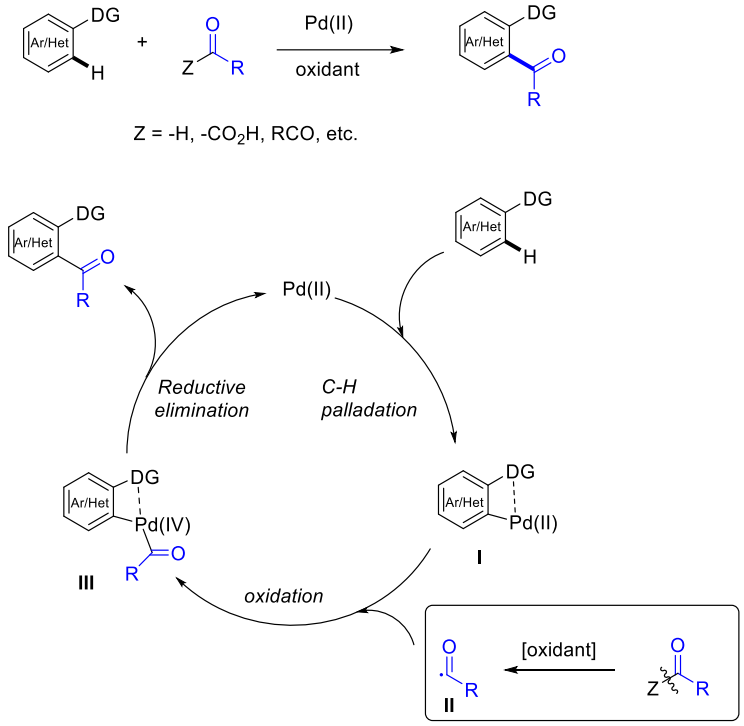
2.1. INTRODUCTION

Transition-metal direct C-H functionalization has emerged as an efficient, atom-economical and environmentally friendly synthetic tool for the preparation of complex multifunctional molecules, which is a good alternative to traditional cross-coupling chemistry. However, this transformation represents a significant challenge in chemical synthesis, largely due to the difficulties associated with the chemoselective activation of relatively inert C-H bonds. Palladium (II) catalysis has been widely used in C-H activation and functionalization of C(sp^2)-H bonds of arenes, heteroarenes or even simple alkenes.[1-2] In this context, Pd(II)-catalyzed acylation of arenes in the presence of an oxidant has emerged as an interesting tool for the synthesis of di(hetero)aryl ketones, important motifs present in natural products, pharmaceuticals or agrochemicals. This procedure constitutes a catalytic alternative to classical acylation methods, reducing the production of toxic metal waste, although it still requires the use of a stoichiometric amount of an oxidant and, in some cases, additives such as acids or metal salts.

A schematic general mechanism proposal is depicted in Scheme 2.1 that implies three distinct fundamental steps. First, palladation of the arene or heteroarene occurs to afford an arylpalladium(II) intermediate **I**, *via* C-H activation. The regioselectivity of this step is generally controlled by the use of a directing group (DG)[3] that provides the *ortho*-arylpalladium(II) intermediate **I**. On the other hand, the oxidant promotes the formation of an acyl radical **II** that, upon reaction with **I,** forms a Pd(IV) intermediate **III** after oxidation. Reductive elimination would afford the corresponding ketone, recovering the Pd(II) catalyst. The first example of Pd(II)-catalyzed acylation reaction with aldehydes was reported in 2009 by Cheng using 2-pyridine as directing group.[4] Since then, significant advances have been made in the field, by the assistance of a wide variety of directing groups for the metalation (DG in

[1] Lei, A.; Shi, W.; Liu, W.; Zhang, H.; He, C. Oxidative Cross-Coupling Reactions; Wiley: Weinheim, Germany, 2017.
[2] Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metal-catalyzed C–H Activation: Examples and Concepts. *Chem. Soc. Rev*. **2016**, *45*, 2900-2936.
[3] Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. Comprehensive Overview of Directing Groups Applied in Metal-Catalysed C–H Functionalization Chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603-6743.
[4] Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. Palladium-Catalyzed Acylation of sp^2 C-H bond: Direct Access to Ketones from Aldehydes. *Org. Lett*. **2009**, *11*, 3120-3123.

arene/heteroarene ring) and by the practical use of different precursors for the acyl radical. The scope of the reaction is wide regarding both the (hetero)aromatic ring and the acyl radical equivalent. The use of the directing group on arene/heteroarene allows the reaction to proceed with both electron-donating and electron-withdrawing substituents on the aromatic ring, although better reactivity is generally obtained with electron-rich aromatic rings.



Scheme 2.1. Schematic mechanism proposed for Pd(II)-catalyzed acylation.

Regarding the acyl radical equivalents, in most cases aroyl groups (ArCO) are introduced. Higher reactivities are generally observed when the aromatic ring of the acyl radical equivalent is substituted with electron-donating groups, what would be in accordance with a more nucleophilic radical intermediate **II**. The use aliphatic acyl equivalents, although possible, generally provides much lower yields. The use of peroxides, such as *t*-

butylhydroperoxide (TBHP), as oxidant for the formation of the acyl radical is the most general method, although more recently their generation *via* photoredox catalysis[5] has also been studied for these reactions.

Although most reactions take place according to Scheme 2.1, the actual mechanism is still not clear. For instance, the exact nature of species **III** formed after radical addition is not known in most cases. Density Functional Theory (DFT) calculations[6] support that the oxidative addition of an acyl radical, obtained by TBHP hydrogen atom abstraction from an aldehyde, to an arylpalladium (**II**) species would generate a Pd(IV) intermediate through a very exergonic process. Reductive elimination would lead to the acylated compound. An alternative aldehyde insertion mechanism was found to be unfavorable. Kinetic isotopic effect experiments have also been used to try to establish the rate-determining step. However, the results obtained for the K_H/K_D ratio in some cases support that the C-H bond cleavage is involved in the rate-determining step[6] but not in other cases.[7] Alternatively, binding of the substrate to palladium and the formation of an aroyl palladium π complex has been proposed.[7] Consequently, further studies are required for mechanistic understanding and further development is necessary for this type of reactions in order to be applied in the synthesis of more complex molecules. A review appeared in 2015 covering the major achievements in this field[8] and the topic has also been included in a broader review. [9] A review covering only the use of toluenes and aroyl surrogate has also appeared very recently.[10] To provide a background for the work developed in this chapter, the next sections are focused on significant recent advances in this type of Pd(II)catalyzed reactions in arenes and heteroarenes and their applications.

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[5] Banerjee, A.; Lei, Z.; Ngai, M. Y. Acyl Radical Chemistry via Visible-Light Photoredox Catalysis. *Synthesis.* **2019**, *51*, 303-333.

[6] Duan, P.; Yang, Y.; Ben, R.; Yan, Y.; Dai, L.; Hong, M.; Wu, Y. D.; Wang, D.; Zhang, X.; Zhao, J. Palladium-catalyzed Benzo[*d*]isoxazole Synthesis by C-H Activation/[4+1] Annulation. *Chem. Sci.* **2014**, *5*, 1574-1578.

[7] Chu, J. H.; Chen, S. T.; Chiang, M. F.; Wu, M. J. Palladium Catalyzed Direct *Ortho* Aroylation of 2-Phenoxypyridines with Aldehydes and Catalytic Mechanistic Investigation. *Organometallics* **2015**, *34*, 953-966.

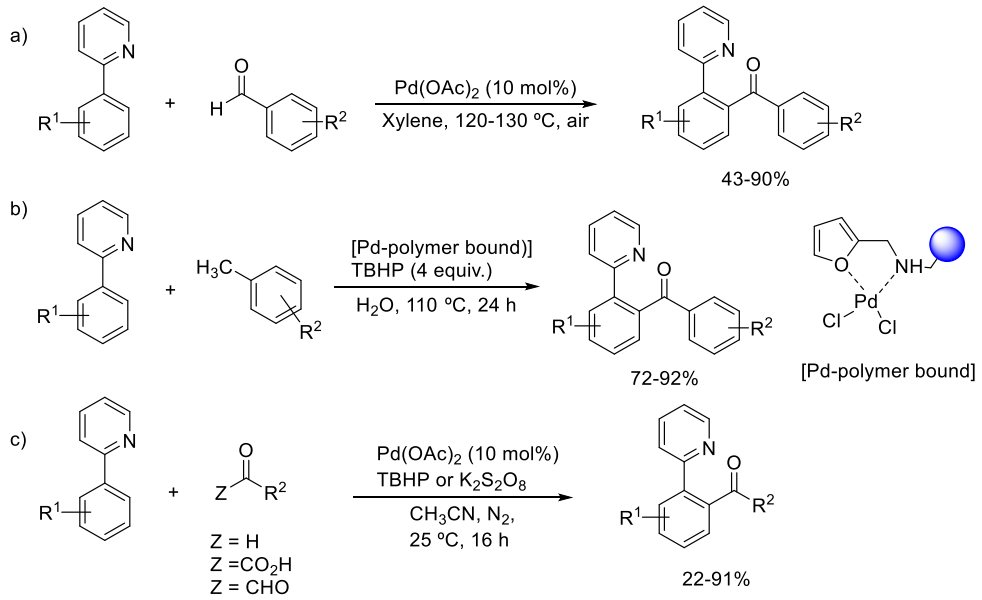
[8] Wu, X.-F. Acylation of (Hetero)Arenes through C-H Activation with Aroyl Surrogates. *Chem. Eur. J.* **2015**, *21*, 12252-12265.

[9] Hummel, J. R.; Boerth, J. A.; Ellman, J. A. Transition-Metal-Catalyzed C−H Bond Addition to Carbonyls, Imines and Related Polarized π Bonds. *Chem. Rev.* **2017**, *117*, 9163-9227.

[10] Joshi, A.; Iqbal, Z.; Jat, J. L.; De, S. R. Pd(II)-Catalyzed Chelation-Induced C(sp^2)-H Acylation of (Hetero)Arenes Using Toluenes as Aroyl Surrogate. *ChemistrySelect.* **2021**, *6*, 12383-12406.

2.1.1. Acylation of Arenes

As indicated, the first example of Pd(II)-catalyzed acylation reaction was reported using 2-pyridine as directing group, aldehydes as the acyl precursor, using air as the oxidant. An aldehyde insertion mechanism was proposed in a Pd(II)/Pd(0)/Pd(II) cycle (Scheme 2.2a).[4] Later, the use of TBHP as an oxidant was reported and a Pd(II)/Pd(IV)/Pd(II) cycle was proposed.[11] Homogeneous conditions are generally used for these reactions, using standard commercial Pd(II) pre-catalysts, such as $Pd(OAc)_2$, $Pd(TFA)_2$, $PdCl_2(CH_3CN)_2$, sometimes in the presence of additives.



Scheme 2.2. Acylation of arenes using a pyridine-directing group.

However, it has been shown that a recyclable heterogeneous palladium complex under on-water conditions, using toluenes as the acyl source (Scheme 2.2b), can replace homogeneous

[11] Baslé, O.; Bidange, J.; Shuai, Q.; Li, C. J. Palladium-Catalyzed Oxidative sp^2 CH Bond Acylation with Aldehydes. *Adv. Synth. Catal.* **2010**, *352*, 1145-1149.

catalysts. The polymer supported furan-2-ylmethanamine complex is stable and could be reused for 5 cycles without loss of efficiency.[12] α-oxoacids have been also used as the acyl source in decarboxylative acylation reactions in the presence of silver salts.[13] Generally these reactions require the use of high temperatures (80–140 °C) but more recently it has been shown that aliphatic and aromatic aldehydes, α-oxoacids and α-oxoaldehydes can be reacted at room temperature in CH_3CN, in presence of $Pd(OAc)_2$ as catalyst and $K_2S_2O_8$ (for α-oxoacids and α-oxoaldehydes) or TBHP (for aldehydes) as oxidants. The formation of an acyl radical intermediate is proposed in all cases. Generally, good yields of acylated 2-arylpyridines are obtained, although aldehydes required longer reaction times (36 h) (Scheme 2.2c).[14] Interestingly, when 2-pyrimidine was used as directing group instead, mixtures of mono- and diacylated products were obtained.

If the pyridine-directing group is linked to the aromatic ring through a heteroatom,[7] it can be easily removed, so further transformations can be performed on the acylated compounds, significantly increasing the synthetic applicability of these transformations. Along these lines, the effect of the substitution on the pyridine ring was studied in the acylation of *N*-aryl-2-pyridinylamines (Scheme 2.3).[15] The introduction of an electron-donating group in C-4 of the pyridine ring (R^3 = OMe) promotes the reactivity of the Pd(II)-catalyzed C-H activation step. On the other hand, the amino nitrogen has to be protected (R^2 = Boc, Ac, Bn, Moc, Piv) and Boc was selected as the most effective group. The reaction was extended to a series of aldehydes obtaining acylated *N*-aryl-2-pyridinylamines in moderate to good yields, although in most cases significant amounts of the diacylated products were also obtained. Both protecting groups could be efficiently removed to obtain amines, which could also be transformed into an acridanone.[15] Besides the use of simple 2-pyridinyl, other related directing groups based on nitrogen coordination have been developed.

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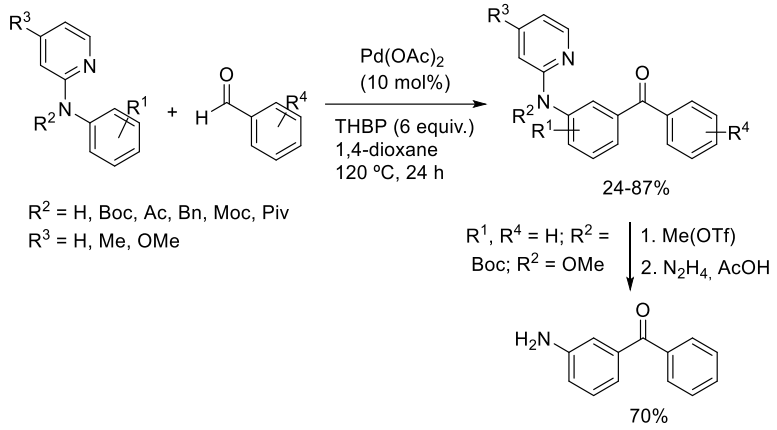
[12] Perumgani, C. P.; Parvathaneni, S. P.; Keesara, S.; Mandapati, M. R. Recyclable Pd(II) Complex Catalyzed Oxidative sp^2 C-H Bond Acylation of 2-Aryl Pyridines with Toluene Derivatives. *J. Organomet. Chem.* **2016**, *822*, 189-195.

[13] Li, M.; Ge, H. Decarboxylative Acylation of Arenes with α-Oxocarboxylic Acids *via* Palladium-Catalyzed C-H Activation. *Org. Lett.* **2010**, *12*, 3464-3467.

[14] Hossian, A.; Manna, M. K.; Manna, K.; Jana, R. Palladium-catalyzed Decarboxylative, Decarbonylative and Dehydrogenative C(sp^2)–H Acylation at Room Temperature. *Org. Biomol. Chem.* **2017**, *15*, 6592-6603.

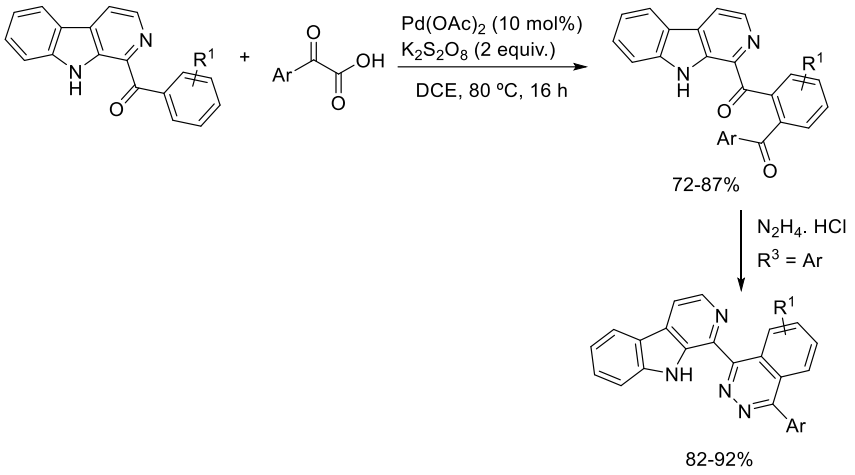
[15] Chu, J. H.; Chiang, M. F.; Li, C. W.; Su, Z. H.; Lo, S. C.; Wu, M. J. Palladium Catalyzed Late Stage *ortho*-C-H Bond Aroylation of anilines using 4-Methoxy-2-pyridinyl as a Removable Directing Group. *Organometallics* **2019**, *38*, 2105-2119.



Scheme 2.3. Pyridine as removable directing group. Effect of the substitution.

As shown in Scheme 2.4, β-carboline was used as directing group for the selective acylation of ketones with α-oxoacids using $K_2S_2O_8$ as oxidant. Diketones were obtained in good yields, which could be derivatized to phthalizines. In this case, the pyridine nitrogen would facilitate the metalation by the formation of a six-membered palladacycle.[16]

[16] Kolle, S.; Batra, S. β-Carboline-directed Decarboxylative Acylation of *Ortho*-C(sp^2)–H of the Aryl Ring of Aryl(β-carbolin-1-yl)methanones with α-Ketoacids under Palladium Catalysis. *RSC Adv.* **2016**, *6*, 50658-50665.

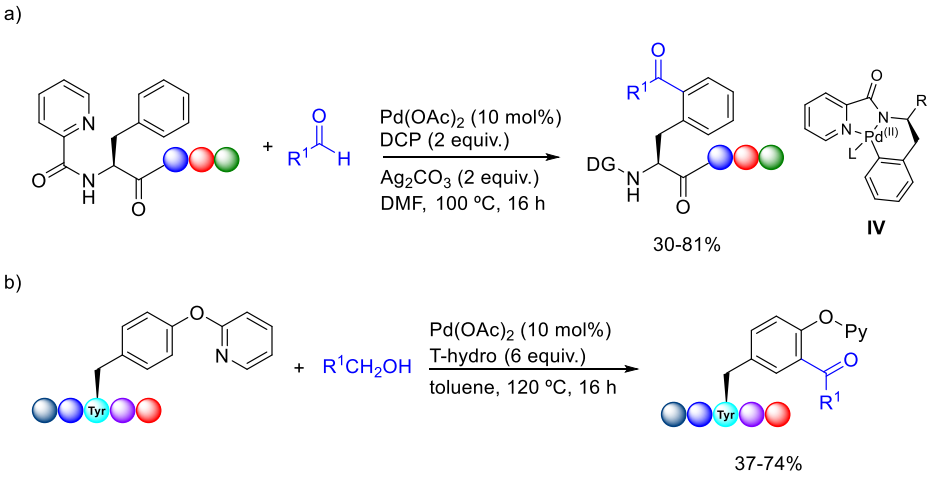


Scheme 2.4. β-Carboline as directing group.

A very interesting application has been developed for the late-stage functionalization of peptides, as shown in Scheme 2.5a. Using a picolinamide directing group it was possible to carry out the selective acylation of phenylalanine-containing peptides (from dipeptides to pentapeptides). The selective palladation would be favored by the bidentate directing group through the formation of a palladacycle intermediate such as **IV** that would later react with the acyl radical to generate a Pd(IV) intermediate. Aromatic, heteroaromatic and aliphatic aldehydes could be used, using dicumyl peroxide (DCP) as oxidant in the presence of silver carbonate (TBHP gave lower yields). Under these conditions, generally excellent yields of the selectively monoacylated peptides were obtained, minimizing the formation of diacylated compounds and with complete retention of stereochemistry.[17] In a related approach, tyrosine containing oligopeptides could be easily acylated using 2-pyridyl ether as an efficient directing group (Scheme 2.5b).[18] Unlike the previous example, the acyl group comes from the oxidation of different alcohols in presence of 6 equivalets of TBHP in aqueous solution (T-hydro). As a result of lower reactivity of alcohols (like EtOH) compared with the

[17] San Segundo, M.; Correa, A. Pd-catalyzed Site-selective C(sp^2)–H Radical Acylation of Phenylalanine Containing Peptides with Aldehydes. *Chem. Sci.* **2019**, *10*, 8872-8879.
[18] Urruzuno, I.; Andrade-Sanpedro, P.; Correa, A. Late-Stage C−H Acylation of Tyrosine-Containing Oligopeptides with Alcohols. *Org. Lett.* **2021**, *23*, 7279-7284.

corresponding aldehydes, the reaction afforded exclusively monoacylated products. The reaction could be scaled to grams, when EtOH and BuOH were used and extended to di-, tri, tetra- and even hexapeptides, including the synthesis of analogues of Endomorphin 2 and Neuromedin N.



Scheme 2.5. Late stage functionalization of peptides using pyridin-based directing-groups.

Besides pyridine, other nitrogen heterocycles have been used as directing groups, such as triazoles. The acylation of 2-aryl-1,2,3-triazoles has been accomplished with aldehydes.[19] More recently, when 1,4-diaryl-1,2,3-triazoles were used, the acylation using aldehydes[20] or oxoacids[21] took place selectively on the aromatic ring on C-4 of the triazole (Scheme 2.6). In the first case (Scheme 2.6a), the yields of acylated 1,4-diaryl-1,2,3-triazoles were improved in the presence of a ligand such as X-Phos. The reaction using oxoacids in the presence of

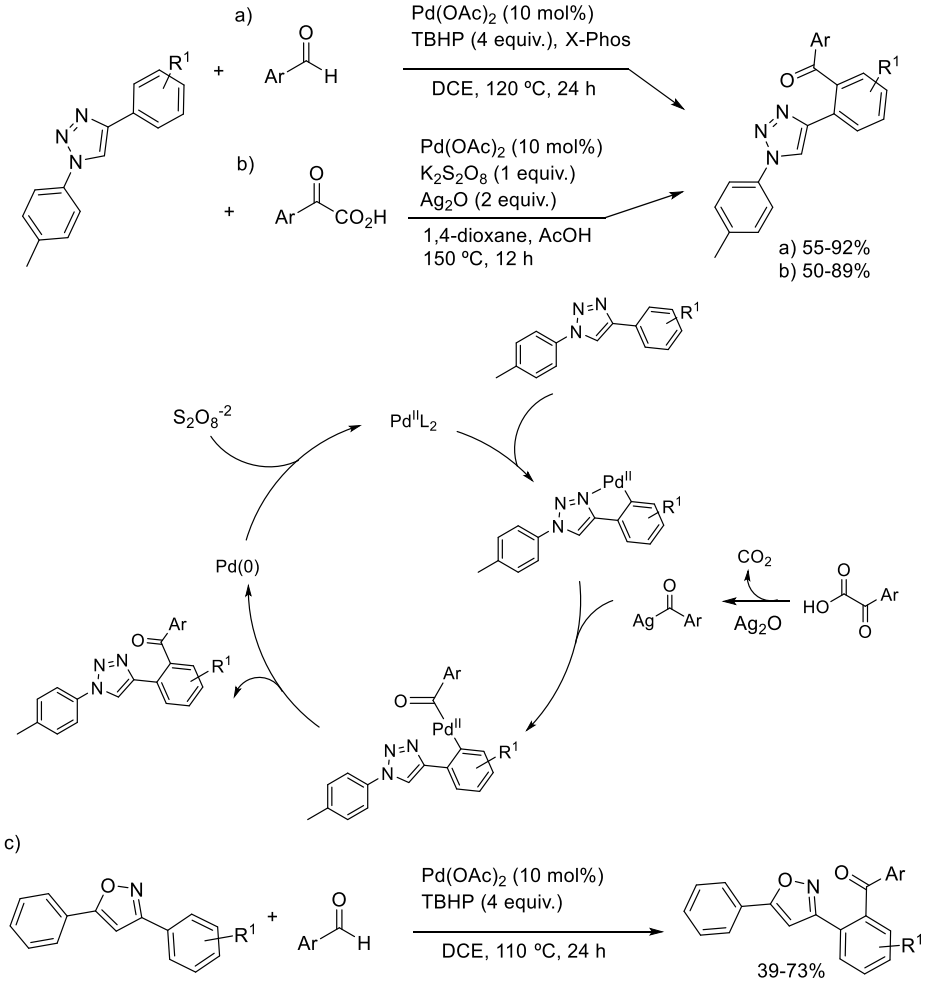
[19] Wang, Z.; Tian, Q.; Yu, X.; Kuang, C. Palladium-Catalyzed Acylation of 2-Aryl-1,2,3-triazoles with Aldehydes. *Adv. Synth. Catal.* **2014**, *356*, 961-966.
[20] Zhao, F.; Chen, Z.; Liu, Y.; Xie, K.; Jiang. Y. Palladium-Catalyzed Acylation of Arenes by 1,2,3-Triazole-Directed C–H Activation. *Eur. J. Org. Chem.* **2016**, 5971-5979.
[21] Ma, X.; Huang, H.; Yang, J.; Feng, X.; Xie, K. Palladium-Catalyzed Decarboxylative *N*-3-*ortho*-C–H Acylation of 1,4-Disubstituted 1,2,3-Triazoles with α-Oxocarboxylic Acids. *Synthesis* **2018**, *50*, 2567-2576.

silver oxide (Scheme 2.6b) does not seem to involve the formation of an acyl radical intermediate, as no change in reactivity was found when the reactions were carried out in the presence of radical scavengers such as 2,2,6,6-tetramethylpiperidin-1-yl-oxydanyl (TEMPO). A mechanism (Scheme 2.6) is proposed in which coordination to the more electron rich *N*-3 atom of the triazole would favor the *ortho*-palladation. The oxoacid would generate an acyl-silver intermediate, which would transmetalate to generate an acylpalladium(II) intermediate. Reductive elimination produces the corresponding acylated products and the resulting palladium(0) species is reoxidized to Pd(II), closing the catalytic cycle. In addition, the higher directing ability of nitrogen over oxygen atom has been applied for the completely regioselective acylation of 3,5-diarylisoxazoles with aldehydes, which are acylated at the *ortho*-position of the C-3 aromatic ring to obtain *ortho* acylated 3,5-diarylisoxazoles [22] (Scheme 2.6c).

The use of tertiary amides as directing groups in *ortho*-metalation reactions is widely recognized and employed.[23,24] Diethyl amides have been used in rhodium-catalyzed aroylation reactions with aldehydes.[25] However, as tertiary amides may undergo insertion of palladium into the *N*-C(O) bond,[26] they have been used as aroyl sources in cross-coupling reactions. Besides, the weak coordination of the amide and the electron deficient aryl ring makes them difficult substrates for palladium catalyzed C-H activation. Despite this, two examples of decarboxylative acylation of benzamides with α-oxocarboxylic acids were

[22] Banerjee, A.; Bera, A.; Santra, S. K.; Guin, S.; Patel, B. K. Palladium-catalysed Regioselective Aroylation and Acetoxylation of 3,5-Diarylisoxazole *via Ortho* C–H Functionalisations. *RSC Adv.* **2014**, *4*, 8558-8566.
[23] Snieckus, V. Directed *Ortho* Metalation. Tertiary Amide and *O*-carbamate Directors in Synthetic Strategies for Polysubstituted Aromatics. *Chem. Rev.* **1990**, *90*, 879-933.
[24] Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. Beyond Thermodynamic Acidity: A Perspective on the Complex-Induced Proximity Effect (CIPE) in Deprotonation Reactions. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206-2225.
[25] Park, J.; Park, E.; Kim, A.; Lee, Y.; Chi, K. W.; Kwak, J. H.; Jung, Y. H.; Kim. I. S. Rhodium-Catalyzed Oxidative *ortho*-Acylation of Benzamides with Aldehydes: Direct Functionalization of the sp^2 C–H Bond. *Org. Lett.* **2011**, *13*, 4390-4393.
[26] Meng, G.; Shi, S.; Szostak, M. Cross-Coupling of Amides by N–C Bond Activation. *Synlett* **2016**, *27*, 2530-2540.

described almost simultaneously (Scheme 2.7).[27,28] In both cases, dialkyl or cyclic amides could be used as directing groups.



Scheme 2.6. 1,2,3-triazole and oxazole as directing group.

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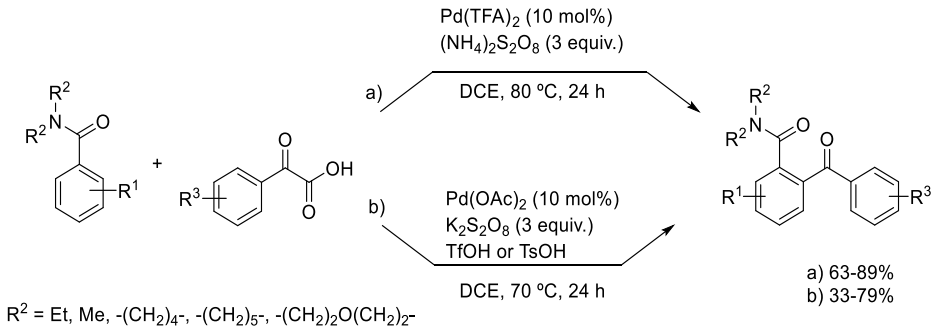
[27] Laha, J. K.; Patel, K. V.; Sharma, S. Palladium-Catalyzed Decarboxylative *Ortho*-Acylation of Tertiary Benzamides with Arylglyoxylic Acids. *ACS Omega.* **2017**, *2*, 3806-3815.

[28] Jing, K.; Yao, J.-P.; Li, Z.-Y.; Li, Q.-L.; Lin, H.-S.; Wang, G.-W. Palladium-Catalyzed Decarboxylative *Ortho*-Acylation of Benzamides with *α*-Oxocarboxylic Acids. *J. Org. Chem.* **2017**, *82*, 12715-12725.

Diethyl amides (R^2 = Et) were selected as the best candidates in the first case (Scheme 2.7a,[27]) using $(NH_4)_2S_2O_8$ as oxidant, while dimethyl amides (R^2 = Me) were selected for extension in the second case (Scheme 2.7b,[28]). The mode of activation of the amide is not clear. Control experiments suggest that the initial palladation is assisted by initial coordination to the amide nitrogen, although DFT calculations showed that an *O*-coordinated intermediate would be more favorable.[27] Besides, intermolecular KIE experiments (K_H/K_D = 2.5) suggest that the C-H cleavage might be the rate determining step. In this case, *O*-coordination to the amide is proposed.[28]

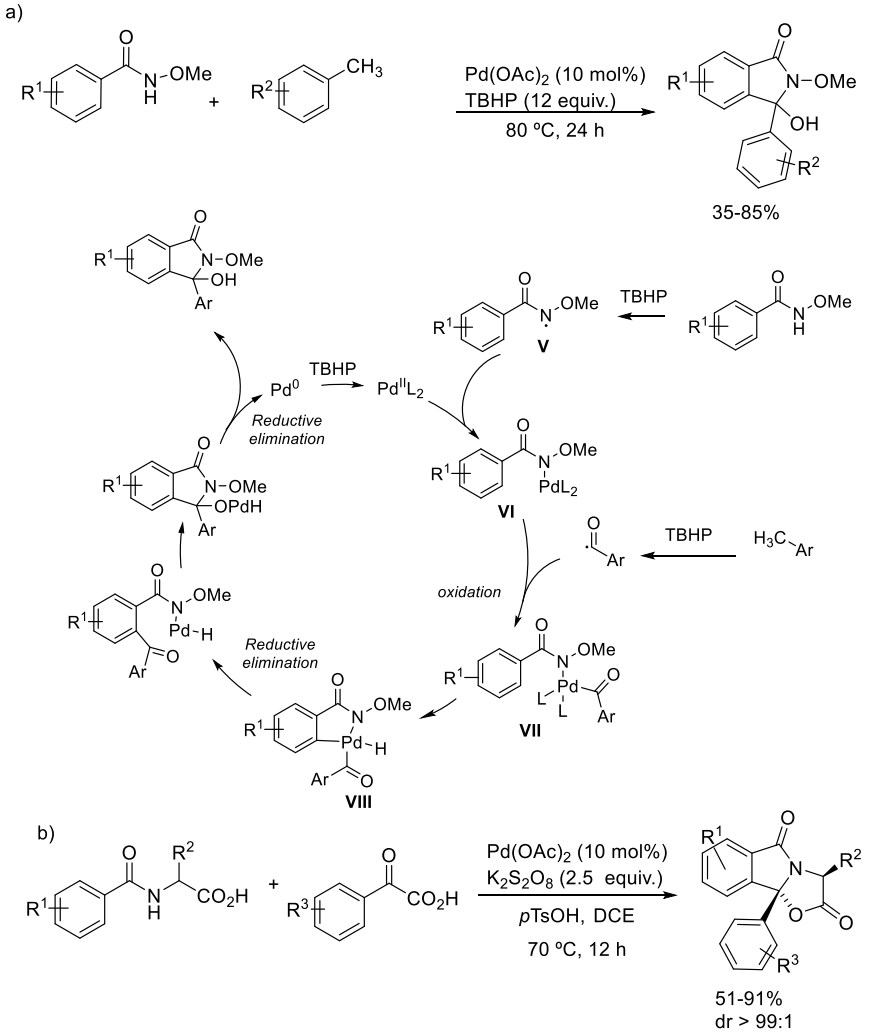


Scheme 2.7. Tertiary amides as directing groups. Acylation of benzamides.

Secondary amides, with a free NH group, have also been successfully used as directing groups in the acylation reaction with aldehydes[29] or α-oxoacids,[28] leading to the formation of hydroxyisoindolones through acylation and subsequent cyclization. More recently, toluene derivatives have been used as acyl source for the acylation of *N*-methoxybenzamides (Scheme 2.8a).[30] In this case, the mechanistic proposal differs from Scheme 2.1, although a coupling with an acyl radical is also involved. In agreement with previous reports,[29] it is proposed that the secondary amide would be activated by TBHP, generating an amide

[29] Yu, Q.; Zhang, N.; Huang, J.; Lu, S.; Zhu, Y.; Yu, X.; Zhao, K. Efficient Synthesis of Hydroxyl Isoindolones by a Pd-Mediated C-H Activation/Annulation Reaction. *Chem. Eur. J.* **2013**, *19*, 11184-11188.
[30] Yang, L.; Han, L.; Xu, B.; Zhao, L.; Zhou, J.; Zhang, H. Palladium-Catalyzed C-H Bond *Ortho* Acylation/Annulation with Toluene Derivatives. *Asian J. Org. Chem.* **2016**, *5*, 62-65.

nitrogen radical **V**, which forms intermediate **VI** after electrophilic palladation. TBHP also oxidizes the toluene derivate to the acyl radical, forming a high-valent Pd(IV) intermediate **VII** prior to a fast C-H activation. Hydroxyindolinones would be obtained through reductive elimination and subsequent cyclization, as depicted in Scheme 2.8a.



Scheme 2.8. Secondary amides as directing groups. Formation of isoindolinones.

Amino acid-derived amides have also been used as bidentate directing groups (Scheme 2.8b).[31] The mechanistic proposal is analogous to the one depicted in Scheme 2.8a, although in this case, C-H activation is assisted by prior coordination of Pd(II) to both the nitrogen atom and the carboxylic oxygen atom forming a palladacycle intermediate. The directing group on benzamides is incorporated in the oxazoloisoindolinones through a cascade reaction, with complete diastereoselectivity.

Besides benzamides, anilides have also been successfully acylated with aldehydes.[32,33,34] Also, an amide-directed metalation was applied in the selective C-7 acylation of indolines with aldehydes.[35]

More recently, acylation of acetanilides has been achieved with inexpensive benzylic alcohols under aqueous conditions at 40 °C in the presence of a catalytic amount of TFA, obtaining very good yields of ketones, with wide functional group tolerance (Scheme 2.9a).[36] A bimetallic palladium 6-membered cyclopalladated complex could be obtained and used as catalyst for this reaction. Recently, carbamates have also been used as directing groups for the acylation with α-oxoacids (Scheme 2.9b) obtaining the corresponding aryl ketones in moderate to good yields.[37] Carbamate directing group could be easily removed obtaining amine that could be derivatized to various heterocyclic systems, such as quinazoline or phenylquinoline.

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[31] Jing, K.; Wang, X.-N.; Wang, G.-W. Diastereoselective Synthesis of Oxazoloisoindolinones via Cascade Pd-Catalyzed *Ortho*-Acylation of *N*-Benzoyl *α*-Amino Acid Derivatives and Subsequent Double Intramolecular Cyclizations. *J. Org. Chem.* **2019**, *84*, 161-172.

[32] Chan, C. W.; Zhou, Z.; Yu, W. Y. Palladium(II)-Catalyzed Direct *Ortho*-C−H Acylation of Anilides by Oxidative Cross-Coupling with Aldehydes using *Tert*-Butyl Hydroperoxide as Oxidant. *Adv. Synth. Catal.* **2011**, *353*, 2999-3006.

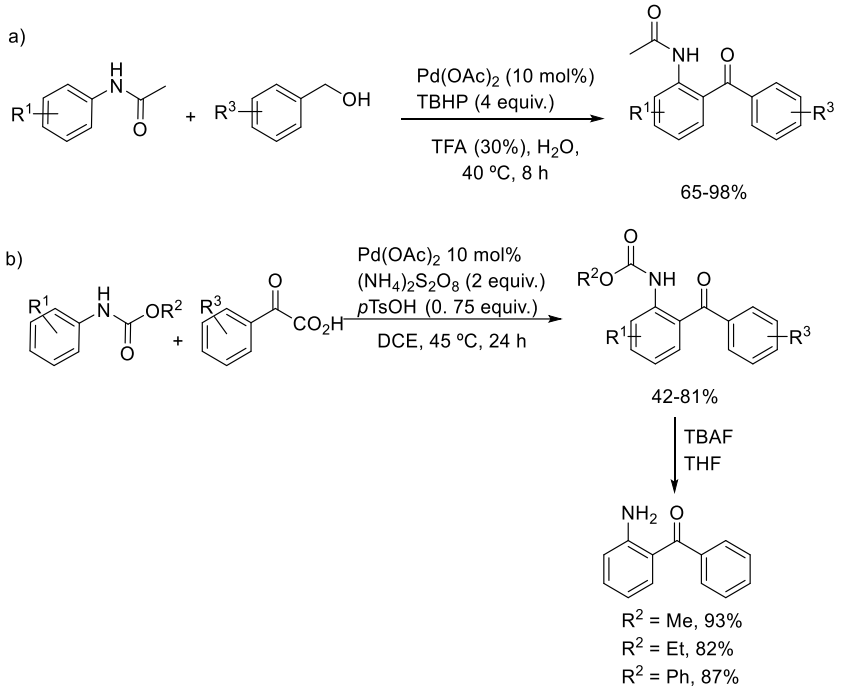
[33] Wu, Y.; Li, B.; Mao, F.; Li, X.; Kwong, F. Y. Palladium-Catalyzed Oxidative C−H Bond Coupling of Steered Acetanilides and Aldehydes: A Facile Access to *ortho*-Acylacetanilides. *Org. Lett.* **2011**, *13*, 3258-3261.

[34] Li, C.; Wang, L.; Li, P.; Zhou, W. Palladium(II)-Catalyzed Direct *Ortho*-C−H Acylation of Anilides by Oxidative Cross-Coupling with Aldehydes using *Tert*-Butyl Hydroperoxide as Oxidant. *Chem. Eur. J.* **2011**, *17*, 10208-10212.

[35] Shin, Y.; Sharma, S.; Mishra, N. K.; Han, S.; Park, J.; Oh, H.; Ha, J.; Yoo, H.; Jung, H.-Y.; Kim, I. S. Direct and Site-Selective Palladium-Catalyzed C-7 Acylation of Indolines with Aldehydes. *Adv. Synth. Catal.* **2015**, *357*, 594-600.

[36] Luo, F.; Yang, J.; Li, Z.; Xiang, H.; Zhou, X. Palladium-Catalyzed C–H Bond Acylation of Acetanilides with Benzylic Alcohols under Aqueous Conditions. *Eur. J. Org. Chem.* **2015**, 2463-2469.

[37] Li, Q.-L.; Li, Z.-Y.; Wang, G.-W. Palladium-Catalyzed Decarboxylative *Ortho*-Acylation of Anilines with Carbamate as a Removable Directing Group. *ACS. Omega.* **2018**, *3*, 4187-4198.

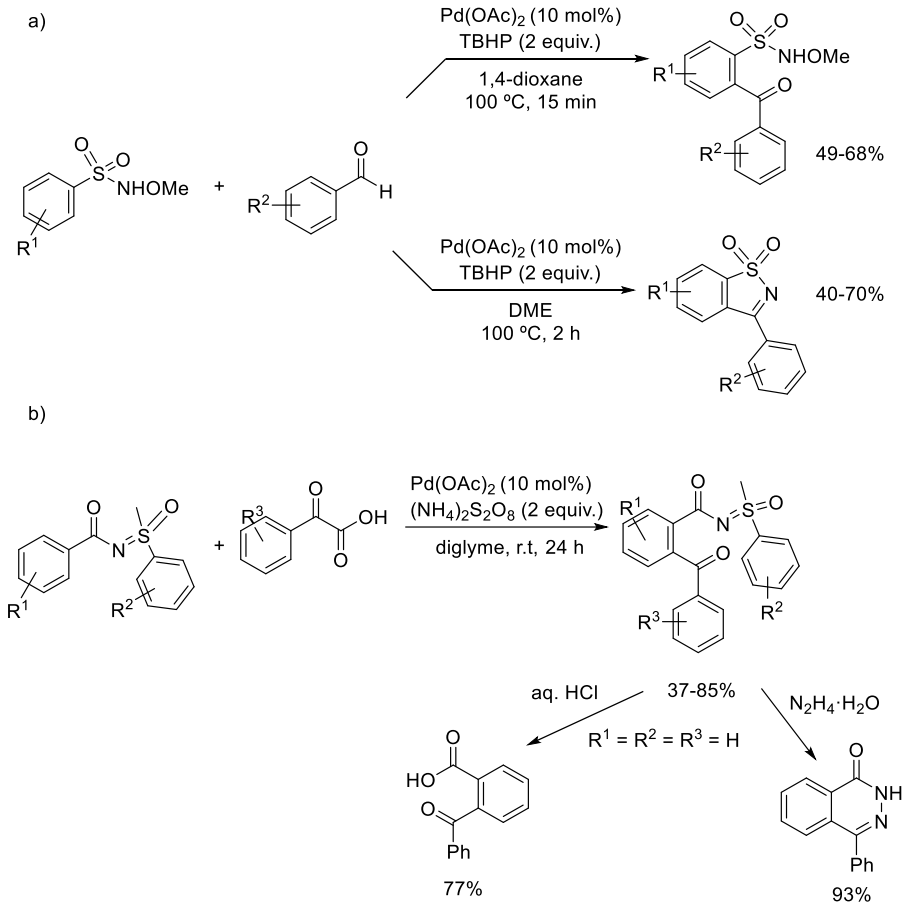


Scheme 2.9. Acylation of acetanilides and *N*-aryl carbamates.

More recently, sulfonamides and *N*-sulfoximine amides have also been developed as directing groups (Scheme 2.10). Sulfonamides are acylated efficiently with aldehydes in good yields in only 15 min.[38] Aliphatic aldehydes can also be used, although with lower yields. Only a change in the solvent and an extension of the reaction time led to the direct formation of cyclic sulfonyl ketimines in generally good yields (Scheme 2.10a). In the case of the *N*-sulfoximine benzamides, the reaction could be efficiently performed with α-oxocarboxylic acids at room temperature. The reactivity was similar when electron-withdrawing and electron-donating groups were introduced in the sulfoximine unit. (Scheme 2.10b). The directing group could be easily hydrolyzed to obtain the corresponding

[38] Ojha, S.; Panda, N. Palladium-Catalyzed *Ortho*-Benzoylation of Sulfonamides through C−H Activation: Expedient Synthesis of Cyclic *N*-Sulfonyl Ketimines. *Adv. Synth. Catal.* **2020**, *362*, 561-571.

carboxylic acid or directly transformed in other heterocyclic systems, such as phthalazinone.[39]



Scheme 2.10. Acylation of sulfonamides and *N*-sulfoximine amides.

Besides these examples, other nitrogen containing directing groups have been also used. For

[39] Das, P.; Biswas, P.; Guin, J. Palladium-Catalyzed Decarboxylative *Ortho*-C(sp^2)−H Aroylation of *N*-Sulfoximine Benzamides at Room Temperature. *Chem. Asian J.* **2020**, *15*, 920-925.

instance, azobenzenes have been selectively *ortho*-acylated with aldehydes,[40] also using aqueous conditions [41] and with α-oxoacids,[42] even at room temperature.[43] The acylated azobenzenes could be very efficiently transformed into indazoles (Scheme 2.11a). More recently, α-hydroxyl ketones have been identified as acylating agents (Scheme 2.11b). In most examples, symmetrically substituted azoarenes are used, leading to the selective formation of monoacylated compounds, although excellent selectivities could also be obtained when non-symmetrically substituted azoarenes were used, depending on the substitution pattern. This acylation reaction could be applied to the synthesis of an indazole system, which has activity as a liver(X) receptor agonist. It is proposed that the hydroxyketone is oxidized to the corresponding diketone, generating the acyl radical. Both acyl fragments are transferred, so symmetrically substituted hydroxyketones have to be used to obtain selective reactions.[44]

Nitrosoamines are also effective directing groups (Scheme 2.12). Thus, nitrosoanilines could be acylated with oxoacids at room temperature, using 5 mol % of the palladium catalyst. Acylated nitrosoanilines are obtained in good yields, with wide functional group tolerance. The nitroso group could be removed or transformed, as exemplified in Scheme 2.12 for the two step synthesis of an indole.[45] Related examples have also been described.[46,47]

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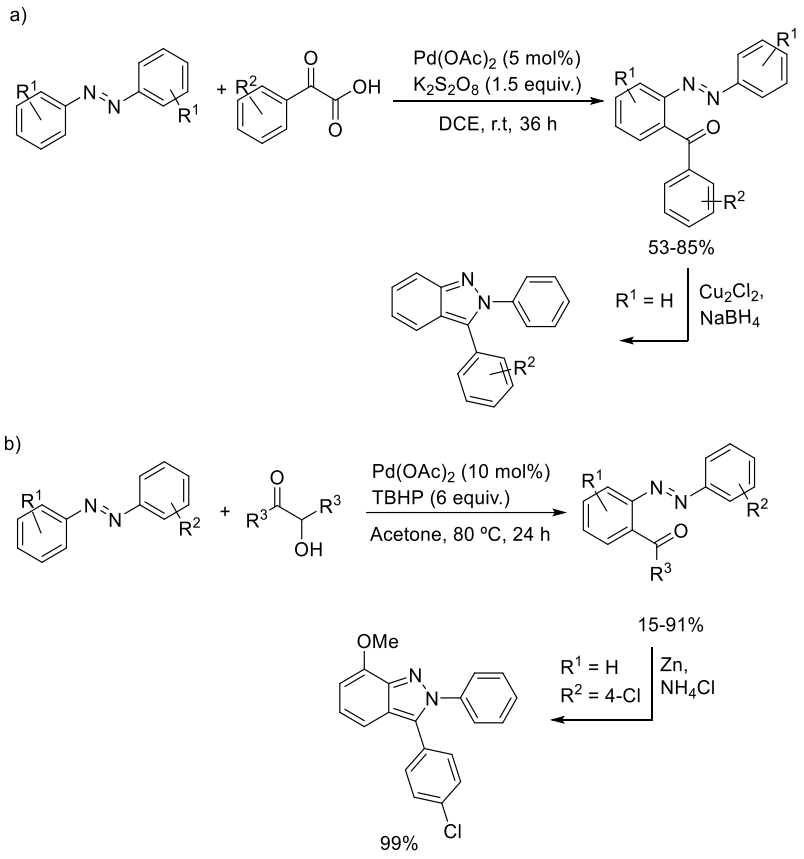
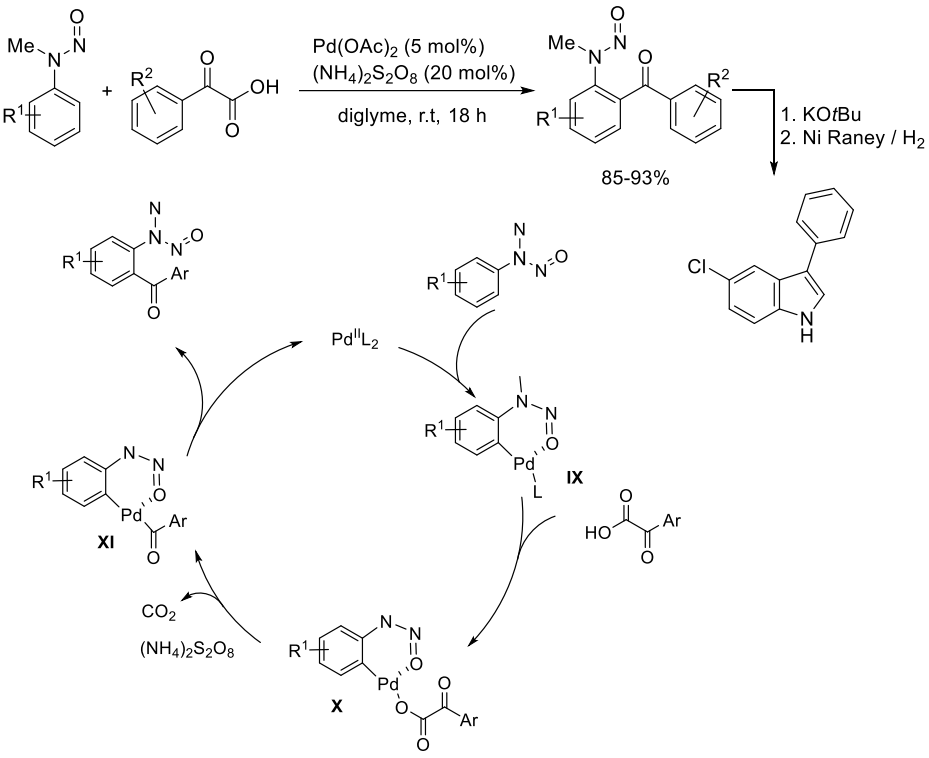
[40] Li, H.; Li, P.; Wang, L. Direct Access to Acylated Azobenzenes via Pd-Catalyzed C–H Functionalization and Further Transformation into an Indazole Backbone. *Org. Lett.* **2013**, *15*, 620-623.
[41] Xiao, F.; Chen, S.; Huang, H.; Deng, G. J. Palladium-Catalyzed Oxidative Direct *Ortho*-C–H Acylation of Arenes with Aldehydes under Aqueous Conditions. *Eur. J. Org. Chem.* **2015**, 7919-7925.
[42] Li, Z.-Y.; Li, D.-D.; Wang, G.-W. Palladium-Catalyzed Decarboxylative *Ortho* Acylation of Azobenzenes with *α*-Oxocarboxylic Acids. *J. Org. Chem.* **2013**, *78*, 10414-10420.
[43] Li, H.; Li, P.; Tan, H.; Wang, L. A. Highly Efficient Palladium-Catalyzed Decarboxylative ortho-Acylation of Azobenzenes with α-Oxocarboxylic Acids: Direct Access to Acylated Azo Compounds. *Chem. Eur. J.* **2013**, *19*, 14432-14436.
[44] Majhi, B.; Ahammed, S.; Kundu, D.; Ranu, B. C. Palladium-Catalyzed Oxidative C−C Bond Cleavage of *α*-Hydroxyketones: Application to C−H Acylation of Azoarenes and Synthesis of a Liver(X) Receptor Agonist. *Asian J. Org. Chem.* **2015**, *4*, 154-163.
[45] Wu, Y.; Sun, L.; Chen, Y.; Zhou Q.; Huang, J. W.; Miao, H.; Luo, H. B. Palladium-Catalyzed Decarboxylative Acylation of *N*-Nitrosoanilines with α-Oxocarboxylic Acids. *J. Org. Chem.* **2016**, *81*, 1244-1250.
[46] Zhang, L.; Wang, Z.; Guo, P.; Sun, W.; Li, Y.-M.; Sun, M.; Hua, C. Palladium-catalyzed *Ortho*-acylation of *N*-Nitrosoanilines with *α*-Oxocarboxylic Acids: A Convenient Method to Synthesize *N*-Nitroso Ketones and Indazoles. *Tetrahedron Lett.* **2016**, *57*, 2511-2514.
[47] Yao, J. P.; Wang, G. W. Palladium-catalyzed Decarboxylative *Ortho*-acylation of *N*-Nitrosoanilines with α-Oxocarboxylic Acids. *Tetrahedron Lett.* **2016**, *57*, 1687-1690.



Scheme 2.11. Acylation of azoarenes.

The mechanism in these cases is still not clear but the formation of an intermediate acyl radical from the ketoacid is not proposed. Instead, palladation of nitrosoanilines lead to an intermediate **IX**, which would react with the ketoacid to obtain a Pd(II)carboxylate such as **X**. Decarboxylation would lead to an acyl-palladium(IV) intermediate **XI** after oxidation.

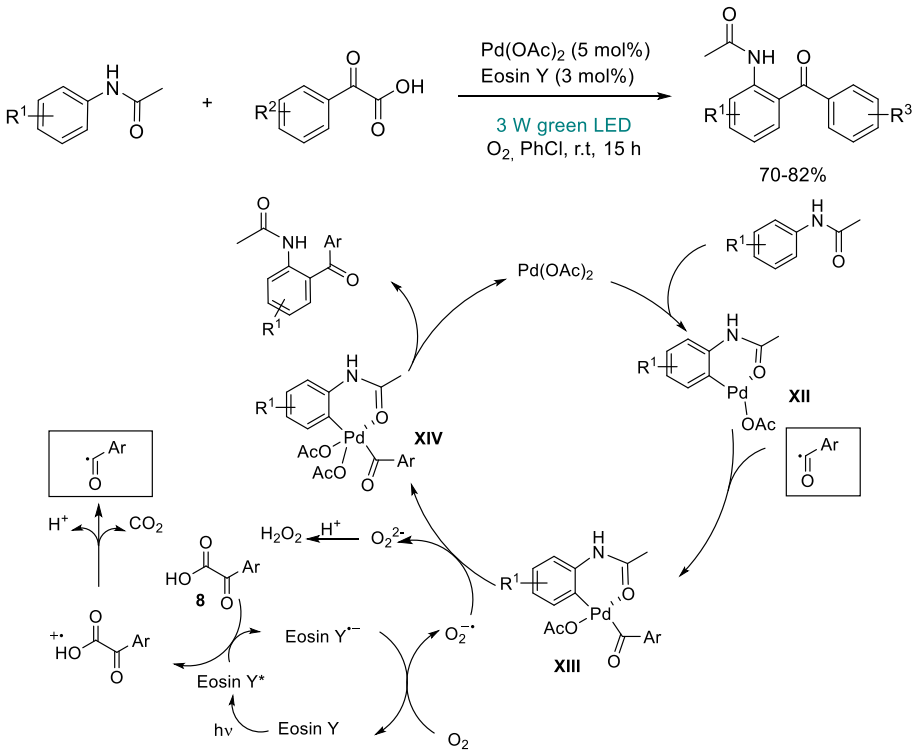


Scheme 2.12. Nitrosoamine as directing group.

To finish this section, an important contribution is depicted in Scheme 2.13. Recently, the combination of visible light photoredox catalysis with transition metal catalysis has attracted much attention, as it can open opportunities for new reactivity.[48] In this context, it has been shown that the acylation reaction of acetanilides[49] (Scheme 2.13), azoarenes[50] (Scheme 2.14a)

[48] De Abreu, M.; Belmont, P.; Brachet, E. Synergistic Photoredox/Transition-Metal Catalysis for Carbon–Carbon Bond Formation Reactions. *Eur. J. Org. Chem.* **2020**, *2020*, 1327-1378.
[49] Zhou, C.; Li, P.; Zhu, X.; Wang, L. Merging Photoredox with Palladium Catalysis: Decarboxylative *Ortho*-Acylation of Acetanilides with α-Oxocarboxylic Acids under Mild Reaction Conditions. *Org. Lett.* **2015**, *17*, 6198-6201.
[50] Xu, N.; Li, P.; Xie, Z.; Wang, L. Merging Visible-Light Photocatalysis and Palladium Catalysis for C-H Acylation of Azo- and Azoxybenzenes with α-Keto Acids. *Chem. Eur. J.* **2016**, *22*, 2236-2242.

and 2-arylpyridines (Scheme 2.14b and 2.14c)[51,52] can be carried out at room temperature using a combination of a photoredox catalyst with a palladium(II) catalyst.



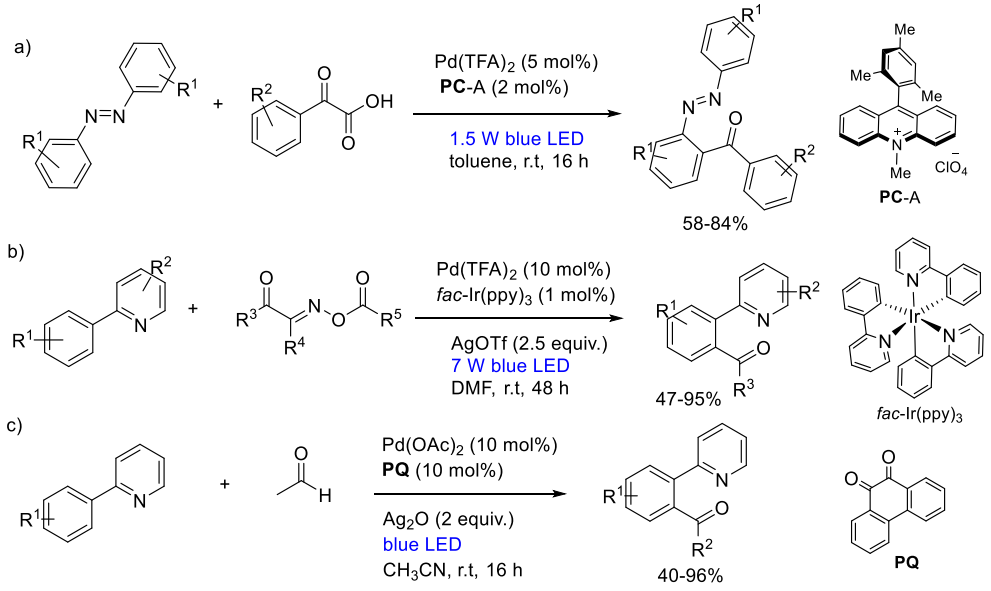
Scheme 2.13. Photoredox/palladium catalyzed acylation of acetanilides.

In all cases, the reaction would work on a Pd(II)/Pd(IV) catalytic cycle, analogous to the one depicted in Scheme 2.1. This cycle would be coupled with the corresponding photocatalytic

[51] He, B-Q.; Gao, Y.; Wang, P-Z.; Wu, H.; Zhou, H-B.; Liu, X-P.; Chen, J-R. Dual Photoredox/Palladium-Catalyzed C–H Acylation of 2-Arylpyridines with Oxime Esters. *Synlett* **2021**, *32*, 373-377.

[52] Wang, H.; Li, T.; Hu, D.; Tong, X., Zheng, L.; Xia, C. Acylation of Arenes with Aldehydes through Dual C−H Activations by Merging Photocatalysis and Palladium Catalysis. *Org. Lett.* **2021**, 23, 3772-3776.

cycle, through which the acyl radical is generated from the oxoacid, α-keto oxime esters or aldehydes. The presence of the acyl radical has been supported by TEMPO trapping experiments and the presence of oxygen (air) is required. In all cases, several photoredox catalysts were screened and Eosin Y, the acridinium salt perchlorate PC-A (Fukuzumi salt), *fac*-Ir(ppy)$_3$ ([*fac*-tris(2-phenylpyridine)iridium(III)]) and PQ (phenanthrene-9,10-dione) were selected as the best candidates. In all cases, yields of the ketones are competitive with the ones obtained in the presence of an oxidant (Schemes 2.2, 2.8 and 2.10), with the advantage of using milder conditions in the absence of an excess of oxidant. The proposed mechanism is illustrated in Scheme 2.13a for the reaction of acetanilides. Palladium catalytic cycle would start by a C-H activation to form palladacycle **XII**, which reacts with the acyl radical to afford a Pd(III) intermediate **XIII**. A one electron oxidation *via* superoxide radical anion generates a Pd(IV) intermediate **XIV**. Reductive elimination leads corresponding acylated products and regenerates the Pd(II) catalyst. The photocatalytic cycle starts with the visible irradiation of Eosin Y to take it to the excited state (Eosin Y*). One electron oxidation of the ketoacid generates the acyl radical, after loss of CO_2 and Eosin Y radical anion (Eosin Y$^{-\cdot}$). Electron transfer by molecular oxygen regenerates Eosin Y and produces superoxide radical anion (detected by Electron Spin Resonance (ESR)), who acts as an oxidant in the palladium cycle.



Scheme 2.14. Photoredox/palladium catalyzed acylation of azoarenes and 2-arylpyridines.

2.1.2. Acylation of Heteroarenes

The Pd(II)-catalyzed oxidative acylation of heteroarenes has been less developed than the acylation of arenes covered in the previous section. In some cases, it is possible to take advantage of the electronic properties of the heteroaromatic ring (mainly electron-rich), so the C-H palladation step can be performed without the need of a directing group. However, directing groups are frequently used to overcome the electronic bias and direct the metalation to other positions in the ring. Among them, the most frequently used are nitrogen-based directing groups (2-pyridine, 2-pyrimidine). The acylation of indole derivatives has received much attention. It has been shown that the Pd(II)-catalyzed acylation of *N*-alkylindoles with aldehydes in the presence of TBHP occurs selectively at the C-3 position, through an acyl radical insertion

into the initially generated 3-indolyl-Pd(II) intermediate.[53] However, C-2 selective acylation of indoles has been described using 2-pyrimidine or 2-pyridine as a directing group on nitrogen and α-oxocarboxylic acids[54] or aldehydes.[55] More recently, using 2-pyrimidine as directing group, it has been shown that the acylation of indoles can be achieved with both aliphatic and aromatic aldehydes at the C-2 position (Scheme 2.15a).[56] The directing group can be efficiently removed leading to 2-acylindoles. Besides, a second metalation at C-7 can also take place, so 2,7-diacylated indoles can be obtained in good yields, using a larger excess of aldehyde. If the reaction is carried out sequentially with different aldehydes, non-symmetrically substituted diacylindoles could also be obtained (Scheme 15 b).[55] In a similar way, diketones (Scheme 2.15c)[57] and toluene derivatives (Scheme 2.15 d)[58] have been used as acyl surrogates.

[53] Kianmehr, E.; Kamezi, S.; Foroumadi, A. Palladium-catalyzed Oxidative C−H bond coupling of Indoles and Benzaldehydes: A New Approach to the Synthesis of 3-Benzoylindoles. *Tetrahedron* **2014**, *70*, 349-354.

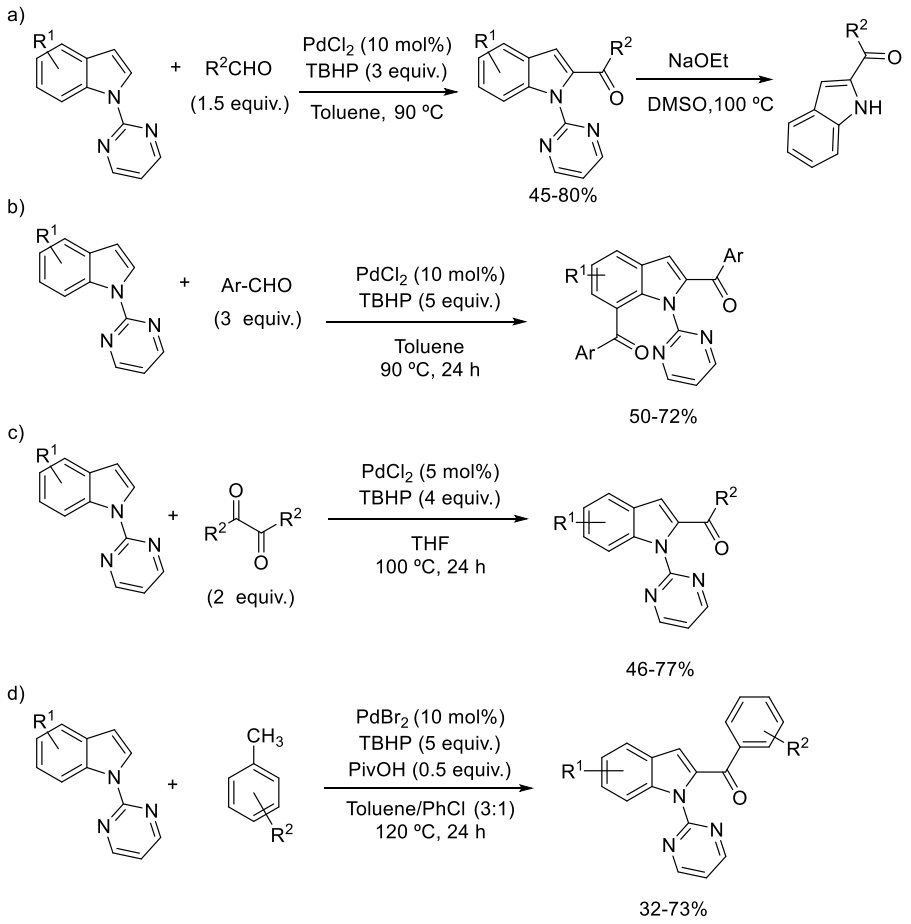
[54] Pan, C.; Jin, H.; Liu, X.; Cheng, Y.; Zhu, C. Palladium-catalyzed Decarboxylative C2-Acylation of Indoles with *α*-Oxocarboxylic Acids. *Chem. Commun.* **2013**, *49*, 2933-2935.

[55] Yan, X.-B.; Shen, Y.-W.; Chen, D.-Q.; Gao, P.; Li, Y.-X.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. Palladium-catalyzed C2-Acylation of Indoles with Aryl and Alkyl Aldehydes. *Tetrahedron* **2014**, *70*, 7490-7495.

[56] Kumar, G.; Sekar, G. Pd-catalyzed Direct C2-Acylation and C2, C7-Diacylation of Indoles: Pyrimidine as an Easily Removable C–H Directing Group. *RSC Adv*. **2015**, *5*, 28292-28298.

[57] Li, C.; Zhu, W.; Shu, S.; Wu, X.; Liu, H. Palladium-Catalyzed C2-Acylation of Indoles with *α*-Diketones Assisted by the Removable *N*-(2-Pyrimidyl) Group. *Eur. J. Org. Chem.* **2015**, *2015*, 3743-3750.

[58] Zhao, Y.; Sharma, U. K.; Schröder, F.; Sharma, N.; Song, G.; Van der Eycken, E. V. Direct C-2 Acylation of Indoles with Toluene Derivatives *via* Pd(II)-catalysed C–H Activation. *RSC Adv*. **2017**, *7*, 32559-32563.



Scheme 2.15. Pyrimidine-directed C-2 acylation of indoles.

In all cases, the oxidative formation of an acyl radical from aldehydes, toluenes or diketones is proposed, so the mechanistic proposal would be in accordance with the general mechanism shown in Scheme 2.1. In all cases, high temperatures and long reaction times are required, but it has been shown that the use of an acid additive (pivalic acid, Scheme 2.15d) increases the reaction rate, presumably by generating more electrophilic palladium species and, consequently, facilitating the C-H activation event. However, the acid may also have a detrimental effect by protonation of the substrate. Both with toluenes and aromatic aldehydes , the

introduction of electron-donating groups on the aromatic ring leads to increased yields of 2-acyl indoles, which would be in accordance with a more nucleophilic acyl radical. However, the opposite trend was observed with diketones. Interestingly, when other directing groups, such as sulfonylpyridyl, Boc or *N*,*N*-dimethylcarbamoyl, were tested, no reaction took place,[57] which is in contrast with related rhodium-catalyzed acylation reactions.[59]

Dual visible light photoredox/palladium catalysis has been also developed for the acylation of indole, using pyrimidine as directing group and aldehydes as the acyl source. Thus, indoles could be efficiently acylated at room temperature in excellent yields with a wide variety of aromatic, heteroaromatic and aliphatic aldehydes (Scheme 2.16a).[60] The reaction was carried out both in batch and into a continuous-flow micro reactors, under blue LED light, using *fac*-$[Ir(ppy)_3]$ as photoredox catalyst and TBHP as the oxidant. In general, much shorter reaction times (2 h *vs*. 20 h), decreased catalyst loading and higher yields were obtained when the reaction was carried out in a continuous-flow reactor (Scheme 2.16a). Almost simultaneously, a dual catalytic system that uses a ruthenium photoredox catalyst was reported, also at room temperature with consistently good yields (Scheme 2.16b).[61]

As in the previously discussed examples (Scheme 2.13 and 2.14), the Pd(II)/Pd(IV) cycle for the C-H activation and acylation would be combined with the photoredox cycle but in these cases, the presence of an oxidant (TBHP) is also necessary. A mechanistic proposal is depicted in Scheme 2.16. In the presence of light, Ir^{3+} or Ru^{2+} are excited to Ir^{3+*} or Ru^{2+*}. Single electron transfer to TBHP produces the *tert*-butoxy radical that, in turn, abstracts a hydrogen from the aldehyde to generate the acyl radical. The addition of the acyl radical to palladium (II) intermediate **XV** generates a Pd(III) intermediate **XVI**, which is oxidized by Ru^{3+} or Ir^{4+} closing the photocatalytic cycle and generating Pd(IV) intermediate **XVII**. Reductive elimination produces the corresponding acylated indoles and regenerates de Pd(II) catalyst.

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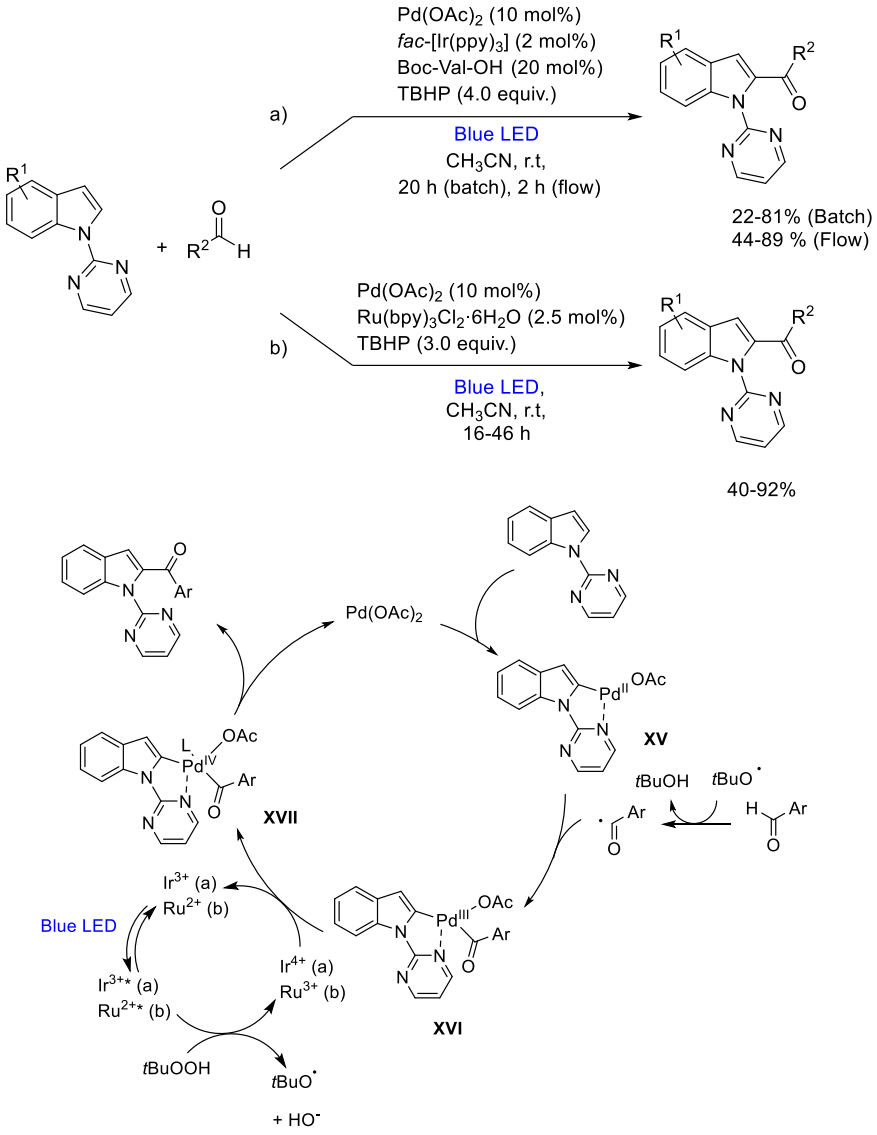
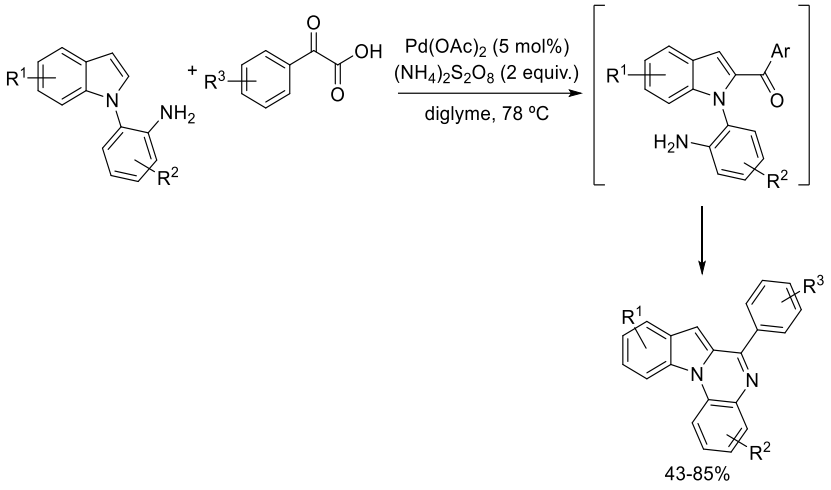
[59] Zhou, B.; Yang, Y.; Li, Y. Rhodium-catalyzed Oxidative C2-Acylation of Indoles with Aryl and Alkyl Aldehydes. *Chem. Commun.* **2012**, *48*, 5163-5165.
[60] Sharma, U. K.; Gemoets, H. P. L.; Schröder, F.; Nöel, T.; Van der Eycken, E.V. Merger of Visible-Light Photoredox Catalysis and C−H Activation for the Room-Temperature C-2 Acylation of Indoles in Batch and Flow. *ACS Catal.* **2017**, *7*, 3818-38232.
[61] Manna, K. M.; Bairy, G.; Jana, R. Dual Visible-light Photoredox and Palladium(II) Catalysis for Dehydrogenative C2-Acylation of Indoles at Room Temperature. *Org. Biomol. Chem.* **2017**, *15*, 5899-5903.



Scheme 2.16. Photoredox/palladium catalyzed C-2 acylation of indoles.

Other directing groups have also been used for C-2 acylation. As shown in Scheme 2.17, the

amine directed palladation of indoles was possible through the formation of a six-membered ring palladacycle. Kinetic isotopic effect (KIE) experiments suggested that the cleavage of the C-H would be rate determining. The acylation takes place efficiently with a variety of aromatic α-oxoacids, obtaining the indolo[1,2-*a*]quinazolines after condensation. The reaction takes also place in the presence of TEMPO and other radical scavengers, suggesting that an acyl radical is not involved. The authors propose an alternate Pd(II)/Pd(0) mechanism, in which the oxidant is required for the reoxidation of the palladium catalyst.[62]

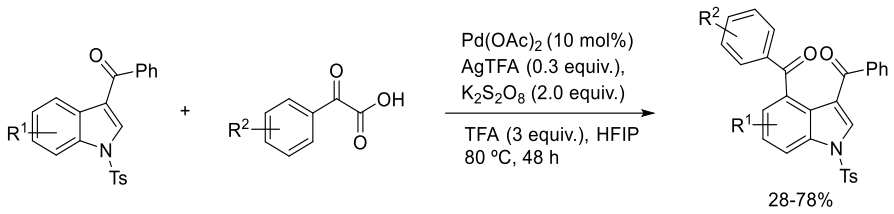


Scheme 2.17. Amine directed acylation/cyclization. Access to indolo[1,2-*a*]quinazolines.

C-4 position of indoles can also be selectively acylated using a ketone carbonyl group in C-3 as directing group (Scheme 2.18).[63] The metalation takes place with complete regioselectivity at the C-4 position, through the formation of a six-membered palladacycle, which would be more favorable than C-2 metalation that would imply a more strained five-

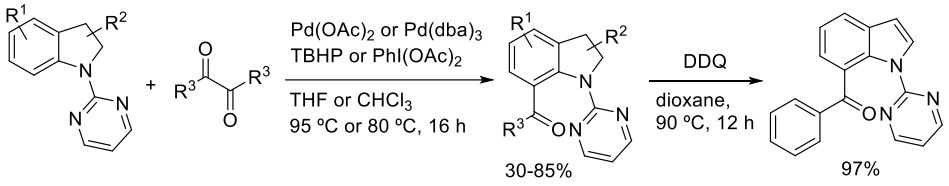
[62] Jiang, G.; Wang, S.; Zhang, J.; Yu, J.; Zhang, Z.; Ji, F. Palladium-Catalyzed Primary Amine-Directed Decarboxylative Annulation of α-Oxocarboxylic Acids: Access to Indolo [1,2-*a*] Quinazolines. *Adv. Synth. Catal*. **2019**, *361*, 1798-1802.
[63] Zhang, J.; Wu, M.; Fan, J.; Xu, Q.; Xie, M. Selective C–H Acylation of Indoles with α-Oxocarboxylic Acids at the C4 Position by Palladium Catalysis. *Chem. Commun.* **2019**, *55*, 8102-8105.

membered palladacycle. The choice of the protecting group on the nitrogen atom is also critical for reactivity.



Scheme 2.18. Ketone directed selective C-4 acylation of indoles.

Selective C-7 acylation of indoles is quite challenging due to competitive C-7 and C-2 diacylation, as it has been shown on Scheme 2.14b. In this context, C-7 acylation of indolines with 1,2-diketones in presence of TBHP as oxidant (Scheme 2.19)[64] has been considered as an appealing strategy to obtain C-7 acylated indols as acylated indolines can be easily oxidated with DDQ (Dichloro-5,6-dicyano-1,4-benzoquinone) to acylated indols .

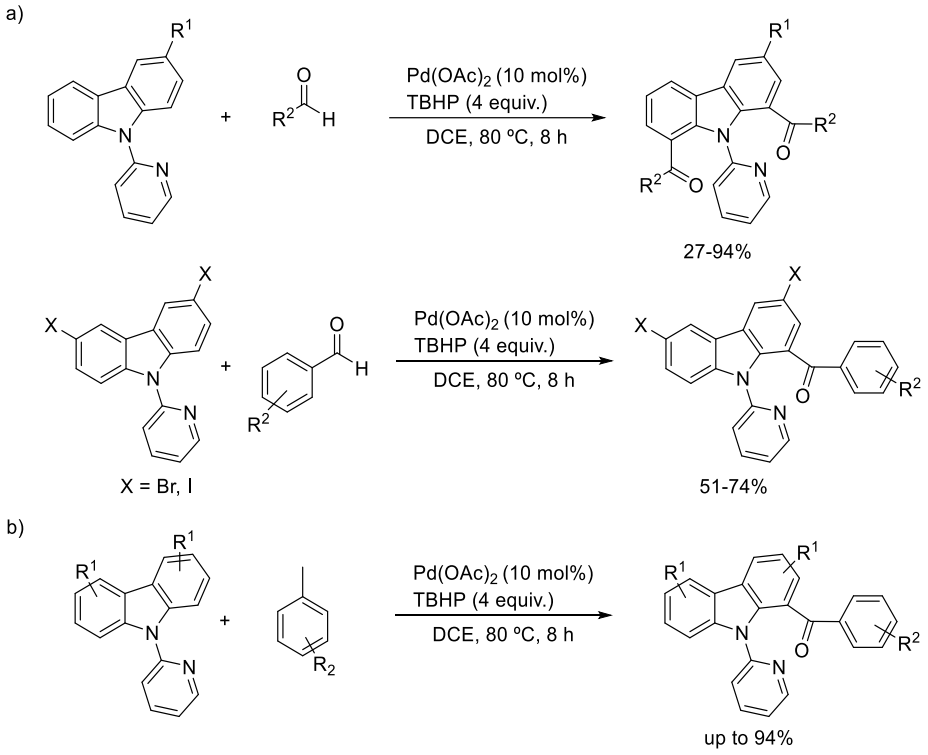


Scheme 2.19. Selective C-7 acylation of indolines.

2-Pyridine has been used for the acylation of carbazoles (Scheme 2.20a)[65] with various aromatic and aliphatic aldehydes. When only one equivalent of the aldehyde was used, a

[64] Xie, G.; Zhao, Y.; Cai, C.; Deng, G-J.; Gong, H. Palladium-Catalyzed Direct and Specific C-7 Acylation of Indolines with 1,2-Diketones. *Org. Lett.* **2021**, *23*, 410-415.
[65] Maiti, S.; Burgula, L.; Chakraborti, G.; Dash, J. Palladium Catalyzed Pyridine Group Directed Regioselective Oxidative C-H Acylation of Carbazoles using Aldehydes as the Acyl Source. *Eur. J. Org. Chem.* **2017**, 332-340.

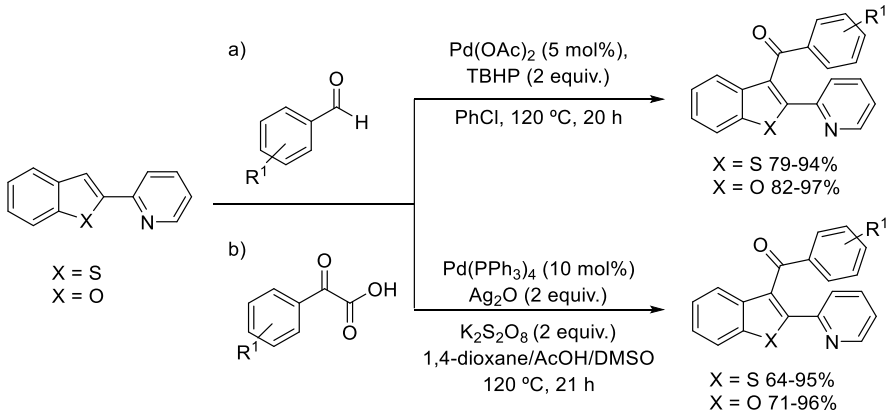
mixture of mono- and diacylated carbazoles were obtained in low yields. However, the use of 4 equivalents of aldehyde led to the selective formation of diacylated carbazoles in generally high yields in the case of aromatic aldehydes. Lower yields were obtained with aliphatic aldehydes. Interestingly, when 3,6-dihalogenated carbazoles (X = Br, I) were used, monoacylated carbazoles were selectively obtained. Toluene derivatives have found to be a proper acyl radical source in palladium catalyzed acylation of carbazoles (Scheme 2.20b).[66]



Scheme 2.20. Pyridine-directed acylation of carbazoles.

[66] Maiti, S.; Mandal, T.; Dash, B. P.; Dash, J. Site Selective Aerobic C–H Monoacylation of Carbazoles Using Palladium Catalysis. *J. Org. Chem.* **2021**, *86*, 1396-1407.

2-Pyridine has also been introduced at the C-2 position of benzothiophenes and benzofurans to obtain the C-3 acylated derivatives and using aromatic aldehydes (Scheme 2.21a)[67] or α-oxoacids (Scheme 2.21b)[68] as the acyl sources. In the latter case, a Pd(0) pre-catalyst is employed that would be oxidized *in situ.*

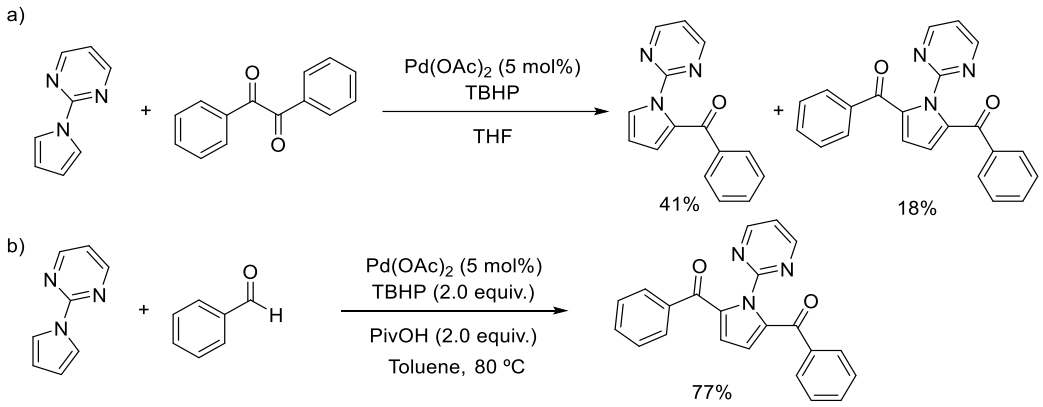


Scheme 2.21. Pyridine-directed acylation of benzofurans and benzothiophenes.

This acylation reaction has been only scarcely applied to pyrrole, and in this case the C2-acylated compound was obtained with a modest yield (41 %), together with the corresponding 2,5-diacylated product in a significant amount (18 %) as shown in Scheme 2.22a.[57] Diacylated products have also been obtained using 2-pyridine as directing group on pyrrole (Scheme 2.22b).[55] The formation of diacylated products has been observed as a side reaction also in related systems, such as carbazoles (Scheme 2.20).[65]

[67] Zhao, J.; Fang, H.; Xie, C.; Han, J.; Li, G.; Pan, Y. Palladium-Catalyzed C3 Acylation of Benzofurans and Benzothiophenes with Aromatic Aldehydes by Cross-Dehydrogenative Coupling Reactions. *Asian J. Org. Chem.* **2013**, *2*, 1044-1047.

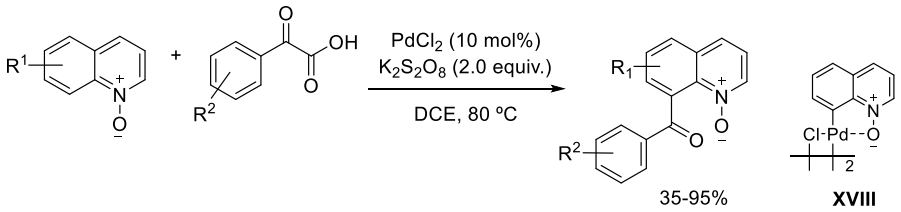
[68] Gong, W.-J.; Liu, D.-X.; Li, F.-L.; Gao, J.; Li, H.-X.; Lang, J.-P. Palladium-catalyzed Decarboxylative C3-Acylation of Benzofurans and Benzothiophenes with α-Oxocarboxylic Acids via Direct sp^2 C-H Bond Activation. *Tetrahedron* **2015**, *71*, 1269-1275.



Scheme 2.22. Examples of Palladium-catalyzed acylation of pyrroles.

The examples of heteroarene acylation shown so far involve electron-rich heteroaromatic rings that, in principle, could be more easily metalated with an electrophilic Pd(II) catalyst. However, selective C-8 palladium catalyzed acylation of quinolines has also been accomplished (Scheme 2.23) [69] using an *N*-oxide as the directing group. The formation of an *N*-oxide chelated palladacycle would favor the regioselective acylation of quinoline *N*-oxides with a variety of aromatic α-oxoacids. Besides, quinolines with electron-donating groups gave better yields of acylquinolines than those with electron-withdrawing groups. Intermolecular KIE experiments indicate that the C-H bond cleavage would be rate determining. Besides, the reaction of quinoline *N*-oxide with stoichiometric $PdCl_2$ gave a chloride-bridged palladacycle dimer **XVIII**. This complex **XVIII** was reacted with an oxoacid in the presence of oxidant, which suggests the formation of a five membered palladacycle in the catalytic cycle.

[69] Chen, X.; Cui, X.; Wu, Y. C8-Selective Acylation of Quinoline *N*-Oxides with *α*-Oxocarboxylic Acids *via* Palladium-Catalyzed Regioselective C−H Bond Activation. *Org. Lett.* **2016**, *18*, 3722-3725.



Scheme 2.23. *N*-oxide directed C-8 acylation of quinolines.

2.2. OBJECTIVES

In the previous section, it has been shown that the oxidative Pd(II)-catalyzed acylation is an effective alternative to the classical acylation methods. This methodology has been applied to the acylation of arenes and heteroarenes using different acyl sources and directing groups to control the regioselectivity. In many cases, long reaction times and relatively high temperatures are required. Besides, the use of aliphatic acyl equivalents, if possible, generally provides lower yields.

On the other hand, this palladium(II) acylation reaction has scarcely been studied on five-membered heteroaromatic rings, such us pyrrole or thiophene. The acylation of these heterocycles would lead to heteroaryl ketones, structures with potential interesting biological activities.

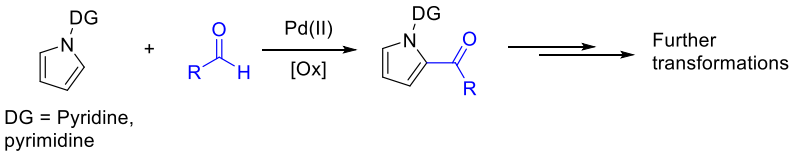
The overall aim of this part of the research was the development of an efficient methodology for the selective acylation of five-membered heteroaromatic rings (pyrrole and thiophene).

a) Selective C-2 acylation of pyrrole ring with aldehydes.

As it has been shown in the previous section (Scheme 2.22), the C-2 acylation of pyrrole with oxoacids or aldehydes under Pd(II) catalysis led to only moderate yields due to competitive diacylation. In this context, our first goal was to study the selective C-2 mono acylation of pyrrole, avoiding or minimizing the diacylation reaction.

For this purpose, the reaction will be studied to select the directing group, and reaction conditions (catalyst, oxidant, solvent, additives). Once the optimized conditions have been selected, the reaction will be extended to a series of aldehydes.

To show the synthetic applicability of the reaction, selected ketones will be used as intermediates in the synthesis of interesting acyl pyrroles (Scheme 2.24).



Scheme 2.24. Selective Pd(II)-catalyzed acylation of pyrroles at C-2 position.

Finally, as a complementary objective, the biological activity of some of the obtained ketones will be evaluated. In connection with previous studies,[70] the anti-leishmanial activity of selected compounds will be tested in order to identify new lead compounds for this disease.

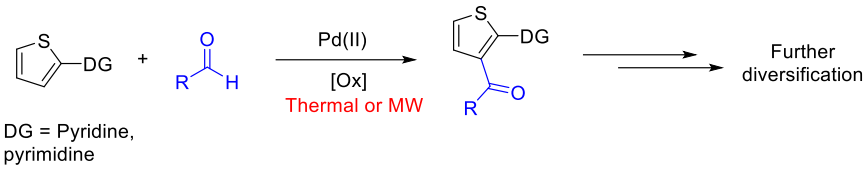
Biological assays against visceral (*L. donovani*) and cutaneous (*L. amazonensis*) leishmaniasis, as well as their cytotoxicity, will be carried out by Dr. M. A. Dea, from University CEU Cardenal Herrera (Valencia).

b) MW assisted Pd(II) catalyzed acylation of thiophenes with aldehydes.

The acylation of thiophenes has also received very little attention. For this part of the work, our goal was to study the selective C-3 acylation of the thiophene ring (Scheme 2.25). To control the selectivity, a directing group will be introduced in C-2. As described for the previous section, the reaction conditions will be optimized, and then extended to a series of aldehydes.

Besides standard thermal conditions, the use of MW irradiation for these reactions will be studied, in order to avoid long reaction times at high temperatures. Finally, to show the synthetic interest of the acylthiophenes obtained, selected examples will be further derivatized.

[70] Barbolla, I.; Hernández-Suárez, L.; Quevedo-Tumailli, V.; Nocedo-Mena, D.; Arrasate, S.; Dea-Ayuela, M. A.; González-Díaz, H.; Sotomayor, N.; Lete, E. Palladium-mediated Synthesis and Biological Evaluation of C-10b substituted Dihydropyrrolo[1,2-*b*]isoquinolines as Antileishmanial Agents. *Eur. J. Med. Chem.* **2021**, *220*, 113458.



Scheme 2.25. C-3 acylation of thiophene catalyzed by Pd(II) under thermal and microwave irradiation conditions.

2.3. RESULTS AND DISCUSSION

2.3.1. Selective Palladium (II) catalyzed C-2 acylation of pyrroles with aldehydes

Di(hetero)aryl ketones are important motifs present in natural products, pharmaceuticals or agrochemicals. In particular, various natural and synthetic molecules containing 2-aroylpyrrole cores have been extensively studied in the development of antibacterial, antifungal, and anticancer agents.[71] Pyrrolomycins[72] are a family of potent natural product antibiotics with nanomolar activity against Gram-positive and Gram-negative bacteria with the ability to target biofilms, which confers them a great potential for the development of new antimicrobial agents to face the antibiotic resistance problem.[73] For example, Pyoluteorin (Figure 2.1), a pyrrolomycin alkaloid isolated from several species of *Pseudomonas*, shows a broad bioprofile, demonstrating antibiotic, antifungal and herbicidal activity.[74] The alkaloid Celastramycin A (Figure 2.1) exhibits high activity against a series of multiresistant bacteria and mycobacteria and has also been identified as a potent innate immune suppressor.[75] Tolmetin (Figure 2.1) is a nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis, osteoarthrosis, pain, and ankylosing spondylitis.[76]

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[71] a) Cascioferro, S.; Raimondi, M. V.; Cusimano, M. G.; Raffa, D.; Maggio B.; Daidone, G.; Schillaci, D. Pharmaceutical Potential of Synthetic and Natural Pyrrolomycins. *Molecules* **2015**, *20*, 21658-21671; b) Liu, Y.-X.; Zhang, P.-X.; Li, Y.-Q.; Song, H.-B.; Wang, Q.-M. Design, synthesis, and biological evaluation of 2-benzylpyrroles and 2-benzoylpyrroles based on structures of insecticidal chlorfenapyr and natural pyrrolomycins. *Mol. Diversity* **2014**, *18*, 593-598.

[72] a) Le Quesne, P. W.; Dong, Y.; Blythe, T. A. in *Alkaloids: Chemical and Biological Perspectives*, *Vol. 13*, (Ed.: S. W. Pelletier), Pergamon, Amsterdam, **1999**, pp. 237–287; b) Gribble. G. W. in *The Alkaloids*, *Vol. 71* (Ed.: H.-J. Knolker), Academic Press, San Diego, **2012**, pp. 1-165.

[73] Valderrama, K.; Pradel, E.; Firsov, A. M.; Drobecq, H.; Bauderlique-le Roy, H.; Villemagne, B.; Antonenko, Y. N.; Hartkoorn, R. C. Pyrrolomycins Are Potent Natural Protonophores. *Antimicrob. Agents Chemother.* **2019**, *63*, e01450-19.

[74] a) Rao, K. V.; Reddy, G. C. Synthesis and herbicidal activity of the halo analogs of pyoluteorin. *J. Agric. Food Chem.* **1990**, *38*, 1260-1263; b) Gross. H.; Loper. J. E. Genomics of secondary metabolite production by *Pseudomonas* spp. *Nat. Prod. Rep.* **2009**, *26*, 1408-1446.

[75] a) Pullen, C.; Schmitz, P.; Meurer.; von Bamberg, D. D.; Lohmann, S.; De Castro Franca, S.; Groth, I.; Schlegel, B.; Möllmann, U.; Gollmick, F.; Gräfe, U.; Leistner, E. New and bioactive compounds from *Streptomyces* strains residing in the wood of Celastraceae. *Planta* **2002**, *216*, 162-167; b) Kikuchi, H.; Sekiya, M.; Katou, Y.; Ueda, K.; Kabeya, T.; Kurata, S.; Oshima. Y. Revised Structure and Synthesis of Celastramycin A, A Potent Innate Immune Suppressor. *Org. Lett.* **2009**, *11*, 1693-1695.

[76] For selected reviews, see: a) Hollingworth, P. The use of non-steroidal anti-inflammatory drugs in paediatric rheumatic diseases. *Rheumatol.* **1993**, *32*, 73-77; b) Calin, A. *Br. J. Rheumatol*. **1993**, *23*, 301-308; c) Rama-dan, A. A.; lbakry, A. M.; Esmaeil, A. H.; Khaleel, S. A. Pharmaceutical and

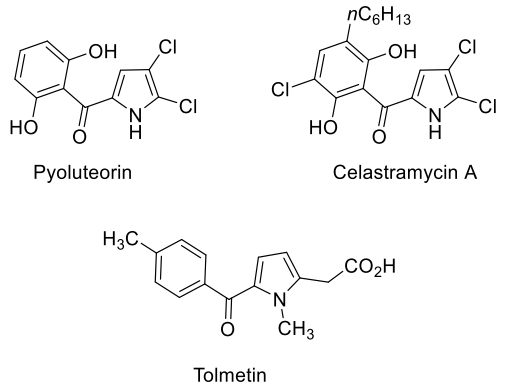

Figure 2.1. Selected alkaloids and pharmaceuticals with the 2-acylpyrrole framework.

Therefore, the construction of 2-aroyl pyrroles has received considerable attention.[77] However, classical methodologies through Friedel-Crafts, Vilsmeier–Haack and Houben–Hoesch type acylations are frequently not regioselective, and require the use of stoichiometric quantities of Lewis or protic acids.[78] However, more environmentally friendly Friedel-Crafts acylation methods based on the use of solid catalysts have been applied only to acetylation of pyrrole.[79]

The development of efficient and catalytic methods to acylate pryrroles at C-2 is of significant value. For example, catalytic Friedel–Crafts acylation of heteroaromatics has been achieved using metal triflates as catalysts, though the procedure has been mainly applied to

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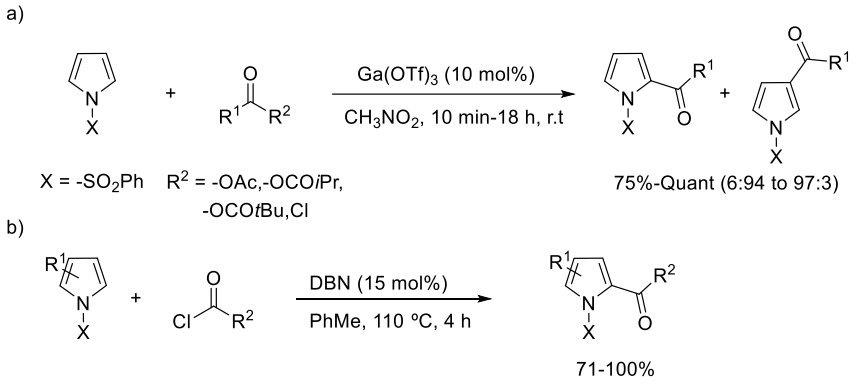
pharmacokinetic evaluation of novel rectal mucoadhesive hydrogels containing tolmetin sodium. *J. Pharm. Investig.* **2018**, *48*, 673-683; d) Akl, M. A.; Ismael, H. R.; Allah, F. I. A.; Kassem, A. A.; Samy, A. M. Tolmetin sodium-loaded thermosensitive mucoadhesive liquid suppositories for rectal delivery; strategy to overcome oral delivery drawbacks. *Drug Dev. Ind. Pharm.* **2019**, *45*, 252-264.

[77] Bergman, J.; Janosik, T. Five-Membered Heterocycles: Pyrrole and Related Systems in *Modern Heterocyclic Chemistry*, *Vol. 1* (Eds.: Álvarez-Builla. J, Vaquero, J. J, Barluenga, J), Wiley-VCH Verlag & Co. KGaA, Weinheim, **2011**, pp. 269-375.

[78] a) Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H.-Y. Regiospecific *C*-Acylation of Pyrroles and Indoles Using *N*-Acylbenzotriazoles. *J. Org. Chem.* **2003**, *68*, 5720-5723, and references cited therein; b) Mullins, R. J.; Schwieter, K. E. in *Name Reactions in Heterocyclic Chemistry II* (Ed.: Li, J. J.), John Wiley & Sons, Inc., Hoboken, New Jersey, **2011**, pp. 53-59.

[79] a) Sartori, G.; Maggi, R. Use of Solid Catalysts in Friedel−Crafts Acylation Reactions. *Chem. Rev.* **2006**, *106*, 1077-1104; b) Sartori, G.; Maggi, R. Use of Solid Catalysts in Friedel−Crafts Acylation Reactions. *Chem. Rev.* **2011**, *111*, PR181-PR214.

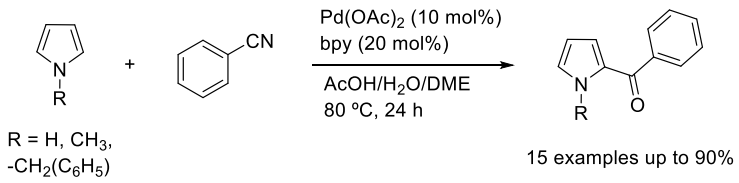
the synthesis of alkanoyl pyrroles (Scheme 2.26a).[80] More recently, an organocatalytic Friedel-Crafts acylation of pyrroles and indoles with acyl chlorides using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as a nucleophilic catalyst has been developed (Scheme 2.26b).[81]



Scheme 2.26. Catalytic Friedel-Craft acylation of pyrroles.

Transition-metal catalyzed acylation of (hetero)-arenes *via* C–H bond activation is a good alternative to access di(hetero)aryl ketones,[82] but the method has been scarcely applied to pyrroles. A notable example is the palladium-catalyzed regioselective acylation of pyrroles with arylnitriles, which has proven successful even with N–H free pyrrole (Scheme 2.27).[83]

[80] Komoto, I.; Matsuo, J.; Kobayashi, S. Catalytic Friedel–Crafts Acylation of Heteroaromatics. *Top. Catal*. **2002**, *19*, 43-47.
[81] Taylor, J. E.; Jones, M. D.; Williams, J. M.; Bull, S. D. Friedel–Crafts Acylation of Pyrroles and Indoles using 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) as a Nucleophilic Catalyst. *Org. Lett.* **2010**, *12*, 5740-5743.
[82] Pan, C.; Jia, X.; Cheng, J. Transition-Metal-Catalyzed Synthesis of Aromatic Ketones via Direct C-H Bond Activation. *Synthesis* **2012**, *44*, 677-685.
[83] Jafarpour, F.; Hazrati, H.; Darvishmolla, M. Acylation of Pyrroles and their Free (N-H)-Derivatives *via* Palladium-Catalyzed Carbopalladation of Nitriles. *Adv. Synth. Catal.* **2014**, *356*, 3784-3788.



Scheme 2.27. Palladium(II) C-H acylation of pyrroles with nitriles.

As has been shown in the introduction, the Pd(II)-catalyzed acylation of (hetero)arenes in the presence of an oxidant has recently emerged as catalytic alternative to classical acylation methods, reducing the production of toxic metal waste. Different directing groups and acyl sources are being studied for this purpose,[8] although further development is required to face mainly selectivity problems in order to be applied in the synthesis of more complex molecules. Examples reported in the literature mainly involve Pd(II)-catalyzed acylation reactions of indole derivatives, where no selectivity problems arise. Thus, C-2 selective acylation of indoles has been described using 2–pyrimidine as a directing group on nitrogen and α-oxocarboxylic acids,[54] aldehydes,[55,84] α-diketones[57] and even toluene derivatives[58] as the acyl surrogates (Scheme 2.15).

As depicted in previous section (Scheme 2.22), the palladium(II)-catalyzed acylation of pyrroles is still unexplored, probably the competitive 2,5 diacylation side reaction could play an important role in this fact. Thus, improved methodologies for selective Palladium(II)-catalyzed acylation are required.

Related protocols, as the ruthenium catalyzed carbonylative direct arylation of pyrroles using the 2-pyrimidine directing group have also been developed with high selectivity, although yields obtained with pyrrole were moderate to good, and generally lower than those obtained with indoles (Scheme 2.28).[85]

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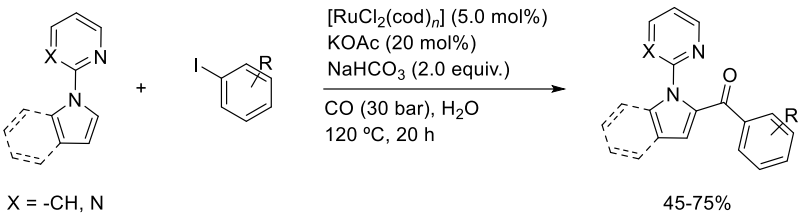
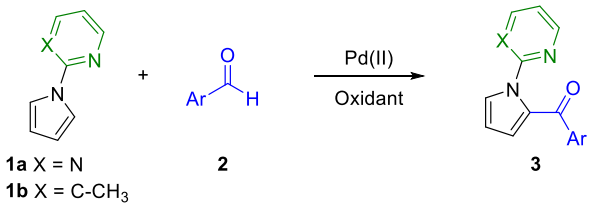
[84] Wang, W.; Liu, J.; Gui, Q.; Tan, Z. Synthesis of 2-Acylated Indoles through Palladium-Catalyzed Dehydrogenative Coupling of *N*-Pyrimidine-Protected Indoles with Aldehydes and Ethyl Glyoxylate**.** *Synlett* **2015**, *26*, 771-778.

[85] Pospech, J.; Tlili, A.; Spannenberg, A.; Neumann, H.; Beller, M. Regioselective Ruthenium-Catalyzed Carbonylative Direct Arylation of Five-Membered and Condensed Heterocycles. *Chem. Eur. J.* **2014**, *20*, 3135-3141.



Scheme 2.28. Ruthenium catalyzed acylation of pyrrole.

In this context, and in connection with our previous work on Pd(II)-catalyzed C–H functionalization reactions,[86] we decided to study the palladium catalyzed acylation of pyrroles **1** for the regioselective formation of C-2 monoacylated pyrroles **3** as shown in Scheme 2.29. For this purpose, we selected first the 2-pyrimidine (**1a**, X = N) as directing group, which has been successfully used in these reactions with indole, but only one example has been reported with pyrrole.[57]

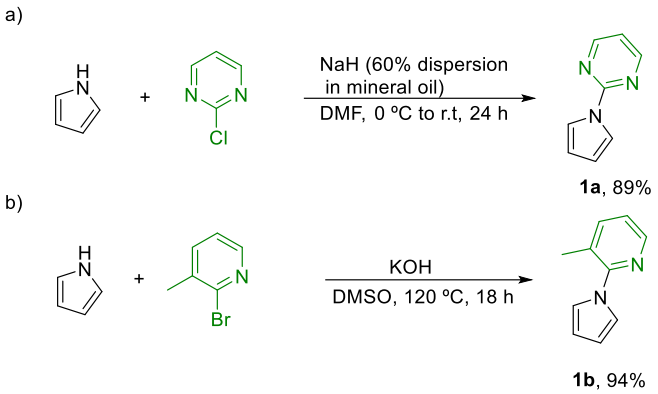


Scheme 2.29. Palladium-catalyzed acylation of *N*-protected pyrroles.

[86] a) Ortiz-de-Elguea, V.; Sotomayor, N.; Lete. E. Two Consecutive Palladium(II)-Promoted C-H Alkenylation Reactions for the Synthesis of 3-Alkenylquinolones. *Adv. Synth. Catal*. **2015**, *357*, 463-473; b) Carral-Menoyo, A.; Ortiz-de Elguea, V.; Martínez-Nunes, M.; Sotomayor, N.; Lete, E. Palladium-Catalyzed Dehydrogenative Coupling: An Efficient Synthetic Strategy for the Construction of the Quinoline Core. *Mar. Drugs.* **2017**, *15*, 276; c) Carral-Menoyo, A.; Misol, A.; Gómez-Redondo, M.; Sotomayor, N.; Lete, E. Palladium(II)-Catalyzed Intramolecular C–H Alkenylation for the Synthesis of Chromanes. *J. Org. Chem.* **2019**, *84*, 2048-2060; d) Carral-Menoyo, A.; Sotorrios, L.; Ortiz-de-Elguea, V.; Díaz- Andrés, A.; Sotomayor, N.; Gómez-Bengoa, E.; Lete, E. 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. *J. Org. Chem.* **2020**, *85*, 2486-2503.

Besides, we decided to study the 3-methyl-2-pyridine as directing group (**1b**, X = C–CH_3). We reasoned that, once the monoacylated compound **3b** is formed, the presence of the C-3 substituent on the directing group could result in a steric interaction with the acyl group in C-2 that may prevent the adoption of the required conformation to assist the second palladation, hampering the formation of diacylated products. For this study, we decided to use aldehydes **2** as the acyl radical source, due to their wide availability and ease of generation in the presence of TBHP as oxidant.[8,17,28,31,62]

The substrate **1a** was synthetized following the procedure described in literature (Scheme 2.30a).[87] A simple treatment of pyrrole with a dispersion of NaH in mineral oil and 2-chloropyrimidine in DMF gave **1a** in very high yield. Regarding substrate **1b**, the synthesis was carried out following the procedure described for indoles,[88] obtaining **1b** in excellent yield (Scheme 2.30b).



Scheme 2.30. Synthesis of substrates **1a** and **1b**.

Thus, we started testing reaction conditions related to those reported for the acylation of

[87] Xu, B.; Xu, S.; Huang, X.; Hong, X. Palladium-Assisted Regioselective C-H Cyanation of Heteroarenes Using Isonitrile as Cyanide Source. *Org. Lett.* **2012**, *14*, 4614-4617.
[88]Hong, X.; Tan, Q.; Liu, B.; Xu, B. Isocyanide-Induced Activation of Copper Sulfate: Direct Access to Functionalized Heteroarene Sulfonic Esters. *Angew.Chem.* **2017**, *129*, 4019-4023.

indoles with aldehydes,[55] using 2-pyrimidine as directing group (**1a**),[89] $Pd(OAc)_2$ as pre-catalyst in the presence of TBHP as oxidant. Using toluene as solvent at 90 °C, the reaction took place obtaining ketone **3aa**, though in a moderate yield (53 %), together with the diacylated product **4aa** (2 %) (Table 2.1, entry 1). In the presence of acetic acid as additive, a similar yield was obtained (Table 2.1, entry 2), while the reactivity was almost completely lost when $Pd(CH_3CN)_2Cl_2$ was used as pre-catalyst (Table 2.1, entry 3). Lower conversions and isolated yields of **3aa** were obtained when the solvent was changed to dioxane, THF or DCE (Table 2.1, entries 4–6), always isolating diketone **4aa** as the minor product, and recovering unreacted **1aa**. We next studied the effect of the acid additive, and we observed that the reactivity was almost completely shut down when strong acids, such as *p*TsOH or TFA were used, recovering unreacted **1aa** (Table 2.1, entries 7–8). The effect of the acid additive has been shown to increase the reactivity by generating more electrophilic palladium species and, consequently, facilitating the C–H activation event. However, the acid may also have a detrimental effect by protonation of the substrate,[90] in accordance with the results obtained in the presence of strong acids. Thus, a significant increase of the reactivity was observed when less strongly acidic pivalic acid was used as an additive (Table 2.1, entries 9–14). The reaction was complete in only 3 hours at 90 °C in the presence of 1 equiv. of pivalic acid, although it also led to a significant increase in the ratio of the formation of the diketone **4aa** (Table 2.1, entry 9). It was also necessary to use an excess of oxidant, as the use of less TBHP led to a loss of reactivity, with a low conversion after 24 h (Table 2.1, entry 10). Finally, the effect of amount of acid additive (0.5 or 0.75 equiv.) and the temperature (90 or 60 °C) were studied (Table 2.1, entries 11–14), obtaining full conversion and a 71 % isolated yield of **3aa** (Table 2.1, entry 13), although minor formation of **4aa** could not be avoided reducing the amount of benzaldehyde (**2a**) used (Table 2.1, entry 14).

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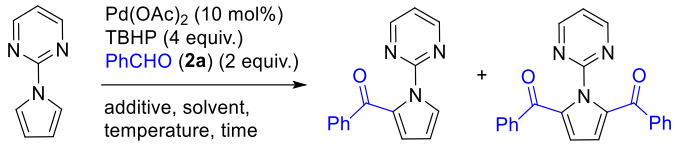
[89] a) Bag, S.; Jayarajan, R.; Dutta, U.; Chowdhury, R.; Mondal, R.; Debabrata Maiti, D. Remote *meta*-C–H Cyanation of Arenes Enabled by a Pyrimidine-Based Auxiliary. *Angew. Chem.* **2017**, *129*, 12712-12716; b) Porey, S.; Zhang, X.; Bhowmick, S.; Singh, V. K.; Guin, S.; Paton, R. S.; Maiti, D. Alkyne Linchpin Strategy for Drug:Pharmacophore Conjugation: Experimental and Computational Realization of a *Meta*-Selective Inverse Sonogashira Coupling. . *J. Am. Chem. Soc.* **2020**, *142*, 3762-3774; c) Brochetta, M.; Borsari, T.; Bag, S.; Jana, S.; .Maiti, S.; Porta, A.; Werz, D.B.; Zanoni, G.; Maiti, D. Direct meta-C-H Perfluoroalkenylation of Arenes Enabled by a Cleavable Pyrimidine-Based Template. *Chem. Eur. J.* **2019**, *25*, 10323-10327.

[90] Vana, J.; Bartacek, J.; Janusek, J.; Roithova, J.; Sedlak, M. C–H Functionalizations by Palladium Carboxylates: The Acid Effect. *J. Org. Chem.* **2019**, *84*, 12746-12754.

Table 2.1. Acylation of **1a**. Optimization of reaction conditions.



1a **3aa** **4aa**

Entry	Additive.	Solvent	*T* [°C]	*t* [h]	3aa [%][a]	4aa [%][b]
1	—	toluene	90	17	53[c]	2
2	AcOH[b]	toluene	90	24	51[c]	9
3[d]	AcOH[b]	toluene	90	24	9[c]	2
4	AcOH[b]	dioxane	90	17	41[c]	6
5	AcOH[b]	THF	60	24	34[c]	3
6	AcOH[b]	DCE	60	24	48[c]	10
7	TsOH[b]	toluene	90	24	3[c]	—
8	TFA[b]	toluene	90	24	7[c]	—
9	PivOH[b]	toluene	90	3	46	23
10[e]	PivOH[b]	toluene	90	24	31[c]	9
11	PivOH[f]	toluene	90	1.5	66	17
12	PivOH[f]	toluene	60	1.5	69	10
13	**PivOH[g]**	**toluene**	**60**	**2**	**71**	**16**
14[h]	PivOH[g]	toluene	60	2.5	61	8

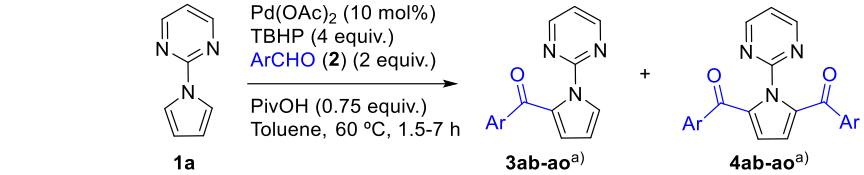
[a]Yield (%) of isolated pure compound. [b] 1 equiv. [c] Unreacted **1a** was recovered. [d] $Pd(CH_3CN)_2Cl_2$ (10 mol %) was used. [e] 3 equiv. of TBHP were used. [f] 0.5 equiv. [g] 0.75 equiv. h) 1.5 equiv. of PhCHO.

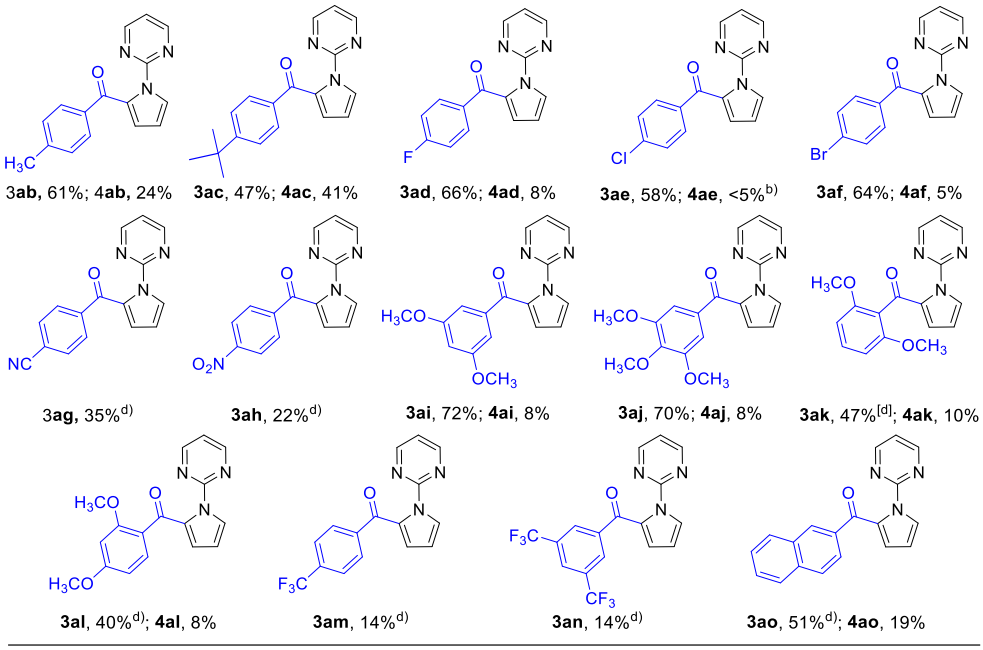
Once the reaction conditions were selected, we studied the application of this procedure to a series of aldehydes **2b**–**2o** with different substitution patterns on the aromatic ring. As depicted in table 2.2, aromatic aldehydes bearing both electron withdrawing and electron-donating groups can be used for the reaction.

The use of *p*-alkyl-substituted aldehydes **2b** and **2c** gave the highest ratio of the corresponding diketones **4ab** and **4ac**. On the other hand, the presence of halogens on the *para* position is well tolerated, giving moderate to good yields on the corresponding ketones **3ad**–**af** in shorter reaction times, and with minor formation of the diketones **4**. The best results were obtained when electron-donating groups are introduced in the aromatic ring **3ai-3aj**, although when an *ortho*-substituent was present, the reaction was slower giving a lower

yield of **3ak** and **3al**, possibly due to a steric effect. 2-Naphthaldehyde **2o** could also be used to obtain **3ao**, although together with a significant amount of the diketone **4ao**.

Table 2.2. Scope Acylation of **1a** with aromatic aldehydes **2b**–**o**.





[a)] Yield % of pure isolated compound. [b)] Detected by ^{1}H NMR but not isolated. [c)] Reaction temperature: 40 °C. [d)] Unreacted **1a** was recovered.

On the other hand, the aldehydes bearing electron-withdrawing groups gave sluggish reactions that required longer reaction times and gave only low yields of the corresponding ketones **3ag**, **3ah** and **3an**. In these cases, the corresponding diketones **4** were not detected. This reactivity pattern has also been described in related palladium catalyzed radical

acylation reactions using aldehydes,[7] but it is opposite to the reactivity observed when α-diketones were used as acyl radical precursors.[57]

Although the change of the structure of the aroyl radical has a small effect on its polar character,[91] the observed trend could be correlated to the nucleophilicity of the resulting acyl radical. Thus, the introduction of donating groups, mainly in the *p*-position, would increase the nucleophilicity of the acyl radical,[92] favoring the reaction with the electrophilic palladium atom in intermediate **I** (see Scheme 2.1). Besides, the electron-donating effect of the aroyl group could also stabilize the resulting palladium intermediate.[15]

As has been shown, ketones **3** have been obtained as the major compounds with moderate to good yields but, in most cases, together with minor amounts of the corresponding diketones **4**. Although both products could be separated by chromatography, we decided to explore the use of 3-methyl-2-pyridine as directing group in order to avoid the formation of the diketones **4**.

Thus, **1b** was treated with benzaldehyde (**2a**), obtaining a moderate yield of ketone **3ba**, not detecting the formation of the corresponding diketone (Table 2.3, entry 1). Therefore, the reaction conditions were further optimized to improve the yield of **3ba** (Table 2.3). An increase in the reaction temperature (Table 2.3, entries 2–3) led to a significant increase of the yield of **3ba**, which was isolated in a 74 %. The use of MW irradiation was also explored (Table 2.3, entries 4–6) but although the reactions were much faster, and full consumption of the staring material was observed in 10–20 minutes, the isolated yields of **3ba** were lower. The use of less aldehyde (1 equiv.) and oxidant (2 equiv.) gave lower yields. However, the reaction could be carried out with similar efficiency using 1.5 equiv. of benzaldehyde at 120 °C in toluene (Table 2.3, entry 7), although unreacted **1b** was recovered in this case. The change of the solvent did not improve the isolated yields of **3ba** (Table 2.3, entries 8–10).

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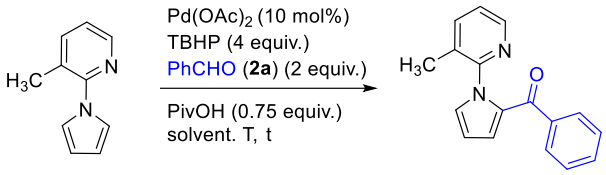
[91] Caronna, T.; Fronza, G.; Minisci, F.; Porta, O. Nucleophilic Character of Acyl Radicals. Substituent Effects on the Homolytic Acylation of Protonated Heteroaromatic Bases. *J. Chem. Soc., Perkin Trans.* **1972**, *2*, 1477-1481.

[92] De Vleeschouwer, F.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. Electrophilicity and Nucleophilicity Index for Radicals. *Org. Lett.* **2007**, *9*, 2721-2724.

Table 2.3 Acylation of **1b**. Optimization of reaction conditions.



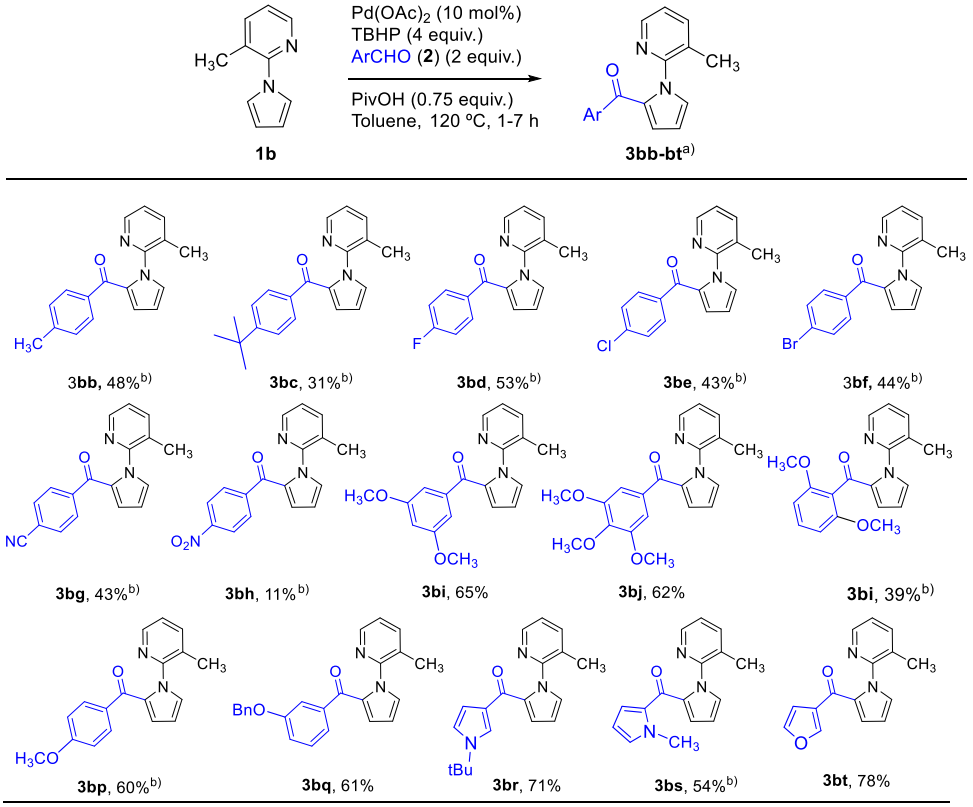
1b **3ba**

Entry	2a [equiv.]	TBHP [equiv.]	Solvent	*T* [°C]	*t* [h]	3ba [%][a)]
1	2	4	toluene	60	2	47
2	2	4	toluene	90	2	67
3	2	4	toluene	120	1.5	74
4	2	4	toluene	90[b)]	0.16	56
5	1	2	toluene	90[b)]	0.3	35
6	1	2	toluene	110[b)]	0.3	50
7	1.5	3	toluene	120	1	74[c)]
8	1.5	3	C_6H_5Cl	120	1	66
9	1.5	3	DCE	90	2.5	69
10	1.5	3	CH_3CN	90	8	30[c)]

[a)] Yield (%) of isolated pure compound. [b)] Microwave irradiation (250 W). [c)] Unreacted **1b** was recovered (20–30 %).

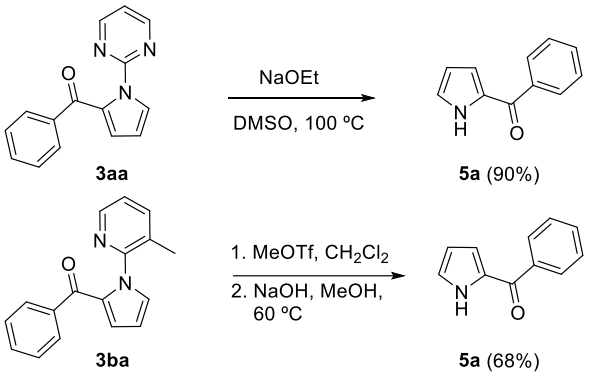
We then extended the procedure to a series of aldehydes **2b**–**t** (Table 2.4). As expected, all reactions afforded selectively the corresponding ketones **3bb**–**bt** not detecting in any case the formation of the diacylated compounds. The same trend of reactivity for the aldehydes was observed, obtaining the best results with electron-rich aromatic rings (**3bi, 3bj** and **3bp**). However, with the exception of **3bg**, the isolated yields of the ketones **3b** were in the same range or below the yields obtained for ketones **3a**. In this case, the procedure could be extended to the use of electron-rich heteroaromatic aldehydes **2r**–**2t**, obtaining diheteroayl ketones **3br**– **bt** with good yields.

Table 2.4. Acylation of **1b** with aromatic aldehydes **2b**–**t**.



[a)]Yield (%) of isolated pure compound. [b)] Unreacted **1b** was recovered.

To test the applicability of these acylation reactions, it was first necessary to remove both directing groups in an efficient manner. Thus, the 2-pyrimidine directing group on **3aa** could be removed under previously described conditions (Scheme 2.31),[57] obtaining **5a** in excellent yield (90 %). On the other hand, the 3-methyl-2-pyridine group could also be removed in good yield using the procedure described for removal of 2-pyridine group.[55]

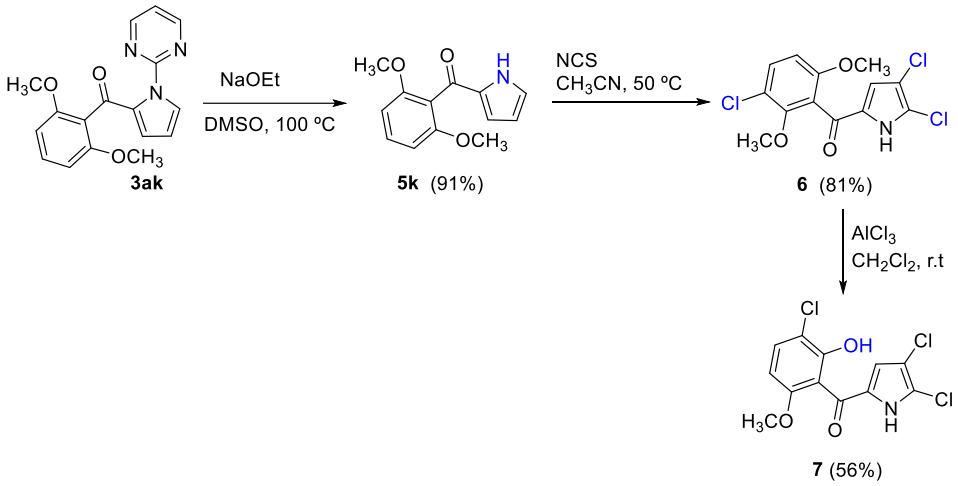


Scheme 2.31. Removal of the directing groups.

2.3.1.1. Synthesis of Celastramycin analogue **7** and Tolmentin **9**

The prepared 2-acyl pyrroles **3** are advanced intermediates for the synthesis of more elaborated compounds. Thus, the compounds obtained could be derivatized to other potentially interesting structures. As shown on Scheme 2.31, the directing group could also be efficiently removed from **3ak** to yield **5k** in high isolated yield. This pyrrole **5k** has already been described as an intermediate in the synthesis of Pyoluteorin (Figure 2.1).[74]Alternatively, the trichlorinated derivative **6** could be selectively obtained in high yield (81 %) using NCS.[93] This compound has been described to have activity as pesticide[94] and as glutamate release inhibitor.[95] Besides, selective demethylation using $AlCl_3$ afforded **7** in moderate yield. Both **6** and **7** could be considered as Celastramycin analogues (Scheme 2.32), structures that have been recently identified to have interesting activity against pulmonary arterial hypertension.[96]

[93] Raimondi, M. V.; Schillaci, D.; Petruso, S. Synthesis of some pyrazolopyrimidines as purine analogues. *J. Heterocycl. Chem.* **2007**, *44*, 1407-1411.
[94] Hayse, Y.; Miki, N.; Ohba, K.; PCT Int. Appl., WO 9953758 A1 19991028, October 28, **1999**; *Chem Abstr*. **1999**, *131*, 296499.
[95] Oshima, T.; Kamigauchi, T.; Fukui, Y.; PCT Int. Appl., WO 9818760 A1 19980507, May 07, **1998**. *Chem Abstr.* **1998**, *128*, 308396.
[96] Kurosawa, R.; Satoh K.; Kikuchi, N.; Kikuchi, H.; Saigusa, D.; Al-Mamun, M.; Siddique, M. A. H.; Omura, J.; Satoh, T.; Sunamura, S.; Nogi, M.; Numano, K.; Miyata, S.; Uruno, A.; Kano, K.; Matsumoto, Y.; Doi, T.; Aoki, J.; Oshima, Y.; Yamamoto, M.; Shimokawa, H. Identification of Celastramycin as a Novel Therapeutic Agent for Pulmonary Arterial Hypertension. *Circ. Res.* **2019**, *125*, 309-327.

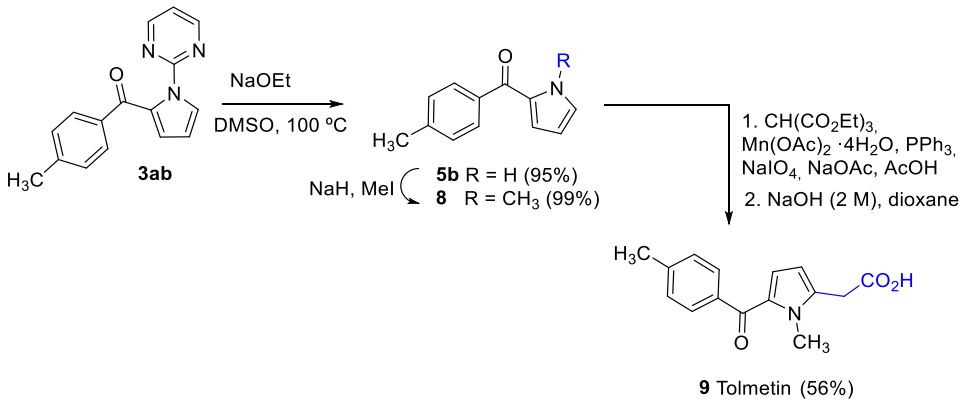


Scheme 2.32. Derivatization of **3ak**.

Finally, the potential application of this acylation protocol in medicinal chemistry and natural products synthesis has also been demonstrated with the synthesis of Tolmetin, a non-steroidal anti-inflammatory drug. As shown on Scheme 2.33, Tolmetin could be easily obtained from C-2 *p*-toluoylpyrrole **3ab** in three steps. Deprotection and methylation of pyrrole was accomplished in nearly quantitative yield. to obtain **8**. The carboxylic acid side chain was introduced as the final step of the synthesis using the manganese-catalyzed intermolecular C–H coupling protocol described by Yamaguchi.[97] Thus, coupling of pyrrole **8** with triethyl methanetricarboxylate in the presence of $Mn(OAc)_2$, followed by hydrolysis and decarboxylation gave Tolmetin (**9**) in a good overall yield starting from pyrrole. This strategy effectively competes with or overcomes other reported procedures for the synthesis of this drug. It is a catalytic approach with atom-economy, which gives comparable or better overall yields. In fact, various described routes involve as key step a classical Friedel-Crafts aroylation of *N*-methylpyrrole acetate, prepared in three steps by traditional methods,[98] or *N*-

[97] Hattori, K.; Ziadi A.; Itami, K.; Yamaguchi, J. Manganese-catalyzed intermolecular C–H/C–H coupling of carbonyls and heteroarenes. *Chem. Commun.* **2014**, *50*, 4105-4107.
[98] Reddy, L. A.; Chakraborty, S.; Swapna, R.; Bhalerao, D.; Malakondaiah, G. C.; Ravikumar, M.; Kumar, A.; Reddy, G. S.; Naram, J.; Dwivedi, N.; Roy, A.; Himabindu, V.; Babu, B.; Bhattacharya,

methylpyrrole acetonitrile.[99] In the last case, it is noteworthy the synthesis of the pyrrole acetonitrile intermediate by photochemical generation of radicals. There is also one example using an organocatalytic Friedel-Crafts reaction using *p*-methyltoluoyl chloride and DBN as catalyst[81] but the overall yield is lower (19.3 % vs. 28.6 %). Alternatively, the methylcarboxyl group has been introduced in the last step by a radical process, after the Friedel-Crafts acylation.[100]



Scheme 2.33. Synthesis of Tolmetin.

In conclusion, the use of 2-pyrimidine as directing group allowed the C-2 metalation of pyrrole with $Pd(OAc)_2$ in toluene, which could be acylated with aldehydes in the presence of TBHP as oxidant. The presence of a moderately acidic additive, such as pivalic acid increases

A.; Bandichhor, R. Synthesis and Process Optimization of Amtolmetin: An Antiinflammatory Agent. *Org. Process Res. Dev.* **2010**, *14*, 362-368, and references cited therein.

[99] Schweitzer-Chaput, B.; Horwitz, M. A.; de Pedro Beato, E.; Melchiorre, P. Photochemical generation of radicals from alkyl electrophiles using a nucleophilic organic catalyst. *Nat. Chem.* **2019**, *11*, 129-135.

[100]a) Liu, Z.-Q.; Li, Z. Radical-promoted site-specific cross dehydrogenative coupling of heterocycles with nitriles. *Chem. Commun.* **2016**, *52*, 14278–14281; b) Flórez-López, E.; Gómez-Pérez, L. B.; Miranda, L. D. Solvent free oxidative radical substitution process. Synthesis of pyrrole fused systems. *Tetrahedron Lett.* **2010**, *51*, 6000-6002. In a previous work of the synthesis of Tolmetin ethyl ester, see: c) Baciocchi, E.; Muraglia, E.; Sleiter, G. Homolytic substitution reactions of electron-rich pentatomic heteroaromatics by electrophilic carbon-centered radicals. Synthesis of .alpha.-heteroarylacetic acids. *J. Org. Chem.* **1992**, *57*, 6817-6820.

the reactivity. The reaction has been extended to a variety of aromatic aldehydes, bearing electron-rich and electron-deficient aromatic rings. However, in most of the cases, a minor amount of the corresponding diacylated product was obtained. This side reaction could be avoided using the 3-methyl-2-pyridinyl group as directing group, obtaining selectively monoacylated pyrroles in moderate to good yields. The so obtained acylated pyrroles have been used as intermediates in the synthesis of celastramycin analogues and in an improved synthesis of Tolmetin.

2.3.1.2. Evaluation of biological activity of 2-acylpyrroles as anti-leishmanial agents

Leishmaniasis is a parasitic disease, caused by *Leishmania* genus protozoan pathogens, that may present different clinical manifestations including cutaneous (CL), visceral or kala-azar (VL), post-kala-azar dermal leishmaniasis (PKDL), and mucocutaneous (MCL) leishmaniasis. As all neglected diseases, Leishmaniasis remains a major global health problem, as it is endemic in around 100 countries with more than 350 million people at risk.[101] Treatment of leishmaniasis relies mainly in a few drugs: pentavalent antimonials (ampB), paromomycin, pentamidine, liposomal amphotericin B, fluconazole, and miltefosine, depending on the etiological species, the infection type, and also the geographical region because of the increasing number of resistant strains. Besides, the use of these drugs is associated with a number of severe side effects related to their toxicity.[102] Therefore, it is clear the need to identify new effective anti-leishmanial compounds with chemotypes other than the prototypes in clinical use. In this context, nitrogen heterocycles are considered privileged scaffolds, because approximately 60% of U.S. FDA approved small-molecule

[101] World Health Organization (WHO): Global leishmaniasis surveillance: 2019-2020, a baseline for the 2030 roadmap https://www.who.int/publications/i/item/who-wer9635-401-419 (accessed 28/12/2021).

[102] a) Gupta, O.; Pradhan, T.; Bhatia, R.; Monga, V. Recent advancements in anti-leishmanial research: Synthetic strategies and structural activity relationships. *Eur. J. Med. Chem.* **2021**, 113606; b) Brindha, J.; Balamurali, M. M.; Kaushik, C. An Overview on the Therapeutics of Neglected Infectious Diseases-Leishmaniasis and Chagas Diseases. *Front. Chem.* **2021**, *9*, 622286; c) Jones, N. G.; Catta-Preta, C. M. C.; Lima, A. P. C. A.; Mottram, J. C. Genetically Validated Drug Targets in *Leishmania*: Current Knowledge and Future Prospects. *ACS Infect. Dis.* **2018**, *4*, 467-477; d) Nagle, A. S.; Khare, S.; Kumar, A. B.; Supek, F.; Buchynskyy, A.; Mathison, C. J. N.; Chennamaneni, N. K.; Pendem, N.; Buckner, F. S.; Geb, M. H.; Moleteni, V. Recent Developments in Drug Discovery for Leishmaniasis and Human African Trypanosomiasis. *Chem. Rev.* **2014**, *114*, 11305-1134.

drugs contain a nitrogen heterocycle.[103] In particular, pyrrole core has attracted our attention because this motif is embedded in a variety of natural products (e.g. prodigenines,[104] bromopyrrole[105] and spiroindimicin alkaloids[106]) with antiparasitic activity.[107] Regarding synthetic derivatives, pyridinyl aryl pyrroles and have proven to be inhibitors of casein kinase 1 that block the growth of *Leishmania major* promastigotes *in vitro*.[108] 1,2-Diarylpyrroles have been identified as a new class of compounds active against amastigote stay of *Leishmania donovani* by inhibiting the Trypanothione reductase.[109] On the other hand, 2-acylpyrrole derivatives also exhibited promising anti-leishmanial profiles (Figure 2.2).[110] Besides, it has been reported that pyrrole-indolinone SU11652, a Sunitinib analog, targets the nucleoside diphosphate kinase from *Leishmania* parasites.[111] The structure of our

[103] Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257-10274.

[104] Papireddy, K.; Smilkstein, M.; Kelly, J. X.; Salem, S. M.; Alhamadsheh, M.; Haynes, S. W.; Challis, G. L.; Reynodls, K. A. Antimalarial Activity of Natural and Synthetic Prodiginines. *J. Med. Chem.* **2011**, *54*, 5296-5306.

[105] Parra, L. L. L.; Bertonha, A. F.; Severo, I. R. M.; Aguiar, A. C. C.; de Souza, G. E.; Oliva, G.; Guido, R. V. C.; Grazzia, N.; Costa, T. R.; Miguel, D. C.; Gadelha, F. R.; Ferreira, A. G.; Hajdu, E.; Romo, D.; Berlinck, R. G. S. Isolation, Derivative Synthesis, and Structure-Activity Relationships of Antiparasitic Bromopyrrole Alkaloids from the Marine Sponge *Tedania brasiliensis*. *J. Nat. Prod.* **2018**, *81*, 188-202.

[106] Zhang, Z.; Ray, S.; Imlay, L.; Callaghan, L. T.; Niederstrasser, H.; Mallipeddi, P. L.; Posner, B. A.; Wetzel, D. M.; Phillips, M. A.; Smith, M. W. Total synthesis of (+)-spiroindimicin A and congeners unveils their antiparasitic activity. *Chem. Sci.* **2021**, *12*, 10388-10394.

[107] Albino, S. L.; da Silva, J. M.; Nobre, M. S. de C.; Silva, Y. M. S. de Santos, M. B.; Araújo, R. S. A.; de Lima, M. do C. A. de; Schmidtt. M.; Moura. R. O. de. Bioprospecting of Nitrogenous Heterocyclic Scaffolds with Potential Action for Neglected Parasitosis: A Review. *Curr. Pharm. Des.* **2020**, *26*, 4112-4150.

[108] Allocco, J. J.; Donald, R.; Zhong, T.; Lee, A.; Tang, Y. S.; Hendrickson, R. C.; Liberator, P.; Nare, B. Inhibitors of casein kinase 1 block the growth of *Leishmania major* promastigotes *in vitro*. *Int. J. Parasitol.* **2006**, *36*, 1249-1259.

[109] Baiocco, P.; Poce, G.; Alfonso, S.; Cocozza, M.; Porretta, G. C.; Colotti, G.; Biava, M.; Moraca, F.; Botta, M.; Yardley, V.; Fiorillo, A.; Lantella, A.; Malatesta, F.; Ilari, A. Inhibition of *Leishmania infantum* Trypanothione Reductase by Azole-Based Compounds: a Comparative Analysis with Its Physiological Substrate by X-ray Crystallography. *ChemMedChem* **2013**, *8*, 1175-1183.

[110] Rizvi, S. U. F.; Siddiqui, H. L.; Parvez, M.; Ahmad, M.; Siddiqui, W. A.; Yasinzai, M. M. Antimicrobial and Anti-leishmanial Studies of Novel (2*E*)-3-(2-Chloro-6-methyl/methoxyquinolin-3-yl)-1-(Aryl)prop-2-en-1-ones. *Chem. Pharm. Bull*. **2010**, *58*, 301-306.

[111] Vieira, P. S.; Souza, T. de A. C. B.; Honorato, R. V.; Zanphorlin, L. M.; Severiano, K. L.; Rocco, S. A.; de Oliveira, A. H. C.; Cordeiro, A. T.; Oliveira, P. S. L.; de Giuseppe, P. O.; Murakami, M. T. Pyrrole-indolinone SU11652 targets the nucleoside diphosphatekinase from *Leishmania* parasites. *Biochem. Biophys. Res. Commun.* **2017**, *488*, 461-465.

synthetized *N*-protected aroyl pyrroles **3** makes them interesting candidates to be tested as potential anti-leishmanial compounds.

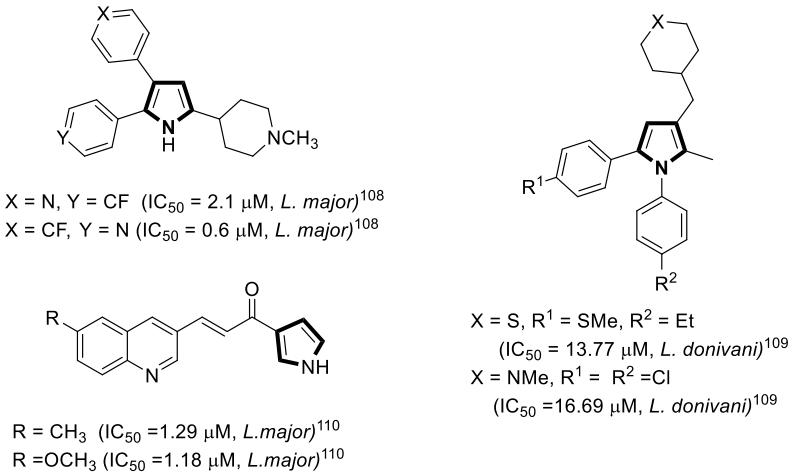
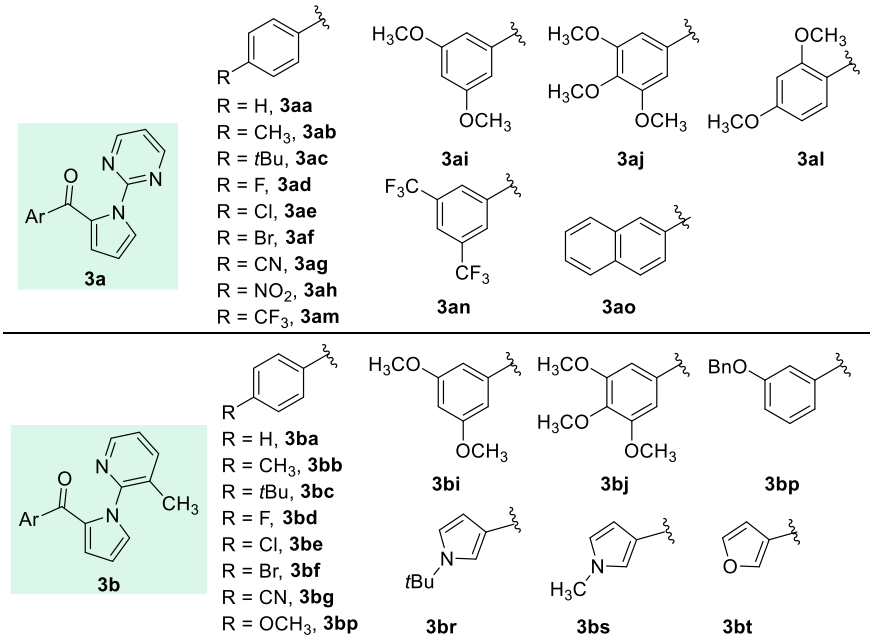


Figure 2.2. Anti-leishmanial activity of some synthetic compounds with the pyrrole motif (IC_{50} values are relative to *in vitro* assays on promastigotes for all compounds, except for 1,2-diarylpyrroles, where the value is relative to amastigotes).

The 2-(hetero)aroylpyrrole derivatives **3a** and **3b** (Scheme 2.34) were tested against *L. amazonensis* and *L. donovani*, which are responsible for the two main clinical forms of this neglected tropical disease, cutaneous and visceral leishmaniasis, respectively (Table 2.5).[112] We performed *in vitro* promastigote and *in vitro* intracellular amastigote susceptibility assays (IC_{50}), and cytotoxicity assays (CC_{50}) on J774 cell line of macrophages using miltefosine as the drug of reference (see experimental section), and the corresponding selectivity indexes (SI) were calculated. The performance of each *N*-pyrimidin-2-yl acylated pyrrole **3a** was compared with that of the corresponding *N*-(3-methylpyridin-2-yl) derivative **3b** (Table 2.5). The bioactivity of some compounds of both series compare well to in terms of activity and selectivity against *L. amazonensis* promastigotes. The aromatic substitution pattern of the acyl group plays an important role on the anti-leishmanial activity of these pyrrole derivatives. In some cases, we observed similar trends in the bioactivity profile for

[112] Anti-leishmanial assays were carried out by Dr. M. A. Dea, from CEU Cardenal Herrera (Valencia).

pyrimidine derivatives **3a** and the corresponding pyridines **3b**. For example, the 4-*t*-butylphenyl pyrrolyl methanones **3ac**/**3bc** and the 3,5-disubstituted phenyl pyrrolyl methanones **3ai**/**3bi**, with electron-donating (MeO) substituents, showed IC_{50} in a similar micromolar range than miltefosine (Table 2.5, entries 3 vs. 17 and 9 vs. 22). The parallel behavior was maintained also for trisubstituted derivatives **3aj**/**3bj**, which were both inactive under our bioassay conditions (Table 2.5, entries 10 vs. 23). However, there were significant differences in the 2-(hetero)aroylpyrroles derivatives with halogenated aromatic rings. In particular, in the pyridine series, **3bd** (R = F) was found to be more active and selective than the drug of reference (miltefosine) (IC_{50} = 16.87 ± 0.73 μM, SI > 10.67), while the corresponding pyrimidine derivative **3ad** (R = F) was inactive (Table 2.5, entry 17 vs entry 4). It also should be pointed out that compound **3ao**, where the phenyl ring had been changed to a naphthyl ring, showed similar activity than the drug of reference with better selectivity (Table 2.5, entry 14).



Scheme 2.34. Selected acylated pirroles **3** screened against *L.* amazonensis and *L. donovani*.

The same set of 2-(hetero)aroylpyrroles **3a,b** was also tested on promastigotes forms of *L. donovani* (Table 2.5). All compounds were considerably less active and selective, than miltefosine. Halogenated pyridine derivatives **3bd-3bf** presented the best profiles, being **3bd** again the most active and selective of all 2-acylpyrroles (IC_{50} = 7.78 ± 0.27 μM and SI > 23.15). However, it should be highlighted that all tested pyrrole derivatives resulted less toxic than miltefosine with values of concentration of the compound that produces 50% reduction of cell viability (Cytotoxic Concentration, CC_{50}) in the range 87 - 401 μM in J774 cells. This is a promising result, taking into account high toxicity (low selectivity) of marketed available drugs.[102b]

Table 2.5. IC_{50} leishmanicidal and cytotoxic effects from 2-acylpyrrole series **3a** and **3b** (expressed as μM) on *in vitro* promastigote assays.

Entry	Comp.	*L. amazonensis*		*L. donovani*		Macrophages J774
		IC_{50} ± SD[a)]	**SI**[b)]	**IC_{50} ± SD**[a)]	**SI**[b)]	**CC_{50} ± SD**[c)]
1	**3aa**	259.58±40.72	>1.55	N/A[d]		401.17[e)]
2	**3ab**	N/A[d)]		N/A[d]		381.24[e)]
3	**3ac**	32.88 ± 0.74	>2.77	58.54±7.04	>1.55	91.02±6.55
4	**3ad**	N/A[d)]		N/A[d]		270.19±26.30
5	**3ae**	117.09±10.92	>3.01	189.77±6.76	>1.86	352,46[e)]
6	**3af**	67.18±4.94	>4.54	118.18±25.81	>2.58	304.72[e)]
7	**3ag**	N/A[d)]		N/A[d)]		364.59[e)]
8	**3ah**	N/A[d)]		N/A[d)]		339.82[e)]
9	**3ai**	32.55±0.64	>2.71	210.90±32.77	>0.42	88.29±3.36[e)]
10	**3aj**	N/A[d)]		N/A[d)]		87.27 ± 7.37[e)]
11	**3al**	N/A[d)]		N/A[d)]		224.28 ± 46.89[e)]
12	**3am**	48.02±1.61	>3.13	42.82±0.61	>3.51	150.36±49.40[e]
13	**3an**	57.34±0.25	>4.53	198.54±25.36	>1.31	259.56[e)]
14	**3ao**	36.11±1.23	>3.12	58.50±3.34	>1.93	112.82±39.19[e)]
15	**3ba**	152.77±21.65	>2.50	N/A[d)]		381.23[e)]

Table 2.5. Continuation.

Entry	Comp.	*L. amazonensis*		*L. donovani*		Macrophages J774
		IC_{50} ± SD[a)]	**SI**[b)]	**IC_{50} ± SD**[a)]	**SI**[b)]	**CC_{50} ± SD**[c)]
16	**3bb**	149.20±3.84	>2.43	119.64±14.98	>3.02	361.87[e)]
17	**3bc**	30.87±3.11	>10.17	221.31±36.90	>1.42	314.05[e)]
18	**3bd**	16.87±0.73	>10.67	7.78±0.27	>23.15	136.96±36.42
20	**3bf**	38.10±0.85	>3.14	19.87±1.47	>6.01	119.51±37.36[e)]
21	**3bg**	191±12.04	>1.81	315.43±60.80	>1.10	348.04[e)]
22	**3bi**	71.06±7.81	>1.53	43.51 ± 0.59	>0.80	108.45±5.76[e)]
23	**3bj**	N/A[d)]		N/A[d)]		283.78
24	**3bp**	224.26±14.71	>1.53	172.92±60.34	>1.98	342.07[e)]
25	**3bq**	207.96±23.62	>1.31	184.22±8.67	>1.47	356.76[e)]
26	**3br**	209.16 ± 4.69	>1.56	92.81±7.68	>1.08	325.31 [e)]
27	**3bs**	226.54±13.42	>1.66	N/A[d)]		376.90 [e)]
28	**3bt**	N/A[d)]		N/A[d)]		396.40 [e)]
29	Miltefosine	30.67±8.80	1.80	0.24 ± 0.02	230.83	55.40±4.19

[a)] IC_{50}: Concentration of the compound that produced a 50% reduction in parasites; SD: Standard Deviation. [b)] SI: Selectivity Index, SI = CC_{50}/IC_{50}. [c)] CC_{50}: Concentration of the compound that produced a 50% reduction of cell viability in treated culture cells with respect to untreated ones. [d)] N/A: not active at the maximum dose tested (100 µg/mL). [e)] CC_{50} values, expressed as µM, correspond to 100 µg/mL, which was the higher doses tested.

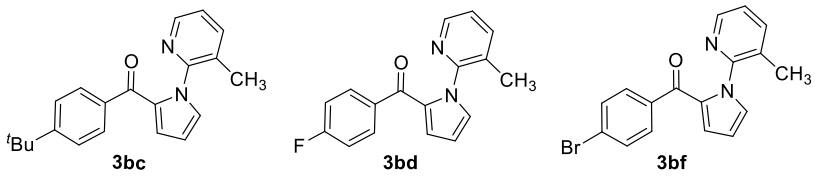
Then, one compound of each series was further tested *in vitro* on *L. amazonensis* and *L. donovani* amastigotes (Table 2.6). Pyrimidine derivative **3bc** showed good performance with and activity similar to miltefosine and better selectivity (IC_{50} = 60.55 ± 7.88 µM, SI > 5.19) against *L. amazonensis*. Nevertheless, pyridine derivative **3bc** presented bad results in terms of activity and selectivity (IC_{50} = 153.27 ± 9.11 µM, SI > 1.99).

Table 2.6. IC_{50} Leishmanicidal and cytotoxic effects from 2-acylpyrroles **3af** and **3bc** (expressed as µM) on *in vitro* amastigote assay.

Entry	Comp.	*L. amazonensis*		*L. donovani*		Macrophages J774
		IC_{50}±SD[a)]	**SI**[b)]	**IC_{50}±SD**[a)]	**SI**[b)]	**CC_{50}±SD**[c)]
1	**3af**	153.27±9.11	>1.99	210.87±30.26	>1.45	304.72[e)]
2	**3bc**	60.55±7.88	>5.19	N/A[d)]		314.05[e)]
3	Miltefosine	47.55±7.04	2.85	0.44±0.05	307.70	135.93±10.19

[a)] IC_{50}: Concentration of the compound that produced a 50% reduction in parasites; SD: Standard Deviation. [b)] SI: Selectivity Index, SI = CC_{50}/IC_{50}. [c)] CC_{50}: Concentration of the compound that produced a 50% reduction of cell viability in treated culture cells with respect to untreated ones. [d)] N/A: not active at the maximum dose tested (100 µg/mL). [e)] CC_{50} values, expressed as µM, correspond to 100 µg/mL, which was the higher doses tested.

In summary, The *in vitro* evaluation of the leishmanicidal activity 2-acylpyrrole series **3a** and **3b** against visceral (*L. donovani*) and cutaneous (*L. amazonensis*) leishmaniasis revealed that all tested 2-acylpyrroles showed very low cytotoxicity, CC_{50}> 100µg/mL in J774 cells (highest tested dose). This in an important feature, as drug toxicity is one of the main limitations of current chemotherapy for leishmaniasis. In particular, **3bd** (IC_{50} = 16.87 µM, SI >10.67) was approximately 6-fold more potent and selective than the drug of reference (miltefosine) in *L. amazonensis* promastigote assays (Figure 2.3). These results point to 2-acylpyrroles as a new class of lead compounds worthy of further optimization as anti-leishmanial hits.



Best IC_{50} values:

L. amazonensis	30.87 µM (**3bc**)	16.87 µM (**3bd**)	
L. donivani		7.78 µM (**3bd**)	19.87 µM (**3bf**)

Figure 2.3. Selected acylpyrroles with best antileishmanial activity (IC_{50} values on *in vivo* promastigotes assays.

2.3.2. Microwave-assisted Palladium (II) C-3 acylation of Thiophenes with aldehydes

As has been explained in objectives, our next goal was to study the C-3 acylation of thiophenes. Thiophene scaffold is found in natural products, pharmaceuticals and other bioactive organic molecules, as well as in functional organic materials.[113] The regioselective acylation of thiophene has attracted the interest of synthetic chemists, because it gives access to biologically active (hetero)aryl and/or cycloalkyl thiophenyl methanones, such as anti-inflammatory drug (NSAID) suprofen[114] and tiaprofenic acid, diuretic tienilic acid[115] or anticancer and antiestrogen Raloxifene,[116] which is being investigated as a treatment option for viral infections as SARS-Cov-2 (Figure 2.4).[117] The (hetero)aryl thiophenyl methanones

[113] For recent reviews, see: a) Ibrahim, S. R. M.; Abdallah, H. M.; El-Halawany, A. M.; Mohamed, G. A. *Phytochem. Rev.* **2016**, *15*,197-220; b) Barbarella, G.; Zangoli, G.; Di Maria, F. Chapter Three - Synthesis and Applications of Thiophene Derivatives as Organic Materials. *Adv. Heterocycl. Chem.* **2017**, *123*, 105-167; c) Pathania, S.; Narang, R. K.; Rawal, R. K. Role of sulphur-heterocycles in medicinal chemistry: An update. *Eur. J. Med. Chem.* **2019**, *180*, 486-508.; d) Archna, P.; Shelly, C.; Chawla, P. A. Thiophene-based derivatives as anticancer agents: An overview on decade's work. *Bioorg. Chem.* **2020**, *101*, 104026.

[114] Todd, P. A.; Heel, R. C. Suprofen. *Drugs.* **1985**, *30*, 514-538.

[115] Gramec, D.; Masic, L. P.; Dolenc, M. S. Bioactivation Potential of Thiophene-Containing Drugs. *Chem. Res. Toxicol.* **2014**, *27*, 1344-1358, and references cited therein.

[116] a) Dadiboyena, S. Recent advances in the synthesis of raloxifene: A selective estrogen receptor modulator. *Eur. J. Med. Chem.* **2012**, *51*, 17-34; b) Levenson, A. S.; Wolf, D. M.; Catherino, W. H.; Takei, H.; Jordan, V. C. Understanding the antiestrogenic actions of raloxifene and a mechanism of drug resistance to tamoxifen. *Breast Cancer*. **1998**, *5*, 99-106.

[117] Hong, S.; Chang, J.; Jeong, K.; Lee, W. *J.* Raloxifene as a treatment option for viral infections**.** *Microbiol.* **2021**, *59*, 124-131.

can also be intermediates in the synthesis of optoelectronic materials.[118]

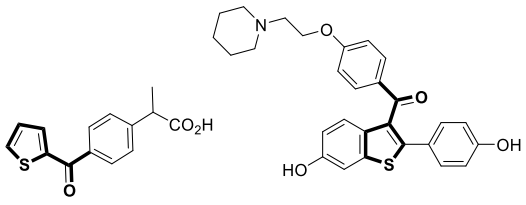


Figure 2.4. Examples of marketed drugs containing acylthiophene nucleus.

Traditional methods to acylate thiophenes mainly rely on the classical Friedel–Crafts acylation reaction[79,119] of (hetero)arenes (Scheme 2.35a), where the regioselectivity is controlled by the electronic properties of the substrate.[120] The addition of aryllithium compounds to carboxylic acid derivatives (Scheme 2.35b)[121] and carbonylative cross-couplings (Scheme 2.35c)[122] from prefunctionalized heteroarenes also constitute two

[118] Wang, S.-A.; Hung, W.-Y.; Chen, Y.-H.; Wong, K.-T. A novel heteroterfluorene for efficient blue and white OLEDs**.** *Org. Electron*. **2012**, *13*, 1576-1582.

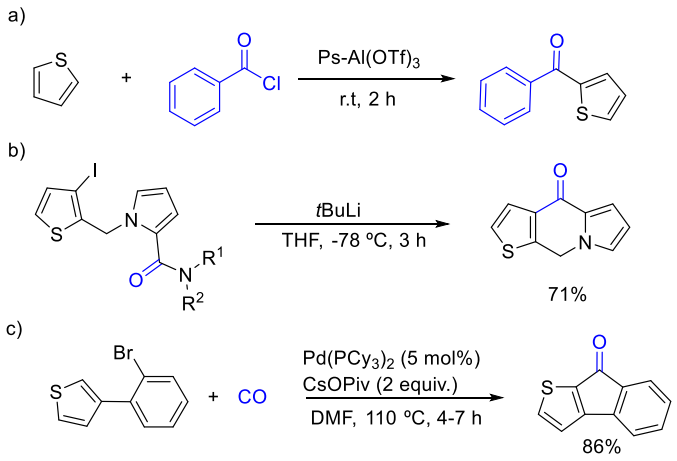
[119] a) Parvanak, B. K. Polystyrene Supported Al(OTf)3: an Environmentally Friendly Heterogeneous Catalyst for Friedel-Crafts Acylation of Aromatic Compounds. *Bull. Korean Chem. Soc*. **2010**, *31*, 3156-3158; For selected reviews, see: b) Olah, G. A.; Reddy, V. P.; Prakash, G. K.S. in: *Kirk-Othmer Encyclopedia of Chemical Technology*, 5th Edition (Ed. A. Seidel), John Wiley & Sons, Inc. Hoboken, N. J., **2005**, Vol. 12, pp 159-199; c) Sartori, G.; Maggi, R. Use of Solid Catalysts in Friedel−Crafts Acylation Reactions. *Chem. Rev*. **2006**, *106*, 1077-1104.

[120] Ryabova,V.; Ignatovich, L. Thiophene Substitution Chemistry. *Top. Heterocycl. Chem.* **2015**, *39*, 43-108.

[121] For a review, see: a) Schatz, J.; Hoffmann, I. Tiophene Metallation and Cross-Coupling Chemistry. *Top. Heterocycl. Chem.* **2015**, *39*, 109-160; see also: b) Ruiz, J.; Sotomayor, N: Lete, E. Parham-Type Cycliacylation with Weinreb Amides. Application to the Synthesis of Fused Indolizinone Systems. *Org. Lett*. **2003**, *5*, 1115-1117; c) Ruiz, J.; Lete, E.; Sotomayor, N. Intramolecular cyclisation of functionalised heteroaryllithiums. Synthesis of novel indolizinone-based compounds. *Tetrahedron* **2006**, *5*, 6182-6189; d) Simón-Vidal, L.; García-Calvo, O.; Oteo, U.; Arrasate, S.; Lete, E.; Sotomayor, N.; González-Díaz, H. Perturbation-Theory and Machine Learning (PTML) Model for High-Throughput Screening of Parham Reactions: Experimental and Theoretical Studies. *J. Chem. Inf. Model.* **2018**, *58*, 1384-1396.

[122] a) Campo, M. A.; Larock, R. C. Synthesis of Fluoren-9-ones by the Palladium-Catalyzed Cyclocarbonylation of *o*-Halobiaryls. *J. Org. Chem.* **2002**, *67*, 5616-5620; For a review, see: b) Wu,

efficient alternative methods to prepare acylthiophenes. However, the environmental problems related to producing strong acidic- or salt-waste are important drawbacks of these procedures.

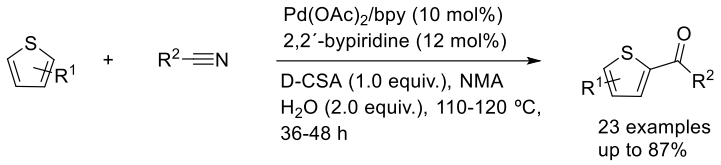


Scheme 2.35. Classical methods for acylation of arenes and heteroarenes.

As has been mentioned in the introduction, in the last years transition-metal-catalyzed direct C-H activation/acylation of (hetero)arenes has revealed as an excellent tool for the synthesis of di(hetero)aryl ketones in an atom-economical way.[2,82] However, these type of reactions have only been scarcely applied to thiophene rings. Thus, 2-acylthiophenes have been synthetized through palladium-catalyzed direct addition of 2-subtituted thiophenes to nitriles (Scheme 2.36). The acylation reaction proceeded well under the $Pd(OAc)_2$/2,2′-bipyridine system using D-(+)-camphorsulfonic acid as additive, although selectivity problems arose when starting from 3-substituted thiophenes, as the reaction takes place under substrate control.[123]

X.-F.; Neumann, H.; Beller, M. Palladium-catalyzed carbonylative coupling reactions between Ar–X and carbon nucleophiles. *Chem. Soc. Rev*. **2011**, *40*, 4986-5009.

[123] Jiang, T.-S.; Wang, G.-W. Synthesis of 2-Acylthiophenes by Palladium-Catalyzed Addition of Thiophenes to Nitriles. *Adv. Synth. Catal*. **2014**, *356*, 369-373.



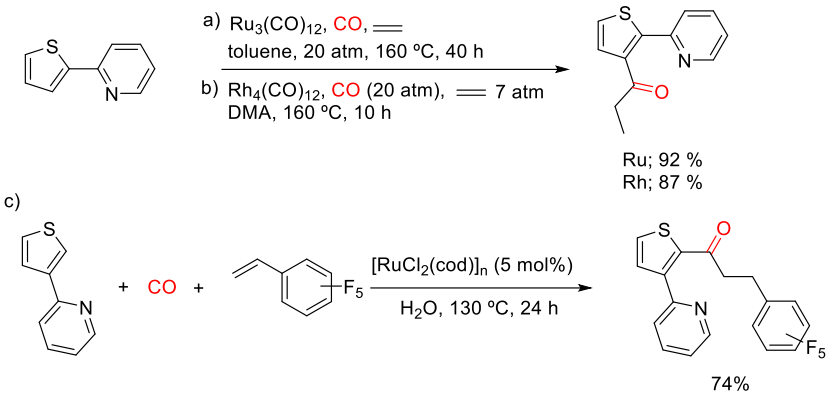
Scheme 2.36. Palladium-catalyzed addition thiophenes to nitriles.

To date, the C-H acylation of thiophene at the C-3 or C-2 position has been achieved by transition metal catalysis *via* C(sp^2)-H bond activation, using directing groups (e.g. pyridine, pyrimidine) to control site selectivity. For example, as it is described in Scheme 2.37a,b, a ruthenium or rhodium-catalyzed carbonylation of 2- and/or 3-pyridinylthiophene with CO (2 MPa) and ethylene in toluene at 160 °C resulted in propionylation at an *ortho* C-H bond.[124] Interesting ruthenium-catalyzed carbonylation reactions of thiophene with aryl iodides[125] or styrenes[126] as coupling partners have been developed by Beller (Scheme 2.37c). The three-component coupling processes proceeded with moderate to good yield in water using both pyridinyl and pyrimidinyl *ortho*-directing groups, but also working at high temperatures (up to 130 ºC) and pressure (3 MPa) for long reaction times (20-24 h).

[124] a) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. $Ru_3(CO)_{12}$-Catalyzed Reaction of Pyridylbenzenes with Carbon Monoxide and Olefins. Carbonylation at a C−H Bond in the Benzene Ring. *J. Org. Chem.* **1997,** *62*, 2604-2610; b) Chatani, N.; Uemura, T.; Asaumi, T.; Ie, Y.; Kakiuchi, F.; Murai, S. Rhodium-catalyzed C-H–CO–olefin coupling reactions- A chelation-assisted direct carbonylation at the ortho C-H bond in the benzene ring of 2-arylpyridines. *Can. J. Chem.* **2005**, *83*, 755-763.

[125] a) Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. Ruthenium-Catalyzed Carbonylative C-C Coupling in Water by Directed C-H Bond Activation. *Angew. Chem. Int. Ed.* **2013**, 52, 6293-6297; b) Pospech, J.; Tlili, A.; Spannenberg, A.; Neumann, H.; Beller, M. Regioselective Ruthenium-Catalyzed Carbonylative Direct Arylation of Five-Membered and Condensed Heterocycles *Chem. Eur. J.* **2014**, *20*, 3135-3141.

[126] Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. Ruthenium-Catalyzed Hydroaroylation of Styrenes in Water through Directed C-H Bond Activation. *ChemCatChem*, **2014**, *6*, 1562-1566.



Scheme 2.37. Rutenium and Rhodium-catalyzed acylation.

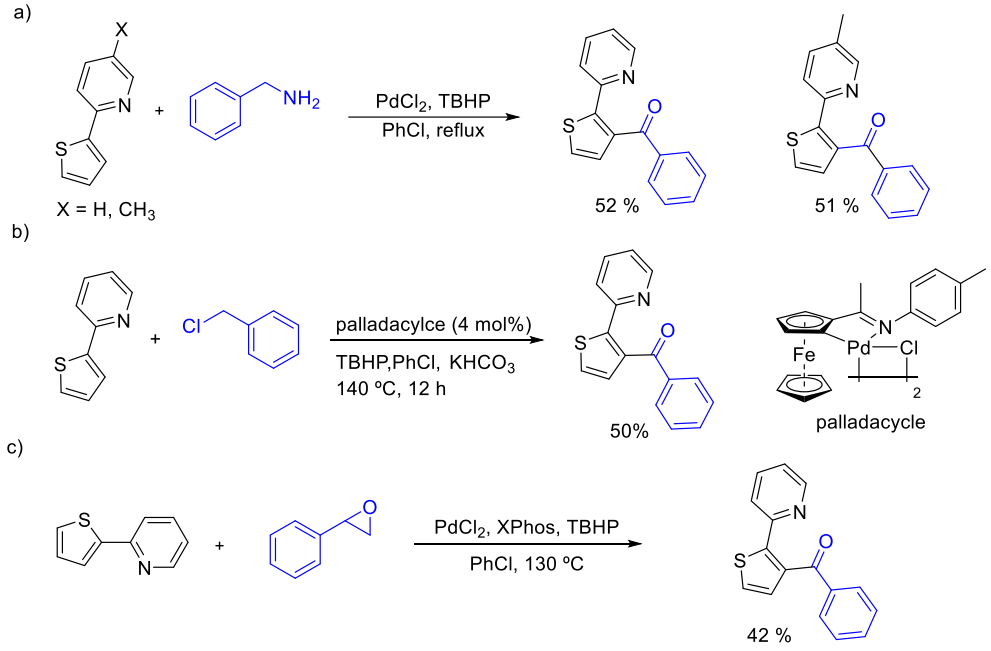
Li *et al.*[127] developed the first Rh(III)-catalyzed mild acylation of both C(sp^3)–H bonds and C(sp^2)–H bonds under redox-neutral conditions, using a ketene as acylation reagent, which was successfully applied to the C-3 acylation of thiophene (Scheme 2.38).

Scheme 2.38. Rhodium-catalyzed acylation using ketenes as acyl source.

In contrast, Pd(II)-catalyzed C-H acylation of thiophenes has been scarcely studied and limited to a few examples using 2-pyridinyl as directing group with benzylamine (Scheme

[127] Yu, S.; Li, Y.; Kong, L.; Zhou, X.; Tang, G.; Lan, Y.; Li, X. Mild Acylation of C(sp^3)–H and C(sp^2)–H Bonds under Redox-Neutral Rh(III) Catalysis. *ACS Catal.* **2016**, *6*, 7744-7748.

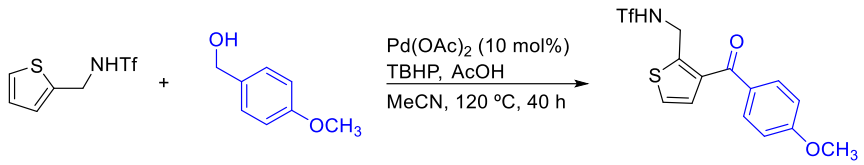
2.39a)[128] or benzyl chloride (Scheme 2.39b), [129] as well as phenyloxirane (Scheme 2.39c)[130] as acylating agents. In all cases, low moderate yields (up to 52%) were obtained under rather harsh reaction conditions (120-140 ºC, 8-12h).



Scheme 2.39. Palladium(II)-catalyzed acylation of thiophene with benzamines, benzylchloride and phenyloxirane.

[128] Zhang, Q.; Yang, F.; Wu, Y. Palladium-catalyzed *ortho*-acylation of 2-aryl pyridine derivatives using arylmethyl amines as new acyl sources. *Chem. Commun.* **2013**, *49*, 6837-6839.
[129] Zhang, G.; Sun, S.; Yang, F.; Zhang, Q.; Kang, J.; Wu, Y.; Wu, Y. Arylmethyl Chlorides: New Bifunctional Reagents for Palladium-Catalyzed *ortho*-Chlorination and Acylation of 2-Arylpyridines. *Adv. Synth. Catal.* **2015**, *357*, 443-450.
[130] Zhang, Q.; Wang, Y.; Yang, T.; Li, L.; Li, D. Palladium catalyzed *ortho*-C–H-acylation of 2-arylpyridines using phenylacetylenes and styrene epoxide. *Tetrahedron Lett.* **2016**, *57*, 90-94.

A related procedure[131] using the triflamidomethyl as directing group with a benzyl alcohol as acyl source required even longer reaction times (40 h) to access the benzoylated thiophene in low yield (30%) (Scheme 2.40).



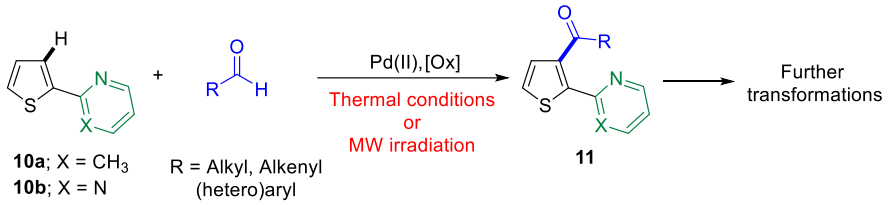
Scheme 2.40. Palladium(II)-catalyzed acylation of thiophenes using the triflamide as directing group.

As has been shown, the absence of examples of palladium(II)-catalyzed acylation of thiophenes leaves a door opened for methodologies that can provide 3-acylthiophenes in an efficient, atom-economical and environmentally friendly way. As indicated before, our goal is to study the selective palladium(II)-catalyzed C-3 acylation of thiophenes with aldehydes *via* C(sp^2)-H activation for the synthesis of (cyclo)alkyl/aryl thienyl ketones. Control of positional selectivity will be achieved by 2-pyridinyl and 2-pyrimidyl *ortho*-directing groups at C-2 of the thiophene scaffold (Scheme 2.41). The reaction will be studied first under standard thermal conditions, and then the application of MW heating will be explored. The efficiency of microwave (MW) irradiation in accelerating transition metal-catalyzed homogeneous cross-coupling reactions (Heck, Suzuki, Sonogashira, Stille, Negishi, etc.) has been recognized for years.[132] More recently, it has been proven that MW heating can also help to develop new, safe, and energy efficient C-C and C-X bond forming C-H activation

[131] Park, J.; Kim, A.; Sharma, S.; Kim, M.; Park, E.; Jeon, Y.; Lee, Y.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. Direct acylation of N-benzyltriflamides from the alcohol oxidation level *via* palladium-catalyzed C–H bond activation. *Org. Biomol. Chem.* **2013**, *11*, 2766-2771.

[132] For selected reviews, see: a) Larhed, M.; Moberg, C.; Hallberg, A. Microwave-Accelerated Homogeneous Catalysis in Organic Chemistry. *Acc. Chem. Res.* **2002**, *35*, 717-727; b) Mehta, P. V.; Van der Eycken, E. V. Microwave-assisted C–C bond forming cross-coupling reactions: an overview. *Chem. Soc. Rev.* **2011**, *40*, 4925-4936; c) Rathi, A. K.; Gawande, M. B.; Zboril, R.; Varma, R.S. Microwave-assisted synthesis – Catalytic applications in aqueous media**.** *Coord. Chem. Rev.* **2015**, *291*, 68-94.

reactions.[133] However, the effect of MW irradiation on palladium(II)-catalyzed radical-H acylation reaction has not been studied. Besides, further transformations of these ketones illustrate the potential of the method, including intramolecular reactions to embed the directing-group in the core-structure of the new molecule.

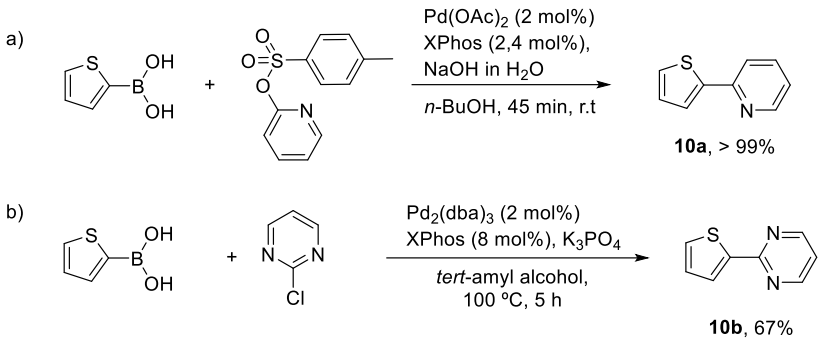


Scheme 2.41. Pd(II)-catalyzed acylation of thiophenes under thermal and MW heating.

Substrates **10a** and **10** were synthetized in excellent and good yields by classical Suzuki-Miyaura reaction described in literature as it is depicted in Scheme 2.42.[134]

[133] a) Zhao, Y.; Sharma, N.; Sharma, U. K.; Li, Z.; Song, G.; V, Van der Eycken, E. V. Microwave-Assisted Copper-Catalyzed Oxidative Cyclization of Acrylamides with Non-Activated Ketones. *Chem. Eur. J.* **2016**, *22*, 5878-5882; b) Sharma, N.; Bahadur, V.; Sharma, U. K.; Saha, D.; Li, Z.; Kumar, Y.; Colaers, J.; Singh, B. K.; Van der Eycken, E. V. Microwave-Assisted Ruthenium-Catalysed *ortho*-C−H Functionalization of *N*-Benzoyl *α*-Amino Ester Derivatives. *Adv. Synth. Catal.* **2018**, *360*, 3083-3089; c) Song, L.; Tian, G.; Blanpain, A.; Van Meervelt, L.; Van der Eycken, E. V. Diversification of Peptidomimetics and Oligopeptides through Microwave-Assisted Rhodium(III)-Catalyzed Intramolecular Annulation. *Adv. Synth. Catal.* **2019**, *361*, 4442-4447.

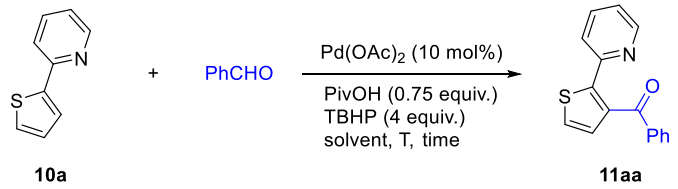
[134] Yang, J.; Liu, S.; Zheng, J-F.; Zhou, J. Room-Temperature Suzuki–Miyaura Coupling of Heteroaryl Chlorides and Tosylates. *Eur. J. Org. Chem.* **2012**, 6248; b) Billingsley, K.; Buchwald, S. L. Highly Efficient Monophosphine-Based Catalyst for the Palladium-Catalyzed Suzuki-Miyaura Reaction of Heteroaryl Halides and Heteroaryl Boronic Acids and Esters. *J. Am. Chem. Soc.* **2007**, *129*, 3358-3366.



Scheme 2.42. Synthesis of substrates **10a** and **10b**.

We started studying the use of pyridine as directing group on C-2, in the reaction of **10a** with benzaldehyde (**2a**) and using TBHP as the oxidant, under the conditions previously optimized for the C2-acylation of pyrroles in toluene at 60 ºC using conventional heating and in the presence of pivalic acid as additive (Table 2.7, entry 1). Gratifyingly, full conversion of **10a** was observed after 2 hours and the expected ketone **11aa** was isolated as the major compound in a good yield (78%), although the formation of decomposition products was also observed. A shorter reaction time (1 h), using a stoichiometric amount of PivOH led to a similar isolated yield of **11aa**, although unreacted **10a** was also recovered (Table 2.7, entry 2). The reaction of **10a** was not complete at lower temperature (40 ºC) for a longer time (Table 2.7, entry 3). However, the use of higher temperatures and longer reaction times led to decomposition products, significantly reducing the isolated yield of **11aa** (Table 2.7, entries 4-5). A change in the solvent to DCE or chlorobenzene did not improve the results, observing once again the formation of decomposition products that lowered the isolated yield of **11aa** (Table 2.7, entries 6-8). The reaction could also be carried out in the absence of any added solvent (TBHP is used as a 5.5 M solution in decane) (Table 2.7, entry 9), and it is compatible also with the use of water as solvent (using in this case a TBHP water solution), although unreacted **10a** was recovered. The reactivity drops significantly when a surfactant is used (Table 2.7, entries 10-12).

Table 2.7. Acylation of **10a** with benzaldehyde (**2a**) under thermal conditions.



10a **11aa**

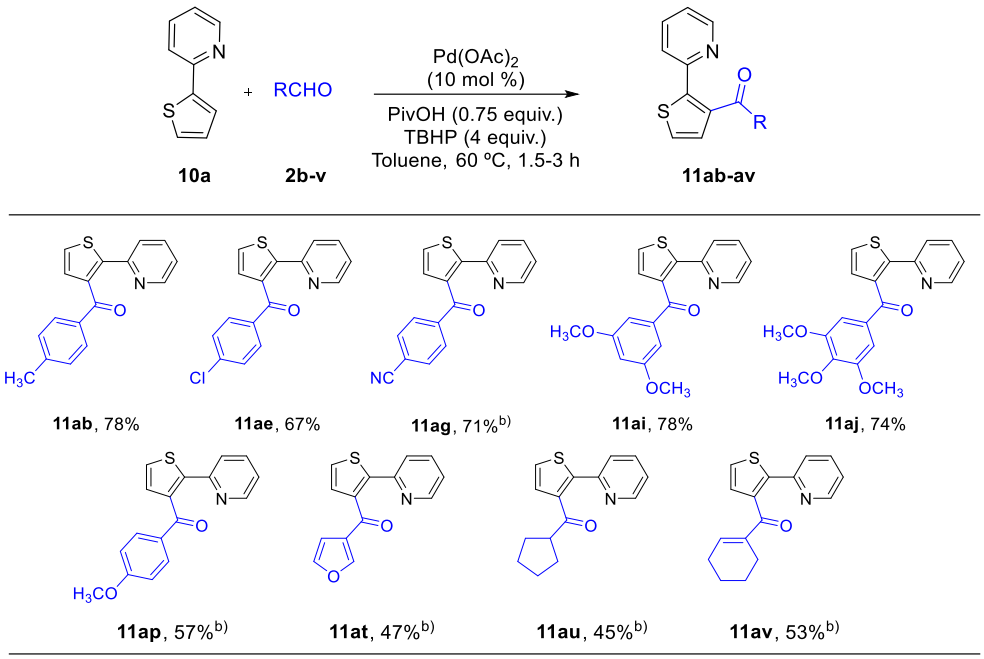
Entry	Solvent	T (ºC)[a)]	time (h)	13a [%][b)]
1	**toluene**	**60**	**2**	**78**
2	toluene	60	1	76[c,d)]
3	toluene	40	3.5	57[c)]
4	toluene	50	17	63
5	toluene	120	1.5	36
6	DCE	60	1.5	65
7	PhCl	60	1.5	74
8	PhCl	60	1	72
9	-	60	1.5	68
10	H_2O	60	2	61[c,e)]
11	H_2O	60	2.5	19[c,e,f)]
12	H_2O	20	24	17[c,e,f)]

[a)] The reactions were carried out in a 0.5 mmol scale using 10 mL sealed reaction tubes inserted in a heating block. The indicated temperature refers to the external temperature of the heating block. [b)] Yield (%) of isolated pure compound. [c)] Unreacted **10a** was recovered. [d)] 1 equiv. of PivOH was used. [e)] TBHP solution in water was used. [f)] SDS (5%) was added.

Toluene at 60 ºC was selected as the optimal solvent and temperature, and the reaction was tested with different aromatic aldehydes (Table 2.8). As shown in Table 2.8, generally higher reactivity is observed when the aromatic ring is substituted with electron-donating groups, what would lead more nucleophilic radical intermediates, but the reaction also works with electron-withdrawing substituents (Table 2.8, **11ab-ap**). 3-Furan-3-carbaldehyde **2t** could also be used, although it presented lower reactivity, obtaining **11at** in a moderate yield. The extension to aliphatic or α,β-unsaturated aldehydes **2u** and **2v** is also possible, but they showed lower reactivity, recovering unreacted **10a**. However, if the reaction times were extended, decomposition of the products started to occur, lowering the isolated yields of ketones **11a**. The examples shown in Tables 2.7 and 2.8 show that longer reaction times or higher temperatures led to decomposition instead of higher conversions, probably due to

oxidation reactions of the thiophene ring.[115]

Table 2.8. Synthesis of 3-acyltiophenes **11ab-av** under thermal conditions.

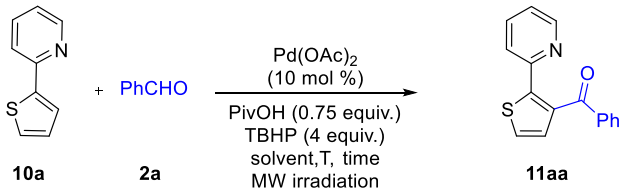


[a)] The reactions were carried out in a 0.5 mmol scale using 10 mL sealed reaction tubes inserted in a heating block. Yield (%) of isolated pure compound.[b)] Unreacted **10a** was recovered.

In view of these results, we decided to test the acylation reaction under MW irradiation assuming that an increase of the reaction rate, usually associated with the use of this technique,[132,133] would lead to shorter reaction times, preventing decomposition of the products and producing higher isolated yields of ketones **11a**. We started using the same reaction conditions used for the thermal heating (toluene at 60ºC), checking the evolution of the reaction at different reaction times (Table 2.9, entries 1-3). Full conversion of the substrate **10a** was achieved only after 50 min, obtaining an improved 85% isolated yield of **11aa**. No decomposition was observed, and unreacted **10a** was recovered with shorter reaction times (20 or 40 min). More polar solvents were checked, and it was found that water

could be used at 60 ºC, but no full conversion was obtained after 40 min (Table 2.9, entries 4-5).

Table 2.9. MW-assisted acylation of **12a** with **2a**.



10a **2a** **11aa**

Entry	Solvent	T (ºC)[a]	time (min)	13a [%][b]
1	toluene	60	20	57[c]
2	toluene	60	40	67[c]
3	toluene	60	50	85
4	H_2O	60	20	33[c]
5	H_2O	60	40	54[c]
6	DCE	80	15	84 (80)[d]
7	DCE[e]	80	15	42[c]
8	DCE[f]	80	15	58
9	DCE[g]	80	15	[c]
10	DCE[h]	80	15	[c]

[a] The reactions were carried out in a 0.5 mmol scale using 10 mL sealed reaction tubes. The indicated temperature, obtained using a maximum power of 200W, refers to the internal reaction temperature measured by an infrared sensor. [b] Yield (%) of isolated pure compound. [c] Unreacted **10a** was recovered. [d] Isolated yield obtained when the reaction was performed in 1 mmol scale. [e] No PivOH was used. [f] 5 mol % of $Pd(OAc)_2$ was used. [g] No $Pd(OAc)_2$ was used. [h] No TBHP was used.

A significant improvement was finally found using DCE at 80 ºC, which led to a 84% isolated yield of **11aa** in only 15 min. The yield was similar (80%) when the reaction was carried out in 1 mmol scale (Table 2.9, entry 6). As shown in previous section, the use of pivalic acid was also important for reactivity, as the yield of **11aa** dropped to 42% in its absence in the same time (Table 2.9, entry 7), the yield also dropped when the catalyst loading was decreased (Table 2.9, entry 8). Finally, it was also checked that both the palladium catalyst and the oxidant are required, as the reaction does not take place at all in their absence (Table 2.9, entries 9-10).

These reaction conditions were applied to a series of aromatic, heteroaromatic, aliphatic and alkenyl aldehydes, as shown in Table 2.10. Ketones **11ab-11aj** were obtained in generally good yields in 15-25 minutes, improving the results obtained under standard thermal conditions (Table 2.8), with the exception of **11ap** and **11ag** that gave only moderate yields and unreacted **10a** was also recovered. This acylation reaction was further extended for the synthesis of ketones **11as-11aac**. Thus, a variety of aromatic aldehydes could be used, tolerating the presence of halogens or alkyl groups (**11ad-11af, 11au ,11ax** and **11aaa**).

The reaction is less efficient when electron-withdrawing groups are introduced in the aromatic ring (**11ag, 11aw**), specially in the case of a nitro group (**11ah**). Heteroaromatic or aliphatic aldehydes could also be used. Interestingly, the reaction is compatible with the use of more complex aldehydes, such as (*S*)-perylladehyde or (*R*)-myrtenal to obtain ketones **11ay** and **11az** in moderate yields. However, adamantane-1-carbaldehyde (**2ac**) showed a low reactivity, obtaining a low yield of **11aac** (23%). Nonetheless, with our optimized conditions, the reaction with high conjugated aldehydes as cinamaldehyde **2aab** proceeds in low yield (23%) and with retinal **2aad** we only obtained decomposition products and the recovery of **10a**.

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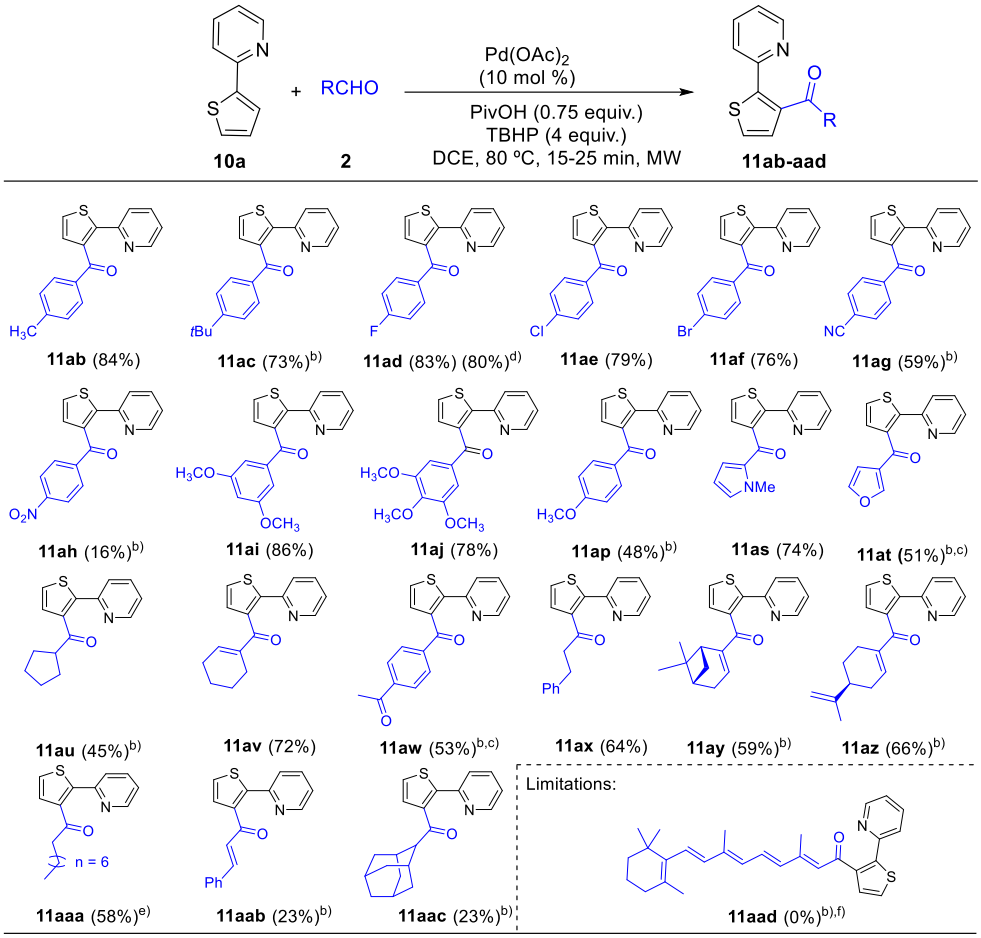
Table 2.10. MW-assisted acylation of **10a** with aldehydes **2**.

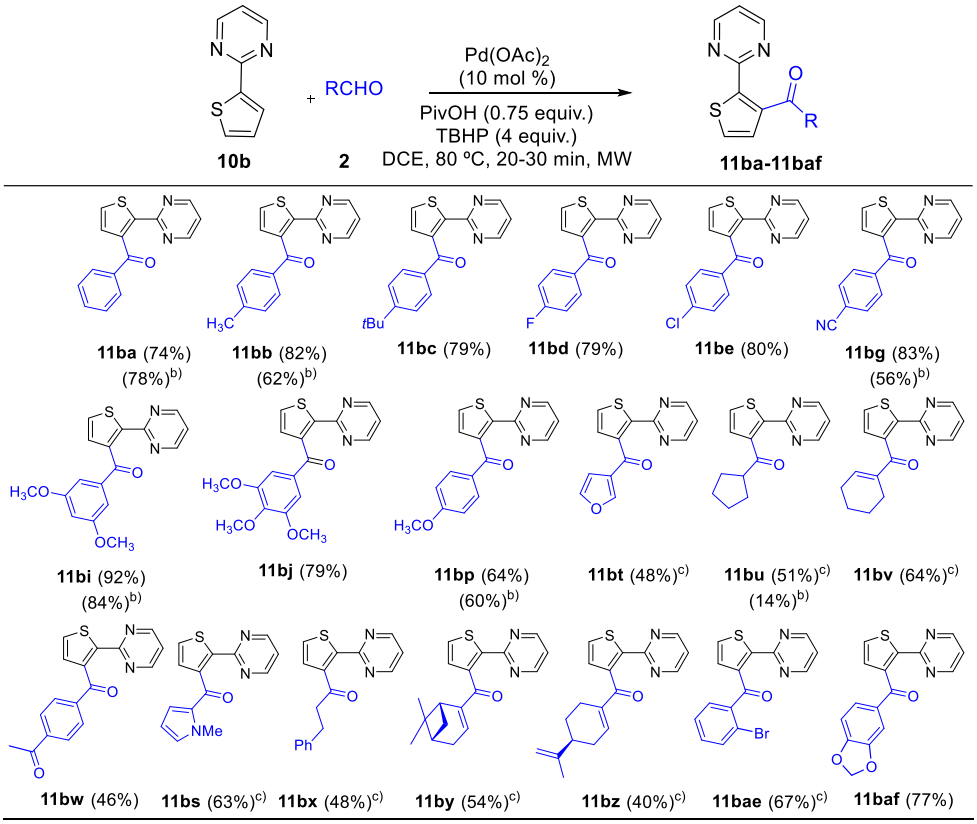


a) Yield (%) of pure isolated product. Reactions done in a 0.5 mmol scale. b) Unreacted **10a** was recovered. c) 15 mol% of catalyst was used. d) Reaction done in 1 mmol scale. e) Reaction done in 2 mmol scale. f) Descomposition products were oberserved.

We next studied the efficiency of 2-pyrimidine as directing group for these reactions (Table 2.11). The reaction times could be extended to 20-30 min without decomposition of the products, and ketones **11b** were obtained in general with comparable yields to those of ketones **11a** (Table 2.10), although some remarkable improvements were achieved. For

instance, ketone **11bg** was obtained with an 84% yield *vs* 59% for **11ag**. Compared to aromatic aldehydes, alkyl or alkenyl aldehydes gave in this case also lower yields of **11bx-bz**, due to recovery of unreacted **10b**. In addition to the results depicted in Tables 2.11 and 2.10 for the acylation of **11a,b**, different reaction times under MW irradiation were tested to try to improve the obtained yields of **11a,b**. The results are summarized in Figure 2.5. As can be seen, the extension of the reaction time can lead to lower isolated yields of **11a,b** due to the formation of decomposition products.

Table 2.11. MW-assisted acylation of **10b** with aldehydes **2**.



a) Yield (%) of pure isolated product. Reactions done in a 0.5 mmol scale. b) Yield (%) of pure compound when the reaction was carried out in toluene at 60 ºC, 1-3 h, with standard heating. c) Unreacted **10b** was recovered.

For comparison, selected examples (**11ba-bb**, **11bg-bi**, **11bp, 11bu**) were also carried out under standard thermal conditions, using toluene at 60 ºC for 1-3 hours. With the exception of **11ba**, the yields obtained were lower than those obtained under MW irradiation, specially in the cases of **11bg** and **11bu**.

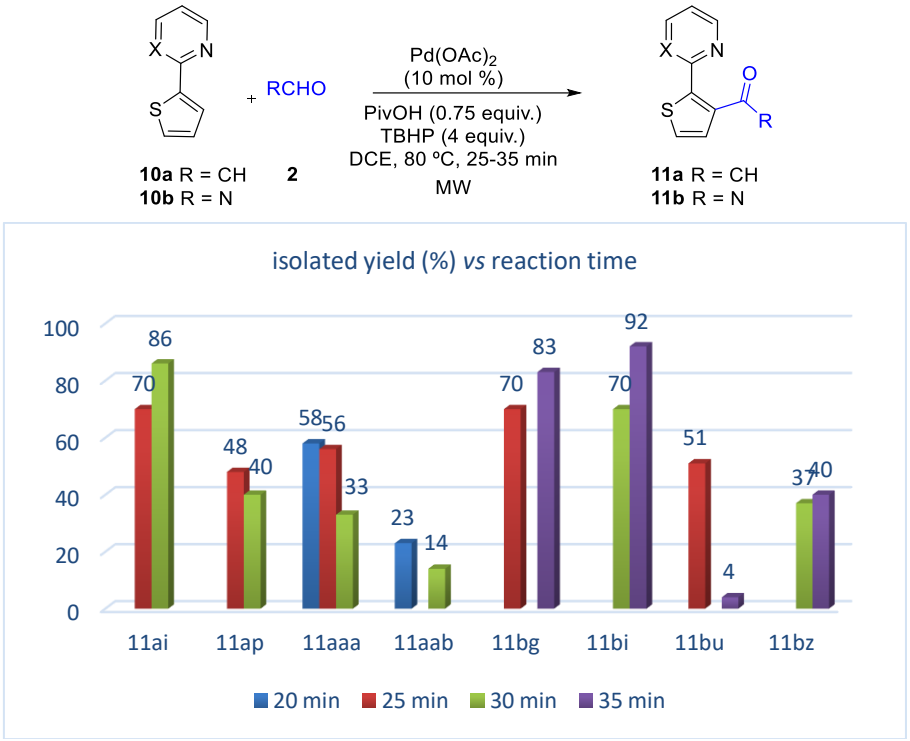
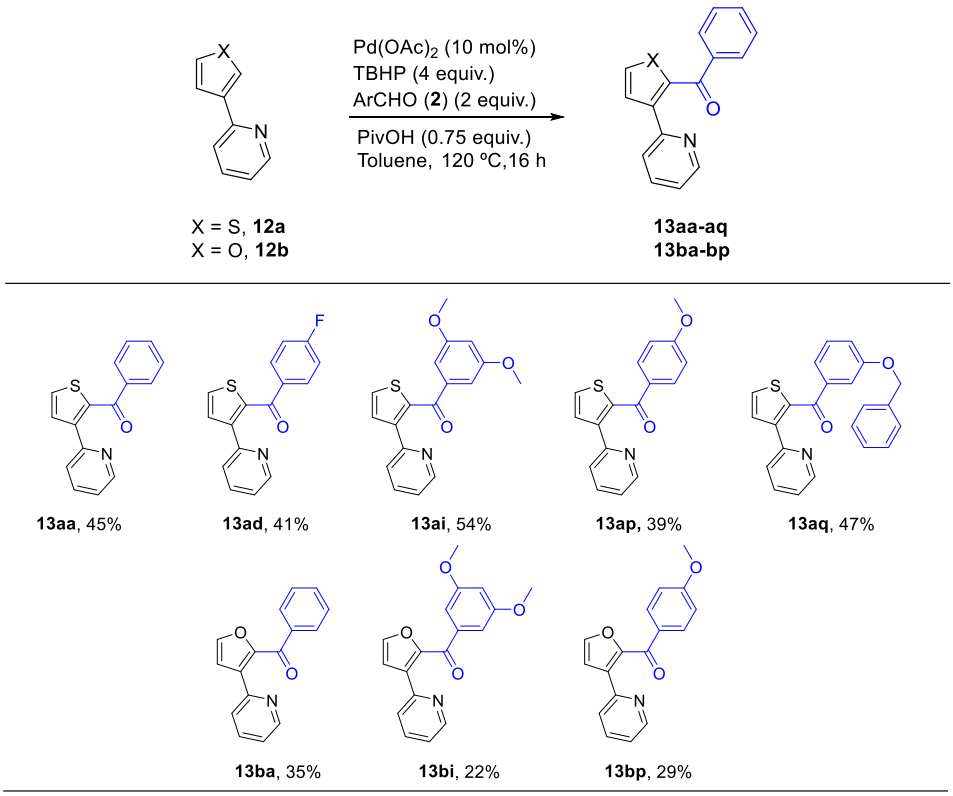


Figure 2.5. Additional essays on substrates **10a,b** with selected aldehydes **2** at different reaction times.

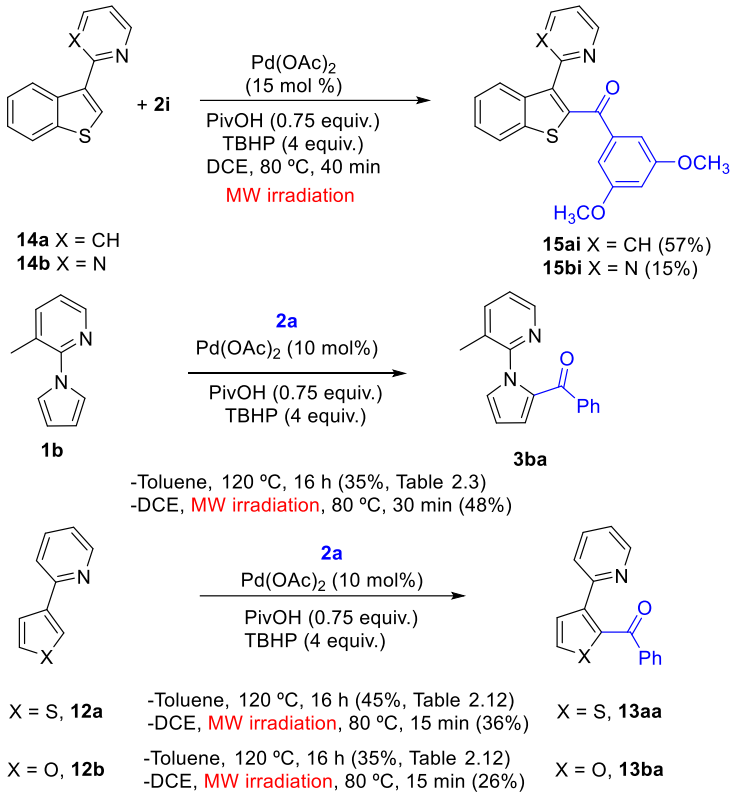
In order to expand of methodology, we applied our optimized thermal conditions for the C-2 acylation of thiophene and furan, using pyridine directing group in C-3 (**12a**,**12b**, Table 2.12). Due to the lower reactivity of those heterocycles, the reaction time and temperature had to be increased, and the aldehydes with the best reactivity in C-2 acylation of pyrroles were selected.

Table 2.12. C-2 acylation of thiophene and furan rings under thermal conditions.



We obtained the corresponding 2-aryl thiophenyl ketones **13aa-aq** in moderate yields, though unreacted **12a** was recovered in all cases, as well as decomposition of the starting material. Furanyl pyridine **12b** showed less reactivity and a greater tendency to decompose compared with thiophenyl pyidine **12a**. When the optimized reaction conditions were applied to **12b**, the corresponding 2-aryl furanyl ketones **13ba-bp** were isolated in low yields, recovering starting material **12b** and decomposition products in all cases.

Finally, the MW-assisted acylation reaction was tested also in different heterocyclic systems (Scheme 2.43). In the case of benzothiophenes **14a,b**, the performance of the pyridine as directing group for the C-2 acylation was clearly superior obtaining **15ai** with a moderate yield (Scheme 2.43).



Scheme 2.43. Acylation of heteroaromatic rings.

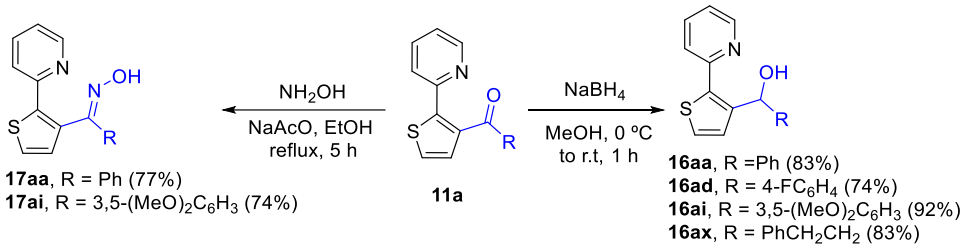
The reaction was applied also to pyrrole **1b**, although in this case, the results previously obtained under thermal conditions (toluene, 120 ºC, 1.5 h, 74%, Table 2.3) could not be improved. The reaction under MW irradiation led to **3ba** in a 48% isolated yield, recovering unreacted pyrrole **1b**. The C-2 acylation of furan **12b** was also tested (Scheme 2.43). Under thermal conditions (toluene, 120 ºC) **13ba** was obtained regioselectively, although in a low yield (35%), mainly due to the formation of decomposition products (Table 2.11).

Unfortunately, this result could not be improved under MW irradiation conditions observing also decomposition. Besides, unreacted **12b** was recovered, obtaining **13ba** in a 26% isolated yield after 15 min. A similar result was obtained for the C-2 acylation of thiophene **12a**, obtaining **13ba** regioselectively but in low isolated yield, not improving the result obtained

under thermal conditions.

2.3.2.1. Diversification of 3-acylthiophenes

The acyl thiophenes obtained provide a platform for a rich array of downstream manipulations. In this way, this approach enables relatively straightforward access to a plethora of analogues that may present interesting applications. Thus, the versatile reactivity of the carbonyl group can used to perform reduction or other nucleophilic additions, as illustrated by a few representative examples shown in Scheme 2.44. Reduction of acyl thiophenes **11a** with $NaBH_4$ under mild conditions provide access to compounds containing a benzylic functionality **16** [i.e. heteroaryl benzyl alcohol], which can be inhibitors of PI3K and/or VPS34, useful for treating proliferative, inflammatory, or cardiovascular disorders.[135] Besides, addition of hydroxylamine to acyl thiophenes **11a** in the presence of NaOAc led to (*E*)-oximes **17** also in good yields. It has been recently reported that the presence of a thiophene moiety in pinane-derived oximes can be crucial for their anti-influenza activity.[113]



Scheme 2.44. Synthesis of heteroaryl phenyl alcohols **15** and (*E*)-oximes **16** from acylthiophenes **11**.

In addition, the reaction of acyl thiophenes **11a** with thiosemicarbazide in acid media (HCl, EtOH, reflux) furnished (*Z*)-thiosemicarbazones **18** in high yield (Scheme 2.45). This type

[135] Freeze, B. S.; Hirose, M.; Hu, Y.; Hu, Z.; Lee, H. M.; Sells, T. B.; Shi, Z.; Vyskocil, S.; Xu, T. (Millennium Pharmaceuticals, Inc., USA), PCT Int. Appl. WO 2012021696 A1 20120216, 2012; *Chem. Abstr*. **2012**, *156*, 284873.

of thiosemicarbazones are cathepsin L inhibitors (e.g. SSAA09E1), which may be a therapeutic option for COVID-19[136] because they can prevent the progression of pulmonary fibrosis.[137] They are also inhibitors of trypanosomal cathepsins rhodesain and TbcatB[138]and potential antileukemic agents.[139] The obtained thiosemicarbazones **18** also served as good precursors to prepare more complex heterocycles, as illustrated in Scheme 2.45, with the synthesis of 4-(3-nitrophenyl)thiazol-2-ylhydrazones **19** by the Hantzsch reaction with 2-bromo-3'-nitroacetophenone (EtOH, r.t). It should be noted that **19**-like thiazol-2-ylhydrazones have been proven promising antioxidants and selective hMAO-B inhibitors, so they are potential leads for the design of novel therapies for neurodegenerative disorders.[140]

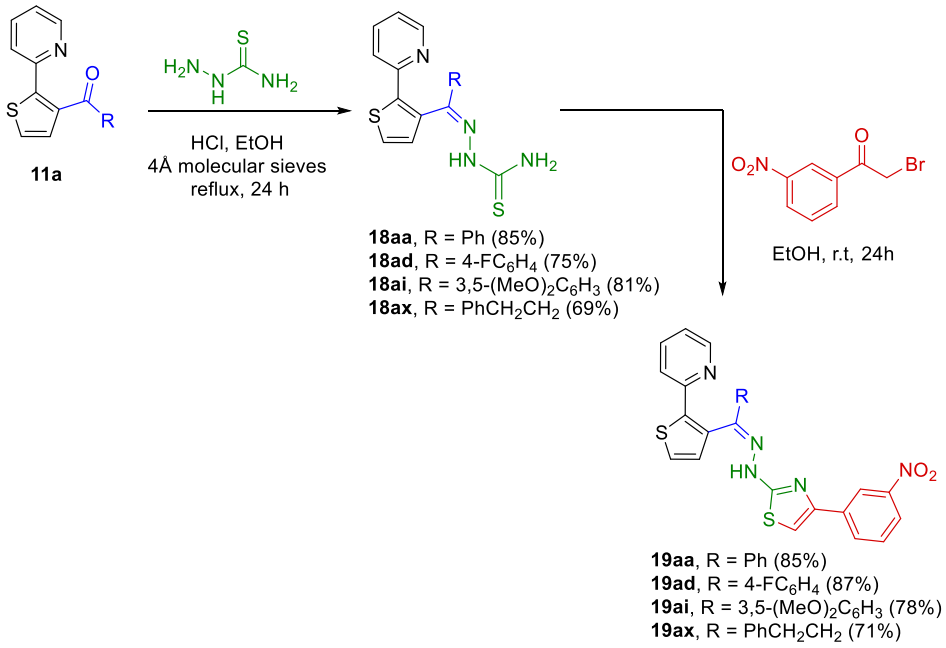
[136] Gil, C.; Ginex, T.; Maestro, I.; Nozal, V.; Barrado-Gil, L.; Cuesta-Geijo, M. A.; Urquiza, J.; Ramírez, D.; Alonso, C.; Campillo, N. E.; Martinez, A. COVID-19: Drug Targets and Potential Treatments. *J. Med. Chem.* **2020**, *63*, 12359-12386.

[137] Yuan, L.; Zou, C.; Ge, W.; Liu, Y.; Hu, B.; Wang, J.; Lin, B.; Li, Y.; Ma, E. A novel cathepsin L inhibitor prevents the progression of idiopathic pulmonary fibrosis *Bioorg. Chem.* **2020**, *94*, 103417.

[138] Mallari, J. P.; Shelat, A.; Kosinski, A.; Caffrey, C. R.; Connelly, M.; Zhu, F.; McKerrow, J. H.; Guy, R. K. Discovery of trypanocidal thiosemicarbazone inhibitors of rhodesain and TbcatB. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2883–2885.

[139] Gu, X.; Guan, M.; Jiang, C.; Song, Q.; Li, X.; Sun, N.; Chen, J.; Qiu, J. Assessment of Thiosemicarbazone-Containing Compounds as Potential Antileukemia Agents against P-gp Overexpressing Drug Resistant K562/A02 Cells. *Chem. Biodiversity.* **2021**, *18*, e2000775.

[140] Secci, D.; Carradori, S.; Petzer, A.; Guglielmi, P.; D'Ascenzio, M.; Chimenti, P.; Bagetta, D.; Alcaro, S.; Zengin, G.; Petzer, J. P.; Ortuso, F. 4-(3-Nitrophenyl)thiazol-2-ylhydrazone derivatives as antioxidants and selective HmaoB inhibitors: synthesis, biological activity and computational analysis. *J. Enzym. Inhib. Med. Chem.* **2019**, *34*, 597-612.



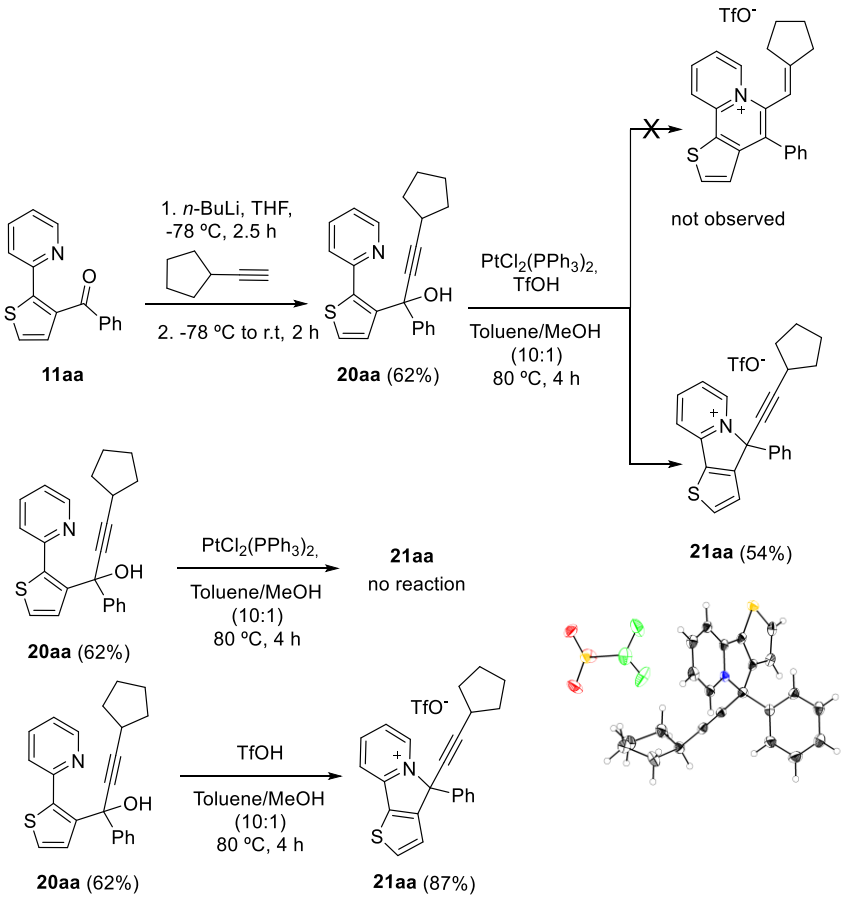
Scheme 2.45. Synthesis of thiosemicarbazones **18** and 4-(3-nitrophenyl)thiazol-2-ylhydrazones **19.**

To expand the synthetic utility of the methodology, we decided to incorporate the directing group in the final coupled products. For this purpose, we selected a recently described Pt(II)-catalyzed intramolecular C−N bond formation between the pyridine nitrogen and metal-activated alkyne to access quinolizinium-type heteroaromatics.[141]

Thus, addition of lithium cyclopentylacetylide, generated by deprotonation of cycopentylacetylene with *n*-BuLi at -78 ºC, to **11aa** led to the formation of the tertiary alcohol **20aa**. However, treatment of **20aa** with $PtCl_2(PPh_3)_2$ in the presence of triflic acid led to the 4*H*-thieno[2,3-*a*]indolizin-5-ium salt **21aa**, instead of the expected quinolizinium-type heteroaromatic. The structure of the indolizinium salt **21aa** was unambiguously confirmed

[141] Li, F.; Cho, J.; Tan, S.; Kim, S. Synthesis of Quinolizinium-Type Heteroaromatics via a Carbene Intermediate. *Org. Lett.* **2018**, *20*, 824-827.

by X-ray analysis[142] (Scheme 2.46). The role of the acid in the formation of the quinolizinium salt would be to protonate the pyridine, which enables the alkyne to coordinate the platinum catalyst.[141]

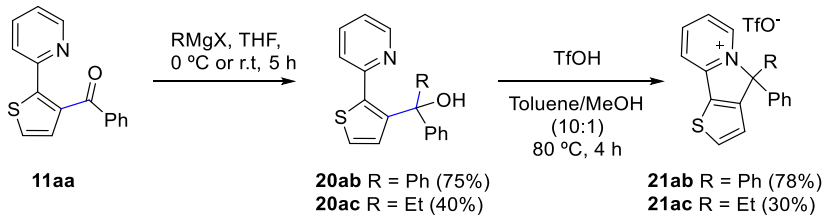


Scheme 2.46. Obtention of 4*H*-thieno[2,3-*a*]indolizin-5-ium salt **21aa**.

[142] CCDC2107402 contains the supplementary crystallographic data for **21aa**. These data can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

However, in our case the formation of **21aa** would arise from intramolecular reaction of pyridine nitrogen with a stable tertiary benzylic carbocation, generated from the alcohol in the acidic reaction media. Control experiments were carried out with **11aa**. As expected, in the absence of acid, with the platinum catalyst, the reaction does not take place at all and unreacted **20aa** was recovered after 3 h at 80 ºC. On the contrary, when the reaction was carried out just with triflic acid, in the absence of the platinum catalyst, **21aa** was isolated in excellent yield (87%). This unprecedented fused heterocyclic structure could be considered as a thiophene analogue of pyridoisoindoles or pyridoisoindolium salts found in fluorescent materials and bioactive compounds, and recently obtained by molybdenum–catalyzed cyclization of analogous ketones,[143] and also present in more complex pyridoisoindolium structures used as fluorophores.[144]

Intrigued by this reactivity, we extended this cyclization to the tertiary diarylmethanol **20ab** and alkyl aryl methanol **20ac**, obtained by simple Grignard addition to ketone **11aa** (Scheme 2.47). In both cases, the indolizinium salts could be obtained, although the low yield of **21ac** probably is related to the ease of formation of the intermediate cations. In any case, the synthesis of thienoindoliziniums **21** showcases a route to incorporate the directing group into the final product.



Scheme 2.47. Obtention of 4*H*-thieno[2,3-*a*]indolizin-5-ium salts **21ab,ac**.

[143] Asako, S.; Kobayashi, T.; Ishihara, S.; Takai, K. Molybdenum-Catalyzed Deoxygenative Cyclization of Carbonyl Compounds for the Synthesis of Pyrido[2,1-a]isoindoles. *Asian J. Org. Chem.* **2021**, *10*, 753-756.

[144] Shaikh, A. C.; Varma, M. E.; Mule, R. D.; Banerjee, S.; Kulkarni, P. P.; Patil, N. T. Ionic Pyridinium–Oxazole Dyads: Design, Synthesis, and Application in Mitochondrial Imaging. *J. Org. Chem.* **2019**, *84*, 1766-1777.

These indolizinium salts exhibit fluorescent properties.[145] Figure 2.6 depicts the UV–visible absorption and the fluorescence spectra of **21aa** and **21ab** in acetonitrile 1.15mM. Both salts **21aa,ab** showed similar absorption spectra (λem = 308-313 nm). The emission wavelengths are in the indigo region (λem = 424-427 nm) with high Stoke's shift values (>110) (Table 2.13), which could be interesting for potential biological applications[146] of these ionic fluorophores The small differences on the absorption/emission wavelengths of both compounds reflect that there is no much influence of the nature of the substituent at the quaternary center C-4 of the 4*H*-thieno[2,3-*a*]indolizin-5-ium moiety, as they are non-conjugated with the heterocyclic nucleus (see X-Ray structure of **21aa** in Scheme 2.46). This is one of the few examples of ionic fluorophores with a quaternary pyridinium core.[144]

Table 2.13. Absorption and Emission maxima of ionic fluorophores **21aa** and **21ab**.

Entry	Comp.	λabs[a)] (nm)	λem[b)] (nm)	ΔStoke[c)] (nm)
1	**21aa**	308	427	119
2	**21ab**	313	424	111

[a)] The maximum absorption wavelength in acetonitrile (1.15 mM). [b)] Excited at the maximum absorption wavelength in acetonitrile (1.15 mM). c) Stoke shift = λem _ λabs..

[145] Fluorescence studies were carried out by Dr. M. G. Lete at CICbioGune, Derio, Bizkaia.

[146] a) Lavis, L. D.; Raines, R. T. Bright Ideas for Chemical Biology. *ACS Chem. Biol*. **2008**, 3, 142-155; b) Lavis, L. D.; Raines, R. T. Bright Building Blocks for Chemical Biology. *ACS Chem. Biol*. **2014**, 9, 855-866; c) Gao, Z.; Hao, Y.; Zheng, M.; Chen, Y. A fluorescent dye with large Stokes shift and high stability: synthesis and application to live cell imaging**.** *RSC Adv*. **2017**, *7*, 7604-7609.

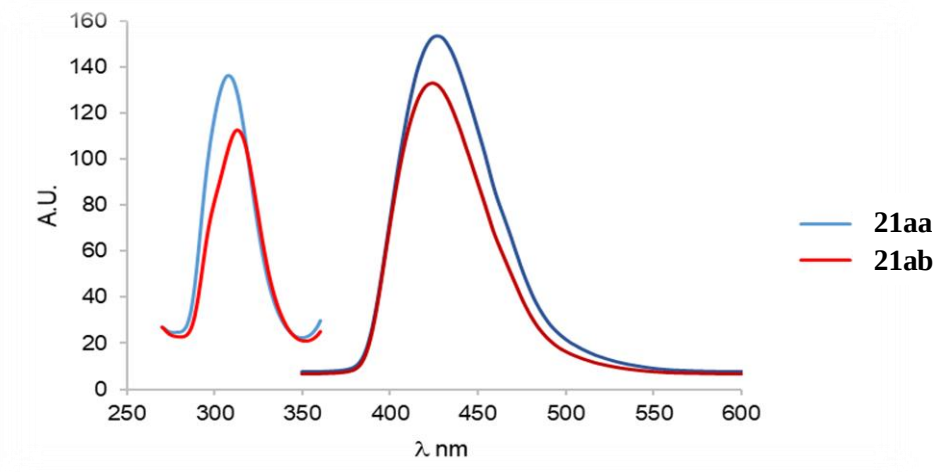


Figure 2.6. Excitation and emission spectra of indolizinium salts **21aa,ab** at 1.15 mM in acetonitrile.

To sum up, we have developed an efficient microwave-assisted Palladium(II)-catalyzed C-3 acylation of thiophenes with aldehydes. The reaction can be applied to aromatic, heteroaromatic, and also aliphatic aldehydes. The use of MW allows the obtention of ketones **11a** and **11b** in higher yields at 80 ºC and in short reaction times (15 to 30 min), avoiding formation of decomposition products associated with longer reaction times required under standard thermal conditions. Further transformations of these ketones illustrate the potential of the method, including intramolecular reactions to embed the directing-group in the core-structure of the new molecule. The described methodology provides a useful extension to existing C-H bond functionalization strategies and should find broad utility in synthetic applications for the synthesis of complex target molecules.

III

Cobalt(III)-catalyzed C-H acylation and aminoarbonylation of heteroaromatics

3.1. INTRODUCTION

3.1.1. Cobalt(III)-catalyzed nucleophilic addition to C=X bond

3.1.2. Cobalt(III)-catalyzed acylation and related reactions

3.2. OBJECTIVES

3.3. RESULTS AND DISCUSSION

3.3.1. C-H acylation of pyrroles catalyzed by Co(III)

3.3.2. Cobalt(III)-catalyzed C-H aminocarnonylaions of thiophenes

3.1. INTRODUCTION

As has been exemplified in previous chapter, transition-metal C-H functionalization is a powerful tool in organic synthesis, and therefore extensive research attention and great efforts have been realized in this field.[1] In recent years, major breakthroughs in this area have been accomplished using complexes of noble transition-metals such as Rh, Pd, Ru, Pt and Ir, as catalysts. Nonetheless, due to their toxicity, high cost and low earth abundance, research efforts have been recently focused on the use of cheaper, non-toxic and more abundant first-row transition metals, such as Fe, Ni, Co or Mn, to perform C-H functionalization with reactions with comparable catalytic efficiencies.[2] In particular, cobalt[3] has emerged as one of the most promising 3d metals and therefore the development of new methodologies for C-H functionalization has increased considerably in the last years.[4]

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[1] a) Miura, M.; Satoh, T.; Hirano, K. Development of Direct Aromatic Coupling Reactions by Transition-Metal Catalysis. *Bull. Chem. Soc. Jpn.* **2014**. *87*, 751-764; b) Wencel-Delord, J.; Glorius, F. C–H bond activation enables the rapid construction and late-stage diversification of functional molecules. *Nat. Chem.* **2013**, *5*, 369-375; c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C-H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed*. **2012**, *51*, 8960-9009; *Angew. Chem.* **2012**, *124*, 9092-9142; d) Schlummer, B.; Scholz, U. Palladium-Catalyzed C–N and C–O Coupling–A Practical Guide from an Industrial Vantage Point. *Adv. Synth. Catal*. **2004**, *346*, 1599-1626.

[2] a) Su, B.; Cao, Z-C.; Shi, Z-J. Exploration of Earth-Abundant Transition Metals (Fe, Co, and Ni) as Catalysts in Unreactive Chemical Bond Activations. *Acc. Chem. Res*. **2015**, *48*, 886-896; b) Shang, R.; Ilies. L.; Nakamura, E. Iron-Catalyzed C−H Bond Activation. *Chem. Rev.* **2017**, *117*, 9086-9139; c) Sun, X.; Li, J.; Huang. X.; Sun. C. Recent Advances in Iron-Catalyzed C-H Bond Activation Reactions. *Curr. Inorg. Chem*. **2012**, *2*, 64-85; d) Campbell, M. W.; Yuan, M.; Polites, V. C.; Molander, G. A. Photochemical C–H Activation Enables Nickel-Catalyzed Olefin Dicarbofunctionalization *J. Am. Chem. Soc*. **2021**, *143*, 3901-3910; e) Liang, L-C.; Chien, P-S.; Huang, Y-L. Intermolecular Arene C-H Activation by Nickel(II). *J. Am. Chem. Soc.* **2006**, *128*, 15562-15563; f) Khake, S. M.; Chatani, N. Nickel-Catalyzed C-H FunctionalizationUsing A Non-directed Strategy. *Chem.* **2020**, *6*, 1056-1081; g) Aneeja, T.; Neetha, M.; Afsinaa, C. M A.; Anilkumar, G. Recent advances and perspectives in manganese catalyzed C–H activation. *Catal. Sci. Technol*. **2021**, *11*, 444-458; h) Cano. R.; Mackeyab. K.; McGlacken. G. P. Recent advances in manganese-catalysed C–H activation: scope and mechanism. *Catal. Sci. Technol*. **2018**, *8*, 1251-1266.

[3] a) Hapke, M.; Hilt. G. Cobalt Catalysis in Organic Synthesis: Methods and Reactions, Wiley-VCH, Weinheim, 2020; b) Yoshino, T.; Matsunaga, S. Chapter Four - High-Valent Cobalt-Catalyzed C-H Bond Functionalization**.** *Adv. Organomet. Chem.* **2017**, *68*, 197.

[4] Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann. L. 3d Transition Metals for C−H Activation. *Chem. Rev.* **2019**, *119*, 2192-2452.

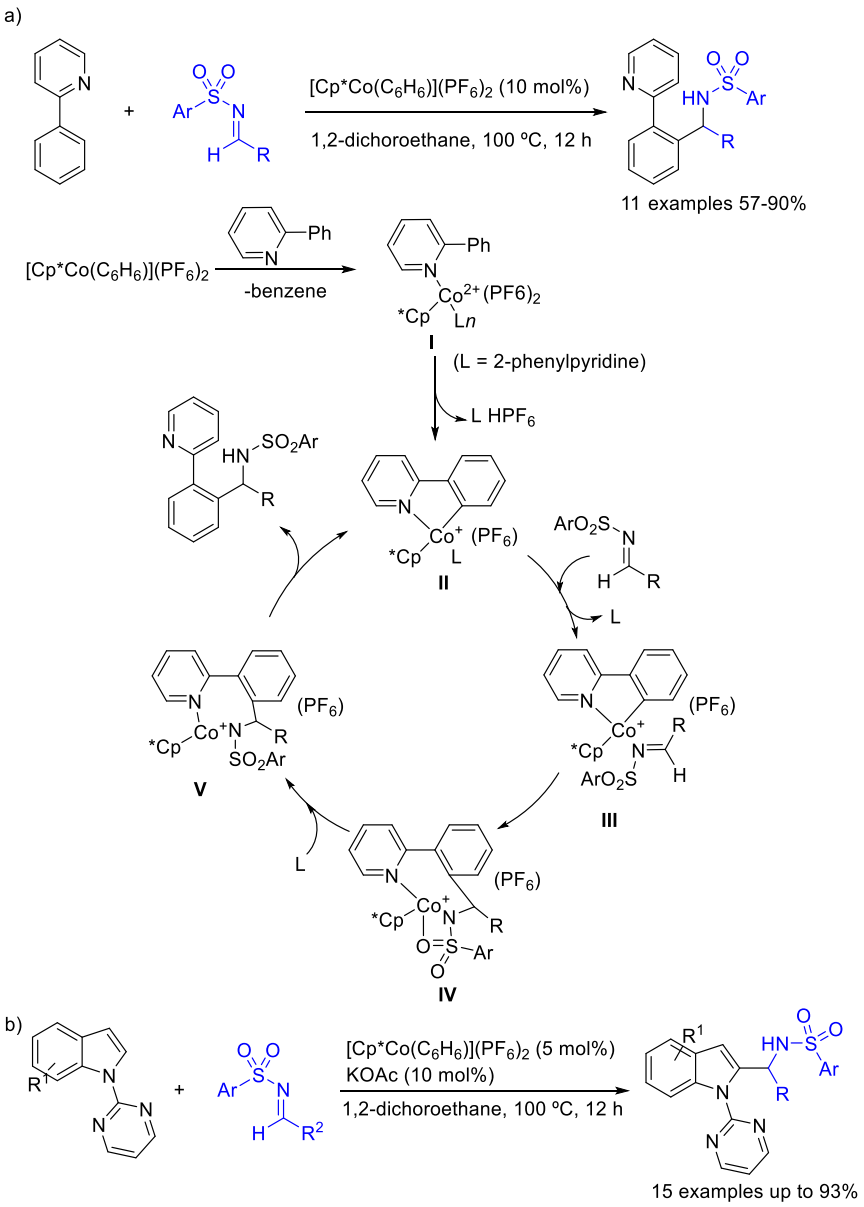
3.1.1. Cobalt(III)-catalyzed nucleophilic addition to C=X bonds

The reduced electronegativity of Cobalt (1.88 in Pauling scale), as compared to Rhodium (2.28) or Palladium (2.20), results in more nucleophilic organometallic Cobalt complexes, allowing new reactivities.

In this context, cobalt catalysts bearing pentamethylcyclopentadienyl ligands (Cp*) stand out in this field. Matsunaga and Kanai reported in 2013 their work about C-H activation reactions catalyzed by air-stable high-valent Cp*Co(III) catalysts, where they demonstrated the utility and versatility of the nucleophilic Co(III) organometallic species generated *via* C-H activation, in different types of C-H functionalizations. After an screening of some Cobalt(III) complexes, they demonstrated that $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ was the most balanced in terms of reactivity and stability, for the nucleophilic addition of phenylpyridine to sulphenyl imines (Scheme 3.1a).[5] The proposed mechanism for this reaction is based on Rh^{III} catalysis[6] and would start with the dissociation of benzene ligand of the Co(III) complex upon heating, followed by coordination with the nitrogen of phenylpyridine to afford intermediate **I**. Then, C-H activation occurs through electrophilic aromatic substitution or CMD process, where pyridine works as *orto* directing group, to form cyclometalated intermediate **II**. After ligand/imine exchange to lead intermediate **III** and the insertion of electrophile to give intermediate **IV**, proto-demetalation from **V** with another molecule of 2-phenylpyridine would induce the dissociation of the products and regenerate the active intermediate **II**.

[5] Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. A Cationic High-Valent Cp^*Co^{III} Complex for the Catalytic Generation of Nucleophilic Organometallic Species: Directed CH Bond Activation. *Angew. Chem. Int. Ed.* **2013**, *52*, 2207-2211.

[6] a)Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. Mechanism of the Rhodium(III)-Catalyzed Arylation of Imines via C–H Bond Functionalization: Inhibition by Substrate. *J. Am. Chem. Soc*. **2012**, *134*, 1482-1485; b) Li, Y.; Zhang, X.-S.; Li, H.; Wang, W.-H.; Chen. K.; Li, B.-J.; Shi, Z.-J. Mechanistic understanding of Rh-catalyzed *N*-sulfonylaldimine insertion into aryl C–H bonds**.** *Chem. Sci.* **2012**, *3*, 1634-1639.



Scheme 3.1. Co(III)-catalyzed addition of arenes and indoles to imines.

The procedure could be extended to the unfavored C-2 addition of indoles to imines using $[Cp^*Co(III)(C_6H_6)](PF_6)_2$ as catalyst, pyrimidine as directing group and KOAc as additive, leading to the corresponding products in high yield (Scheme 3.1b).[7]

Therefore, this procedure would be an environmentally friendly alternative to the classical nucleophilic addition of organometallic reagents to polar electrophiles, which require the use of stoichiometric amounts of strong bases/or reducing metals, such as Mg or Li.[8] As related Rh(III)-catalyzed addition reactions of arene C-H bonds to imines or aldehydes, this Co(III)-catalyzed reactions have the advantage of having higher functional group tolerance.

Aldehydes have also been used as electrophiles in Cobalt(III) catalyzed addition reactions. In 2015, Ellman and Hummel studied the synthesis of indazoles and furans through Cobalt(III)-catalyzed C-H addition/cyclization process (Scheme 3.2), where the use of new catalyst such as $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$ found to be the best one, and the directing groups (arylazo and oxime) could be incorporated to final complex structures indazoles and furans after a cyclization.[9] After mechanistic studies, they concluded that the reversible mechanism of the reaction would start with the heating-provoked loss of benzene from $[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$, leading to the active catalyst **VI** which would reversibly coordinate with azobenzene to provide cobaltacycle **VII**. After reversible coordination with aldehyde, migratory insertion would lead intermediate **IX**. Finally, a protonation of **IX** regenerate the active catalyst and release corresponding alcohol, which after a protonation of the alcohol group *via* intramolecular nucleophilic substitution would lead to intermediate **X**. The corresponding indazole would be obtained after a rearomatization of **X**.

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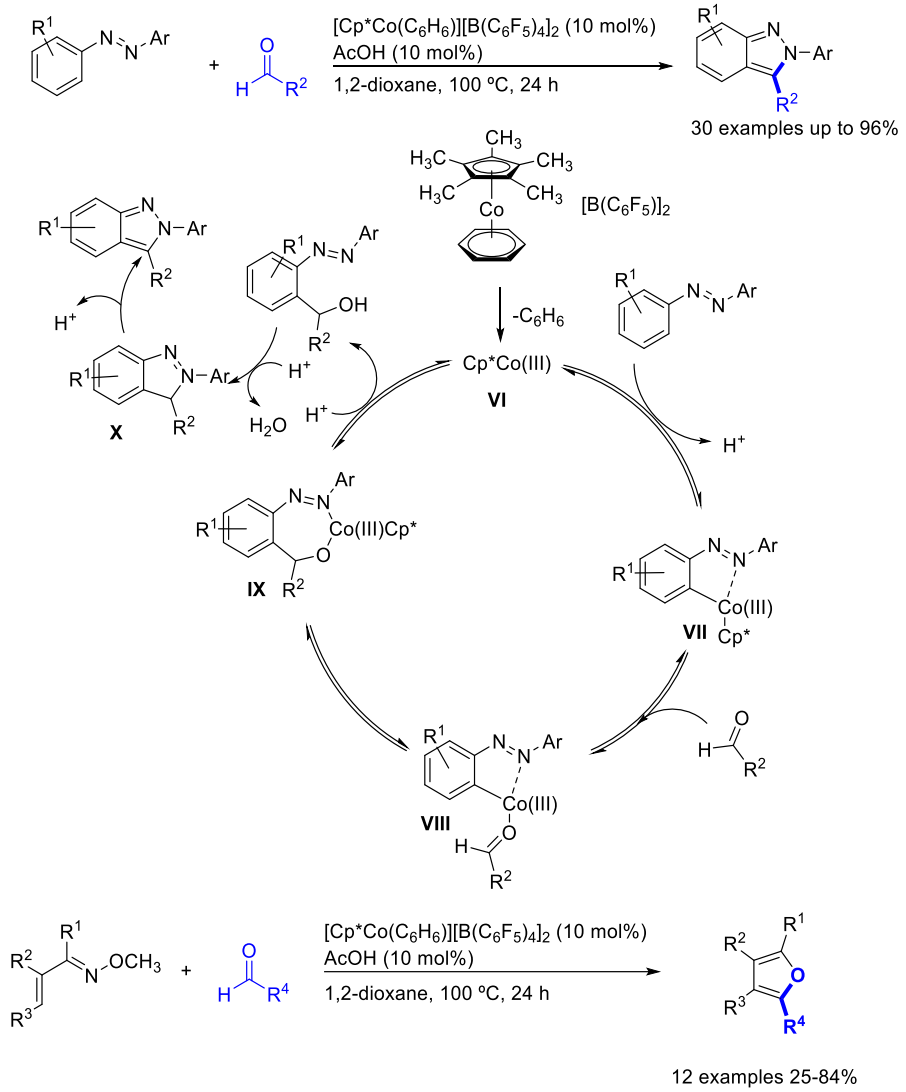
[7] Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. Cp*CoIII-Catalyzed C2-Selective Addition of Indoles to Imines. *Chem. Eur. J.* **2013**, *19*, 9142-9146.

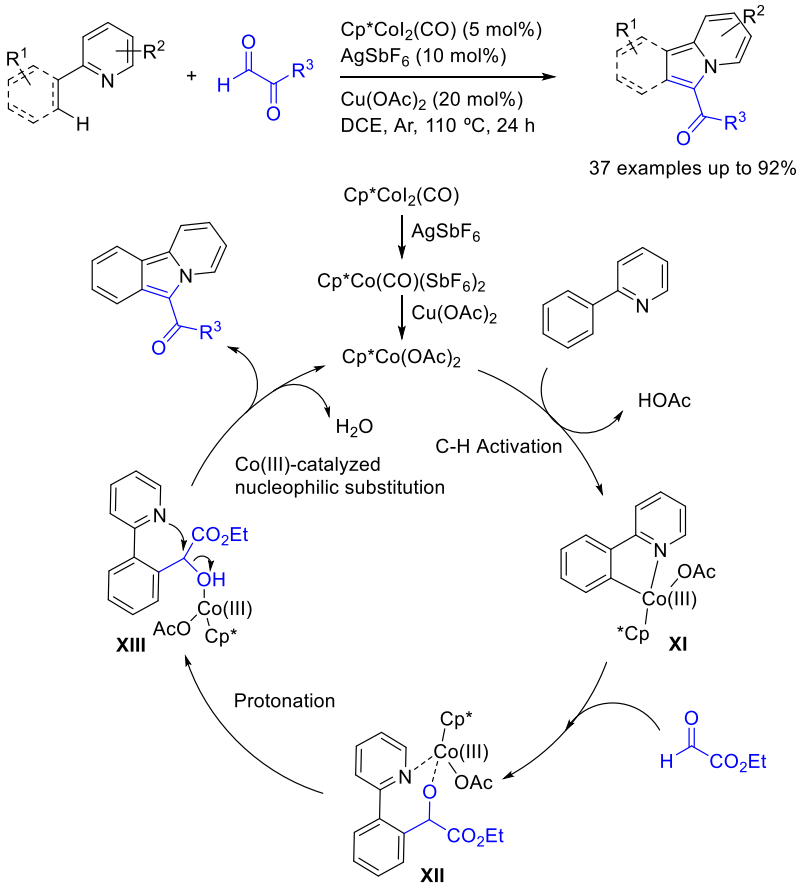
[8] a) Cheng, L.; Liu, L.; Sui, Y.; Wang, D.; Chen, Y-J. Highly diastereoselective reactions of 2-lithiated indoles with chiral *N-tert*-butanesulfinyl aldimines for the synthesis of chiral (2-indolyl) methanamine derivatives**.** *Tetrahedron: Asymmetry* **2007**, *18*, 1833-1843; b) Martínez-Estíbalez, U.; Gómez-San Juán, A.; Calvo, O. G.; Aranzamendi, E.; Sotomayor, N.; Lete, E. Strategies based on aryllithium and *N*-acyliminiun ion cyclizations for the stereocontrolled synthesis of alkaloids and related systems. *Eur. J. Org. Chem.* **2011**, 3610-3633; c) Arrasate, S.; Lete, E. Sotomayor, N. Synthesis of enantiomerically enriched β-aminoalcohol derivatives *via* asymmetric lithiation of *O*-benzyl carbamates-imine additionusing (-)-sparteine complexes. *Tetrahedron: Asymmetry*, **2002**, *13*, 311-316; d) Arrasate, S.; Lete, E.; Sotomayor, N. Synthesis of enantiomerically enriched benzylamines by chiral ligand mediated addition of organolithium reagents to imines *Tetrahedron: Asymmetry* **2001**, *12*, 2077-2082.

[9] Hummel, J. R.; Ellman, J. A. Cobalt(III)-Catalyzed Synthesis of Indazoles and Furans by C−H Bond Functionalization/Addition/Cyclization Cascades. *J. Am. Chem. Soc.* **2015**, 137, 490-498.



Scheme 3.2. Synthesis of indazoles and furans through C-H addition/cyclization process.

Zeng and co-workers followed a similar strategy to build a variety of indolizines.[10] They reacted 2-arylpyridines with different oxoacetates, in presence of Cp*CoI_2(CO) as catalyst, $AgSbF_6$ as silver salt and $Cu(OAc)_2$ as additive (Scheme 3.3). In this case, the pyridine ring acts as directing group for the C-H activation, but it is also incorporated in the final structure.



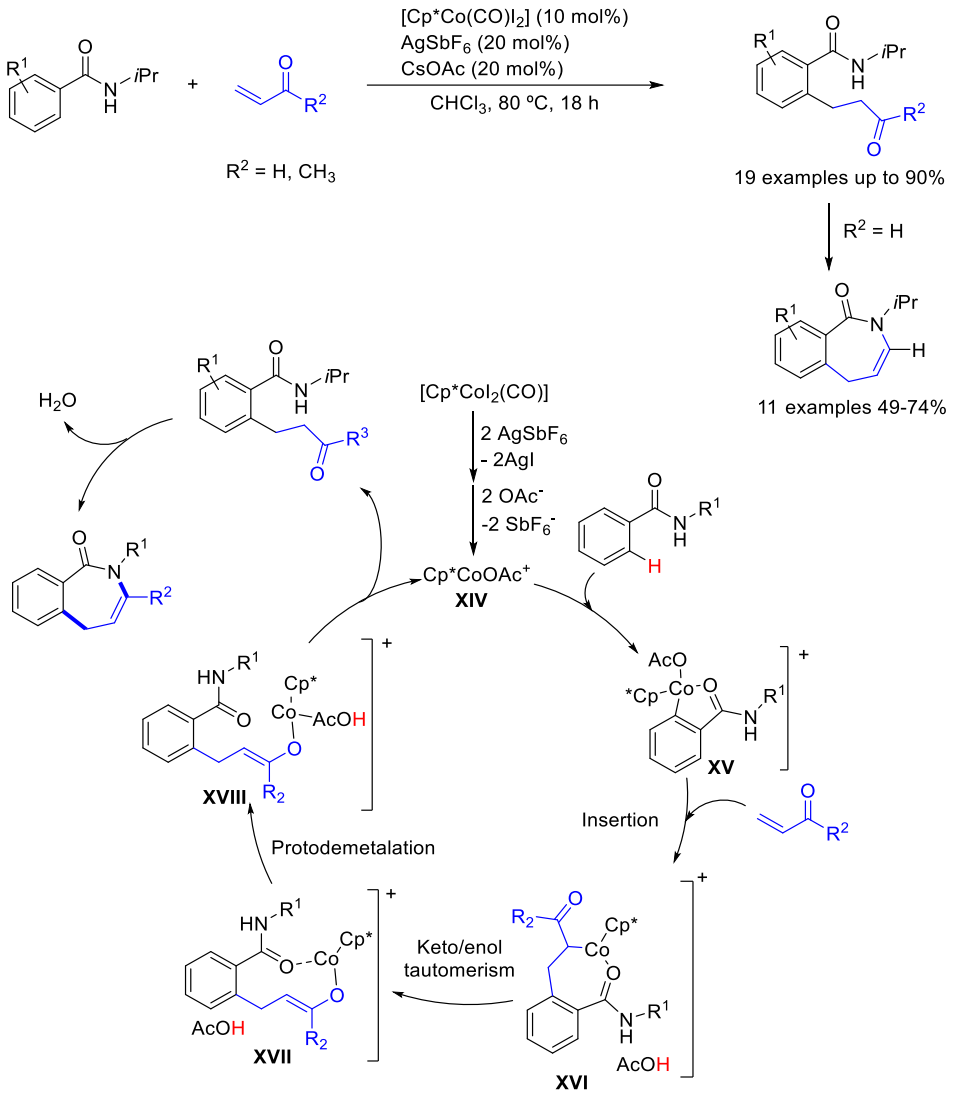
Scheme 3.3. Synthesis of indolizines catalyzed by Co(III) and mechanism of the reaction.

[10] Chen, X.; Hu, X.; Deng, Y.; Jiang, H.; Zeng, W. A [4 + 1] Cyclative Capture Access to Indolizines via Cobalt(III)-Catalyzed Csp^2 −H Bond Functionalization. *Org. Lett.* **2016**, *18*, 4742-4745.

The reaction could be applied to a large series of 2-arylpyridines. However, only α-oxoaldehydes (as ethyl 2-oxoacetae) could be used. The reaction failed with simple aldehydes (PhCHO, MeCHO). Unlike the example of Ellman and Hummel (Scheme 3.2), Co(III) species not only catalyzed the nucleophilic addition of Csp^2-H to oxoacetates, but also played a role in the cyclization as it activates the resulting hydroxymethylene group, promoting the nucleophilic attack of the pyridyl nitrogen (Scheme 3.3). The mechanistic studies carried out suggested that the mechanism would start with the activation of the catalyst by additives $AgSbF_6/Cu(OAc)_2$, forming the catalytically active species $Cp^*Co(OAc)_2$, which would coordinate with 2-arylpyridine, affording corresponding cobaltacycle **XI**. Then, the insertion of oxoacetate would occur to form intermediate **XII**, which undergoes a protonation leading corresponding alcohol **XIII**. Finally, Co(III)-catalyzed nucleophilic addition of the pyridine nitrogen to activated hydroxymethylene group would occur to afford the resulting indolizine.

Besides the 1,2-addition to aldehydes, when α,β-unsaturated aldehydes or ketones are used, the conjugated addition 1,4 takes place instead, as exemplified in the Co(III) catalyzed C-H functionalization of benzamides with α,β-unsaturated carbonyl compounds to obtain the corresponding aliphatic ketones or azepinones as depicted in Scheme 3.4.[11] A monosubstituted amide is used as directing group in this case. They observed that, when alkyl vinyl ketones were used as coupling partners and the substituent of the nitrogen atom of the amide was isopropyl, generally, the corresponding alkylated product was obtained. Nonetheless, when alkyl vinyl ketones were replaced by acrolein, the reaction leaded to the corresponding azepinones. Based on their DFT studies of the reaction, they proposed the mechanism would start with the activation of the catalyst, followed by the C-H activation event leading to the formation of Co(III)-O chelated species **XV**. Then, the addition of α,β-unsaturated aldehyde or ketone would take place to form intermediate **XVI**, which after a key keto/enol tautomerism and proto-demetallation would lead to the corresponding aliphatic aldehyde or ketones. Finally, azepinones would form after a Lewis acid catalyzed dehydrative ring closure.

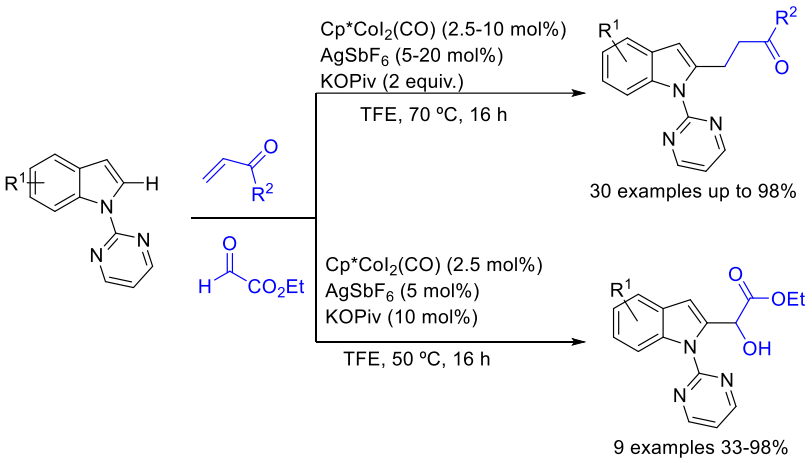
[11] Chirila, P. G.; Adams, J.; Dirjal, A.; Hamilton, A.; Whiteoak, C. J. Cp*Co(III)-Catalyzed Coupling of Benzamides with α,β-Unsaturated Carbonyl Compounds: Preparation of Aliphatic Ketones and Azepinones. *Chem. Eur. J.* **2018**, 24, 3584-3589.



Scheme 3.4. Synthesis of aliphatic ketones and azepinones.

This alkylation reactions can also be applied to heteroaromatic systems. For instance, Li and co-workers described the conjugate addition of indoles to α,β-unsaturated aldehydes and

ketones (Scheme 3.5),[12] using pyrimidine as C-2 selective directing group, in presence of $Cp^*CoI_2(CO)$ as catalyst, $AgSbF_6$ as additive and KOPiv as base. When glycoxalates were used, 1,2-addition could be achieved. The base was crucial for regioselectivity as in absence of it, the reaction afforded to C-3 substitued products.

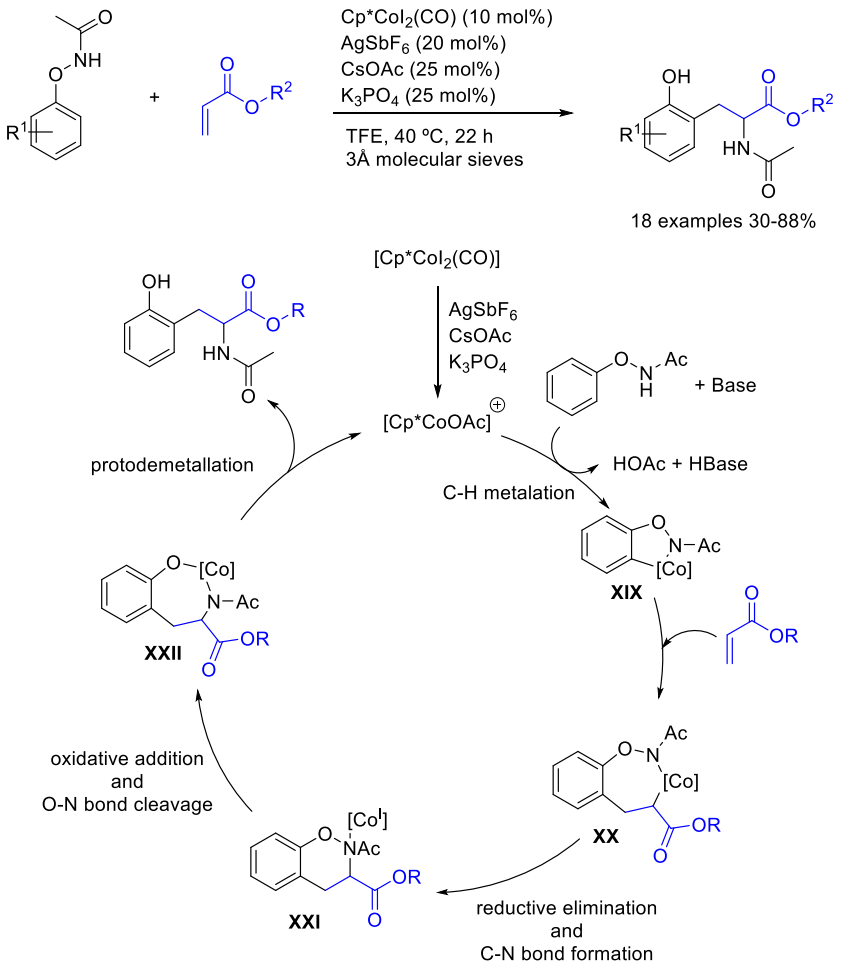


Scheme 3.5. Co(III)-catalyzed hydroarylation of α,β-unsaturated aldehydes/ ketones and oxalates.

Glorius and co-workers used a related reactivity for the carboamination of acrylates. In this case, an aryloxyacetamide is used as a directing group, which also participates in the amination reaction. Thus, aminoacids are obtained *via* Co(III)-catalyzed reaction of phenoxyacetamides and acrylates, as shown on Scheme 3.6.[13] Mechanistic studies of the reaction concluded that the catalytic cycle would start, as in the examples before, with the activation of the catalyst promoted by $AgSbF_6$, CsOAc and K_3PO_4. Then, C-H activation step occurs, by the assistance of the amide, leading to cobaltacycle **XIX**, followed by the insertion

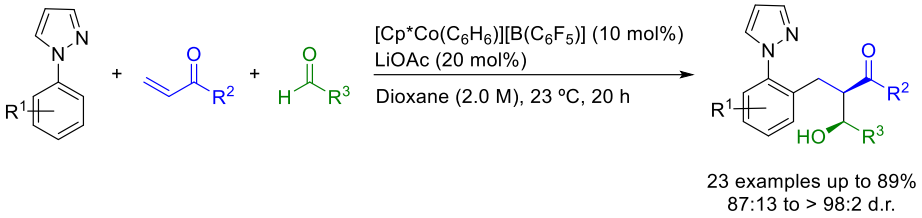
[12] Li, J.; Zhang, Z.; Ma, W.; Tang, M.; Wang, D.; Zou, L.-H. Mild Cobalt(III)-Catalyzed C–H Hydroarylation of Conjugated C=C/C=O Bonds. *Adv. Synth. Catal.* **2017**, *359*, 1717-1724.
[13] Lerchen, A.; Knecht, T.; Daniliuc, C. G.; Glorius, F. Unnatural Amino Acid Synthesis Enabled by the Regioselective Cobalt(III)-Catalyzed Intermolecular Carboamination of Alkenes. *Angew. Chem. Int. Ed.* **2016**, *55*, 15166-15170.

of the olefin to form 7-membered intermediate **XX**. In this case, the C-N bond formation occurs *via* a reductive elimination leading to a Co(I) intermediate **XXI**. Afterwards, the O-N bond undergoes an oxidative addition to the Co(I) species to lead intermediate **XXII** (Co(III)). Finally, the desired aminoacid derivative and the catalytically active species are formed by proto-demetalation of intermediate **XXII**.



Scheme 3.6. Co(III)-catalyzed conjugate addition to α,β-unsaturated esters and catalytic cycle.

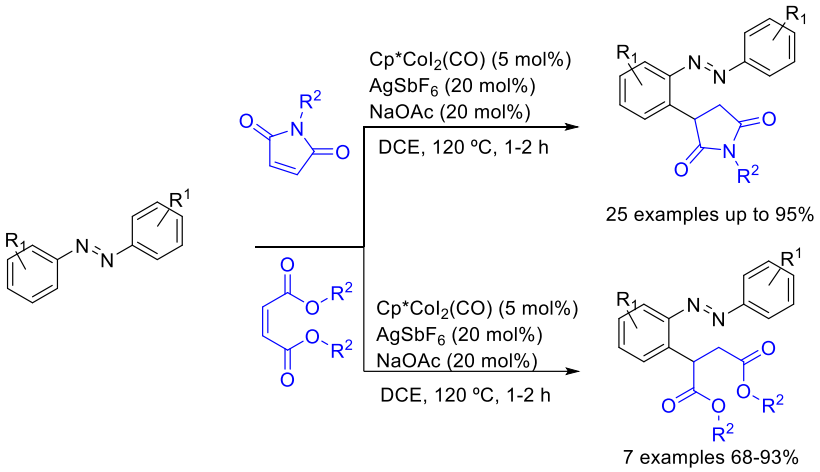
The first example of three-component C-H functonalization cascade was carried out by Ellman and coworkers (Scheme 3.7). In this case, the cobalt enolate formed after the olefin insertion step could be trapped with aldehydes.[14] Their methodology showed high tolerance with a wide range of aldehydes and high diastereoselectivity.



Scheme 3.7. Co(III)-catalyzed three-component transformation.

Maleimides have also been employed in Co(III)-catalyzed conjugate addition of arenes. In this context, the reaction of azobenzenes with maleimides provided the corresponding 1,4-adducts in good yields (Scheme 3.8).[15] This methodology was also applied for maleate derivatives.

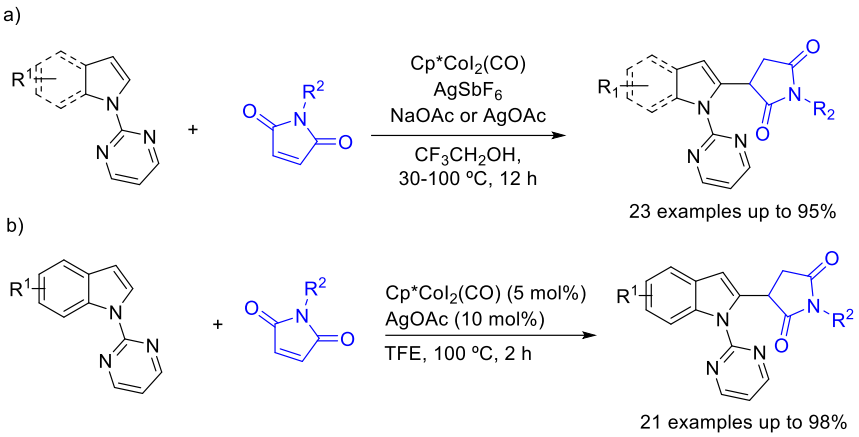
[14] Boerth, J. A.; Hummel, J. R.; Ellman, J. A. Highly Stereoselective Cobalt(III)-Catalyzed Three-Component C−H Bond Addition Cascade. *Angew. Chem. Int. Ed.* **2016**, *55*, 12650-12654.
[15] Muniraj, N.; Prabhu, K. R. Cobalt(III)-Catalyzed C−H Activation: Azo Directed Selective 1,4-Addition of Ortho C−H Bond to Maleimides. *J. Org. Chem.* **2017**, *82*, 6913-6921.



Scheme 3.8. Co(III)-catalyzed azobenzene C-H addition to maleimides and maleate derivatives.

This reactivity could also be extended to heteroarenes. As shown in Scheme 3.9a,b, indoles and pyrroles could be selectively alkylated at C-2, using a pyrimidine directing group.[16,17] The reaction was extended also to thiophenes.

[16] Zhang, Z.; Han, S.; Tang, M.; Ackermann, L.; Li, J. C–H Alkylations of (Hetero)Arenes by Maleimides and Maleate Esters through Cobalt(III) Catalysis. *Org. Lett.* **2017**, *19*, 3315-3318.
[17] Muniraj, N.; Prabhu, K. R. Co(III)-Catalyzed C–H Activation: A Site-Selective Conjugate Addition of Maleimide to Indole at the C-2 Position. *ACS Omega* **2017**, *2*, 4470-4479.

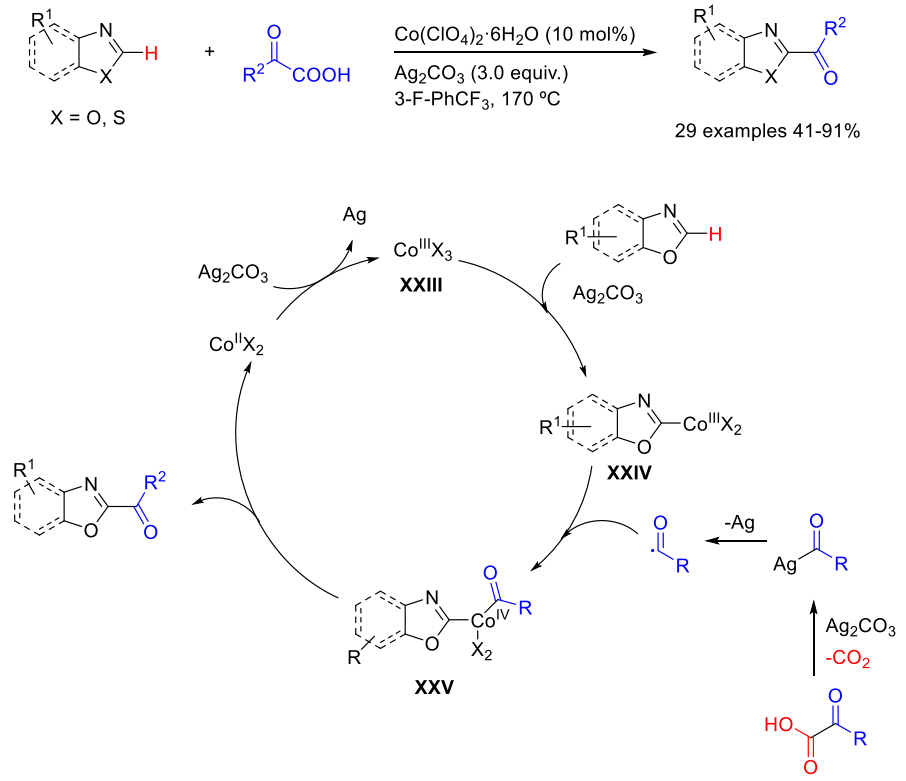


Scheme 3.9. Cobalt(III)-catalyzed conjugate addition of (hetero)arenes to maleimides.

3.1.2. Cobalt(III)-catalyzed acylation and related reaction

In connection with Chapter II, decarboxylative acylation reactions involving any radicals have also been carried out by Co(III) catalysis. In this context, as shown in Scheme 3.10, Co(III)-catalyzed acylation reactions of oxazoles and thiazoles were studied using α-oxocarboxylic acids as radical source.[18] The mechanism of this reaction is still unclear. However, the authors proposed a catalytic cycle based on their previous work that implies a Co(II)-Co(III)-Co(IV)-Co(II) cycle.[19] The precatalyst employed is a Co(II) salt, so the first step would correspond to the silver intermediated oxidation of Co(II) catalyst to a Co(III) species **XXII**. C-H activation mediated by silver salt, leads to intermediate **XXIV** would be formed. After the addition of acyl radical, which would come from the oxidation of α-oxocarboxylic acid in presence of Ag_2CO_3, afforded intermediate Co(IV) **XXV**. Finally, a reductive elimination would lead to the acylated product and Co(II) catalyst, thus completing catalytic cycle.

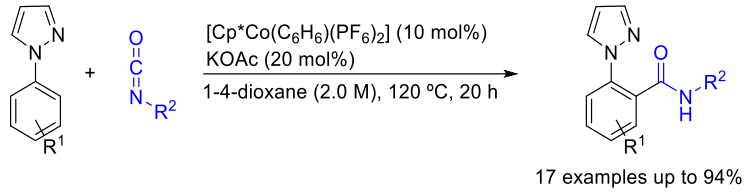
[18] Yang, K.; Chen, X.; Wang, Y.; Li, W.; Kadi, A. A.; Fun, H-K.; Sun, H.; Zhang, Y.; Li, G.; Lu, H. Cobalt-Catalyzed Decarboxylative 2-Benzoylation of Oxazoles and Thiazoles with α-Oxocarboxylic Acids. *J. Org. Chem.* **2015**, *80*, 11065-11072.
[19] Wu, X.; Yang, K.; Zhao, Y.; Sun, H.; Li, G.; Ge, H. Cobalt-catalysed site-selective intra- and intermolecular dehydrogenative amination of unactivated sp^3 carbons. *Nat. Commun.* **2015**, *6*, 6462.



Scheme 3.10. Cobalt-catalyzed acylation of oxazoles and thiazoles and proposed catalytic cycle.

Besides this acylation reactions, related aminocarbonylation reactions have also been described by Cobalt(III)-catalyzed C-H bond additions to isocyanates to obtain the corresponding amides. In this context, Ellman and Hummel studied the Co(II) redox neutral catalyzed reaction of arenes with several isocyanates and directing groups under Cobalt(III) catalysis. The combination of $[Cp^*Co(C_6H_6)](PF_6)_2$ complex and pyrazole as directing group gave best results (Scheme 3.11).[20]

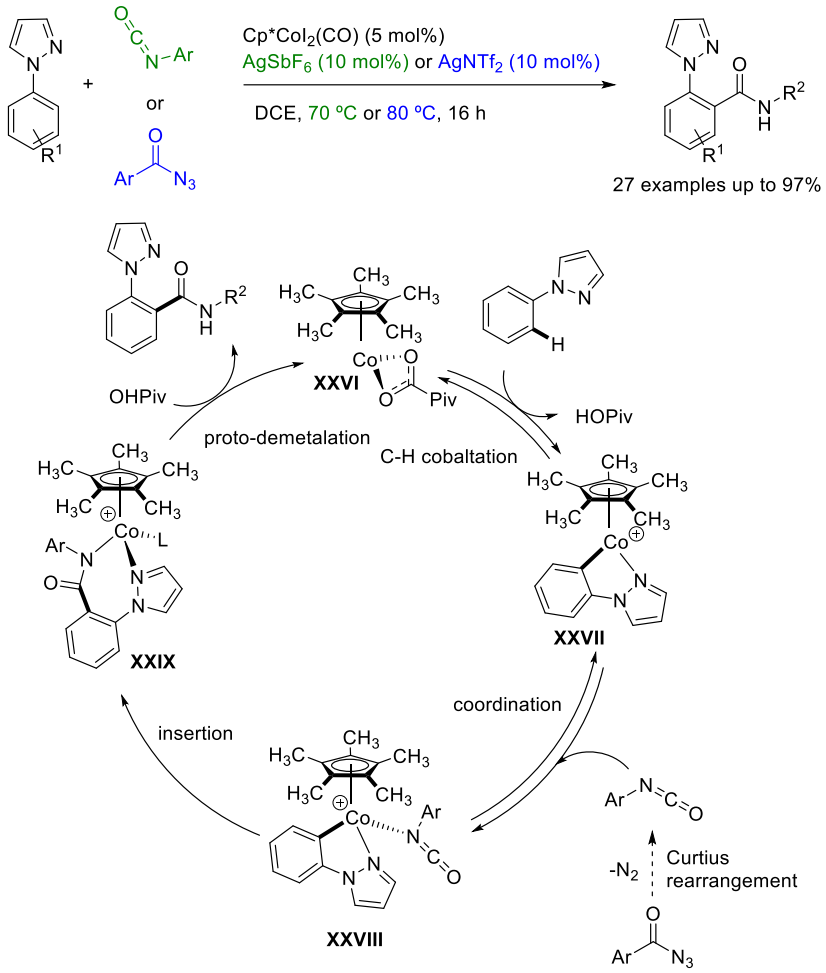
[20] Hummel, J. R.; Ellman, J. A. Cobalt(III)-Catalyzed C−H Bond Amidation with Isocyanates. *Org. Lett.* **2015**, *17*, 2400-2403.



Scheme 3.11. Co(III)-catalyzed aminocarbonylation of arenes with isocyanetes.

Simultaneously and using the same pyrazole as directing group, Ackermann and Li described a related reaction using isocyanates and also acylazides to afford the desired amides in good yields.[21] In this case, as depicted in Scheme 3.12, Cp*Co(CO)I_2 complex was used as catalyst. The proposed mechanism for this reaction would start with the reversible carboxylate assisted C-H cobaltation, generating intermediate **XXVII**, followed by the coordination between the nitrogen of the isocyanate and cobalt, leading cyclometalated complex **XXVIII**. Then, nucleophilic attack of metalated arene on the coodinated isocyanate, gives intermediate **XXIX**, which, after a protodemetalation, generates corresponding amide and the catalytically active complex **XXVI**. When an acylazide is used, the isocyanate is generated *in situ* through a Curtius rearrangement.

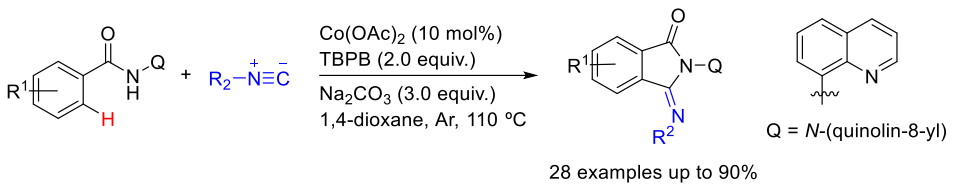
[21] Li, J.; Ackermann, L. Cobalt(III)-Catalyzed Aryland Alkenyl C-H Aminocarbonylation with Isocyanates and Acyl Azides. *Angew. Chem. Int. Ed.* **2015**, *54*, 8551-8554.



Scheme 3.12. Cobalt(III)-catalyzed carboamidation with isocyanates and azides. Proposed mechanism.

Besides isocyanates can also be used as electrophiles, as exemplified by the synthesis of iminolactames *via* Co(III)-catalysis using bidentate directing groups such as *N*-(quinolin-8-yl)amides (Scheme 3.13). In this context, Ji, Wang and co-workers, reported in 2017 their studies of Co(III)-catalyzed anulation of amides with isocyanides, in presence $Co(OAc)_2$ as

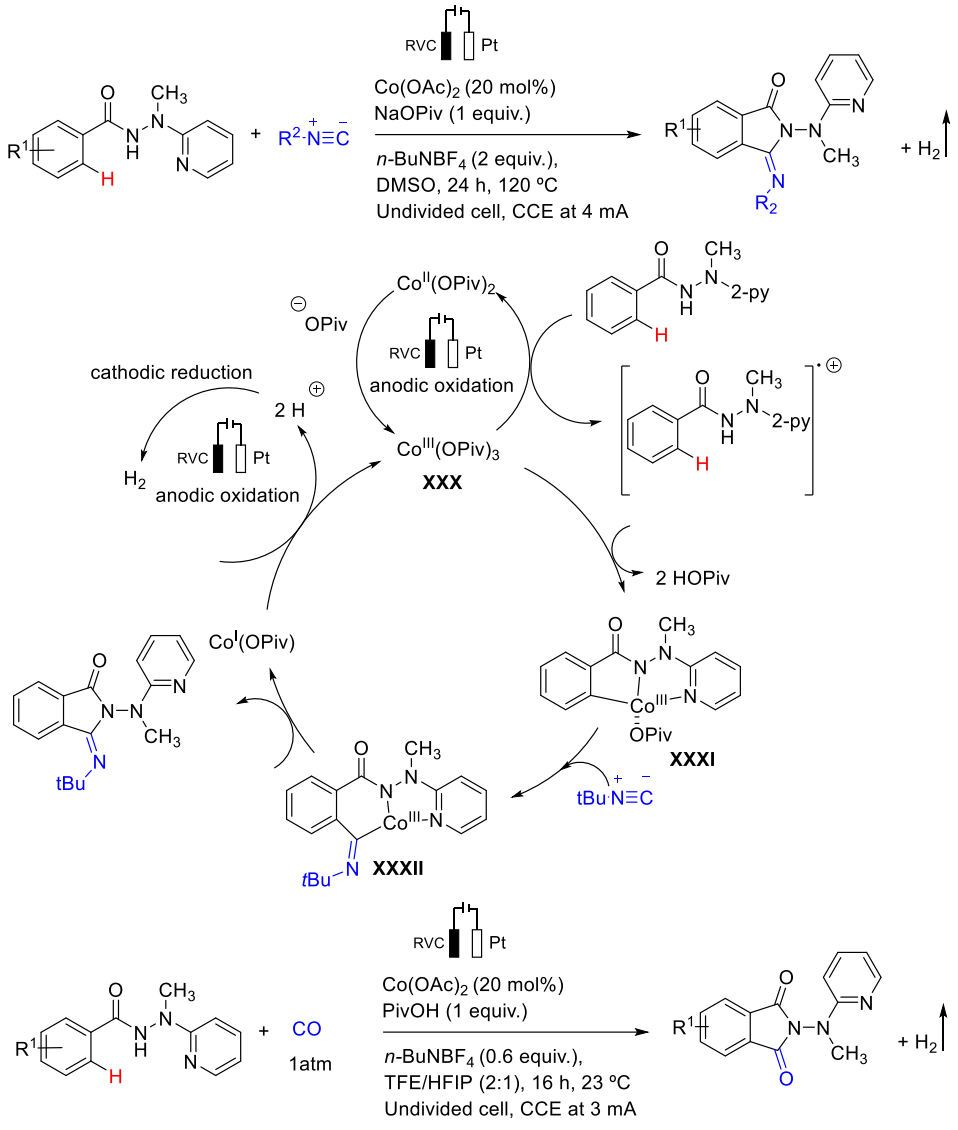
catalyst, TBPB as oxidant and Na_2CO_3 as base, affording corresponding iminolactams in good yields (Scheme 3.13).[22] In this example, the directing group is also incorporated in the final structure.



Scheme 3.13. Co(III)-catalyzed synthesis of iminolactams from isocyanides and amides.

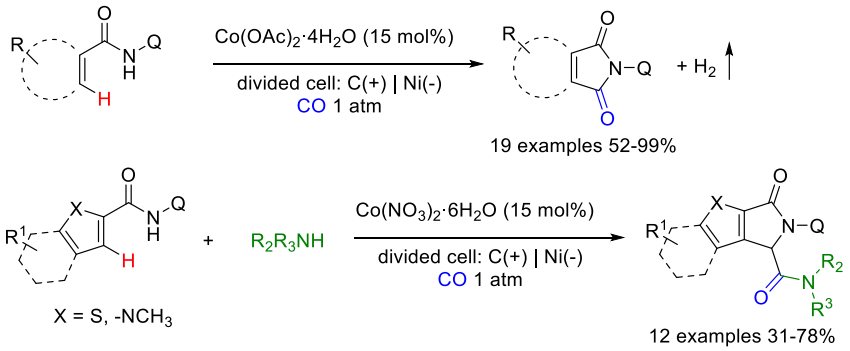
A related reactivity could be obtained by a cobaltaelectrocatalytic C-H activation. The reaction of different benzhydrazides with a variety of isonitriles, using $Co(OAc)_2$ as catalyst, nBu$_4$NBF$_4$ and NaOPiv as additives into an undivided cell with a constant current of 4 mA (Scheme 3.14a).[23] In this case, the use of electrocatalytic cell avoids the use of chemical oxidants, which otherwise are used in stoichiometric quantities, as shown in the previous examples. Similarly, carbonylation reactions could also be accomplished (Scheme 3.14b). The mechanism of this reaction would start with the anodic oxidation of the Cobalt(II) precatalyst to catalytically active Cobalt(III) species **XXX.** Then, the C-H activation would occur to give cobaltacycle **XXXI**. The insertion of the isonitrile would afford the six-membered intermediate **XXXII** which after a reductive elimination would release corresponding product and Co(I) species. Finally, the catalytically active species **XXX** would be regenerated by anodic oxidation of Co(I) species, closing the cycle.

[22] Gu, Z.-Y.; Liu, C.-G.; Wang, S.-Y.; Ji, S.-J. Cobalt-Catalyzed Annulation of Amides with Isocyanides via C(sp^2)−H Activation. *J. Org. Chem.* **2017**, *82*, 2223-2230.
[23] Sau, C. S.; Mei, R.; Struwe, J.; Ackermann, L. Cobaltaelectro-Catalyzed C−H Activation with Carbon Monoxide or Isocyanides. *ChemSusChem* **2019**, *12*, 3023-3027.



Scheme 3.14. Cobaltaelectro-catalyzed C-H/N-H activation with isocyanides and carbonylation. Proposed mechanism.

Using similar concept, Lei and co-workers focused on the study of cobalt-catalyzed electrochemical oxidative C-H/C-N carbonylation of (hetero)aromatic amides with CO and amines. They used $Co(OAc)_2$ or $Co(NO_3)_2$ and the reaction was carried out in a divided cell (Scheme 3.15).[24]

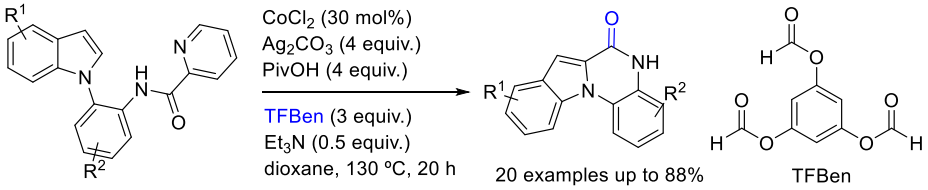


Scheme 3.15. Cobalt(III) catalyzed carbonylation of amides.

Finally, carbon monoxide could also been used for the synthesis of complex tetracycles such as free N-*H* indoloquinoxalinones *via* cobalt-catalyzed C-H carbonylation of indoles, utilizing $CoCl_2$ as catalyst, Ag_2CO_3 as oxidant and TFBen as CO source, and removable picolamide directing group (Scheme 3.16).[25]

[24] Zeng, L.; Li, H.;Tang, S., Gao, X.; Deng, Y.; Zhang, G.; Pao, C.-W.; Chen, J.-L.; Lee, J.-F.; Lei, A. Cobalt-Catalyzed Electrochemical Oxidative C−H/N−H Carbonylation with Hydrogen Evolution. *ACS Catal*. **2018**, *8*, 5448-5453.

[25] Gao, Q.; Lu, J.-M.; Yao, L.; Wang, S.; Ying, J.; Wu, X.-F. Cobalt-Catalyzed Direct C–H Carbonylative Synthesis of Free (N*H*)-Indolo[1,2-a]quinoxalin-6(5*H*)-ones. *Org. Lett.* **2021**, *23*, 178-182.



Scheme 3.16. Synthesis of indoloquinoxalinones *via* Co(III)-catalyzed carbonylation.

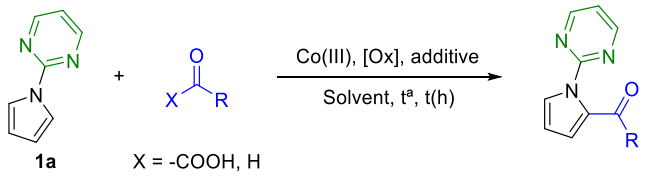
3.2.OBJECTIVES

In the previous section, it has been shown that cobalt(III)-catalyzed C-H functionalization arises as an effective alternative to replace the use of 4d noble transition-metal such as Pd, Ru or Rh, among others, which are toxic, less abundant and more expensive than cobalt.

In chapter II, we focused on palladium(II) C-H acylation of five membered heterocycles such as pyrrole and thiophene. However, to the best of our knowledge, there are no examples described for the cobalt-catalyzed C-H acylation of pyrroles or thiophenes as an alternative to the reactivity described in the previous chapter.

Therefore, the first aim of this part of the research was to study the possibility of developing a methodology for Cobalt(III)-catalyzed acylation of heteroarenes using acyl radical equivalents.

For this purpose, we selectd pyrrole **1a** as the model substrate. The reaction will be studied to select the reaction conditions (acyl radical source, cobalt catalyst, solvent, oxidant, additive), taking the cobalt(III)-catalyzed acylation of oxazoles and thiazoles described in the introduction (Scheme 3.10) as starting point and using, in this case, pyrimidine as directing group (Scheme 3.17).

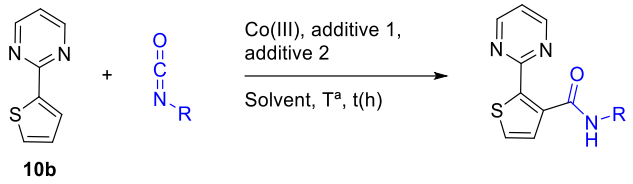


Scheme 3.17. Cobalt(III)-catalyzed acylation of pirroles.

On the other hand, as depicted in previous section, the aminocarbonylation of heteroarenes has not been studied. Thiophene 2- and 3-carboxamides are found in structures with biological activity and therefore, new synthetic pathways to obtain that kind of molecules would be interesting.

Therefore, we decided to study this reactivity using thiophene **10b** as a model compound. Thus, this part of the work will be focused on the optimization of reaction conditions

(catalyst, additives, solvent) and the extension with aryl, alkyl isocianates (Scheme 3.18), taking the reaction conditions described in Schemes 3.11 and 3.12 as starting points. The reaction will be assisted by pyrimidin as directing group in order to control the regioselectivity of the reaction.



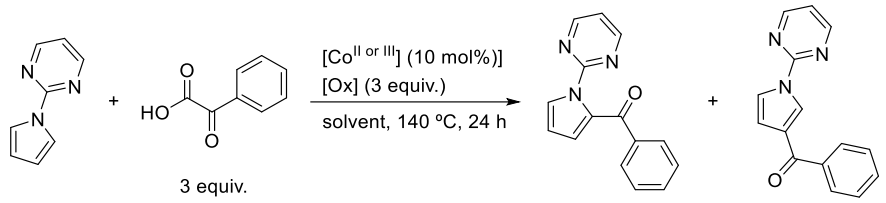
Scheme 3.18. Co(III)-catalyzed aminocarbonylation of thiophenes.

3.3. RESULTS AND DISCUSSION

3.3.1. C-H acylation of pyrroles catalyzed by Co(III)

To test the viability of the Co(III)-catalyzed radical acylation reaction, we selected pyrrole **1a** as substrate and phenylglyoxylic acid **22a** as acyl radical source. Firstly, we took the reaction conditions described in literature for oxazoles as starting point[18] but with no result (Table 3.1, entry 1). Different Cobalt(II) pre-catalysts were tested, but the reaction did not proceed (Table 3.1, entries 2-3). A change in the oxidant (Table 3.1, entry 4) or the solvent (Table 3.1, entry 5) did not give any reactivity. However, using $Cp^*CoI_2(CO)$ as Co(III) catalyst, 20% yield of **3aa** was obtained and unexpected C-3 acylated product **23aa** was observed in 6% yield (Table 3.1, entry 6). The formation of **23aa** would be derived from a non-directed C-H activation of the pyrrole nucleus. The yield of **3aa** dropped to 6% when $[Cp^*CoI_2]_2$ was utilized (Table 3.1, entry 7). Some oxidants as AgOAc, TBHP or $K_2S_2O_8$ were assayed with no result (entries 8-10), only the recovery of **1a** was observed. Where acyl radical source was changed to benzaldehyde, the yield turned down dramatically to 2% (Table 3.1, entry 11). The increase the temperature from 140 ºC to 160 ºC did not afford better results (Table 3.1, entry 12). Finally, the use of 3-Fluorobenzotrifluoride as solvent provided similar yields of **3aa**, 17% (Table 3.1, entry 12).

Table 3.1. Cobalt(III)-catalyzed acylation of **1a**. Optimization of reaction conditions.



1a **22a** **3aa** **23aa**

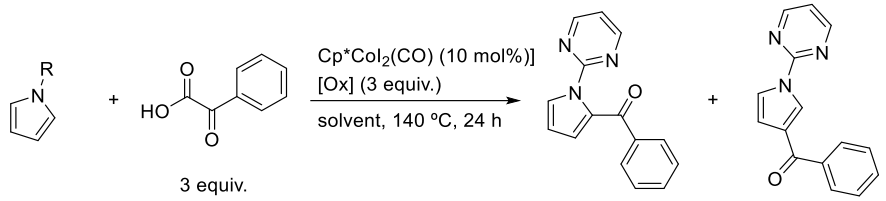
Entry	[Co]	[Ox]	Additive	Solvent[a)]	3aa [%][b)]	23aa [%]
1	$Co(ClO_4)\cdot 6H_2O$	Ag_2CO_3	-	$C_6H_5CF_3$	-[c)]	-
2	$CoCl_2$	Ag_2CO_3	-	$C_6H_5CF_3$	-[c)]	-
3	$CoBr_2$	Ag_2CO_3	-	$C_6H_5CF_3$	traces[c)]	-
4	$Co(ClO_4)\cdot 6H_2O$	TBHP[d)]	-	$C_6H_5CF_3$	traces[c)]	-
5	$Co(ClO_4)\cdot 6H_2O$	Ag_2CO_3	-	DCE	-[c)]	-
6	**$Cp^*CoI_2(CO)$**	**Ag_2CO_3**	**$AgSbF_6$** [e)]	**$C_6H_5CF_3$**	**20[c)]**	**6**
7	$[Cp^*CoI_2]_2$	Ag_2CO_3	$AgSbF_6$ [e)]	$C_6H_5CF_3$	6[c)]	-
8	$Cp^*CoI_2(CO)$	AgOAc	$AgSbF_6$ [e)]	$C_6H_5CF_3$	-[c)]	-
9	$Cp^*CoI_2(CO)$	TBHP[d)]	$AgSbF_6$ [e)]	$C_6H_5CF_3$	-[c),f)]	-
10	$Cp^*CoI_2(CO)$	$K_2S_2O_8$	$AgSbF_6$ [e)]	$C_6H_5CF_3$	-[c)]	-
11	$Cp^*CoI_2(CO)$	Ag_2CO_3	$AgSbF_6$ [e)]	$C_6H_5CF_3$	2[c),g)]	-
12	$Cp^*CoI_2(CO)$	Ag_2CO_3	$AgSbF_6$ [e)]	$C_6H_5CF_3$	16[c),h)]	4
13	$Cp^*CoI_2(CO)$	Ag_2CO_3	$AgSbF_6$ [e)]	3-F-$C_6H_4CF_3$	17[c)]	traces

[a)] The reactions were carried out in a 0.4 mmol scale using 10 mL sealed reaction tubes inserted in a heating block. The indicated temperature refers to the external temperature of the heating block. [b)] Yield (%) of isolated pure compound. [c)] Unreacted **1a** was recovered. [d)] 5.5 M solution in decane. [e)] 0.2 equiv. of $AgSbF_6$ was used as additive. [f)] Decomposition of starting material observed. [g)] Benzaldehyde **2a** was used. h) the reaction was carried out at 160 ºC.

An increase of the yield of **23aa** was observed when the equivalents of $AgSbF_6$ additive were increased from 0.2 to 0.5 (Table 3.2, entry 2). It was also checked that cobalt catalyst was necessary for the reaction, as the reaction did not take place in its absence (Table 3.2, entry 3). The use of Ag_2O gave almost no reactivity (Table 3.2, entry 4). As the pyrimidine group was not acting as a directing group, we selected different substituents on the pyrrole, but no reaction took place (Table 3.2, entries 5-6). Triisopropylsilyl TIPS group provided **23aa** in

very low yield (Table 3.2, entry 7) and the change of the oxidant to Ag_2O and solvent to toluene gave similar results (Table 3.2, entries 8-9).

Table 3.2. Cobalt(III)-catalyzed acylation of **1a**. Optimization of the reaction conditions.



1a **22a** **3aa** **23aa**

Entry	R	[Ox]	$AgSbF_6$ (equiv.)	Solvent[a)]	3aa [%][b)]	25aa [%]
1	Pyrimidine	Ag_2CO_3	0.2	$C_6H_5CF_3$	20[c)]	6
2	**Pyrimidine**	**Ag_2CO_3**	**0.5**	**$C_6H_5CF_3$**	**3[c)]**	**25**
3	Pyrimidine[d)]	Ag_2CO_3	0.5	$C_6H_5CF_3$	-[c)]	-
4	Pyrimidine	Ag_2O	0.5	$C_6H_5CF_3$	4[c)]	5
5	Methyl	Ag_2CO_3	0.5	$C_6H_5CF_3$	-[c)]	-
6	*p*-Tolylsulfonyl	Ag_2CO_3	0.5	$C_6H_5CF_3$	-[c)]	-
7	TIPS[e)]	Ag_2CO_3	0.5	$C_6H_5CF_3$	-[c)]	6
8	TIPS	Ag_2CO_3	0.5	Toluene	-[c)]	12
9	TIPS	Ag_2O	0.5	$C_6H_5CF_3$	-[c)]	9

a) The reactions were carried out in a 0.4 mmol scale using 10 mL sealed reaction tubes inserted in a heating block. The indicated temperature refers to the external temperature of the heating block. b) Yield (%) of isolated pure compound. c) Unreacted **1a** was recovered. d) No $Cp^*CoI_2(CO)$ was used. e) The reaction was carried out at 100 ºC.

Considering results obtained, we decided to quit the optimization of the reaction. A deeper study should be carried out, in terms of reaction conditions and directing groups, to try to improve the reactivity. In this case, we believe that the C-H cobaltation step is failing, or, also, the recycling of the catalyst. Further experimentation should be carried out.

3.3.2. Cobalt(III)-catalyzed C-H aminocarbonylation of thiophenes

As mentioned in objectives, the last work related with cobalt catalyzed C-H functionalization was based on C-H aminocarbonylation of thiophenes. The synthesis of *N*-arylthiophen-3-carboxamides has attracted the interest of synthetic chemists as they have found to be a potent antitumorasls (Figure 3.1A-B)[26] and DHODH inhibitors,[27] involved in diseases such as sclerosis (Figure 3.1C).

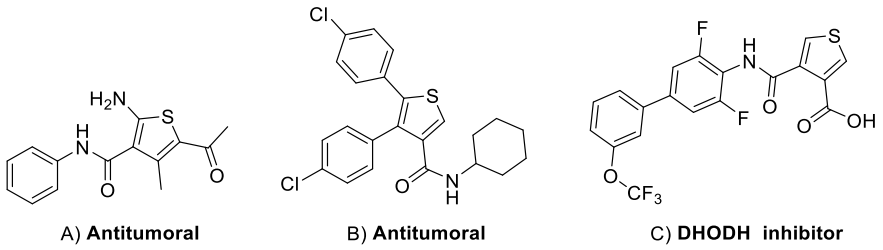
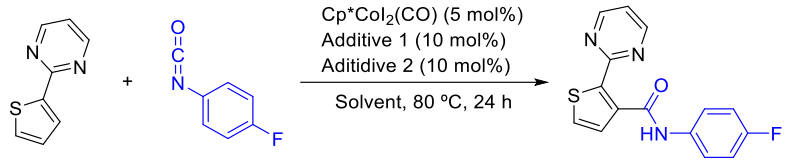


Figure 3.1. Biological activity of thiohen-3-carboxamides.

To optimize the reaction conditions, we selected thiophene **10b** and 4-Fluorophenyl isocyanate **24a** as model compounds, using Cp*CoI_2(CO) as catalyst with the reaction conditions described by Ackerman and Li as starting point (Table 3.3).[21] Under this reaction conditions (Table 3.3, entry 1.), the amide **25ba** was obtained in low yield, recovering unreacted starting material. When the temperature was increased to 80 ºC and the reaction time was extended to 24 h, the yield increased to 78% (Table 3.3, entry 2).

[26] Mahmoud, M. A. A. Design and synthesis of new thiophene derivatives together with their antitumor evaluations. *Eur. J. Chem.* **2015**, *6*, 444-450; b) Wang, W.; Zhu, X.; Hong, X.; Zheng, L.; Zhu, H.; Hu. Y. Identification of novel inhibitors of p53–MDM2 interaction facilitated by pharmacophore-based virtual screening combining molecular docking strategy. *Med. Chem. Commun.* **2013**, *4*, 411-416.
[27] Leban, J.; Kralik, M.; Mies, J.; Baumgartner. R.; Gassen, M.; Tasler, S.; Biphenyl-4-ylcarbamoyl thiophene carboxylic acids as potent DHODH inhibitors. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 267-270.

Table 3.3. Co(III)-catalyzed aminocarbonylation of **10b**. Optimization of reaction conditions.



Entry	Solvent[a)]	Additive1	Additive2	Yield[b)]
1	DCE	$AgSbF_6$	AgOAc	27[c)]
2	DCE	$AgSbF_6$	AgOAc	78[c)]
3	DCE	$AgSbF_6$	CsOAc	84[c)]
4	DCE	$AgSbF_6$	RbOAc	84[c)]
5	DCE	$AgSbF_6$	AgTFA	55[c)]
6	DCE	$AgSbF_6$	CsOPiv	57[c)]
7	DCE	$AgSbF_6$	$NaOPiv·H_2O$	91
8	DCE	$AgNTf_2$	$NaOPiv·H_2O$	85[c)]
9	DCE	$AgPF_6$	$NaOPiv·H_2O$	65[c)]
10	DCE	$AgBF_4$	$NaOPiv·H_2O$	-[c)]
11	Toluene	$AgSbF_6$	$NaOPiv·H_2O$	82[c)]
12	$PhCF_3$	$AgSbF_6$	$NaOPiv·H_2O$	81[c)]
13	DCE	$AgSbF_6$	$NaOPiv·H_2O$	67[c),d)]

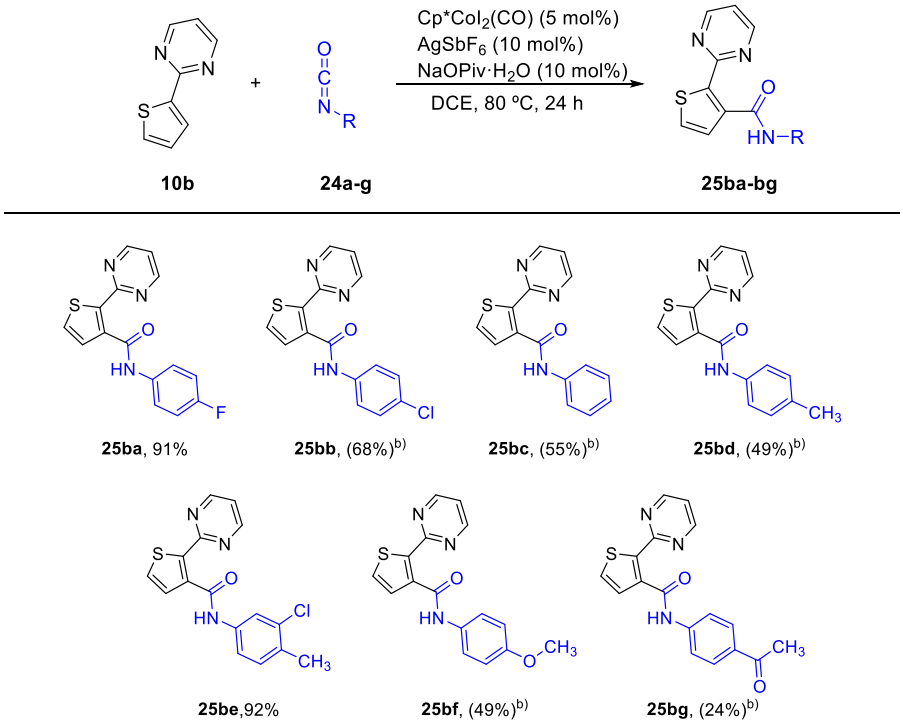
[a)] The reactions were carried out in a 0.5 mmol scale using 20 mL sealed vials inserted in a heating block. The indicated temperature refers to the external temperature of the heating block. [b)] Yield (%) of isolated pure compound. [c)] Unreacted **10b** was recovered. [d)] The reaction was carried out at 70 ºC for 16 h. [d)] The reaction was proceed under MW irradiation 35 min at 100 ºC in a 10 mL sealed reaction tube.

Next, different bases were tesed. When acetates CsOAc and RbOAc were used, amide **25ba** was obtained in 84% yield (Table 3.3, entries 3 and 4). The yield dropped when AgTFA (55%) or CsOPiv (57%) where used, recovering unreacted **10b** (Table 3.3, entries 5 and 6). An excellent result was obtained when hydrated pivalate salt ($NaOPiv·H_2O$) was used as base (91%), in this case no **10b** was recovered (Table 3.3, entry 7). The use of $AgNTf_2$ or $AgPF_6$ as silver salts did not improve the yield (Table 3.3, entries 8-9), and the reaction did not proceed in presence of silver tetrafluoroborate $AgBF_4$ (Table 3.3, entry 10). Regarding solvents, the use toluene and trifluorotoluene lowered the yield to 82% and 81% respectively

(Table 3.3, entries 11-12). Finally, and in order to shorten the reaction time, optimized reaction conditions were carried out under MW irradiation at 100 ºC for 35 min, but the yield dropped significantly to 67% and **10b** was also recovered (Table 3.3, entry 13).

Once the optimal reaction conditions were selected, the reaction was extended to a few aromatic isocyanates (Table. 3.4). The reaction with 4-chloroisociante **24b** provided corresponding product in lower yield (Table 3.4, **27bb**). Isocyanates with no activation on aromatic ring or the introduction of inductive donor groups as *p*-tolyl showed lower reactivity (Table 3.4, **25bc-bd**).

Table 3.4. Synthesis of Thiophene-3-carboxamides **25ba-bg**.



a) Yield (%) of pure isolated product. Reactions done in a 0.4 mmol scale. b) Unreacted **10b** was recovered.

An excellent yield was achieved when 3-Chloro-4-methylphenyl isocyanate **26e** was used. Electron-donating group -OCH_3 in *para* position provided **27bf** in moderate yield, instead, the reaction performed in low yield when electron-withdrawing groups are introduced in aromatic ring (Table 3.4, **27bg**).

As can be seen in Table 3.4, the yields of amides **27** obtained with most of isocyanates **26a-g** employed so far are moderate, lower than the yield optimized for **27ba**. Although the reaction takes place, further optimization of the reaction conditions is required (time, temperature, solvent…) to obtain higher yields with a wider scope of isocyanates. In addition, it would be interesting to decrease the catalyst loading, and reduce the reaction time, (for instance, with MW heating) to obtain a more efficient procedure.

IV

Dual Ligand-Enabled Late-Stage Fujiwara-Moritani reaction

4.1. INTRODUCTION

In this chapter, the research carried out over the course of my three-month pre-doctoral stay in Prof. Manuel Antonio van Gemmeren´s research group at the Organic Chemistry Institute of the University of Münster is explained. During that time, I extended the research van Gemmeren´s group performed in 2018 about Palladium(II)-catalyzed nondirected C-H olefination in the presence of two complementary ligands, to be used for late-stage functionalization of complex molecules.

Methods for the so-called late-stage functionalization (LSF) of complex organic compounds play an important role in various fields of research.[1] For example, derivatives of drug candidates can be accessed without having to repeat the compound synthesis for every desired variant.[2] Likewise, structural diversity can be introduced into complex scaffolds during the generation of compound libraries. In natural-product synthesis, streamlining can be achieved because key late-stage functionalization steps permit the use of simpler precursors and intermediates in the preceding synthesis, for example by obviating the need for protecting groups.[3] It is therefore not surprising that substantial efforts continue to be directed toward LSF of important scaffolds such as aromatic cores. Such methods can be enabled through various mechanistic approaches, ranging from modern methods of electrophilic aromatic substitution, through radical-based methods (which can, for example,

[1] a) Moir, M.; Danon, J. J.; Reekie, T. A.; Kassiou, M. An overview of late-stage functionalization in today's drug discovery. *Expert Opin. Drug Discovery* **2019**, *14*, 1137-1149; b) Börgel, J.; Ritter, T. Late-Stage Functionalization. *Chem* **2020**, *6*, 1877-1887.

[2] a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C-H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009; b) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016**, *45*, 546-576; c) Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M. Expanding the medicinal chemistry synthetic toolbox. *Nat. Rev. Drug Discovery* **2018**, *17*, 709-727.

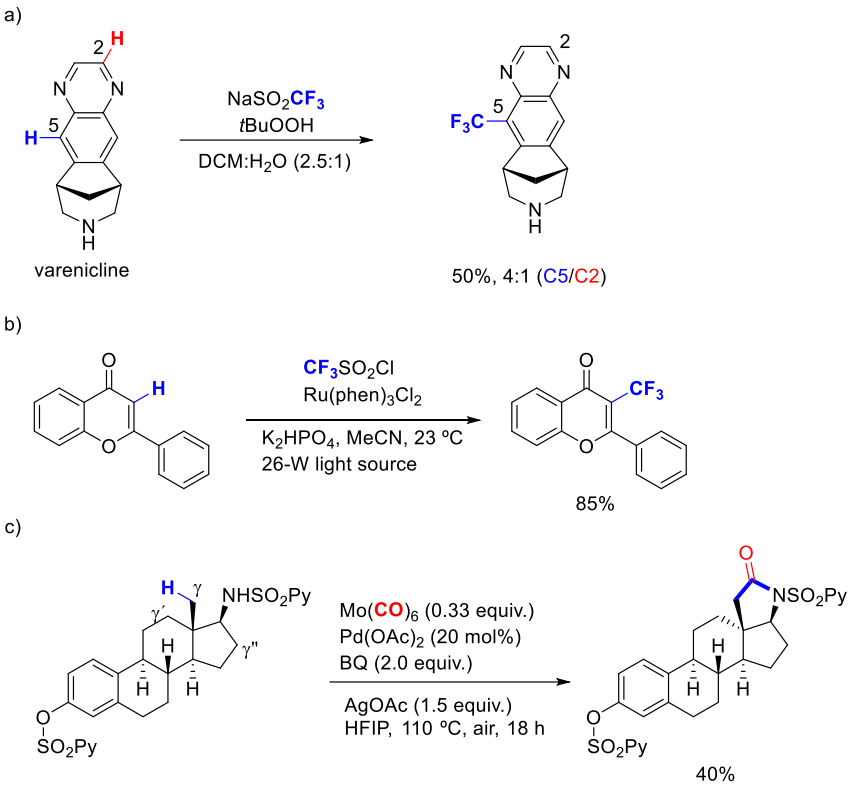
[3] a) Baudoin, O. Multiple Catalytic C−H Bond Functionalization for Natural Product Synthesis. *Angew. Chem. Int. Ed.* **2020**, *59*, 17798-17809; b) McMurray, L.; O'Hara, F.; Gaunt, M. Recent developments in natural product synthesis using metal-catalysed C–H bond functionalisation. *J. Chem. Soc. Rev.* **2011**, *40*, 1885-1898; c) Lam, N. Y. S.; Wu, K.; Yu, J.-Q. Advancing the Logic of Chemical Synthesis: C−H Activation as Strategic and Tactical Disconnections for C−C Bond Construction. *Angew. Chem. Int. Ed.* **2021**, *60*, 15767-15790.

also be photoredox catalyzed or based on electrochemistry), to transition metal-enabled C–H activation processes.[1,4] Thus, Baran and coworkers have reported a new method of C-H trifluoromethylation of a great variety of nitrogen-containing heterocycles, using a benchtop stable trifluoromethyl radical source. It works with both electron-rich and electron-deficient systems and presents a high functional group tolerance. The procedure has been applied in LSF, as illustrated in the regioselectively trifluoromethylate at the C-5 position of the drug varenicline, a drug used for smoking cessation (Scheme 4.1a).[5]

Similarly, McMillan and Nagib reported the trifluoromethylation of (hetero)arenes through, in this case, photoredox catalysis. They used CF_3SO_2Cl as CF_3 radical source and $Ru(phen)_3Cl_2$ as photocatalyst, under 26-W light source. The methodology was applied to LSF of biological active molecules, such as Vitamin P (Scheme 4.1b).[6]

On the other hand, palladium-catalyzed carbonylation/cyclization *via* C(sp^3)-H activation was used on LSF of an estrone derivative where the *N*-SO_2Py directing group could act successfully, even in the presence of the potentially coordinating *O*-SO_2Py group (Scheme 4.1c).[7]

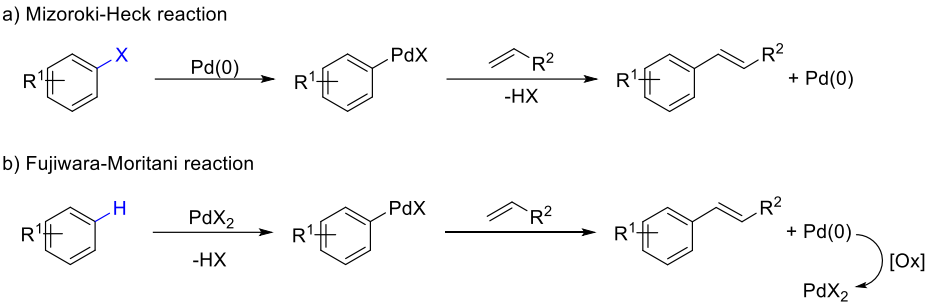
[4] Mondal, A.; Wedi, P.; van Gemmeren, M. In *Remote C–H Bond Functionalization: Methods and Strategies in Organic Synthesis*; Maiti. D.; Guin. S., Ed.; Wiley-VCH: Weinheim, **2021**, Chap. 7, 191.
[5] Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. Innate C-H trifluoromethylation of heterocycles. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *35*, 14411-14415.
[6] Nagib, D. A.; MacMillan, D. W. C. Trifluoromethylation of arenes and heteroarenes by means of photoredox catalysis. *Nature* **2011**, *480*, 224-228.
[7] Hernando, E.; Villalva, J.; Martínez, A. M.; Alonso, I.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. Palladium-Catalyzed Carbonylative Cyclization of Amines *via* γ-C(sp^3)-H Activation: Late-Stage Diversification of Amino Acids and Peptides. *ACS Catal.* **2016**, *6*, 6868-6882.



Scheme 4.1. Examples of LSF.

In this context, the Fujiwara-Moritani reaction presents a useful procedure for LSF of (hetero)arenes. The Fujiwara-Moritani reaction, also called oxidative Mizoroki-Heck reaction, is more efficient, atom economical and environmentally friendly version than the Mizoroki-Heck reaction, as it does not require the use of functionalized coupling partners. Mizoroki-Heck reaction is a Pd(0)-catalyzed cross coupling reaction between aryl or vinyl halides or triflates and alkenes (Scheme 4.2a). In contrast, the Fujiwara-Moritani reaction consists of the direct coupling between the alkene and an unfunctionalized arene catalyzed by Pd(II) in presence of an oxidant. Although the high energy to break C-H bond (e.g.,

Benzene = 110 kcal/mol) limits the functionalization, tremendous efforts have been made in this area to enhance reactivity and also the regioselectivity.[8]

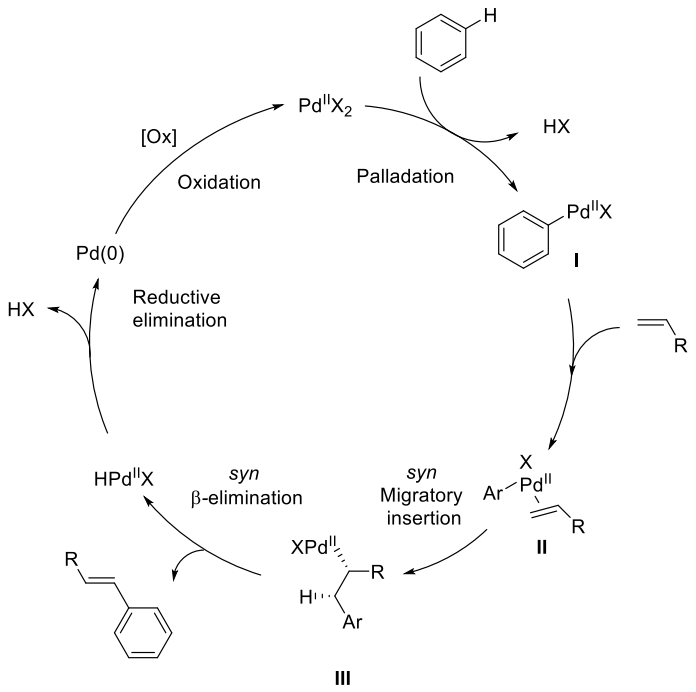


Scheme 4.2. Comparative Mizoroki-Heck reaction and Fujiwara-Moritani reaction.

The generally accepted mechanism of Fujiwara-Moritani reaction starts with the palladation of arene ring to form aryl-palladium intermediate **I**, which coordinates to the alkene. Then, the 1,2-migratory insertion occurs to afford σ-aryl-Pd(II) intermediate **III**. Subsequent β-hydride *syn* elimination generates the olefinated product and a Pd(II) hydride that is

[8] For selected reviews, see: a) Shilov, A. E.; Shul'pin, G. B. Activation of C−H Bonds by Metal Complexes. *Chem. Rev.* **1997**, *97*, 2879-2932; b) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. Oxidative Heck-Type Reactions (Fujiwara−Moritani Reactions). In *The Mizoroki−Heck Reaction*; Oestreich, M. Ed.; Wiley: Chichester, 2009; pp 345−382; c) Le Bras, J.; Muzart, J. Intermolecular Dehydrogenative Heck Reactions. *Chem. Rev*. **2011**, *111*, 1170-1214; d) Suna, E.; Shubin, K. Intramolecular Coupling *via* C(sp^2)-H Activation. In Science of Synthesis. Cross Coupling and Heck-Type Reactions 3. Metal-Catalyzed Heck-Type Reactions and C−H Couplings *via* C−H Activation; Larhed, M., Ed.; Georg Thieme Verlag: Stuttgart, 2013; pp 643-653; e) Zhou, L.; Lu, W. Towards Ideal Synthesis: Alkenylation of Aryl C−H Bonds by a Fujiwara−Moritani Reaction. *Chem. Eur. J.* **2014**, *20*, 634-642; f) Topczewski, J. J.; Sanford, M. S. Carbon−Hydrogen (C−H) Bond Activation at PdIV: a Frontier in C−H Functionalization *Catalysis. Chem. Sci.* **2015**, *6*, 70-76; g) Kitamura, T.; Fujiwara, Y. RSC Green Chemistry Series: From C−H to C−C Bonds: Cross-Dehydrogenative-Coupling; Li, C.-J., Ed.; Royal Society of Chemistry: London, UK, 2015; Vol. 26, pp 33-54; h) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metal-Catalyzed C−H Activation: Examples and Concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900-2936; i) Carral-Menoyo, A.; Sotomayor, N.; Lete, E. Palladium-catalysed Heck-type alkenylation reactions in the synthesis of quinolines. Mechanistic insights and recent applications. *Catal. Sci. Technol.* **2020**, *10*, 5345-5361; j) Le Bras, J.; Muzart, J. Pd-Catalyzed Intermolecular Dehydrogenative Heck Reactions of Five-Membered Heteroarenes. *Catalysts* **2020**, *10*, 571.

transformed into Pd(0) after a reductive elimination. Finally, an oxidant is required to recover the catalytically active Pd(II) species (Scheme 4.3).[9]



Scheme 4.3. Mechanistic proposal for Fujiwara-Moritani reaction.

Due to the wide range of C-H bonds in organic molecules, different approaches have been developed to control the regioselectivity in the metalation step of the Fujiwara-Moritani reaction. Initially, the reaction was carried out using $Pd(OAc)_2$ as catalyst and had low catalytic efficiency, so it was necessary the use of large excess of the arene coupling partner [generally as (co)solvent]. The key C-H activation step is proposed to take place *via* a concerted metalation-deprotonation (CMD) process, where the acetate ion acts as

[9] Mulligan, C. J.; Jeremy, S., Parker, J. S.; Hii, K.-K. M. Revisiting the mechanism of the Fujiwara–Moritani reaction. *React. Chem. Eng.* **2020**, *5*, 1104-1111.

intramolecular base.[10] As no additional ligand or directing groups are used, the selectivity comes from the electronic and steric properties of arene, i.e. substrate control (Scheme 4.4a). A significant improvement of the catalytic efficiency of the reaction was achieved with the incorporation of pyridine ligands, where a modified acetate-based CMD was proposed (Scheme 4.4b).[11] However, excess of arene is still required. Another strategy relies on the use of directing groups (DGs)[12] that coordinate to the catalyst and thereby render the decisive C-H activation intramolecular in nature. This precoordination induces the reactivity and controls the regioselectivity of the process due to the proximity effect, which enables the use the arene coupling partner as limiting reagent (Scheme 4.4c).[13] In this context, *N*-acetyl amino acids have been found to modulate the activity and selectivity of the catalyst, as the acetyl group can act as the internal base abstracting the proton during CMD step (Scheme 4.4c).[14]

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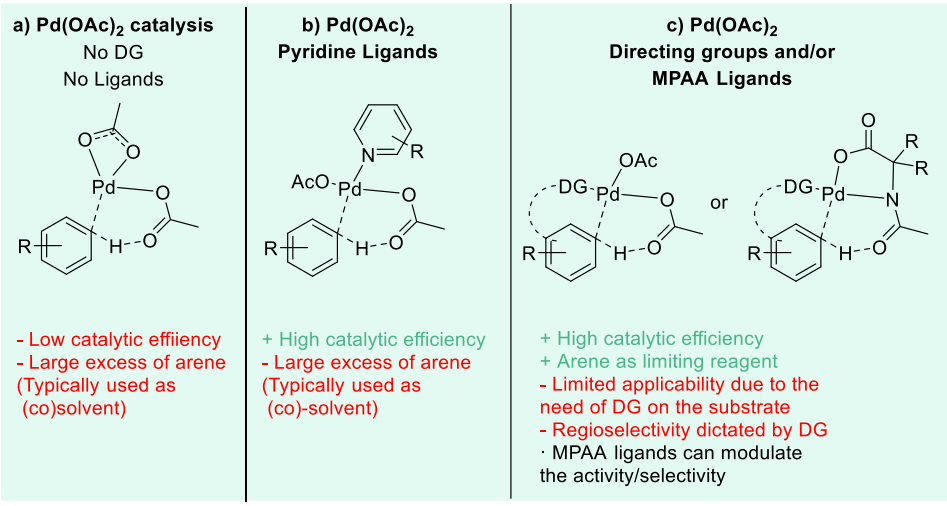
[10] a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. Computational Study of the Mechanism of Cyclometalation by Palladium Acetate**.** .*J. Am. Chem. Soc.* **2005**, *127*, 13754-13755; b) Lapointe, D.; Fagnou. K. Overview of the Mechanistic Work on the Concerted Metallation-Deprotonation Pathway. *Chem. Lett.* **2010**, *39*, 1118-1126.

[11] Zhang, S.; Shi, L.; Ding, Y. Theoretical Analysis of the Mechanism of Palladium(II) Acetate-Catalyzed Oxidative Heck Coupling of Electron-Deficient Arenes with Alkenes: Effects of the Pyridine-Type Ancillary Ligand and Origins of the *meta*-Regioselectivity. *J. Am. Chem. Soc.* **2011**, *133*, 20218-20229.

[12] a) Gandeepan, P.; Ackermann, L. Transient Directing Groups for Transformative C–H Activation by Synergistic Metal Catalysis. *Chem.* **2018**, *4*, 199-222; b) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A comprehensive overview of directing groups applied in metal-catalysed C–H functionalisation chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603-6743.; c) Rej, S.; Ano, Y.; Chatani. N. *Chem. Rev.* **2020**, *120*, 1788-1887.

[13] Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. Beyond Thermodynamic Acidity: A Perspective on the Complex-Induced Proximity Effect (CIPE) in Deprotonation Reactions. *J. Am. Chem. Soc.* **2013**, *135*, 7567-7571.

[14] a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. Pd(II)-Catalyzed Enantioselective Activation of $C(sp^2)$-H and $C(sp^3)$-H Bonds Using Monoprotected Amino Acids as Chiral Ligands. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882-4886; *Angew. Chem.* **2008,** *120*, 4960-4964; b) Cheng, G.-J.; Yang, Y.-F.; Liu, P.; Chen, P.; Sun, T.-M.; Li, G.; Zhang, X.; Houk, K. N.; Yu, J.-Q.; Wu, Y.-D. Role of *N*-Acyl Amino Acid Ligands in Pd(II)-Catalyzed Remote C–H Activation of Tethered Arenes. *J. Am. Chem. Soc.* **2014**, *136*, 894-897; c) Yang, Y.-F.; Hong, X.; Yu, J.-Q.; Houk, K. N. Experimental–Computational Synergy for Selective Pd(II)-Catalyzed C–H Activation of Aryl and Alkyl Groups. *Acc. Chem. Res.* **2017**, *50*, 2853-2860.



Scheme 4.4. Proposed transition state models for Pd(II)-catalyzed C-H functionalization of arenes (such as Fujiwara-Moritani reaction).

The use of DGs has permitted a plethora of synthetically highly useful transformations for late-stage modification. One of the mayor disadvantages of this strategy could be the necessity to develop such reactions individually for each functionalization to be achieved and for each directing group on the substrate. Recent studies have shown, however, that it is possible to develop methods for LSF that are suitable for a broad range of DGs under identical conditions and/or that are able to use naturally occurring functional groups as DGs.[15]

However, the ideal approach toward late-stage C-H activation would be to develop nondirected methods, in which no donor functionality is required on the substrate for the reaction to occur.[16] In contrast to directed methods that typically deliver a single regioisomer,

[15] a) Friis, S. D.; Johansson, M. J.; Ackermann, L. Cobalt-catalysed C–H methylation for late-stage drug diversification. *Nat. Chem.* **2020**, *12*, 511-519; b) Evano, G.; Theunissen, C. Beyond Friedel and Crafts: Innate Alkylation of C−H Bonds in Arenes. *Angew. Chem. Int. Ed.* **2019**, *58*, 7558-7598; c) Uttry, A.; van Gemmeren, M. The Direct Pd-Catalyzed β-C(sp^3)–H Activation of Carboxylic Acids. *Synlett* **2018**, 1937-1943; d) Uttry, A.; van Gemmeren, M. Direct C(sp^3)–H Activation of Carboxylic Acids. *Synthesis* **2020**, *52*, 479-488.

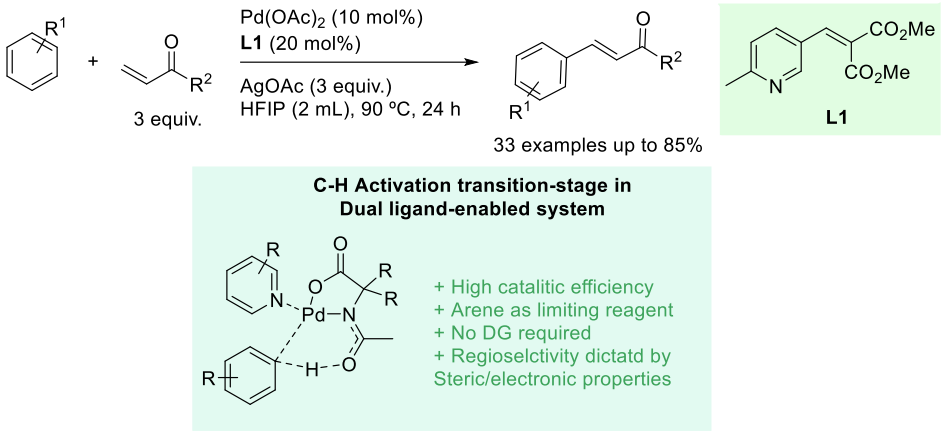
[16] a) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. Beyond Directing Groups: Transition-Metal-Catalyzed C-H Activation of Simple Arenes. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236-10254; b)

nondirected reactions often deliver a mixture of regioisomeric products. This aspect can be considered a disadvantage, but can, in fact, often be exploited, because these mixtures frequently contain regioisomers that would otherwise only be accessible through tedious multistep synthesis. Therefore, in conjunction with modern separation techniques, the generation of regioisomeric mixtures through late-stage nondirected C–H activation can be a valuable tool, for example in the synthesis of compound libraries.[2] As stated above, historically, methods for nondirected C–H activation have required an excess of the substrate to overcome the lack of a directing group. This need for an excess of the substrate is inherently incompatible with the use of such methods in LSF. In this context, van Gemmeren´s group developed dual-ligand-enabled Pd-catalysts centered on the C–H olefination of arenes that permits the Pd-catalyzed nondirected C–H activation to occur efficiently, with the arene as the limiting reactant (Scheme 4.5).[17] The strategy consists of combining two complementary ligands, an amino acid derived ligand and a pyridine ligand which generates a catalyst species that can facilitate CMD through a species that resembles those involved in transition-stage shown in Scheme 4.5, albeit without the linkage between the donor (DG *vs.* pyridine ligand) and the substrate, as confirmed by mechanistic studies.[18]

Hartwig, J. F.; Larsen, M. A. Undirected, Homogeneous C−H Bond Functionalization: Challenges and Opportunities. *ACS Cent. Sci.* **2016**, *2*, 281-292; c) Wedi, P.; van Gemmeren, M. Arene-Limited Nondirected C−H Activation of Arenes. *Angew. Chem. Int. Ed.* **2018**, *57*, 13016-13027; d) Zhou, L.; Lu, W. Towards Ideal Synthesis: Alkenylation of Aryl C-H Bonds by a Fujiwara–Moritani Reaction. *Chem. Eur. J.* **2014**, *20*, 634-642.

[17] a) Chen, H.; Wedi, P.; Meyer, T.; Tavakoli, G.; van Gemmeren, M. Dual Ligand-Enabled Nondirected C−H Olefination of Arenes. *Angew. Chem. Int. Ed.* **2018**, *57*, 2497-2501; b) Naksomboon, K.; Valderas, C.; Gómez-Martínez, M.; Álvarez-Casao, Y.; Fernández-Ibáñez, M. Á. S, O-Ligand-Promoted Palladium-Catalyzed C–H Functionalization Reactions of Nondirected Arenes**.** *ACS Catal.* **2017**, *7*, 6342-6346; c) 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. Ligand-accelerated non-directed C–H functionalization of arenes. *Nature* **2017**, *551*, 489-493.

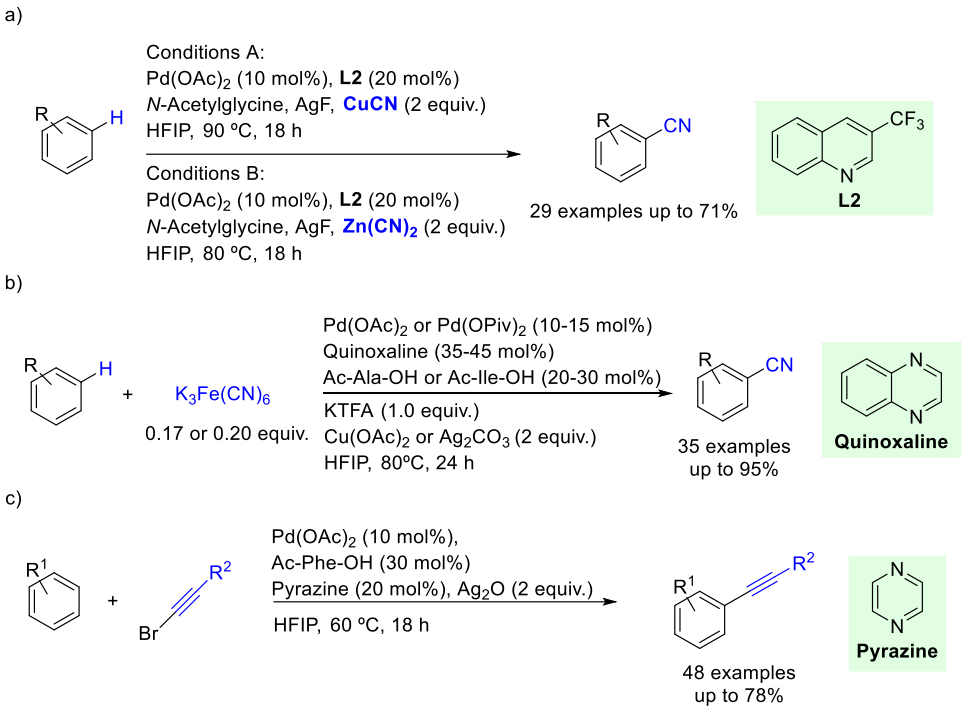
[18] Wedi, P.; Farizyan, M.; Bergander, K.; Mück-Lichtenfeld, C.; van Gemmeren, M. Mechanism of the Arene-Limited Nondirected C–H Activation of Arenes with Palladium. *Angew. Chem. Int. Ed.* **2021**, *60*, 15641-15649.



Scheme 4.5. Dual-ligand-enabled C-H olefination of arenes and proposed transition-state.

In later studies, this design principle was also applied to further valuable transformations. In 2019, the groups of van Gemmeren and Ritter reported dual-ligand-enabled methods for the nondirected cyanation of arenes (Scheme 4.6a-b).[19] van Gemmeren´s group selected an excess (2 equiv.) of CuCN or $Zn(CN)_2$ as cyanide source and quinoline type and *N*-acetyl glycine as ligands, while Ritter's group opted for a substoichiometric amount of $K_3Fe(CN)_6$ (0.17-0.2 equiv.) as cyanide source and quinoxaline/*N*-acetyl-L-alanine as ligand combination. Furthermore, van Gemmeren´s group described an analogous alkynylation utilizing *N*-acetyl-phenylalanine/pyrazine ligand combination, which allowed the synthesis of a wide variety of alkynylated arenes, including complex structures as cholesterol ether, in good yields (Scheme 4.6c).[20]

[19] a) Chen, H.; Mondal, A.; Wedi, P.; van Gemmeren, M. Dual Ligand-Enabled Nondirected C–H Cyanation of Arenes. *ACS Catal*. **2019**, *9*, 1979-1984; b) Zhao, D.; Xu, P.; Ritter, T. Palladium-Catalyzed Late-Stage Direct Arene Cyanation. *Chem.* **2019**, *5*, 97-107.
[20] Mondal, A.; Chen, H.; Flämig, L.; Wedi, P.; van Gemmeren, M. Sterically Controlled Late-Stage C-H Alkynylation of Arenes. *J. Am. Chem. Soc.* **2019**, *141*, 18662-18667.



Scheme 4.6. Dual-ligand-enabled palladium-catalyzed cyanation and alkynylation.

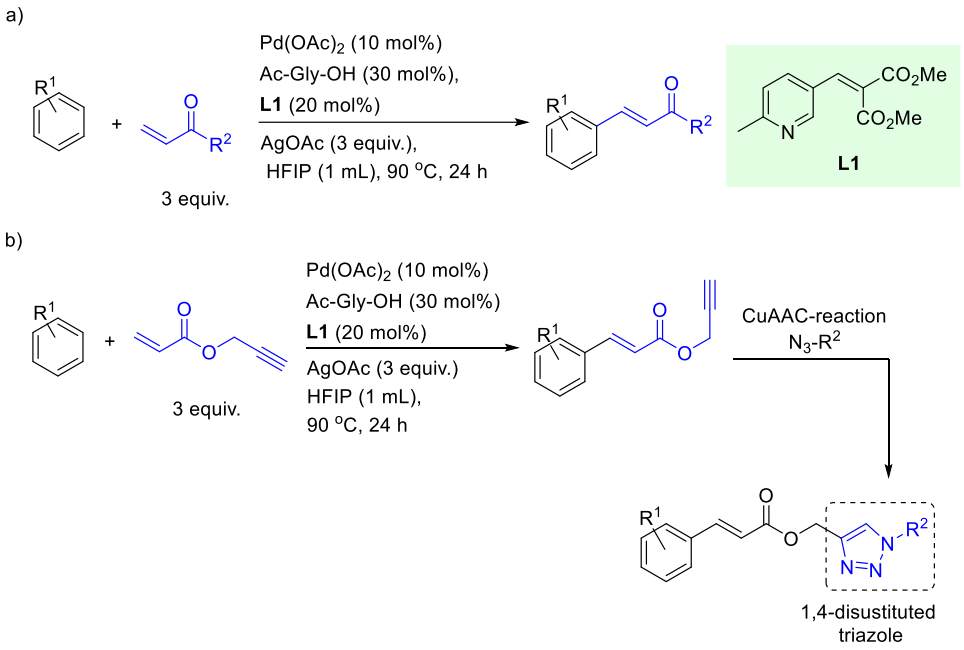
4.2. OBJECTIVES

As explained above, the van Gemmeren´s group has recently reported a dual ligand-enabled nondirected C-H olefination of arenes. The development of a catalyst system through the combination of two complementary ligands makes it possible to use directing-group-free arenes as limiting reagents. In this study on the Fujiwara–Moritani reaction, van Gemmeren hypothesized that this method could, in principle, be used for late-stage functionalization (LSF) of arenes, but the suitability of this protocol was not experimentally evaluated. It should be noted that Ritter and co-workers demonstrated the broad utility of the cyanation reaction for LSF.[19b] Likewise, van Gemmeren demonstrated the possibilities of their procedure of late-stage alkynylation of arenes.[20] Despite these findings, which implied that the late-stage olefination of arenes should indeed be possible, we envisaged that an experimental assessment would be required to encourage practitioners in the various fields that rely on LSF to adopt this technology.

Therefore, the aims of this work performed during my Ph.D stay were:

a) to study the late-stage nondirected Fujiwara-Moritani reaction of complex bioactive arenes and acrylates with dual-ligand-based palladium catalysts (Scheme 4.7a).
b) to explore the Fujiwara-Moritani reaction with propargylic acrylates and the subsequent CuAAc-reaction with corresponding substituted azides, so as to build, after a simple click reaction, 1,4-disubstituted triazoles which are appealing scaffolds in medicinal chemistry (Scheme 4.7b).[21]

[21] a) Dheer, D.; Singh, V.; Shankar, R. Medicinal attributes of 1,2,3-triazoles: Current developments. *Bioorg. Chem.* **2017**, *71*, 30-54; b) Malik, M. S.; Ahmed, S. A.; Althagafi, I. I.; Ansari, M. A.; Kamal. A. *RSC Med. Chem.* **2020**, *11*, 327-348; c) Forezi, L. da S. M.; Lima, C. G. S.; Amaral, A. A. P.; Ferreira, P. F.; de Souza, M. C. B. V.; Cunha, A. C.; da Silva, F de C.; Ferreira, V. F. *Chem. Rec.* **2021**, *21*, 2782 -2807.



Scheme 4.7. General objectives of my Ph.D three-months stay.

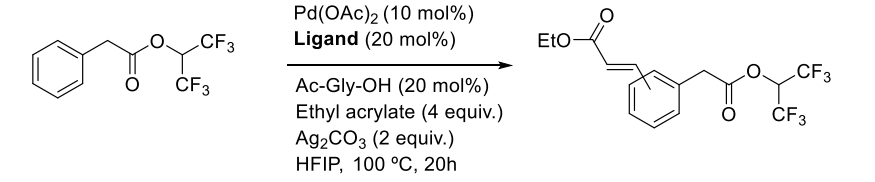
4.3. RESULTS AND DISCUSSION

As has been mentioned in the introduction of this chapter, van Gemmeren´s group has developed the Pd(II)-catalyzed nondirected C-H olefination (Fujiwara-Moritani reaction) of simple arenes, based on the use of two complementary ligands: an amino acid derived ligand and pyridine ligand. They carried out an optimization of the procedure, which is summarized below to put my work in context.

4.3.1. Previous optimization of Pd(II)-catalyzed nondirectd C-H olefination reaction of simple arenes carried out in van Gemmeren´s group

An extensive optimization of the reaction conditions was conducted using a phenylacetic acid ester derivative, the 1,1,1,3,3,3-hexafluoropropan-2-yl 2-phenylacetate, and ethyl acrylate in excess (4 equiv.) as coupling partners.[17a] Firstly, they tested pyridine type ligands. As shown in Table 4.1, at 110 º C, electron-donating groups in the pyridine ring decreased the conversion and yield, halogenated pyridines and electron-withdrawing groups presented high conversions and moderate yields, while ligands **L1** and **L3** showed good conversions and moderate yields at 90 ºC.

Table 4.1. Preliminary screening of Pyridine ligands.

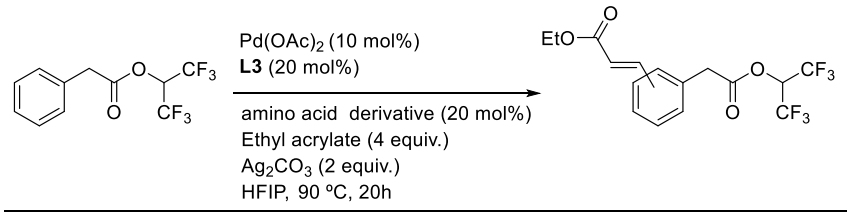


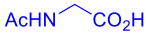
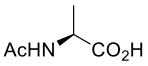
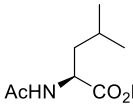
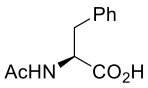
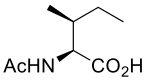
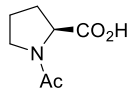
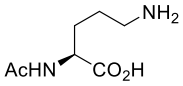
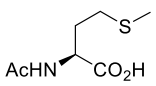
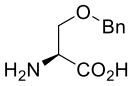
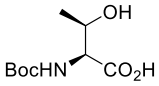
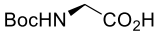
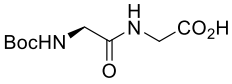
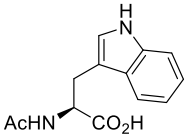
R = -Alkyl, -aryl Conversion: 60-74% Yield: 21-46%	Conversion: 90% Yield: 36%	Conversion: 41% Yield: 14%	X = -H (**L3**); Conversion: 63% Yield: 47% o.m:p = 12:58:30[a)] X = -CH_3 (**L1**); Conversion: 71% Yield: 37% o:m:p = 4:55:41[a)]
R = -F, -Cl Conversion: 68-93% Yield: 31-45%			

[a)] Reactions conducted at 90 ºC.

After selecting **L3** as pyridine ligand amino acid-derivatives were also validated. Although several ones were tested, only *N*-acetyl glycine led to the olefinated product in good conversion and moderate yield (Table 4.2).

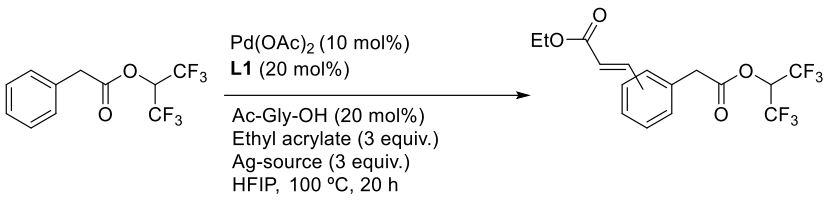
Table 4.2. Preliminary screening of amino acid-derived ligands.



				
Conversion: 63% Yield: 47% o:m:p = 12:58:30	Conversion: 54% Yield: 28%	Conversion: 52% Yield: 22%	Conversion: 50% Yield: 23%	Conversion: 36% Yield: 14%
				
Conversion: 29% Yield: 2%	Conversion: 29% Yield: 2%	Conversion: 26% Yield: 2%	No Reaction	No Reaction
				
No Reaction	No Reaction	No Reaction		

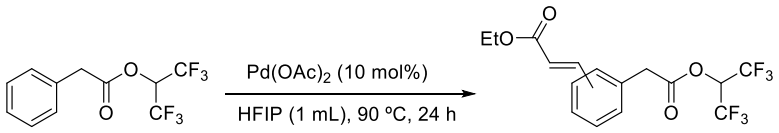
After the screening of ligands, the Ag-source was optimized. In this case, they used **L1** as pyridine ligand and *N*-acetyl glycine as amino acid. Many inorganic and organic silver salts were tested but only few of them gave good results, as shown in Table 4.3. Remarkably, the increase of equivalents of silver salt from 2 to 3 equivalents and the reduction of the amount of ethyl acrylate to 3 equivalents led to best results, obtaining higher yields using silver acetate as silver source (72%).

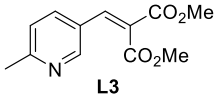
Table 4.3. Optimization of Ag-source.



Ag-source	Conversion	Yield	o:m:p
Ag_2CO_3	50%	49%	5:60:35
AgOAc	**80%**	**72%**	**7:59:34**
$AgNO_3$	74%	59%	8:61:30
Ag_3PO_4	53%	47%	2:54:44

Table 4.4. Optimized reaction conditions.



Amino acid-derived ligand	Pyridine Ligand	Ag-source	Yield (%)[a)]	o:m:p
Ac-Gly-OH (30 mol%)	 L3 30 mol%	AgOAc (3 equiv.)	75	7:58:35

[a)] The reaction was conducted on a 0.2 mmol scale.

In view of these results, they carried out a re-optimization of the pyridine ligands (also including quinoline derivatives) and the amino acid-derived ligands. The reaction time, temperature and the amount of solvent (HFIP) were also adjusted. Thus, the best reaction conditions are shown in Table 4.4, obtaining the desired product in good yield.

As was explained in the introduction of this section (see Scheme 4.5), these optimized reaction conditions had been successfully applied to a great variety of simple arenes and acrylates.[17a]

4.3.2. Late-stage nondirected Fujiwara-Moritani reaction of complex bioactive arenes and acrylates with dual-ligand-based palladium catalysts

With the above precedents in mind, the aim of the work during my three-month Ph.D stay was to extend the reaction to a variety of more complex substrates with a broad range of electronic properties without individually fine-tuning the reaction conditions for each separate case. The results of these experiments are summarized in Table 4.5.

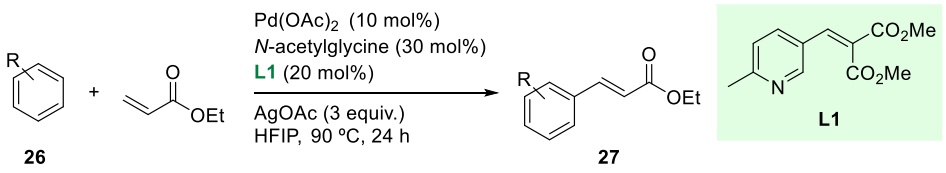
We began with comparably highly reactive electron-rich substrates. First, the methyl ether derived of the narcotic propofol reacted to give product **27a** in 61% yield as a single regioisomer. Next, a series of substrates were tested that, due to their substitution pattern, featured no sterically unhindered positions. The synthetic estrogen estrone methyl ether was olefinated to give **27b** in a moderate yield of 28%. The lipid-lowering agents clofibrate and gemfibrozil (as its methyl ester) gave **27c** and **27d**, in yields of 48 and 28%, respectively. These products were obtained as regioisomeric mixtures derivatized at the sterically most accessible positions. These examples showed that, due to the steric sensitivity of our catalyst system, yields remain limited when no unhindered C–H bonds were available in the substrate. We therefore continued to explore electron-rich substrates in which such positions occur. The methyl ether of guaifenesin delivered **27e** in a good overall yield of 63% as a mixture of the two expected regioisomers. When we used the pesticide carbofuran as a substrate, the product **27f** was again obtained in good yield. We observed that the carbamate group acts as a directing group, leading to *ortho* substitution in the major product.

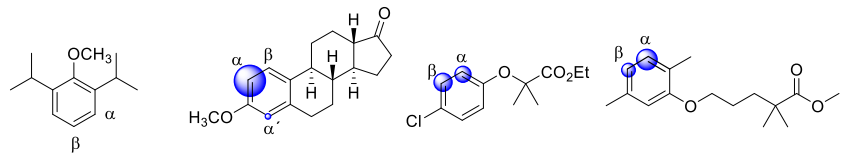
Next, a substrate bearing both electron-rich and electron-deficient positions was tested. Substrate **26g**, an intermediate in the synthesis of the chemotherapeutic sonidegib, was olefinated to give **27g** in 55% overall yield of the two major regioisomers, the olefination occurring in the sterically unhindered position and the position *ortho* to the trifluoromethyl ether. The menthol ester of benzoic acid was tested as a representative of an electron-deficient substrate. The product **27h** was obtained in 42% yield with good *meta* selectivity. We next tested **26i**, an intermediate in the synthesis of palonosetron, a medication used against chemotherapy-induced nausea. The product **27i** was obtained in a synthetically useful yield

and with a high selectivity toward the β-regioisomer. The methyl ester of nateglinide, a blood-glucose-lowering agent for the treatment of diabetes, containing both ester and amide groups, was olefinated to give **27j** in 64% yield. Analogously, the olefination of Evans-type reagent **26k** gave **27k** in 51% yield. The olefination product of chromanone, **27l** was obtained in 46% yield with the two electronically preferred positions leading to the major isomers. In agreement with a report in the literature regarding a related catalyst system, the α′-position was favored in this reaction.[17c] Analogously, two suberone derivatives led to **27m** and **27n** with electronic selectivity between the sterically accessible positions. Finally, we confirmed that the protocol can be used to combine structural complexity in both the arene substrate and the olefin coupling partner. When a fenchol-derived olefin was combined with propofol methyl ether as substrate, product **28** was obtained in 39% yield.

As expected on the basis of literature reports on the Fujiwara–Moritani reaction, all products were obtained with an *E*-configuration of the double bond.[17] The regioselectivities shown in Scheme 4.6, in line with our previous studies,[17a,19,20] can serve as a basis for predicting the reaction outcome with future substrates. In essence, the electrophilic palladium catalyst prefers to activate electron-rich positions of the arene substrate. At the same time, the catalyst is comparatively encumbered and therefore avoids sterically hindered positions whenever possible. The reaction thus proceeds under a combined steric and electronic control. Finally, strongly Lewis-basic functional groups can interrupt the nondirected C–H activation, leading to *ortho* isomers through a directed pathway.

Table 4.5. Scope studies for the nondirected late-stage olefination of arenes.



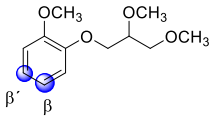


propofol methyl ether
27a, 61%
β-only

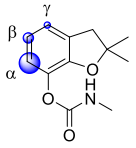
estrone methyl ether
27b, 28%
α:α´ = 91:9

clofibrate
27c, 48%
α:β = 53:47

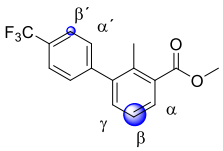
gemfibrozil methyl ester
27d, 28%
α:β= 60:40



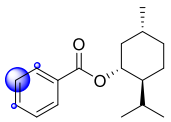
guaifenesin di-methlyether
27e, 63%
β:β´ = 54:46



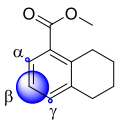
carbofuran
27f, 64%
α:β:γ = 60:30:10



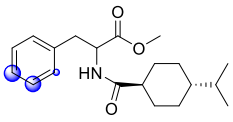
sonidegib precursor
27g, 55%
β:β´:(others) = 64:24:12



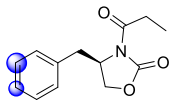
(–)-menthol benzoate
27h, 42%
o:m:p = 16:70:14



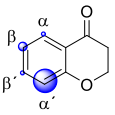
palonosetron precursor
27i, 45%
β:(α+γ) = 93:7



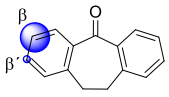
nateglinide methyl ester
27j, 64%
o:m:p = 8:45:47



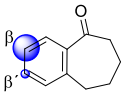
Evans-type reagent
27k, 51%
m:p = 57:43



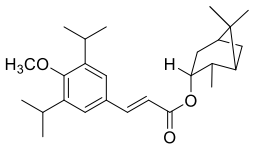
chromanone
27l, 46%
α´:β´:β:α = 68:3:25:4



dibenzosuberone
27m, 31%
β:β´ = 85:15



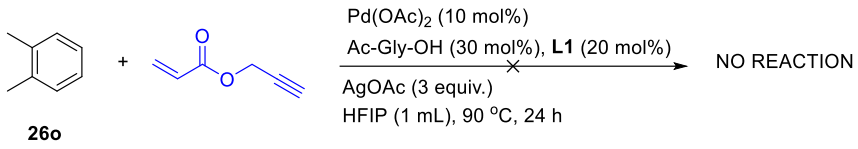
1-benzosuberone
27n, 53%
β:β´ = 76:24



fenchol-derived acrylate
28, 39%

4.3.3. Attempts to extend the Fujiwara-Moritani reaction to propargylic acrylates

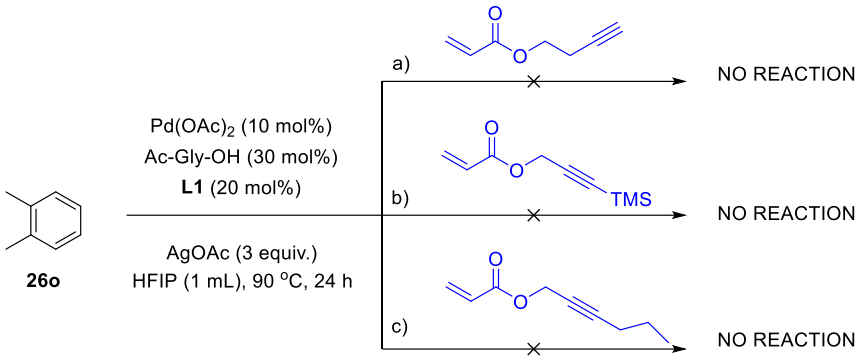
After our study of late-stage olefination of complex and bioactive arenes, we focused on the application of dual ligand-enabled nondirected olefination of arenes to propargylic acrylates so as to obtain, after a simple click reaction, 1,4-disubtituted triazoles as shown in Scheme 4.7. In our first approach, we reacted *o*-xylene **26o** with prop-2-yn-1-yl acrylate, using optimized reaction conditions. However, the reaction did not proceed, instead, starting materials were recovered (Scheme 4.8).



Scheme 4.8. First approach for olefination with propargilic acrylate.

Then, we hypothesized that palladium could coordinate in a competitive way with the carbonyl group or the terminal alkyne. Therefore, we followed the strategies described in Scheme 4.9. The first one consisted on the elongation of the carbon chain in order to avoid the coordination between palladium and the carbonyl group and/or the alkyne, which would block the coordination with the olefin (Scheme 4.9a). Palladium could coordinate also, after deprotonation,[22] with terminal alkyne C-H bond, therefore, the second strategy consisted on the protection of terminal C-H bond with TMS (Scheme 4.9b). The last strategy was the use of an internal alkyne to ensure that the alkyne could not be deprotected or a transmetalation between palladium and silicon could not occur in our reaction conditions (Scheme 4.9c). Unfortunately, none of the followed strategies were successful, so an optimization of reaction conditions should be carried out.

[22]a) García-Melchor, M.; Pacheco, M. C.; Najera, C.; Lledos, A.; Ujaque, G. Mechanistic Exploration of the Pd-Catalyzed Copper-Free Sonogashira Reaction. *ACS Catal.* **2012**, *2*, 135-144; b) Gazvoda, M.; Virant, M.; Pinter, B.; Košmrlj, J. Mechanism of copper-free Sonogashira reaction operates through palladium-palladium transmetallation. *Nat. Commun*. **2018**, *9*, 4814.



Scheme 4.9. Different strategies for olefination of arenes with propargilic acrylates.

To conclude, the results summarized in Scheme 4.6 shows that our initial working hypothesis the suitability of our protocol for the nondirected C–H olefination of arenes in the context of late-stage functionalization-was indeed verified. By using the protocol previously developed for simple arenes, a wide variety of complex substrates could be functionalized. As expected on the basis of related transformations and our mechanistic data, the reactions proceed with a mixture of steric and electronic control, providing access to the desired products in moderate to good yields. Importantly, on the basis of literature studies,[17a,c,19–23] individual yields could probably be increased substantially by fine-tuning the reaction conditions. In this study we provide evidence that our protocol can be used to introduce olefins into complex molecular scaffolds.[13] These results are expected to encourage practitioners in the various fields that rely on late-stage functionalization to include dual-ligand-based palladium catalysts in their toolboxes as valuable tools that often prove complementary to established technologies. Unfortunately, our efforts to extend the reaction to propargylic acrylates to obtain, after a simple CuAAc reaction, 1,4-disubtituted triazoles failed because of the incompatibility of alkyne group with our reaction conditions, and therefore, a re-optimization of reaction conditions must be done.

[23] Chen, H.; Farizyan, M.; Ghiringhelli, F.; van Gemmeren. M. Sterically Controlled C-H Olefination of Heteroarenes. *Angew. Chem. Int. Ed.* **2020**, *59*, 12213-12220.

V

Final Conclusions

5.1. CONCLUSIONS

5.1 CONCLUSIONS

- The palladium(II)-catalyzed radical acylation of pyrroles has proven to be an efficient procedure for the synthesis of a variety of 2-acylpyrroles. The use of 2-pyrimidinyl as directing group allowed the C-2 metalation of pyrrole with $Pd(OAc)_2$ in toluene, which could be acylated with aldehydes in the presence of TBHP as oxidant. The presence of a moderately acidic additive, such as pivalic acid increases the reactivity. The procedure could be extended to a variety of aromatic aldehydes, bearing both electron-rich and electron-deficient aromatic rings. However, in most of the cases, it is not possible to avoid the formation of a minor amount of the corresponding diacylated product. This side reaction can be avoided using the 3-methyl-2-pyridinyl group as directing group, obtaining selectively monoacylated pyrroles in moderate to good yields. The so obtained acylated pyrroles have been used as intermediates in the synthesis of celastramycin analogues and in an improved synthesis of Tolmetin.

- The *in vitro* evaluation of the leishmanicidal activity of 2-acylpyrroles against visceral (*L. donovani*) and cutaneous (*L. amazonensis*) leishmaniasis revealed that all tested 2-acylpyrroles showed lower cytotoxicity CC_{50}> 100 µg/mL in J774 cells (highest tested dose). This is an important feature, as drug toxicity is one of the main limitations of current chemotherapy for leishmaniasis. In particular, (4-fluorophenyl)(1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl)methanone **3bd** (IC_{50} = 16.87 µM, SI > 10.67) was approximately 6-fold more potent and selective than the drug of reference (miltefosine) in *L. amazonensis* promastigote assays. These results point to 2-acylpyrroles as a new class of lead compounds worthy of further optimization as antileishmanial hits.

- The use of MW allows the efficient palladium(II)-catalyzed C-3 acylation of thiophenes with aldehydes *via* C(sp^2)–H activation for the synthesis of (cyclo)alkyl/aryl thienyl ketones. Compared to standard thermal conditions, the use of MW reduces the reaction time (15 to 30 min *vs*. 1 to 3 hours), leading to improved yields of the ketones (up to 92%). The control of positional selectivity is achieved by 2-pyridinyl and 2-pyrimidyl *ortho*-directing groups at C-2 of the thiophene scaffold. The reaction can be applied to aromatic, heteroaromatic, and also aliphatic aldehydes. Further transformations of these ketones led to compounds with potential biological activities (e.g. thiazol-2-ylhydrazones) or fluorescent 4*H*-thieno[2,3-*a*]indolizin-5-ium salts, in which the directing group is embedded in the core structure of the new molecule. The described methodology provides an improved procedure for C–H bond functionalization of thiophenes, with a high atom economy (99%), and would find broad utility in the synthesis of complex target molecules.

- Cp*Co(III) complexes have not shown to be good catalysts for the radical acylation reactions of heteroarenes under the reaction conditions tested. In contrast, they have allowed us to accomplish the high-valent-cobalt-catalyzed aminocarbonylation of thiophenes with isocyanates. Nevertheless, more experimentation is needed to determine the scope of the procedure.

- The dual ligand-enabled Fujiwara-Moritani reaction is a suitable protocol for the nondirected C–H olefination of arenes in the context of late-stage functionalization. This study provides evidence that this protocol can be used to introduce olefins into complex molecular scaffolds. As expected, the reaction proceeds with a mixture of steric and electronic control, providing access to the desired products in moderate to good yields. These results are expected to encourage practitioners in the various fields that rely on late-stage functionalization to include dual ligand-based palladium catalysts in their toolboxes as valuable tools that often prove complementary to established technologies.

- Our attempts to extend the reaction to propargylic acrylates to obtain, after a simple CuAAc reaction, 1,4-disubtituted triazoles failed, due to the incompatibility of alkyne group with our optimized reaction conditions. Therefore, further optimization of reaction conditions is required to apply this methodology to compounds containing carbon-carbon triple bonds.

VI

Experimental section

6.2.2.5. Diversification of 3-acylthiophenes

6.3. COBATL(III)-CATALYZED C-H ACYLATION AND AMINOCARBONYLATION OF HETEROAROMATICS

6.3.1. C-H acylation of pyrroles catalyzed by Co(III)

6.3.1.1. Cobalt(III)-catalyzed acylation of **1a**

6.3.2. Cobalt(III)-catalyzed C-H aminocarbonylation of thiophenes

6.3.2.1. Aminocarbonylation of **10b** with isocyanates

6.4. DUAL LIGAND-ENABLED LATE-STAGE FUJIWARA-MORITANI REACTION

6.4.1. Late-stage nondirected Fujiwara-Moritani reaction of complex bioactive arenes and acrylates with dual-ligand-based palladium catalysts

6.4.1.1. Pd(II)-catalyzed olefination of arenes **26**

6.1. GENERAL METHODS AND MATERIAL

NMR

Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (1H NMR and ^{13}C NMR) were acquired at 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 and 77.0 ppm for ^{13}C NMR; $(CD_3)_2CO$, 2.05 ppm for ^{1}H NMR and 28.8 ppm for ^{13}C NMR; D_2O, 4.79 ppm for 1H), 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; sept, septuplet; m, multiplet; br s, broad singlet. Assignments of individual ^{13}C and ^{1}H resonances are supported by DEPT experiments and 2D correlation experiments (COSY, HSQCed or HMBC). Selective nOe or NOESY experiments were performed when necessary.[1]

In Münter: ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra were recorded at room temperature on a Bruker Avance II 300 MHz, Bruker Avance II 400 MHz, Agilent DD2 500 or Agilent DD2 600 spectrometer. Chemical shifts (*δ*) of 1H- and ^{13}C-NMR spectra are given in ppm relative to tetramethylsilane (TMS) using the residual solvent peaks for calibration ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm).[2] For the spectra of regioisomeric mixtures signals clearly assigned to a particular regioisomer are labelled with a superscript at the integration. The number of protons in such cases refers to the number of protons of the respective isomer. The absence of such an index indicates that the signals of all observed regioisomers overlap, the integration given corresponds to the number of protons in each isomer. The ^{13}C-NMR spectra of mixtures are reported as observed. Due to the low signal intensity and potentially an

[1] Kinss, M.; Sanders, J. K. M. Improved frequency selectivity in nuclear overhauser effect difference spectroscopy. *J. Mag. Res.* **1984**, *56*, 518-520.
[2] 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. Ligand-accelerated non-directed C–H functionalization of arenes. *Nature* **2017**, *551*, 489-493.

overlap of signals, the number of signals can deviate from the hypothetical value, however, the signals of the major components are clearly recognizable in all cases and correspond to the literature values whenever the respective compounds are literature known.

Chromatography

The reactions were monitored by thin layer chromatography (TLC) in pre-coated aluminium-backed plates Merck F254. Visualization was accomplished with UV light (λ = 254 nm and 360 nm) or by immersion in phosphomolybdic acid or vanillin solution (0.07 M in ethanol).[3] For column chromatographic separations Silica Flash P60 (Silicycle), 230-400 mesh ASTM, or aluminum oxide neutral active 90 (Merck), 70-230 mesh ASTM, were used.

In Münster: Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 aluminum plates (Merck). Visualization was achieved by exposure to ultraviolet light (254 nm, 366 nm) and/or by staining. For staining the TLC plates were dipped into a solution of $KMnO_4$ (1 g $KMnO_4$, 6 g K_2CO_3 and 0.1 g KOH in 100 mL H_2O) and developed with a heat gun if necessary. Flash column chromatography was performed on silica gel (35-70 μm mesh, 60A, Acros) with a positive argon overpressure.

GC-FID

In Münster: GC-FID analyses were performed using an Agilent Technologies 7890B setup equipped with an HP5 column (30 m, 0.32mm × 0.25 μm).

GC-MS

[3] Stahl, E. *Thin Layer Chromatography*. Springler-Verlag: Berlin, **1969**.

In Münster: GC-MS spectra were recorded on an Agilent Technologies 7890A GC-system with an Agilent 5975C VL MSD or an Agilent 5975 inert Mass Selective Detector (EI) and an HP-5MS column (30 m, 0.32mm × 0.25 μm). The major signals are quoted in m/z with the relative intensity in parentheses.

IR

IR spectra were obtained using an ATR in a JASCO FT/IR 4100 in the interval between 4000 and 400 cm^{-1} with 4 cm^{-1} resolution. Only characteristic bands are given in each case.

MS

Mass spectra (MS) and high resolution mass spectra (HRMS) were performed by the Mass Spectrometry General Service at the University of Basque Country using an Ultra Performance Liquid Chromatography (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 (ESI) in a positive mode.

In Münster: High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics MicroTof or on a Thermo-Fisher Scientific Orbitrap LTQ XL spectrometer using electron spray ionization (ESI).

m.p

Melting points were measured in a Büchi B-450 apparatus in open capillary tubes.

MW

MW assisted reactions were carried out using a CEM Discover Lab Mate Reactor. The reaction temperature was measured by an integrated infrared sensor, and the reaction times indicated refer to the time at the given temperature. The maximum power supplied to reach the stated temperature was 200 W.

Reagents and Solvents

All solvents used in reactions were anhydrous and purified according to standard procedures.[4]

Commercially available starting materials and reagents (Sigma-Aldrich, Fluka and Acros Organics) were used without further purification. Palladium catalysts were commercially available, and were used without further purification: $Pd(OAc)_2$: 98% purity, $PdCl_2(CH_3CN)_2$, 99% purity. Cobalt catalyst were commercially available, and were used without further purification. $Cp^*CoI_2(CO)$ and $[Co^*CoI]_2$ were synthetized following procedures described in literature.[5]

In Münster: The following solvents were dried by distillation over the drying agents indicated in parentheses: HFIP (activated 3Å MS), THF (Na/benzophenone), toluene (CaH_2), Et_2O (Na/benzophenone), CH_2Cl_2 (CaH_2). Additional anhydrous solvents (<50 ppm water) were purchased from Acros Organics, Sigma-Aldrich, or Carl Roth and stored over molecular sieves under an argon atmosphere. For optimal yields of the reported Fujiwara-Moritani reaction, the quality of the HFIP was found to be essential. HFIP was freshly distilled and utilized within a few days during the course of this project.

[4] a) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 6th Ed., Elsevier Science: Burlington, Massachusetts, **2009**; b) Williams, D. B. G.; Lawton, M. Drying of Organic Solvents: Quantitative Evaluation of the Efficiency of Several Desiccants. *J. Org. Chem.* **2010**, *75*, 8351-8354.

[5] Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M.; A Cp^*CoI_2-dimer as a precursor for cationic Co(III)-catalysis: application to C–H phosphoramidation of indoles. *Chem. Commun.* **2015**, *51*, 4659-4661.

Commercially available chemicals were obtained from ABCR, Acros Organics, Aldrich Chemical Co., Alfa Aesar, Combi-Blocks, Fluorochem, and TCI Europe and used as received unless otherwise stated. The AgOAc utilized during these studies was purchased from ABCR. A strong dependency of the reaction on the quality and morphology of the AgOAc was observed, leading to varying results with AgOAc purchased from other suppliers. The AgOAc was stored in a glove box and batches for short term use were extracted as required.

Miscellaneous

For anhydrous conditions, all the glassware was previously dried for 12 h prior to utilizing in an oven at 130 ^{o}C and allowed to cool down under a dehumidified atmosphere and purged with argon. The addition of solutions and liquids was carried out by over-dried syringe or cannula.[6]

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.

In Münster: All reactions were conducted in oven-dried glassware and under a dry argon atmosphere. Reaction temperatures are reported as the temperature of the oil bath or metal block surrounding the vessel.

X-RAY diffraction

Intensity data were collected on an Agilent Technologies Super-Nova diffractometer, which was equipped with monochromated Mo kα radiation (λ= 0.71073 Å) and Eos CCD detector. Measurement was carried out at 150.01(10) K with the help of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (united cell determination, analytical

[6] Harwood, L. M.; Moody, C. J.; Percy, J. M. *Experimental Organic Chemistry: Standard and Microscale*, 2nd Ed., Blackwell Science: Oxford, **1999**.

absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) using the Crysalis software package.[7] The structure was solved using SHELXT[8] and refined by full-matrix least-squares with SHELXL-97.[9] Final geometrical calculations were carried out with Mercury[10] and PLATON[11] as integrated in WinGX.[12]

Anti-leishmanicidal assays

The following species of *Leishmania* were used: *L. donovani* (MHOM/IN/80/DD8) was purchased (ATCC, USA) and *L. amazonensis* (MHOM/Br/79/Maria) were kindly provided by Prof. Alfredo Toraño (Instituto de Salud Carlos III, Madrid). Promastigotes were cultured in Schneider's Insect Medium supplemented with 10% heat-inactivated Foetal Bovine Serum (FBS) and 1000 U/L of penicillin plus 100 mg/L of streptomycin in 25 mL culture flasks at 26 °C.

[7] CrysAlisPro, Agilent Technologies,Version 1.171.37.31 (release 14-01-2014 CrysAlis171 .NET)(compiled Jan 14 2014,18:38:05)
[8] Sheldrick, G. M. SHELXT-Integrated space-group and crystal-structure determination. *Acta Cryst*. **2015**, *71*, 3-8.
[9] Sheldrick, M. G. A short history of *SHELX*. *Acta Cryst*. **2008**, *64*, 112-122.
[10] 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. *Mercury CSD 2.0* – new features for the visualization and investigation of crystal structures. *J. Appl. Cryst*. **2008**, *41*, 466-470.
[11] a) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*, Utrecht University: Utrecht, The Netherlands; 2010; b) Spek, A. L. Single-crystal structure validation with the program *PLATON*. *J. Appl. Cryst.* **2003**, *36*, 7-13.
[12] Farrugia, L. J. *WinGX* suite for small-molecule single-crystal crystallography. *J. Appl. Cryst.* **1999**, *32*, 837-838.

The in vitro promastigote susceptibility assay,[13] in vitro intracellular amastigote susceptibility assay[14] and cytotoxicity assay[15] were carried out following the procedures previously described in literature.

[13] a) Bilbao-Ramos, P.; Galiana-Roselló, C.; Dea-Ayuela, M. A.; González-Alvarez, M.; Vega, C.; Rolón, M.; Pérez-Serrano, J.; Bolás-Fernández, F.; González-Rosende, M. E. Nuclease activity and ultrastructural effects of new sulfonamides with anti-leishmanial and trypanocidal activities. *Parasitol. Int.***2012**, *61*, 604-613; b) Dea-Ayuela, M. A.; Bilbao-Ramos, P.; Bolás-Fernández, F.; González-Cardenete, M. A. Synthesis and anti-leishmanial activity of C7- and C12-functionalized dehydroabietylamine derivatives. *Eur. J. Med. Chem.* **2016**, *121*, 445-450.

[14] Bilbao-Ramos, P.; Sifontes-Rodríguez, S.; Dea-Ayuela, M. A.; Bolás-Fernández, F. A fluorometric method for evaluation of pharmacological activity against intracellular *Leishmania* amastigotes. *J. Microbiol. Meth.* **2012**, *89*, 8-11.

[15] Galiana-Roselló, C.; Bilbao-Ramos, P.; Dea-Ayuela, M. A.; Rolón, M.; Vega, C.; Bolás-Fernández, F.; García-España, E.; Alfonso, J.; Coronel, C.; González-Rosende, M. E. *In vitro* and *in viv*o anti-leishmanial and trypanocidal studies of new *N*-benzene- and *N*-naphthalenesulfonamide derivatives. *J. Med. Chem.* **2013**, *56*, 8984-8998.

6.2. PALLADIUM (II)-CATALYZED ACYLATION OF FIVE-MEMBERED HETEROAROMATIC RINGS.

6.2.1. Selective Pd(II)-catalyzed C-2 acylation of pyrroles with aldehydes

6.2.1.1. Syntheis of *N*-protected pyrroles **1a**, **1b**

2-(1H-pyrrol-1-yl)pyrimidine (1a). Pyrrole (0. 28 mL, 4 mmol) was added dropwise to suspension of NaH (60% dispersion in mineral oil, 176.0 mg, 4.4 mmol) in DMF (8 mL) at 0 ºC. After stirring for 30 min at 0 °C, 2-chloropyrimidine (549.7 mg, 4.8 mmol) was added and the mixture was stirred at room temperature for 24 h. Then, mixture was poured onto H_2O (30 mL), and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over Na_2SO_4. After evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc 7/3) affording 1a as a white solid, whose data are coincidental with those reported[16] (516 mg, 89 %): m.p. (CH_2Cl_2): 85-87 °C (Lit.[16] 88-91 ºC); IR (ATR): 3149, 1573, 1480, 1437, 1333 cm^{-1}; ^1H NMR (300 MHz, $CDCl^3$): δ 6.35-6.37 (m, 2H), 7.01 (t, J = 4.8 Hz, 1H), 7.79-7.81 (m, 2H), 8.59 (d, J = 4.8 Hz, 2H) ppm;^{13}C NMR (75.5 MHz, $CDCl_3$): δ 112.0, 117.1, 119.0, 156.2, 158.3 ppm; MS (ESI^+) *m/z* (rel intensity): 146 (MH^+,100). HRMS (ESI^+): calcd. for $C_8H_8N_3$ [MH^+]146.0718; found, 146.0721.

3-methyl-2-(1H-pyrrol-1-yl)pyridine (1b). A mixture of pyrrole (0.42 mL, 6 mmol), 2-bromo-3-methyl pyridine (0.86 mL, 7.2 mmol), and KOH (841.6 mg, 15 mmol) in DMSO (8 mL) was stirred at 120 °C for 18 h. The mixture was cooled to room temperature, was diluted with EtOAc (25 mL) and washed with H_2O (2 × 25 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL), the combined organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Then, the crude product was purified by column chromatography (silica gel, petroleum

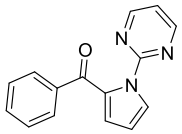
[16] Xu, S.; Huang, X.; Hong, X.; Xu, B. Palladium-Assisted Regioselective C–H Cyanation of Heteroarenes Using Isonitrile as Cyanide Source. *Org. Lett.* **2012**, *14*, 4614-4617.

ether/EtOAc 8/2) to give **1b** as an orange solid (888 mg, 94%): m.p. (CH_2Cl_2): 37-39 °C; IR (ATR): 3008, 2987, 1577, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 6.31 (s, 2H), 7.05-6.97 (m, 1H), 7.12 (s, 2H), 7.48 (d, J = 7.6 Hz, 1H), 8.27 (d, J = 4.8 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.8, 109.6, 121.0, 121.9, 125.6, 140.8, 146.5, 151.6 ppm; MS (ESI^+): *m/z* (rel intensity): 159 (MH^+, 100), 132 (1), 92 (1). HRMS (ESI^+): calcd. for $C_{10}H_{11}N_2$ [MH^+] 159.0922; found, 159.0928.

6.2.1.1. Acylation Reactions of **1a** with Aldehydes.

Acylation Reactions of 1a with Aldehydes. General Procedure: Under argon atmosphere, a sealable reaction tube equipped with a stirring bar was charged with **1a** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), PivOH (0.75 mmol) and corresponding aldehyde **2a–o** (2 mmol). Toluene was added (2 mL), and the mixture was stirred for 2 min until solids were dissolved. Then, TBHP (5.5 M in decane, 4 mmol) was added, the reaction tube was sealed and the reaction mixture was stirred at 60 °C for 1.5–7 h. After cooling to room temperature, the reaction mixture was filtered through silica gel and the filtrate was concentrated under vacuum. The residue was purified by column chromatography affording **3aa–ao** and **4aa–ao**.

Phenyl[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3aa): Following the general procedure, **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1mmol), PivOH (76.6 mg, 0.75 mmol), benzaldehyde **2a** (0.20 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 2 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/EtO_2 4/6) afforded **3aa** as a white solid whose data are coincidental to those reported[17] (179.7 mg, 71%): m.p. (CH_2Cl_2): 115-117°C (Lit.[17] 105-107 ºC); IR (ATR): 1740, 1641, 1566 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 6.35 (t, J = 3.2 Hz, 1H), 6.80 (dd, J = 3.2 , 1.5 Hz, 1H), 7.07 (t, J = 4.9 Hz, 1H), 7.41 (t, J = 7.3 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.71 (t, J = 1.5 Hz, 1H), 7.93 (d, J = 7.3 Hz, 2H), 8.57 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 110.4, 118.5, 122.5, 127.9, 128.2, 129.6, 132.2, 132.4, 138.3, 156.8, 158.2, 185.9



[17] Li, C.; Zhu, W.; Shu, S.; Wu, X.; Liu, H. Palladium-Catalyzed C2-Acylation of Indoles with α-Diketones Assisted by the Removable *N*-(2-Pyrimidyl) Group. *Eur. J. Org. Chem.* **2015**, 3743-3750.

ppm; MS (ESI^+): *m/z* (rel intensity): 250 (MH^+, 100), 105 (1). HRMS (ESI^+): calcd. for $C_{15}H_{12}N_3O$ [MH^+]: 250.0980; found: 250.0986.

[1-(Pyrimidin-2-yl)-1*H*-pyrrol-2-yl](*p*-tolyl)methanone (3ab). Following the general procedure 1a (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-methylbenzaldehyde **2b** (0.22 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1,5 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 6/4) afforded **3ab** as white solid (160.7 mg, 61%): m.p. (CH_2Cl_2): 159-161 °C ; IR (ATR): 1641, 1570 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 6.35 (m, 1H), 6.79 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.08 (t, *J* = 4.8 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.70 (dd, J = 2.9, 1.6 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 8.58 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.7, 110.3, 118.4, 122.2, 127.6, 128.9, 129.8, 132.4, 135.6, 143.3, 156.9, 158.2, 186.7 ppm; MS (ESI^+) m*/z* (rel intensity): 264 (MH^+ , 100), 172(1), 119 (8). HRMS (ESI^+): calcd. for $C_{16}H_{14}N_3O$ [MH^+] 264.1137; found, 264.1143.

[4-(*tert*-Butyl)phenyl][1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3ac). Following the general procedure, **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-(*tert*-butyl)benzaldehyde **2c** (0.33 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **3ac** as white solid (144.8 mg, 47%): m.p. (CH_2Cl_2): 121-123 °C; IR (ATR): 1735, 1641, 1573 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 6.35 (m, 1H), 6.82 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.10 (t, *J* = 4.8 Hz, 1H), 7.45-7.48 (m, 2H), 7.70 (dd, *J* = 2.9, 1.6 Hz, 1H), 7.90-7.93 (m, 2H), 8.60 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 31.2, 35.1, 110.3, 118.4, 122.4, 125.2, 127.8, 129.7, 132.4, 135.6, 156.2, 156.9, 158.2, 186.5 ppm; MS (ESI^+): *m/z* (rel intensity): 306 (MH^+, 100), 161 (1). HRMS (ESI^+): calcd. for $C_{19}H_{20}N_3O$ [MH^+] 306.1606; found, 306.1614.

(4-Fluorophenyl)[1-(pyrimidin-2-yl)-1H-pyrrol-2-yl]methanone (3ad). Following the general procedure 1a (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-fluorobenzaldehyde **2d** (0.21 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3 h at 70 °C, purification by column

chromatography (silica gel, petroleum ether/Et_2O 3/7) afforded **3ad** as white solid, whose data are coincidental to those reported[18] (177.0 mg, 66%): m.p. (CH_2Cl_2): 153-155 °C; IR (ATR): 1645, 1602, 1570 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 6.35 (dd, J = 3.5, 3.0 Hz, 1H), 6.79 (dd, J = 3.6, 1.6 Hz, 1H), 7.06-7.12 (m, 3H), 7.71 (dd, J = 2.9, 1.6 Hz, 1H), 7.92-7.97 (m, 2H), 8.59 (d, J = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 110.5, 115.4 (d, J = 21.9 Hz), 118.5, 122.5, 128.0, 131.9, 132.1 (d, J = 9.1 Hz), 134.6, 156.7, 158.3, 165.4 (d, J = 25 3.5 Hz), 184.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -106.41 ppm; MS (ESI^+): *m/z* (rel intensity): 268 (MH^+, 100), 123 (11). HRMS (ESI^+): calcd. for $C_{15}H_{11}FN_3O$ [MH^+] 268.0886; found, 268.0896.

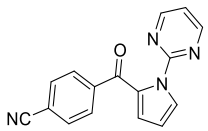
(4-Chlorophenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3ae). Following the general procedure 1a (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-chlorobenzaldehyde **2e** (281.1 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded none **3ae** as white solid (164.4 mg, 58%): m.p. (CH_2Cl_2): 134-136 °C; IR (ATR): 1645, 1573 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 6.35 (t, J = 3.5 Hz, 1H), 6.79 (dd, J = 3.5, 1.5 Hz, 1H), 7.10 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.72 (dd, J = 3.5, 1.5 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 8.57 (d, J = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 110.6, 118.9, 122.5, 128.0, 128.5, 130.9, 131.8, 136.7, 138.7, 156.7, 158.2, 184.6 ppm; MS (ESI^+): *m/z* (rel intensity): 286 (MH^{++2}, 26), 284 (MH^+, 100), 140 (2) 138 (6). HRMS (ESI^+): calcd. for $C_{15}H_{11}ClN_3O$ [MH^+] 284.0591; found, 284.0591.

(4-Bromophenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3af). Following the general procedure **1a** (145.2 mg, 1mmol), $Pd(OAc)_2$ was treated with (22.5 mg, 0.1mmol), PivOH (76.6 mg, 0.75 mmol), 4-bromobenzaldehyde **2f** (281.1 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1.5 h at 70 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 6/4) afforded **3af** as white solid (211.0 mg, 64%): m.p. (CH_2Cl_2): 139-140 °C; IR (ATR): 1741, 1645, 1573 cm^{-1} ; ^1H NMR

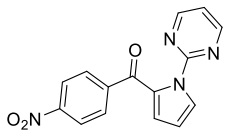
[18] Pospech, J.; Tlili, A.; Spannenberg, A.; Neumann, H.; Beller, M. Regioselective Ruthenium-Catalyzed Carbonylative Direct Arylation of Five-Membered and Condensed Heterocycles. *Chem. Eur. J.* **2014**, *20*, 3135-3141.

(300 MHz, $CDCl_3$): δ 6.34-6-36 (m, 1H), 6.79 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 7.10 (t, J = 4.8 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.72 (dd, J = 2.9, 1.6 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 8.57 (d, J = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 110.6, 118.5, 122.5, 127.3, 128.0, 131.1, 131.5, 131.8, 137.1, 156.6, 158.2, 184.8 ppm; MS (ESI^+): *m/z* (rel intensity): 330 (MH^{++2},99), 328 (MH^+, 100), 184 (4), 182 (4). HRMS (ESI^+): calcd. for $C_{15}H_{11}BrN_3O$ [MH^+] 328.0085; found, 328.0094.

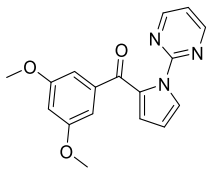
4-[1-(Pyrimidin-2-yl)-1H-pyrrole-2-carbonyl]benzonitrile (3ag). Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4- formylbenzonitrile **2g** (262.3 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 5 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 3/7) afforded **3ag** as light brown solid (95.4 mg, 35%): m.p. (CH_2Cl_2): 176-178 °C; IR (ATR): 2230, 1645, 1570, cm^{-1} ; ^{1}H NMR (300 MHz, CDCl3): δ 6.38-6.40 (m, 1H), 6.83 (dd, J = 3.7, 1.6 Hz, 1H), 7.13 (t, J = 4.8 Hz, 1H), 7.70-7.72 (m, 2H), 7.76 (dd, J = 2.9, 1.6 Hz, 1H), 7.96-7.98 (m, 2H), 8.58 (d, J = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 110.9, 115.5, 118.2, 118.7, 123.1, 129.0, 129.7, 131.4, 132.1, 141.9, 156.5, 158.6, 184.1 ppm; MS (ESI^+): *m/z* (rel intensity): 275 (MH^+ , 100), 130 (12). HRMS (ESI^+): calcd. for $C_{16}H_{11}N_4O$ [MH^+] 275.0933; found, 275.0935.



(4-Nitrophenyl)[1-(pyrimidin-2-yl)-1H-pyrrol-2-yl]methanone (3ah): Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-nitrobenzaldehyde **2h** (302.2 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3ah** as yellow solid (58.8 mg, 22%): m.p. (CH_2Cl_2): 173-174 °C; IR (ATR): 1649, 1570, cm^{-1} ; ^{1}H NMR (300 MHz, DMSO-d^6): δ 6.48-6.50 (m, 1H), 6.95 (dd, J = 3.7, 1.6 Hz, 1H), 7.42 (t, J = 4.9 Hz, 1H), 7.85 (dd, J = 2.8, 1.6 Hz, 1H), 7.99-8.02 (m, 2H), 8.31-8.34 (m, 2H), 8.75 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 111.0, 118.7, 123.3, 123.4, 128.7, 130.2, 131.4, 143.6, 149.8, 156.5, 158.3, 183.8 ppm; MS (ESI^+): *m/z* (rel intensity): 295 (MH^+, 100), 150 (7). HRMS (ESI^+): calcd. for $C_{15}H_{11}N_4O_3$ [MH^+] 295.0831; found, 295.0835.

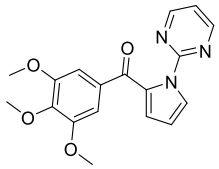


(3,5-Dimethoxyphenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3ai). Following



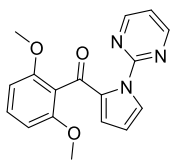
the general procedure **1a** (145.2 mg, 1 mmol), was treated with $Pd(OAc)_2$ (22.5 mg, 0.1mmol), PivOH (76.6 mg, 0.75 mmol), 3,5-dimetoxibenzaldehyde **2i** (332.3 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 2.5 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3ai** as white solid (222.8 mg, 72%): m.p. (CH_2Cl_2): 107-109 °C ; IR (ATR): 1737, 1595 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 6H), 6.34 (t, J = 3.2 Hz, 1H), 6.58 (t, J = 2.3 Hz, 1H), 6.81 (dd, J = 3.5, 1.5 Hz, 1H), 7.04-7.07 (m, 3H), 7.69 (dd, J = 3.1 Hz, 1.5 Hz, 1H), 8.58 (d, J = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.6, 106.2, 107.4, 110.4, 118.5, 122.7, 128.0, 132.0, 140.1, 156.8, 158.3, 160.5, 185.3 ppm; MS (ESI^+): *m/z* (rel intensity): 310 (MH^+, 100), 165 (1). HRMS (ESI^+): Calcd. for $C_{17}H_{16}N_3O_3$ [MH^+] 310.1192; found. 310.1201.

[1-(Pyrimidin-2-yl)-1*H*-pyrrol-2-yl](3,4,5- trimethoxyphenyl)methanone (3aj).



Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 3,4,5-trimethoxybenzaldehyde **3j** (392.4 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 2,5 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 6/4) afforded **3aj** as yellow solid (237.9 mg, 70%): m.p. (CH_2Cl_2): 124-126 °C ; IR (ATR): 1741, 1577 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 6H), 3.87 (s, 3H), 6.32 (dd, J = 3.5, 2.9 Hz, 1H), 6.81 (dd, J = 3.5, 1.6 Hz, 1H), 7.08 (t, J = 4.8 Hz, 1H), 7.20 (s, 2H), 7.68 (dd, J = 2.9, 1.6 Hz, 1H), 8.57 (d, J = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.2, 60.9, 107.1, 110.4, 118.2, 122.2, 127.9, 131.9, 133.2, 141.9, 141.9, 152.8, 156.8, 158.2, 184.7ppm; MS (ESI+): m/z (rel intensity): 340 (MH^+, 100), 172 (1). HRMS (ESI^+): calcd. for $C_{18}H_{18}N_3O_4$ [MH^+] 340.1297; found, 340.1310.

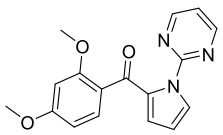
(2,6-Dimethoxyphenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3ak). Following



the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 2,6-dimetoxibenzaldehyde **2k** (332.3 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 6 h at 90 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 3/7) afforded **3ak** as

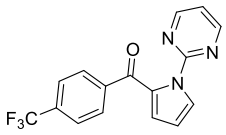
yellow solid (143.9 mg, 47%): m.p. (CH_2Cl_2): 156-158 °C; IR (ATR): 1649, 1591 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 6H), 6.27 (dd, *J* = 3.8, 2.9 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 6.76 (dd, *J* = 3.8, 1.7 Hz, 1H), 7.20 (t, *J* = 4.8 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 2.9, 1.7 Hz, 1H), 8.71 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.1, 104.1, 110.3, 119.0, 119.1, 123.9, 129.9, 130.7, 134.1, 157.8, 158.1, 158.2, 182.5 ppm; MS (ESI^+): m/z (rel intensity): 310 (MH^+, 20), 172 (100), 158 (20), 98 (50). HRMS (ESI^+): calcd. for $C_{17}H_{16}N_3O_3$ [MH^+] 310.1192; found, 310.1185.

(2,4-Dimethoxyphenyl)[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3al). Following



the general procedure 1a (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 2,4-dimetoxibenzaldehyde 2l (332.3 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 6/4) afforded 3al as yellow solid (124.1 mg, 40%): m.p. (CH_2Cl_2): 137-138 °C; IR (ATR): 1602, 1570, 1441 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 3H), 3.79 (s, 3H), 6.27 (dd, J = 3.5, 3.1 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.43 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.70 (dd, *J* = 3.6, 1.7 Hz, 1H), 7.05 (t, *J* = 4.8 Hz, 1H), 7.58 (dd, *J* = 3.1, 1.7 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 8.54 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.5, 55.8, 98.7, 102.0, 110.1, 118.4, 121.5, 121.8, 127.1, 133.4, 134.3, 157.0, 158.0, 160.0, 161.6, 181.9 ppm; MS (ESI^+): m/z (rel intensity): 310 (MH^+, 100), 172 (31). HRMS (ESI^+): Calcd. for $C_{17}H_{16}N_3O_3$ [MH^+] 310.1192; found, 310.1196.

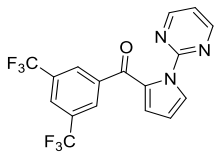
[1-(Pyrimidin-2-yl)-1*H*-pyrrol-2-yl[[4- (trifluoromethyl)phenyl]methanone (3am).



Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-(trifluoromethyl)benzaldehyde **2m** (0.27 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 40 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 3/7) afforded **3am** as white solid (105.8 mg, 33%): m.p. (CH_2Cl_2): 103-104 °C; IR (ATR): 1649, 1570 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 6.38 (s, 1H), 6.83 (d, *J* = 1.7 Hz, 1H), 7.13 (t, *J* = 4.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.74-7.76 (m, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 8.60 (d, *J* = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 110.8, 118.7, 123.7 (q, *J* = 271.1 Hz), 125.2 (q, *J* = 3.8 Hz), 128.5, 129.8, 130.3, 131.7, 133.6 (q, *J* = 32.5 Hz), 141.3, 156.6, 158.3, 184.6 ppm; ^{19}F NMR

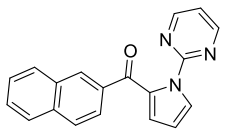
(376 MHz, $CDCl_3$): δ -62.9 ppm; MS (ESI^+): *m/z* (rel intensity): 318 (MH^+, 100), 173 (4). HRMS (ESI^+): Calcd. for $C_{16}H_{11}F_3N_3O$ [MH^+] 318.0854; found, 318.0861.

[3,5-bis(Trifluoromethyl)phenyl][1-(pyrimidin-2-yl)-1*H*-pyrrol-2- yl]methanone (3an).



Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 3,5-bis(trifluoromethyl)benzaldehyde **3n** (0.33 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 40 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 3/7) afforded **3an** as light-brown solid (52.9 mg, 14%): m.p. (CH_2Cl_2): 96- 98 °C; IR (ATR): 1656, 1573 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 6.43 (s, 1H), 6.87 (s, 1H), 7.18 (t, *J* = 4.3 Hz, 1H), 7.82 (s, 1H), 8.04 (s, 1H), 8.38 (s, 2H), 8.62 (d, *J* = 4.6 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 111.0, 118.8, 122.9 (q, *J* = 271.6 Hz), 123.6, 125.5 (q, *J* = 3.65 Hz), 129.4, 129.4 (q, *J* = 3.2 Hz), 130.8, 131.9 (q, *J* = 33.9 Hz), 140.1, 156.5, 158.3, 182.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9 ppm; MS (ESI^+): *m/z* (rel intensity): 386 (MH^+, 100), 241 (1). HRMS (ESI^+): calcd. for $C_{17}H_{10}F_6N_3O$ [MH^+] 386.0728; found, 386.0728.

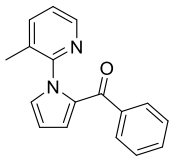
Naphthalen-2-yl[1-(pyrimidin-2-yl)-1*H*-pyrrol-2-yl]methanone (3ao). Following the general procedure **1a** (145.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 2-naphthaldehyde **2o** (312.4 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1,5 h at 60 °C, purification by column chromatography (silica gel, petroleum ether/Et_2O 1/1) afforded **3ao** as white solid (152.2 mg, 51%): m.p. (CH_2Cl_2): 110-112 °C; IR (ATR): 3052, 2999, 1739, 1641, 1573, 1530, 1444 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.39-6.41 (m, 1H), 6.88-6.89 (m, 1H), 7.02 (t, *J* = 4.7 Hz, 1H), 7.51-755 (m, 2H), 7.78 (d, *J* = 1.1 Hz, 1H), 7.85-7.91 (m, 3H), 8.04 (d, *J* = 8.4 Hz, 1H), 8.47 (s, 1H), 8.55 (d, *J* = 4.7 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 110.5, 118.4, 122.5, 125.4, 126.4, 127.8, 128.2, 128.2, 129.5, 131.3, 132.4, 135.4, 135.7, 156.8, 158.2, 186.0 ppm; MS (ESI^+): *m/z* (rel intensity): 300 (MH^+, 100), 155 (3). HRMS (ESI^+): calcd. for $C_{19}H_{14}N_3O$ [MH^+] 300.1137; found, 300.1141.



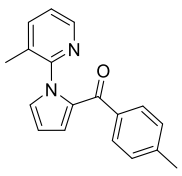
6.2.1.2. Acylation Reactions of **1b** with Aldehydes

Acylation Reactions of 1b with Aldehydes. General procedure: Under argon atmosphere, a sealable reaction tube equipped with a stirring bar was charged with **1b** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), PivOH (0.75 mmol) and corresponding benzaldehyde **2a-t** (2 mmol). Toluene was added (2 mL), mixture was stirred for 2 min until solids were dissolved. Then, TBHP (5.5 M in decane, 4 mmol) was added, reaction tube was sealed and the reaction mixture was stirred at 120 °C for 1.5-7 h. After cooling to room temperature, AcOEt (15mL) was added to reaction mixture and organic phase was washed with an aqueous solution of NaOH 2M (3 × 20 mL) the combined aqueous phase was extracted with AcOEt (2 × 15 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography affording **3ba-3bt**.

[1-(3-Methylpyridin-2-yl)-1*H*-pyrrol-2-yl](phenyl)methanone (3ba). Following the general procedure **1b** (158.2 mg, 1mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), benzaldehyde **2a** (0.20 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1.5 h at 120 ºC, purification by column chromatography (silica gel, petroleum ether/ AcOEt 7/3) afforded **3ba** as a yellow oil (202.5 mg, 74%): IR (ATR): 1739, 1634 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H), 6.37 (dd, J = 3.9, 2.6 Hz, 1H), 6.90 (dd, J = 3.9, 1.6 Hz, 1H), 7.10 (dd, J = 2.6, 1.6, 1H), 7.20-7.25 (m, 1H), 7.40 (dd, J = 8.2, 6.6 Hz, 2H), 7.43-7.54 (m, 1H), 7.56-7.64 (m, 1H), 7.79-7.91 (m, 2H), 8.33-8.38 (m, 1H) ppm; ^{13}C NMR (75.5 MHz, CDCl3): δ 17.3, 109.8, 122.2, 123.7, 128.2, 129.4, 129.6, 130.0, 131.7, 131.9, 138.7, 139.4, 146.4, 152.4, 184.6 ppm; MS (ESI^+): *m/z* (rel intensity): 263 (MH^+, 100), 106 (2), 105 (33). HRMS (ESI^+): calcd. for $C_{17}H_{15}N_2O$ [MH^+] 263.1184; found, 263.1198.

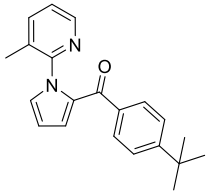


1-(3-Methylpyridin-2-yl)-1*H*-pyrrol-2-yl](*p*-tolyl)methanone (3bb). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-methylbenzaldehyde **2b** (0,24 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether /AcOEt 7/3) afforded **3bb** as yellow oil (132.6 mg, 48 %): IR (ATR): 1739, 1458 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ



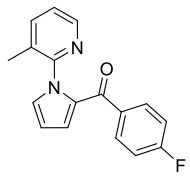
2.14 (s, 3H), 2.44 (s, 3H), 6.41 (dd, *J* = 3.9, 2.7 Hz, 1H), 6.94 (dd, *J* = 3.9, 1.6 Hz, 1H), 7.13 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.27 (d, *J* =8.1 Hz, 2H), 7.30-7.34 (m, 1H), 7.67 (dd, *J* = 7.5,1.2 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 8.41 (dd, *J* = 4.7, 1.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.3, 21.6, 109.8, 121.8, 123.6, 128.8, 129.3, 129.6, 130.1, 131.8, 136.0, 139.4, 142.5, 146.4, 152.4, 184.5, ppm; MS (ESI^+): *m/z* (rel intensity): 277 (MH^+, 100), 119 (37). HRMS (ESI^+): calcd. for $C_{18}H_{17}N_2O$ [MH^+] 277.1341; found, 277.1350

[4-(*tert*-Butyl)phenyl][1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2- yl]methanone (3bc).



Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-(tert-butyl)benzaldehyde **2c** (0.33 mL; 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3,5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bc** as brown solid (100 mg, 31%): m.p. (CH_2Cl_2): 75-79 °C; IR (ATR): 1741, 1454 cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (s, 9H), 2.12 (s, 3H), 6.39 (dd, J = 3.9, 2.7 Hz, 1H), 6.95 (dd, *J* = 3.9, 1.6 Hz, 1H), 7.12 (dd, *J* = 2.7, 1.6Hz, 1H), 7.24-7.32 (m, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.64 (dd, *J* = 7.5, 1.2Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 8.38 (dd, *J* = 4.8, 1.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.2, 31.2, 35.0, 109.8, 121.8, 123.6, 125.1, 129.2, 129.4, 130.0, 130.0, 131.8, 135.9, 139.4, 146.3, 152.4, 155.4, 184.4, ppm; MS (ESI^+): *m/z* (rel intensity): 319 (MH^+, 100), 162 (1), 161 (7). HRMS (ESI^+): calcd. for $C_{21}H_{23}N_2O$ [MH^+] 319.1810; found, 319.1819.

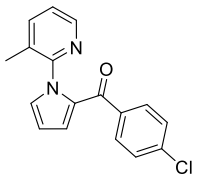
(4-Fluorophenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (3bd): Following



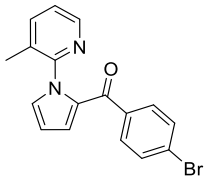
the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-fluorobenzaldehyde **2d** (0.21 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bd** as white solid (148.7 mg, 53%): m.p. (CH_2Cl_2): 76-78 °C; IR (ATR): 1634, 1595, cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.12 (s, 3H), 6.39 (d, *J* = 2.9 Hz, 1H), 6.89 (d, *J* = 3.8 Hz, 1H), 7.09-7.12 (m, 3H), 7.26-7.29 (m, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.96-7.82 (m, 2H), 8.37 (d, *J* = 4.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl3): δ 17.2, 110.0, 115.2 (d, *J* = 21.7 Hz), 122.0, 123.8, 129.7, 130.0, 131.4, 131.8 (d, *J* = 9.0 Hz), 134.9 (d, *J* = 3.4 Hz), 139.5, 146.4, 152.2, 165.1 (d, *J* = 253.2 Hz), 183.2 ppm; MS (ESI^+): *m/z* (rel intensity): 281 (MH^+, 100),

265 (<1), 243 (1), 123 (21). HRMS (ESI$^+$): calcd. for $C_{17}H_{14}FN_2O$ [MH$^+$] 281.1090; found, 281.1092.

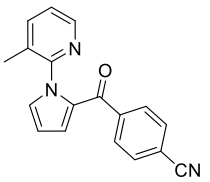
(4-Chlorophenyl)[1-(3-methylpyridin-2-yl)-1H-pyrrol-2-yl]methanone (3be). Following the general procedure,**1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-chlorobenzaldehyde **2e** (281.2 mg; 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3be** as white solid (128.6 mg, 43%): m.p. (CH_2Cl_2): 99-102 °C; IR (ATR): 1739, 1631, cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H), 6.40 (dd, *J* = 3.9, 2.7 Hz, 1H), 6.89 (dd, *J* = 3.9, 1.6 Hz, 1H), 7.13 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 4.8Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.65 (dd, J = 7.6, 1.2 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 8.37 (dd, *J* = 4.8, 1.2 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.2, 110.1, 122.1, 123.8, 128.5, 129.9, 130.0, 130.8, 131.3, 137.0, 138.1, 139.5, 146.4, 152.2, 183.3, ppm; MS (ESI$^+$): m/z (rel intensity): 299 (MH^{++2}, 29), 297 (MH$^+$, 100), 271 (1), 141 (5), 139 (17). HRMS (ESI$^+$): calcd. for $C_{17}H_{14}ClN_2O$ [MH$^+$] 297.0795; found, 297.0802.



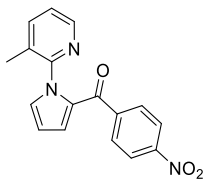
(4-Bromophenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (3bf). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-bromobenzaldehyde **2f** (370.0 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bf** as white solid (149.2mg, 44 %): m.p. (CH_2Cl_2): 109-111 °C; IR (ATR): 1739 cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.11 (s, 3H), 6.40 (dd, *J* = 3.8, 2.7 Hz, 1H), 6.89 (dd, *J* = 3.8, 1.5 Hz, 1H), 7.10–7.16 (m, 1H), 7.29 (dd, *J* = 7.6, 4.8 Hz, 1H),7.57 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 8.37 (d, *J* = 3.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4, 110.1, 122.2, 123.8, 126.7, 129.9, 130.1, 130.9, 131.3, 131.4, 137.5, 139.5, 146.4, 152.2, 183.4 ppm; MS (ESI$^+$): *m/z* (rel intensity): 343(MH^{++2}, 99), 341 (MH$^+$, 100), 185 (9), 183 (10). HRMS (ESI$^+$): calcd. for $C_{17}H_{14}BrN_2O$ [MH$^+$] 341.0290; found, 341.0293.



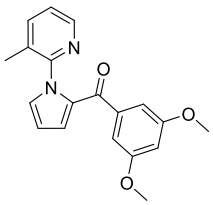
4-[1-(3-Methylpyridin-2-yl)-1*H*-pyrrole-2-carbonyl]benzonitrile (3bg). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4- formylbenzonitrile **2g** (262.2 mg; 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bg** as yellow solid (124.4 mg, 43%): m.p. (CH_2Cl_2): 112-115 °C; IR (ATR): 2230, 1739, 1634 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 2.11 (s, 3H), 6.41 (dd, *J* = 4.0, 2.7 Hz, 1H), 6.87 (dd, *J* = 4.0, 1.5 Hz, 1H), 7.16 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.30 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.67 (dd, *J* = 7.5,1.0 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 8.36 (dd, J = 4.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.2, 110.4, 115.1, 118.2, 122.9, 124.0, 129.7, 130.1, 130.7, 131.0, 132.1, 139.6, 142.4, 146.5, 151.9, 182.6 ppm; MS (ESI^+): *m/z* (rel intensity): 288 (MH^+, 100), 130 (6). HRMS (ESI^+): calcd. for $C_{18}H_{14}N_3O$ [MH^+] 288.1137; found, 288.1141.



[1-(3-Methylpyridin-2-yl)-1*H*-pyrrol-2-yl](4-nitrophenyl)methanone (3bh). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-nitrobenzaldehyde **2h** (302.2 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded as yellow oil **3bh** (32.4 mg, 11%): IR (ATR): 1745, 1637 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H), 6.46 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.92 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.20 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.35 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.71 (ddd, *J* = 7.6, 1.8, 0.8 Hz, 1H), 7.94-8.08 (m, 2H), 8.20-8.35 (m, 2H), 8.41 (ddd, *J* = 4.8, 1.8, 0.7 Hz, 1H), ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.2, 110.5, 123.1, 123.4, 124.1, 130.1, 130.2, 130.9, 130.9, 139.6, 144.0, 146.50, 149.6, 151.9, 182.4 ppm; MS (ESI^+): *m/z* (rel intensity): 308 (MH^+, 100), 274 (1), 150 (3). HRMS (ESI^+): calcd. for $C_{17}H_{14}N_3O_3$ [MH^+] 308.1035; found, 308.1033.

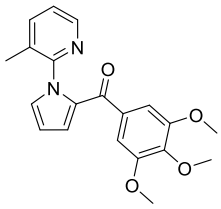


(3,5-Dimethoxyphenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2- yl]methanone (3bi). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 3,5-dimethoxybenzaldehyde **2i** (332.2, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3)



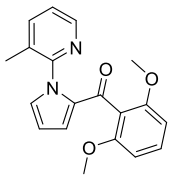
afforded **3bi** as yellow oil (209.2 mg, 65%): IR (ATR): 1727, 1627 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (s, 3H), 3.78 (s, 6H), 6.38 (dd, *J* = 3.9, 2.6 Hz, 1H), 6.61 (t, *J* = 2.3 Hz, 1H), 6.98 (dd, *J* = 3.9, 1.6 Hz, 1H), 7.00 (d, *J* = 2.3 Hz, 2H), 7.11 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.27 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.63 (ddd, *J* = 7.5, 1.8, 0.8 Hz, 1H), 8.36 (ddd, *J* = 4.8, 1.8, 0.7 Hz, 1H) ppm;^{13}C NMR (75 MHz, $CDCl_3$): δ 17.2, 55.5, 104.5, 107.2, 110.0, 122.2, 123.7, 129.7, 130.1, 131.5, 139.4, 140.4, 146.3, 152.3, 160.5, 184.1 ppm; MS (ESI^+): *m/z* (rel intensity): 323 (MH^+, 100), 165 (18). HRMS (ESI^+): calcd. for $C_{19}H_{19}N_2O_3$ [MH^+] 323.1396; found, 323.1406.

[1-(3-Methylpyridin-2-yl)-1*H*-pyrrol-2-yl](3,4,5- trimethoxyphenyl)methanone (3bj).



Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 3,4,5-trimethoxybenzaldehyde **3j** (392.4 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 3.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bj** as yellow oil (217.9 mg, 62%): IR (ATR): 1726, 1630 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.80 (s, 6H), 3.84 (s, 3H), 6.32 (dd, *J* = 3.9, 2.8 Hz, 1H), 6.91 (dd, *J* =3.9, 1.4 Hz, 1H), 7.03-7.08 (m, 1H), 7.10 (s, 2H), 7.20 (dd, *J* = 7.0, 3.5 Hz, 1H), 7.57 (d, *J* = 7.0Hz, 1H), 8.28 (d, *J* = 3.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 56.2, 60.8, 107.0, 109.7, 121.5, 123.7, 129.4, 130.0, 131.4, 133.6, 139.4, 141.5, 146.2, 152.2, 152.7, 183.5 ppm; MS (ESI^+): *m/z* (rel intensity): 353 (MH^+, 100), 195 (10). HRMS (ESI^+): calcd. for $C_{20}H_{21}N_2O_4$ [MH^+] 353.1501; found, 353.1508.

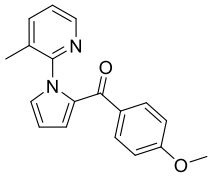
(2,6-Dimethoxyphenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2- yl]methanone (3bk).



Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 2,6-dimethoxybenzaldehyde **2k** (332.2, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 7 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bk** as yellow oil (126.0 mg, 39%): IR (ATR): 1641, 1595 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H); 3.71 (s, 6H), 6.31 (dd, *J* = 3.9, 2.6 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 6.65 (dd, *J* = 3.9, 1.7 Hz, 1H), 7.05 (dd, *J* = 2.6, 1.7 Hz, 1H), 7.33-7.22 (m, 2H), 7.66-7.61 (m, 1H), 8.41 (ddd, *J* = 4.8, 1.8, 0.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7, 55.8, 103.9, 109.9, 118.9, 121.8, 123.7, 129.3, 130.3, 131.1, 133.5, 139.1, 146.1, 152.5, 157.7, 182.9 ppm; MS

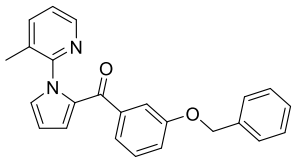
(ESI$^+$): *m/z* (rel intensity): 323 (MH$^+$, 100), 185 (50), 165 (24). HRMS (ESI$^+$): calcd. for $C_{19}H_{19}N_2O_3$ [MH$^+$]: 323.1396; found, 323.1398.

(4-Methoxyphenyl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2- yl]methanone (3bp).



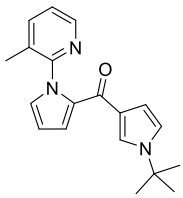
Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 4-methoxybenzaldehyde **2p** (0.24 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 1,5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bp** as yellow solid (174.9 mg, 60%): m.p. (CH_2Cl_2): 109-111 °C; IR (ATR): 3009., 2991, 1735, 1627, 1595, 1451, 1408 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09 (s, 3H), 3.80 (s, 3H), 6.36 (dd, *J* = 3.9, 2.7 Hz, 1H), 6.86-6.94 (m, 3H), 7.08 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.23 (dd, *J* = 7.6, 4.6 Hz, 1H), 7.55-7.64 (m, 1H), 7.80-7.92 (m, 2H), 8.34 (dd, *J* = 4.6, 1.4 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.3, 55.5, 109.7, 113.5, 121.4, 123.6, 129.0, 130.0, 131.2, 131.6, 131.8, 139.4, 146.3, 152.4, 162.8, 183.6 ppm; MS (ESI$^+$): *m/z* (rel intensity): 293 (MH$^+$, 100), 185 (2), 136 (2), 135 (29). HRMS (ESI$^+$): calcd. for $C_{18}H_{17}N_2O_2$ [MH$^+$] 293.1290; found, 293.1293.

[3-(Benzyloxy)phenyl][1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2- yl]methanone (3bq).

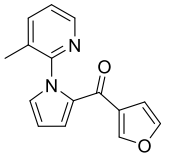


Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 3-(benzyloxy)benzaldehyde **3q** (424.5 mg, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 2 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded as yellow oil **3bq** (224.2 mg, 61%): IR (ATR): 1645, 1595 cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H), 5.11 (s, 2H), 6.40 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.91 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.14 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.18 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 7.28 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.41-7.31 (m, 4H), 7.46-7.42 (m, 2H), 7.51-7.53 (m, 2H), 7.64 (ddd, *J* = 7.6, 1.8, 1.0 Hz, 1H), 8.40 (dd, *J* = 4.8, 1.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 70.1, 110.0, 114.9, 119.3, 122.3, 122.4, 123.7, 127.5, 128.1, 128.7, 129.3, 129.6, 130.1, 131.6, 136.7, 139.4, 140.0, 146.4, 152.4, 158.6, 184.3 ppm; MS (ESI$^+$): *m/z* (rel intensity): 369 (MH$^+$, 100), 211 (6). HRMS (ESI$^+$): calcd. for $C_{24}H_{21}N_2O_2$ [MH$^+$] 369.1603; found, 369.1602.

[1-(*tert*-Butyl)-1*H*-pyrrol-3-yl][1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2- yl]methanone (3br). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 1-(*tert*-butyl)-1*H*-pyrrole-3-carbaldehyde **3r** (226.8 mg, 1.5 mmol) and TBHP (5.5 M in decane, 0.54 mL, 3 mmol). After 1.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **3br** as white solid (216.7 mg, 71 %): m.p. (CH_2Cl_2): 133-134 °C; IR (ATR): 1612, 1526, cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 1.51 (s, 9H), 2.10 (s, 3H), 6.34 (dd, *J* = 3.8, 2.7 Hz, 1H), 6.66 (dd, *J* = 2.9, 1.8 Hz, 1H), 6.79 (t, *J* = 2.9 Hz, 1H), 7.00 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.04 (dd, *J* = 3.8, 1.5 Hz, 1H), 7.21 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.49 (t, *J* = 1.8 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 8.38-8.26 (m, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.4, 30.6, 55.7, 109.4, 110.0, 118.5, 118.9, 123.4, 123.8, 124.0, 127.7, 130.2, 133.0, 139.2, 146.1, 152.8, 179.1 ppm; MS (ESI^+): *m/z* (rel intensity): 308 (MH^+, 100), 185 (33), 150 (5). HRMS (ESI^+): calcd. for $C_{19}H_{22}N_3O$ [MH^+] 308.1763; found, 308.1764.



(1-Methyl-1*H*-pyrrol-2-yl)[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2- yl]methanone (3bs). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), 1-methyl-1*H*-pyrrole-2-carbaldehyde **2s** (0.20 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After 4.5 h at 85 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bs** as a brown solid (142.0 mg, 54 %): m.p. (CH_2Cl_2): 108-111°C; IR (ATR): 1739, 1609 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H), 3.81 (s, 3H), 6.14 (dd, *J* = 4.0, 2.4 Hz, 1H), 6.36 (dd, *J* = 3.8, 2.7 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 6.97-7.01 (m, 2H), 7.05 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.25 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 8.38 (dd, *J* = 4.9, 1.8 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.3, 36.7, 107.8, 109.4, 120.0, 120.5, 123.5, 128.3, 129.7, 130.4, 130.8, 133.0, 139.5, 146.4, 152.4, 175.1 ppm; MS (ESI^+): *m/z* (rel intensity): 266 (MH^+, 14), 185 (100), 108 (1). HRMS (ESI^+): calcd. for $C_{16}H_{16}N_3O$ [MH^+]: 266.1293; found, 266.1297.

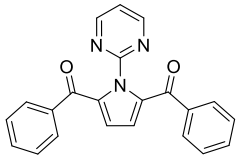


Furan-3-yl[1-(3-methylpyridin-2-yl)-1*H*-pyrrol-2-yl]methanone (3bt). Following the general procedure **1b** (158.2 mg, 1 mmol) was treated with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), PivOH (76.6 mg, 0.75 mmol), furan-3- carbaldehyde **2t** (0.17 mL, 2 mmol) and TBHP (5.5 M in decane, 0.72 mL, 4 mmol). After

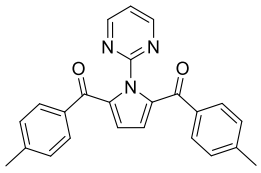
1.5 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **3bt** as a brown-red oil (196.7 mg, 78 %): IR (ATR): 1627, 1454 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 3H), 6.36 (dd, *J* = 3.7, 2.8 Hz, 1H), 6.76 (m, 1H), 7.08 – 7.04 (m, 2H), 7.24 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.40 (t, *J* = 1.7 Hz, 1H), 7.61 (dd, *J* = 7.6, 1.0 Hz, 1H), 8.01 (t, *J* = 1.1 Hz, 1H), 8.33 (dd, *J* = 4.9, 1.8 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.2, 110.0, 110.1, 119.7, 123.8, 126.8, 129.3, 130.2, 132.2, 139.4, 143.6, 146.3, 146.7, 152.2, 177.2 ppm; MS (ESI^+): *m/z* (rel intensity): 253 (MH^+, 100), 95 (16). HRMS (ESI^+): calcd. for $C_{15}H_{13}N_2O_2$ [MH^+] 253.0977; found, 253.0982.

6.2.1.3. Characterization data of diacylated compounds **4**

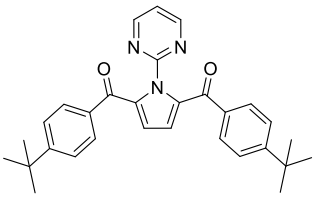
[1-(Pyrimidin-2-yl)-1*H*-pyrrole-2,5-diyl]bis(phenylmethanone) (**4aa)** Obtained as a byproduct in the reaction between **1a** and **2a** as white solid, whose data are coincidental to those reported[17] (53.6 mg, 16%): m.p. (CH_2Cl_2): 143-145 °C (Lit.[17] 139-142 ºC); IR (ATR): 1649, 1573 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (s, 2H), 7.31 (t, *J* = 4.7 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 4H), 7.52-7.61 (m, 2H), 7.87-7.96 (m, 4H), 8.73 (d, *J* = 4.7 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 119.2, 120.2, 128.5, 129.7, 133.0, 136.2, 137.5, 158.2, 158.4, 185.7 ppm; MS (ESI^+): *m/z* (rel intensity): 354 (MH^+, 100). HRMS (ESI^+): calcd. for $C_{22}H_{16}N_3O_2$ [MH^+] 354.1243; found, 354.1247.



[1-(Pyrimidin-2-yl)-1*H*-pyrrole-2,5-diyl]bis(*p*-tolylmethanone) (**4ab).** was obtained as a byproduct in the reaction between **1a** and **2b** as white solid (91.8 mg, 24%): m.p. (CH_2Cl_2): 148-151 °C; IR (ATR): 1645, 1606, 1570 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 6H), 6.82 (s, 2H), 7.28 (d, *J* = 8.2 Hz, 4H), 7.32 (t, *J* = 4.9 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 4H), 8.75 (d, *J* = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.7, 118.9, 120.0, 129.1, 129.9, 135.0, 136.2, 143.7, 158.4, 185.4 ppm; MS (ESI^+): *m/z* (rel intensity): 382 (MH^+, 100), 339 (1), 220 (1). HRMS (ESI^+): calcd. for $C_{24}H_{20}N_3O_2$ [MH^+] 382.1556; found, 382.1560.

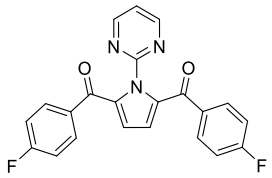


[1-(Pyrimidin-2-yl)-1*H*-pyrrole-2,5-diyl]bis{[4-(*tert*-butyl)phenyl]methanone} (4ac). Obtained as a byproduct in the reaction between **1a** and **2c** as white solid (190.6 mg, 41%):



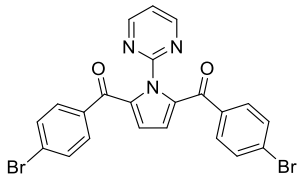
m.p. (CH_2Cl_2): 81-83 °C; IR (ATR): 1649, 1606, 1570cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 18H), 6.85 (s, 2H), 7.32 (t, J = 4.6 Hz, 1H), 7.50 (d, J = 8.1 Hz, 4H), 7.89 (d, J = 8.1 Hz, 4H), 8.75 (d, J = 4.6 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 31.1, 35.2, 118.9, 120.0, 125.4, 129.7, 134.9, 136.3, 156.7, 157.1, 158.4, 185.4 ppm; MS (ESI$^+$): *m/z* (rel intensity): 466 (MH^+, 100), 282 (1), 253 (1). HRMS (ESI$^+$): calcd. for $C_{30}H_{32}N_3O_2$ [MH^+]: 466.2495; found, 466.2501.

[1-(Pyrimidin-2-yl)-1*H*-pyrrole-2,5-diyl]bis[(4-fluorophenyl)methanone] (4ad).



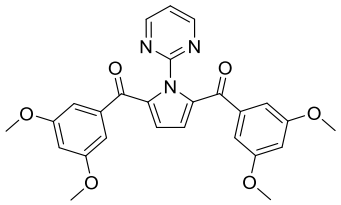
Obtained as a byproduct in the reaction between **1a** and **2d** as white solid (31.1 mg, 8%): m.p. (CH_2Cl_2): 209-211 °C; IR (ATR): 1739, 1649, 1595 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 (s, 2H), 7.16 (t, J = 8.5 Hz, 4H), 7.35 (t, J = 4.5 Hz, 1H), 7.94-7.98 (m, 4H), 8.76 (d, J = 4.7 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 118.9, 120.3, 132.2 (d, J = 9.2 Hz), 133.7 (d, J = 2.9 Hz), 136.0, 155.7 (d, J = 22.0 Hz), 157.9, 158.4, 165.7 (d, J = 254.9 Hz), 184.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -106.0 ppm; MS (ESI$^+$): m/z (rel intensity): 390 (MH^+, 100), 368 (1), 209 (1). HRMS (ESI$^+$): calcd. for $C_{22}H_{14}F_2N_3O_2$ [MH^+] 390.1054; found, 390.1054.

[1-(Pyrimidin-2-yl)-1*H*-pyrrole-2,5-diyl]bis[(4-bromophenyl)methanone] (4af).



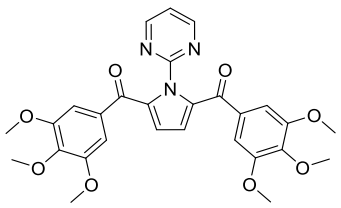
Obtained as a byproduct in the reaction between **1a** and **2f** as white solid (23.2 mg, 5%): m.p. (CH_2Cl_2): 200-203 °C; IR (ATR): 1649, 1595 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82 (s, 2H), 7.36 (t, J = 4.9 Hz, 1H), 7.63 (d, J = 8.5 Hz, 4H), 7.78 (d, J = 8.5 Hz, 4H), 8.76 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 119.1, 120.2, 128.2, 131.3, 131.8, 135.9, 136.2, 157.9, 158.5, 184.6 ppm; MS (ESI$^+$): *m/z* (rel intensity): 514 (MH^{++2}, 40), 512 (MH^+, 100), 510 (MH^{+-2}, 42), 385 (7), 301 (30). HRMS (ESI$^+$): calcd. for $C_{22}H_{14}Br_2N_3O_2$ [MH^+] 509.9453; found, 509.9452.

[1-(Pyrimidin-2-yl)-1*H*-pyrrole-2,5-diyl]bis[(3,5-dimethoxyphenyl)methanone] (4ai).



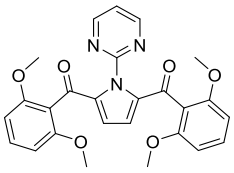
Obtained as a byproduct in the reaction between **1a** and **2i** as white solid (38.3 mg, 8%): m.p. (CH_2Cl_2): 169-172 °C; IR (ATR): 1739, 1662 cm^{1-}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 12H), 6.68 (s, 2H), 6.88 (s, 2H), 7.06 (s, 4H), 7.35 (t, J = 4.8 Hz, 1H), 8.78 (d, J = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.6, 106.6, 107.4, 119.2, 120.1, 136.2, 139.3, 158.4, 160.6, 185.3 ppm; MS (ESI^+): *m/z* (rel intensity): 474 (MH^+, 100), 340 (3), 286 (1). HRMS (ESI^+): calcd. for $C_{26}H_{24}N_3O_6$ [MH^+] 474.1665; found: 474.1671.

[1-(Pyrimidin-2-yl)-1*H*-pyrrole-2,5-diyl]bis[(3,4,5-trimethoxyphenyl)methanone] (4aj).



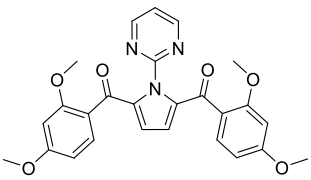
Obtained as a byproduct in the reaction between **1a** and **2j** as yellow solid (83.5 mg, 8%): m.p. (CH_2Cl_2): 200-203 °C; IR (ATR): 1645, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 12H), 3.91 (s, 6H), 6.85 (s, 2H), 7.20 (s, 4H), 7.33 (t, J = 4.9 Hz, 1H), 8.74 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.3, 61.0, 107.3, 118.6, 120.0, 132.4, 136.2, 142.5, 153.0, 158.0, 158.4, 184.7 ppm; MS (ESI^+): *m/z* (rel intensity): 534 (MH^+, 100), 316 (1), 287 (1). HRMS (ESI^+): calcd. for $C_{28}H_{28}N_3O_8$ [MH^+] 534.1876; found, 534.1873.

[1-(Pyrimidin-2-yl)-1*H*-pyrrole-2,5-diyl]bis[(2,6-dimethoxyphenyl)methanone] (4ak):



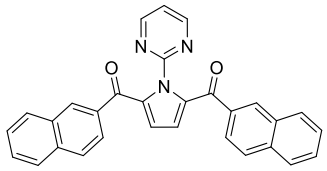
Obtained as a byproduct in the reaction between **1a** and **2k** as white solid (47.8 mg, 10%): m.p. (CH_2Cl_2): 156-158 °C; IR (ATR): 1645, 1570 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 3.70 (s, 12H), 6.44 (s, 2H), 6.73 (d, J = 8.4 Hz, 4H), 7.38 (t, J = 8.4 Hz, 2H), 7.65 (t, J = 4.9 Hz, 1H), 8.93 (d, J = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, DMSO): δ 56.3, 104.8, 117.3, 119.5, 121.6, 131.8, 136.9, 157.5, 158.6, 159.2, 184.0 ppm; MS (ESI^+): *m/z* (rel intensity): 474 (MH^+, 100), 336 (14), 165 (2); HRMS (ESI^+): calcd. for $C_{26}H_{24}N_3O_6$ [MH^+] 474.1665; found: 474.1674.

[1-(Pyrimidin-2-yl)-1*H*-pyrrole-2,5-diyl]bis[(2,4-dimethoxyphenyl)methanone] (4al).



Obtained as a byproduct in the reaction between **1a** and **2l** as colorless solid (39.8 mg, 8%): m.p. (CH_2Cl_2): 117-120 °C; IR (ATR): 1598, 1469cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 6H), 3.81 (s, 6H), 6.43 (d, J = 2.1 Hz, 2H), 6.47 (dd, J = 8.5, 2.1 Hz, 2H), 6.59 (s, 2H), 7.25 (t, J = 4.8 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 8.71 (d, J = 4.8 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.5, 55.7, 98.8, 104.1, 118.5, 119.7, 121.1, 133.1, 137.4, 158.2, 158.6, 160.1, 161.7, 184.1 ppm; MS (ESI$^+$): *m/z* (rel intensity): 474 (MH^+, 100), 336 (1), 257 (1). HRMS (ESI$^+$): calcd. for $C_{26}H_{24}N_3O_6$ [MH^+] 474.1665; found, 474.1668.

[1-(pyrimidin-2-yl)-1*H*-pyrrole-2,5-diyl]bis(naphthalen-2-ylmethanone) (4ao).



Obtained as a byproduct in the reaction between **1a** and **2o** as white solid (85.5 mg, 19%): m.p. (CH_2Cl_2): 80-83 °C; IR (ATR): 1739, 1645 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (s, 2H), 7.35 (t, J = 4.9 Hz, 1H), 7.57-7.61 (m, 2H), 7.61-7.66 (m, 2H), 7.92-8.05 (m, 8H), 8.57 (s, 2H), 8.80 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 119.2, 120.1, 125.2, 126.9, 127.9, 128.5, 128.5, 130.0, 131.7, 132.3, 134.9, 136.0, 136.5, 158.2, 158.5, 185.8 ppm; MS (ESI$^+$): *m/z* (rel intensity): 454 (MH^+, 100), 301 (1), 255 (1). HRMS (ESI$^+$): calcd. for $C_{30}H_{20}N_3O_2$ [MH^+] 454.1556; found, 454.1559.

6.2.1.4. Removal of the 2-Pyrimidyl and 3-Methyl-2-Pyridyl Directing Groups

Removal of the 2-Pyrimidyl Directing Group.[19] **General procedure:** Under argon atmosphere, a solution of **3aa**, **3ab** or **3ak** (1 mmol) and NaOEt (3 mmol) in DMSO (5 mL) was stirred at 100 °C for 2.5-3.5 h. The reaction was allowed to cool down, and EtOAc (10 mL) and H_2O (15 mL) were added. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layer were washed with H_2O (3 × 10 mL) and dried over Na_2SO_4.

[19] Li, C.; Zhu, W.; Shu, S.; Wu, X.; Liu, H. Palladium-Catalyzed C2-Acylation of Indoles with α-Diketones Assisted by the Removable *N*-(2-Pyrimidyl) Group. *Eur. J. Org. Chem.* **2015**, 3743-3750.

The solvent was removed under reduced pressure and the crude product was purified by column chromatography affording **5a,b,k**.

Phenyl(1*H*-pyrrol-2-yl)methanone (5a). Following the general procedure **3aa** (249.6 mg, 1 mmol) was treated with NaOEt (204.3 mg, 3mmol) in DMSO (5 mL). After 2.5 h at 100 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **5a** as a white solid, whose data are coincidental to those reported[20] (153.6 mg, 90%): m.p. (CH_2Cl_2): 76-78 °C (Lit.[20] 77-78 ºC); IR (ATR): 3282, 1609 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 6.35-6.38 (m, 1H), 6.92 (ddd, J = 3.8, 2.4, 1.3 Hz, 1H), 7.19 (td, J = 2.4, 1.3 Hz, 1H), 7.43-7.52 (m, 2H), 7.56-7.61 (m, 1H), 7.92-7.96 (m, 2H), 10.53 (br s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 111.0, 119.9, 125.8, 128.3, 129.0, 131.2, 131.8, 138.5, 186.1 ppm; MS (ESI^+): *m/z* (rel intensity): 172 (MH^+, 100), 105 (45). HRMS (ESI^+): Calcd. for $C_{11}H_{10}NO$ [MH^+] 172.0762; found, 172.0767.

(1*H*-Pyrrol-2-yl)(p-tolyl)methanone (5b). Following the general procedure **3ab** (287.0 mg, 1.09 mmol) was treated with NaOEt (222.1 mg, 3.27 mmol) in DMSO (10 mL). After 3 h at 100 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **5b** as white solid whose data are coincidental to those reported[20] (191.3 mg, 95%): m.p. (CH_2Cl_2): 120-122 °C (Lit.[20] 118-119 ºC); IR (ATR) 3429, 1733, 1612 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H), 6.36 (dt, J = 3.8, 2.5 Hz, 1H), 6.94 (ddd, J = 3.8, 2.5, 1.4 Hz, 1H), 7.19 (td, J = 2.7, 1.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 10.54 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.6, 110.9, 119.5, 125.5, 129.0, 129.2, 131.3, 135.8, 142.5, 184.8 ppm; MS (ESI^+): *m/z* (rel intensity): 186 (MH^+, 89), 119 (29), 94 (8). HRMS (ESI^+): calcd. for $C_{12}H_{12}NO$ [MH^+] 186.0919; found, 186.0914.

(2,6-Dimethoxyphenyl)(1H-pyrrol-2-yl)methanone (5k). Following the general procedure **3ak** (347.1 mg, 1.12 mmol) was treated with NaOEt (229.1 mg, 3.37 mmol) in DMSO (10 mL). After 3.5 h at 100 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **5k** as orange

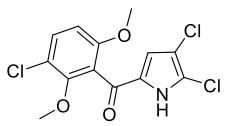
[20] Jafarpour. F.; Hazrati. H.; Darvishmolla. M. Acylation of Pyrroles and their Free (N-*H*)-Derivatives *via* Palladium-Catalyzed Carbopalladation of Nitriles. *Adv. Synth. Catal.* **2014**, *356*, 3784-3788.

solid, whose data are coincidental to those reported[21](234.6 mg, 91%): m.p. (CH_2Cl_2):192-194 °C; IR (ATR): 3278, 1623, 1595 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 6H), 6.24 (dt, J = 3.8, 2.4 Hz, 1H), 6.57 (ddd, J = 3.8, 2.4, 1.4 Hz, 1H), 6.63 (d, J = 8.4 Hz, 2H), 7.10 (td, J = 2.7, 1.4 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 10.00 (br s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.0, 104.1, 110.7, 118.0, 119.2, 125.4, 130.7, 133.4, 157.8, 183.9 ppm; MS (ESI^+): *m/z* (rel intensity): 254 (MNa^+, 100), 232 (MH^+, 2), 165 (7). HRMS (ESI^+): calcd. for $C_{13}H_{13}NNaO_3$ [MNa^+] 254.0793; found, 254.0785.

Deprotection of 3ba.[22] Methyl trifluoromethanesulfonate (0.07 mL, 0.62 mmol) was added dropwise to a solution of **3ba** (131.9 mg, 0.50 mmol) in dry CH_2Cl_2 (7 mL) at 0 °C, and the resulting solution was stirred for 24 h at room temperature. Then, the solvent was removed under vacuum, and the residue was dissolved in MeOH (10 mL). A 2 M aq. NaOH solution (6 mL) was added. The resulting solution was stirred at 60 °C for 24 h. The solvents were removed, and the resulting residue was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O (2 × 15mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography afforded **5a** as a white solid (58.0 mg, 68 %).

6.2.1.5. Synthesis of celastramycine analoge **7**

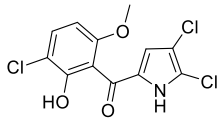
(3-Chloro-2,6-dimethoxyphenyl)(4,5-dichloro-1*H*-pyrrol-2- yl)methanone (6). To a stirred solution of **5k** (113.5 mg, 0.49 mmol) in acetonitrile (6 mL), NCS (164.2 mg, 1.23 mmol) was added and the resulting solution was stirred 24 h at 50 °C. Then, the solvent was evaporated, and the residue was partitioned between water (100 mL) and diethyl ether (100 mL). The aqueous layer was separated and extracted with diethyl ether (2 × 50 ml). The combined extracts were washed with water (20 mL), dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/AcOEt 9/1) affording **6** as light brown solid (132.6 mg, 81%): m.p. (CH_2Cl_2): 171- 173 ºC; IR (ATR,):



[21] Rao, K. V.; Reddy, G. C. J. Synthesis and herbicidal activity of the halo analogs of pyoluteorin. *Agric. Food Chem.* **1990**, *38*, 1260-1263.
[22] Yan, X.-B.; Shen, Y.-W.; Chen, D.-Q.; Gao, P.; Li, Y.-X.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. Palladium-catalyzed C2-acylation of indoles with aryl and alkyl aldehydes**.** *Tetrahedron* **2014**, *70*, 7490-7495.

3219, 1729, 1627 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$): 3.77 (s, 3H), 3.85 (s, 3H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.9 Hz, 1H), 7.42 (d, *J* = 8.9 Hz, 1H), 10.60 (br s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.2, 62.6, 107.9, 112.3, 119.0, 119.7, 122.3, 123.3, 129.8, 131.7, 153.9, 156.4, 181.1 ppm; MS (ESI^+): *m/z* (rel intensity): 340 (MH^{++6}, 1), 338 (MH^{++4}, 13), 336 (MH^{++2}, 52), 334 (MH^+, 53), 201 (24), 199 (110); HRMS (ESI^+): calcd. for $C_{13}H_{11}Cl_3NO_3$ [MH^+] 333.9805; found: 333.9803.

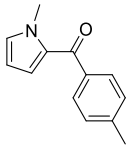
(3-Chloro-2-hydroxy-6-methoxyphenyl)(4,5-dichloro-1*H*-pyrrol-2- yl)methanone (7). A



solution of **6** (121.0 mg, 0.36 mmol) in dry dichloromethane (4 mL) was added dropwise *via* syringe to a stirred suspension of $AlCl_3$ (964.4 mg, 7.23 mmol) in dichloromethane (4 mL) in ice bath. The reaction mixture was stirred for 24 hours at room temperature. Aqueous 5% sulfuric acid on ice was added to quench the reaction mixture, the organic phase was collected and the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/AcOEt 8/2) affording **7** as white solid (64.5 mg, 56%): m.p. (CH_2Cl_2): 180-182 ºC; IR (ATR,): 3518, 3246, 1587 cm^{-1} ; ^{1}H NMR (300 MHz, Acetone-d^6): 3.77 (s, 3H), 6.65 (s, 1H), 6.70 (d, *J* = 8.9 Hz, 1H), 7.42 (d, **J** = 8.9 Hz, 1H), 8.71 (br s, 1H), 12.00 (br s, 1H) ppm; ^{13}C NMR (75.5 MHz, Acetone-d^6): δ 55.5, 104.2, 110.8, 113.2, 116.7, 117.0, 120.1, 130.8, 131.0, 151.2, 157.0, 180.7 ppm; MS (ESI^+): m/z (rel intensity): 326 (MH^{++6}, 2), 324 (MH^{++4}, 23), 322 (MH^{++2}, 99), 320 (MH^+, 100), 187 (18), 185 (77); HRMS (ESI^+): calcd. for $C_{12}H_9Cl_3NO_3$ [MH^+] 319.9651; found: 319.9648.

6.2.1.6. Synthesis of Tolmentin **9**

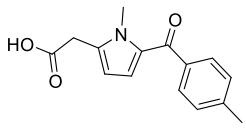
(1-Methyl-1H-pyrrol-2-yl)(p-tolyl)methanone (8). A solution of **5b** (166.5 mg, 0.9 mmol)



in dry dimethylformamide (3 mL) was added dropwise to a stirred suspension of NaH (60% in mineral oil, 39.6 mg, 0.99 mmol) in anhydrous DMF (3 mL). Then, CH_3I (0.07 mL, 1.8 mmol) was added and after 3.5 h at room temperature the reaction was quenched with water (20 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic phase was washed with water (2 × 15 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue

was purified by column chromatography (silica gel, petroleum ether/AcOEt 9/1) affording **8** as colorless oil, whose data are coincidental to those reported[20] (177 mg, 99%): IR (ATR): 1736, 1623 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 4.03 (s, 3H), 6.16 (dd, J = 4.1, 2.5 Hz, 1H), 6.76 (dd, J = 4.1, 1.7 Hz, 1H), 6.90 (t, J = 2.1 Hz, 1H), 7.26 (d, J = 7.9 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.5, 37.3, 108.0, 122.4, 128.8, 129.4, 130.6, 131.2, 137.2, 141.9, 186.0 ppm; MS (ESI^+): *m/z* (rel intensity): 200 (MH^+, 100), 119 (77). HRMS (ESI^+): calcd. for $C_{13}H_{14}NO$ [MH^+] 200.1075; found: 200.1066.

Synthesis of 2-[1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrol-2-yl]acetic acid (Tolmetin, 9).



Under argon atmosphere, a solution of **8** (154.4 mg, 0.80 mmol), $Mn(OAc)_2{\cdot}4H_2O$ (4.9 mg, 0.02 mmol), triphenylphosphine (10.5 mg, 0.05 mmol), $NaIO_4$ (102.3 mg, 0.48 mmol), NaOAc (65.6 g, 0.80 mmol) and tri(ethoxycarbonyl)methane (0.08 mL, 0.4 mmol) in dry acetic acid (1 mL) was stirred at 70 °C for 24 h. After cooling the reaction mixture to room temperature, the mixture was added Me_2S (1 mL) and passed through a short pad of Celite (EtOAc) and the filtrate was evaporated under reduced pressure. KOH (2.5 M in water, 10 mL) and 1,4-dioxane (2 mL) were added and the reaction mixture was stirred at 110 °C for 24 h. After cooling the reaction mixture to room temperature, the mixture was evaporated under reduced pressure. The residue was extracted with EtOAc (2 × 15 mL). The water layer was poured into HCl (1.0 M, 20 mL) and extracted with EtOAc (2 × 15 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4, evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, petroleum ether/AcOEt 6/4) affording **9** as a white solid, whose data are coincidental to those reported[23] (57.4 mg, 56%): m.p. (CH_2Cl_2): 154-155 °C (Lit.[23] 160-161 ºC); IR (ATR) 3225, 1739, 1619 cm^{-1} ; ^{1}H NMR (300 MHz, acetone-d^6): δ 2.42 (s, 3H), 3.84 (s, 2H), 3.95 (s, 3H), 6.15 (d, J = 4.0 Hz, 1H), 6.63 (d, J = 4.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, acetone-d^6): δ 20.6, 31.9, 32.5, 109.2, 121.5, 128.6, 129.2, 131.0, 135.9, 137.7, 141.6, 170.2, 184.9 ppm; MS (ESI^+): *m/z* (rel intensity): 258 (MH^+, 100), 236 (54), 119 (54). HRMS (ESI^+): calcd. for $C_{15}H_{16}NO_3$ [MH^+] 258.1130; found: 258.1120.

[23] Hattori, K.; Ziadi, A.; Itami, K.; Yamaguchi, J. Manganese-catalyzed intermolecular C–H/C–H coupling of carbonyls and heteroarenes. *Chem. Commun.* **2014**, *50*, 4105-4107.

6.2.2. Microwave-assisted Palladium (II) C-3 acylation of Thiophenes with aldehydes

6.2.2.1 Synthesis of substrates **10a**, **10b**, **14a**, **14b, 12a** and**12b**

2-(Thiophen-2-yl)pyridine (10a)[24]. Under argon atmosphere, a mixture of pyridin-2-yl 4-methylbenzenesulfonate (1556.7 mg, 6.2 mmol), 2-thienyl boronic acid (879.8 mg, 7.5 mmol), XPhos (71.5 mg, 0.15 mmol), $Pd(OAc)_2$ (26.4 mg, 0.12 mmol) in dry *n*-butanol was stirred for 15 min at room temperature. Then, a solution of NaOH (421.6 mg) in degassed H_2O (8.4 mL) was added to initiate the Suzuki reaction. The mixture was stirred at room temperature for 45 min. The mixture was passed through a short plug of silica gel with ethyl acetate, the solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 7/3) leading to **10a** as light brown solid (994.9 mg, >99 %), whose data were coincidental to those reported:[24] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07–7.14 (m, 2H), 7.38 (dd, J = 5.1, 1.2 Hz, 1H), 7.56 (dd, J = 3.7, 1.2 Hz, 1H), 7.66–7.59 (m, 2H), 8.56 (dt, J = 4.9, 1.4 Hz, 1H ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 118.8, 121.9, 124.6, 127.6, 128.1, 136.7, 144.9, 149.5, 152.6 ppm.

2-(Thiophen-2-yl)pyrimidine 10b.[25] Under argon atmosphere, a mixture of 2-chloropyrimidine (229.1 mg, 2 mmol), 2-thiophene boronic acid (383.8 mg, 3 mmol), K_3PO_4 (849.1 mg, 4 mmol), $Pd_2(dba)_3$ (18.1 mg, 0.02 mmol) and XPhos (38.1 mg, 0.08 mmol) in *tert*-amyl alcohol (4 mL) was heated to 100 °C for 5 h. The mixture was passed through a short plug of silica gel with ethyl acetate, solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 8/2) affording **10b** as white solid (325.3 mg, 67%), whose data were coincidental to those reported:[25] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (t, J = 4.9 Hz, 1H), 7.10 (dd, J = 5.0, 3.7 Hz, 1H), 7.44 (dd, J = 5.0, 1.2 Hz, 1H), 7.98 (dd, J = 3.7, 1.2 Hz, 1H),

[24] Yang, J.; Liu, S.; Zheng, J-F.; Zhou, J. Room-Temperature Suzuki–Miyaura Coupling of Heteroaryl Chlorides and Tosylates. *Eur. J. Org. Chem.* **2012**, 6248- 6259.
[25] Billingsley, K.; Buchwald, S. L. Highly Efficient Monophosphine-Based Catalyst for the Palladium-Catalyzed Suzuki−Miyaura Reaction of Heteroaryl Halides and Heteroaryl Boronic Acids and Esters. *J. Am. Chem. Soc.* **2007**, *129*, 3358-3366.

8.62 (d, J = 4.9 Hz, 2H,) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 118.5, 128.3, 129.0, 129.9, 143.2, 157.2, 161.5 ppm.

2-(Thiophen-3-yl)pyridine (12a).[26] 3-thienylboronic acid (921.3 mg, 7.2 mmol), K_2CO_3 (2321.9 mg, 16.8 mmol.) and $[Pd(PPh_3)_2Cl_2]$ (21.1 mg, 0.03 mmol) were dissolved in DME (18 mL) and H_2O (6.6 mL). Then, 2-bromopyridine (0.57 mL, 6 mmol) was added the mixture was stirred at 80 °C for 18 h. The reaction mixture was quenched with DCM (30 mL) and washed with H_2O (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (petroleum ether/EtOAc 15/1 to 9/1) afforded **12b** (490.0 mg, 51%), whose data are coincidental to those reported:[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (ddd, J = 7.3, 4.9, 1.3 Hz, 1H ·), 7.39 (dd, J = 5.1, 3.0 Hz, 1H), 7.60 (dt, J = 8.0, 1.2 Hz, 1H), 7.64–7.73 (m, 2H), 7.91 (dd, J = 3.0, 1.3 Hz, 1H), 8.63 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 120.3, 121.9, 123.5 , 126.2, 126.4, 136.8, 142.2, 149.6, 153.5 ppm.

2-(Furan-3-yl)pyridine (12b).[26] 3-Furanylboronic acid (805.6 mg, 7.2 mmol), K_2CO_3 (2321.9 mg, 16.8 mmol.) and $[Pd(PPh_3)_2Cl_2]$ (21.1 mg, 0.03 mmol) were dissolved in DME (18 mL) and H_2O (6.6 mL). Then, 2-bromopyridine (0.57 mL, 6 mmol) was added, and the mixture was stirred at 80 °C for 18 h. The reaction mixture was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (petroleum ether/EtOAc 20/1 to 10/1) afforded **12a** (717,5 mg, 82%) as yellow oil whose data are coincidental with those reported:[26] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, J = 1.9, 0.9 Hz, 1H), 7.00 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 7.31 (dt, J = 7.9, 1.1 Hz, 1H), 7.41 (t, J = 1.7 Hz, 1H), 7.50 (td, J = 7.8, 1.9 Hz, 1H), 7.98 (dd, J = 1.8, 0.9 Hz, 1H), 8.50 (ddd, J = 4.9, 1.9, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 108.6, 120.0, 121.6, 127.1, 136.5, 141.2, 143.8, 149.5, 151.7 ppm.

[26] Pospech, J.; Tlili, A.; Spannenberg, A.; Neumann, H.; Beller, M. Regioselective Ruthenium-Catalyzed Carbonylative Direct Arylation of Five-Membered and Condensed Heterocycles. *Chem. Eur. J.* **2014**, *20*, 3135-3141.

2-(Benzo[*b*]thiophen-3-yl)pyridine (14a).[27] Under argon atmosphere, benzo[*b*]thien-3-ylboronic acid (640.9 mg, 3.6 mmol), *n*-butanol (4.5 mL) and 2-bromopyridine (0.29 mL, 3 mmol). The mixture was purged with argon for 30 min; then degassed sodium hydroxide aqueous solution (1.5 mL, 4 M) was slowly added. To this mixture add $Pd(OAc)_2$ (13.5 mg, 0.06 mmol) and tri-*tert*-butylphosphonium tetrafluoroborate (21.8 mg, 0.075 mmol). The resulting reaction mixture was stirred for 6 h at room temperature. Then, reaction was stopped with addition of water (10 mL) and extracted with ethyl acetate (3 x 15 mL), dried over sodium sulphate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 9/1) affording **14a** as colourless oil (466.4 mg, 74 %), whose data are coincidental to those reported:[27] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (ddd, J = 7.4, 4.7, 1.3 Hz, 1H), 7.38–7.51 (m, 2H), 7.71 (dt, J = 7.9, 1.2 Hz, 1H), 7.76–7.85 (m, 2H), 7.91–7.98 (m, 1H), 8.42–8.52 (m, 1H), 8.78 (d, J = 4.7 Hz, 1H,) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 122.0, 122.6, 122.7, 124.1, 124.6, 124.7, 126.4, 136.6, 136.7, 137.3, 140.9, 149.7, 154.7 ppm.

2-(Benzo[*b*]thiophen-3-yl)pyrimidine 14b). Following the previous procedure, Benzo[*b*]thien-3-ylboronic acid (640.9 mg, 3.6 mmol), was treated with *n*-butanol (4.5 mL), 2-chloropyrimidine (342.6 mg, 3 mmol), degassed sodium hydroxide aqueous solution (1.5 mL, 4 M), $Pd(OAc)_2$ (13.5 mg, 0.06 mmol) and tri-*tert*-butylphosphonium tetrafluoroborate (21.8 mg, 0.075 mmol). After 6 h at room temperature, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **14b** as red solid (107.9 mg, 17 %), whose data are coincidental to those reported:[28] m.p. 80-82 °C (Lit:[28] 86 ºC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (t, J = 4.9 Hz, 1H), 7.44 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.55 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H), 7.94 (dt, J = 8.1, 1.1 Hz, 1H), 8.65 (s, 1H), 8.79 (d, J = 4.9 Hz, 2H), 9.18 (d, J = 8.2 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 118.6, 122.7, 124.7, 124.9, 125.8, 132.1, 134.7, 137.1, 141.1,

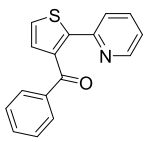
[27] Qu, B.; Mangunuru, H. P. R.; Tcyrulnikov, S.; Rivalti, D.; Zatolochnaya, O. V.; Kurouski, D.; Radomkit, S.; Biswas, S.; Karyakarte, S.; Fandrick, K. R.; Sieber, J. D.; Rodriguez, S.; Desrosiers, J.-N.; Haddad, N.; McKellop, K.; Pennino, S.; Lee, H.; Yee, N. K.; Song, J. J.; Kozlowski, M. C.; Senanayake, C. H. Enantioselective Synthesis of α-(Hetero)aryl Piperidines through Asymmetric Hydrogenation of Pyridinium Salts and Its Mechanistic Insights. *Org. Lett*. **2018**, *20*, 1333-1337.
[28] Zhu, C.; Pinkert, T.; Greßies, S.; F. Glorius, F. One-Pot C–H Formylation Enabled by Relay Catalysis of Manganese(I) and Iron(III). *ACS Catal.* **2018**, *8*, 10036-10042.

156.9, 162.6 ppm; HRMS (ESI-TOF): calcd. for $C_{12}H_9N_2S$ [MH^+]: 213.0481; found: 213.0491.

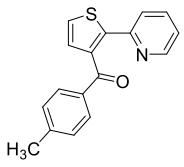
6.2.2.2. Microwave-assisted acylation reactions of **10a,b** with aldehydes

Microwave-assisted acylation reactions of 10a,b with aldehydes. General procedure: Under argon atmosphere, a sealable reaction tube (10 mL, 1.3 × 9 cm) equipped with a stirring bar was charged with **10a,b**, **12a,b** or **14a,b** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PivOH (0.38 mmol) and the corresponding aldehyde **2a-af** (1 mmol). After, DCE was added (1.5 mL), and the mixture was stirred for 2 min until solids were dissolved. Then, TBHP (5.5 M in decane, 2 mmol) was added; the reaction tube was sealed and heated under microwave irradiation at 80 °C for 15-30 min. After cooling to room temperature, the solvent was evaporated under vacuum and the residue was purified by column chromatography affording corresponding ketones.

Phenyl[2-(pyridin-2-yl)thiophen-3-yl]methanone (11aa). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), benzaldehyde **2a** (0.10 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 15 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11aa** as a white solid (110.9 mg, 84%), whose data are coincidental to those reported:[29] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (ddd, J = 7.4, 4.9, 1.2 Hz, 1H), 7.22 (d, J = 5.2 Hz, 1H), 7.29– 7.40 (m, 3H), 7.41 – 7.51 (m, 3H), 7.77 – 7.85 (m, 2H), 8.46 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 122.4 122.5, 126.6, 128.4, 129.8, 129.9, 133.1, 136.3, 137.6, 137.8, 145.8, 149.4, 151.3, 193.7 ppm.



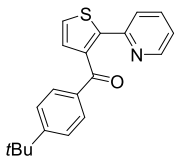
[2-(Pyridin-2-yl)thiophen-3-yl](*p*-tolyl)methanone (11ab). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-methylbenzaldehyde **2b** (0.12 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80°C, purification by column chromatography (silica gel,



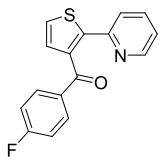
[29] Wu, Y.; Zhang, Q.; Yang, F. Palladium-catalyzed *ortho*-acylation of 2-aryl pyridine derivatives using arylmethyl amines as new acyl sources. *Chem. Commun.* **2013**, *49*, 6837-6839.

petroleum ether/EtOAc 8/2) afforded **11ab** as a white solid (117.6 mg, 84%): m.p. 103-105 °C; IR (ATR): 3013, 2970, 1736, 1658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.08 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 5.2 Hz, 1H), 7.36–7.41 (m, 1H), 7.43 (d, *J* = 5.2 Hz, 1H), 7.48 (td, *J* = 7.7, 1.8 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 8.50 (dt, *J* = 4.8, 1.3 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.7, 122.3, 122.4, 126.6, 129.1, 129.8, 130.1, 135.0, 136.3, 138.1, 144.2, 145.4, 149.4, 151.4, 193.6 ppm; MS (ESI): *m/z* (rel intensity): 280 (MH^+, 100), 188 (1); HRMS (ESI-TOF): calcd. for $C_{17}H_{14}NOS$ [MH^+]: 280.0796.

[4-(*tert*-Butyl)phenyl][2-(pyridin-2-yl)thiophen-3-yl]methanone (11ac). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-(*tert*-butyl)benzaldehyde **2c** (162.2 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 20 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11ac** as a yellow oil (117.9 mg, 73%): IR (ATR): 3056, 2960, 2903, 2868, 1654 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 7.06 (ddd, *J* = 7.3, 4.9, 1.3 Hz, 1H), 7.20 (d, *J* = 5.2 Hz, 1H), 7.33–7.43 (m, 4H), 7.47 (td, *J* = 7.7, 1.8 Hz, 1H), 7.71–7.84 (m, 2H), 8.50 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 31.1, 35.1, 122.3, 122.4, 125.4, 126.5, 129.8, 130.0, 134.9, 136.3, 138.1, 145.6, 149.4, 151.4, 157.1, 193.5 ppm; MS (ESI): *m/z* (rel intensity): 322 (MH^+, 100), 318 (1); HRMS (ESI-TOF): calcd. for $C_{20}H_{20}NOS$ [MH^+]: 322.1266; found: 322.1275.

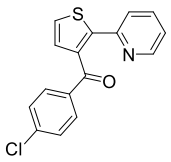


(4-Fluorophenyl)[2-(pyridin-2-yl)thiophen-3-yl]methanone (11ad). Following the general procedure, **10a** (80.6 mg, 1 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-fluorobenzaldehyde **2d** (0.11 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **11ad** as a yellow solid (117.7 mg, 83%) whose data are coincidental to those reported.[26] ^1H NMR (300 MHz, $CDCl_3$) δ 6.97–7.05 (m, 2H), 7.09 (ddd, *J* = 7.9, 4.8, 1.2 Hz, 1H), 7.23 (d, *J* = 5.2 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.50 (td, *J* = 7.9, 1.8 Hz, 1H), 7.79–7.90 (m, 2H), 8.47 (dt, *J* = 4.8, 1.2 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 115.5 (d, *J* = 22.0 Hz) , 122.4, 122.5, 126.8, 129.7, 132.4 (d, *J* = 9.5 Hz), 134.1 (d, *J* = 2.9 Hz), 136.4, 137.6, 145.5, 149.4,

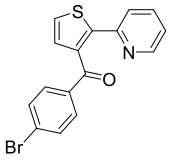


151.1, 165.6 (d, J = 252.6 Hz), 192.2 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -104.94 – -104.84 (m).

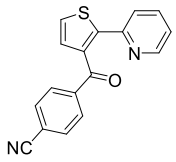
(4-Chlorophenyl)[2-(pyridin-2-yl)thiophen-3-yl]methanone (11ae). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-chlorobenzaldehyde **2e** (140.6 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11ae** as a light yellow solid (118.1 mg, 79%): m.p. (CH_2Cl_2): 77-79 °C; IR (ATR): 3052, 2988, 1736, 1655 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 7.21 (d, J = 5.2 Hz, 1H), 7.27–7.33 (m, 2H), 7.35 (dt, J = 8.0, 1.0 Hz, 1H), 7.43 (d, J = 5.2 Hz, 1H), 7.49 (td, J = 7.7, 1.8 Hz, 1H), 7.71–7.78 (m, 2H), 8.44 (ddd, J = 4.9, 1.7, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 122.4, 122.5, 126.8, 128.7, 129.7, 131.1, 136.0, 136.4, 137.5, 139.4, 145.7, 149.4, 151.1, 192.5 ppm; MS (ESI): *m/z* (rel intensity): 302 (MH^{++2}, 37), 300 (MH^+, 100); HRMS (ESI-TOF): calcd. for $C_{16}H_{11}ClNOS$ [MH^+]: 300.0250; found: 300.0258.



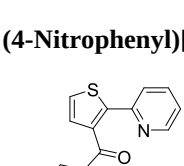
(4-Bromophenyl)[2-(pyridin-2-yl)thiophen-3-yl]methanone (11af). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-bromobenzaldehyde **2f** (185.0 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **3l** as a light brown solid (130.6 mg, 76%): m.p. (CH_2Cl_2): 101-103 °C; IR (ATR): 3109, 3006, 1743, 1658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.22 (d, J = 5.2 Hz, 1H), 7.37 (dt, J = 8.0, 1.1 Hz, 1H), 7.41–7.55 (m, 4H), 7.60–7.72 (m, 2H), 8.45 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 122.4, 122.5, 126.8, 128.2, 129.7, 131.2, 131.7, 136.4, 136.5, 137.4, 145.7, 149.4, 151.1, 192.6 ppm; MS (ESI): *m/z* (rel intensity): 345 (MH^{++2}, 100), 343 (MH^+, 97); HRMS (ESI-TOF): calcd. for $C_{16}H_{11}BrNOS$ [MH^+]: 343.9745; found: 343.9745.



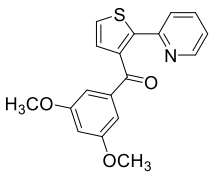
4-[2-(Pyridin-2-yl)thiophene-3-carbonyl]benzonitrile (11ag). Following the general procedure, **10a** (80.6 mg, 1 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-formylbenzonitrile **2g** (131.1 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 15 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **11ag** as a white solid (85.5 mg, 59%). m.p. (CH_2Cl_2): 100-102 °C; IR (ATR): 2228, 1669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 7.24 (d, J = 5.2 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.44 (d, J = 5.2 Hz, 1H), 7.50 (td, J = 7.7, 1.8 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 8.31 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 115.7, 118.0, 122.4, 122.7,126.9, 129.7, 132.1, 136.5, 137.1, 141.2, 146.1, 149.3, 150.7, 191.9 ppm; MS (EI): *m/z* (rel intensity): 290 (M^+, 11), 261 (100), 188 (21), 102 (13); HRMS (ESI-TOF): calcd. for$C_{17}H_{11}N_2OS$ [MH^+]: 291.0592; found: 291.0598.



(4-Nitrophenyl)[2-(pyridin-2-yl)thiophen-3-yl]methanone (11ah). Following the general procedure, **10a** (80.6 mg, 1 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-nitrobenzaldehyde **2h**(151.1 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11ah** as an orange solid (24.6 mg, 16%): m.p. (CH_2Cl_2): 132-115 °C; IR (ATR): 3006, 2988, 1669, 1527 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 7.30 (d, J = 5.1 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 5.2 Hz, 1H), 7.55 (td, J = 7.7, 1.8 Hz, 1H), 7.88–7.97 (m, 2H), 8.09–8.21 (m, 2H), 8.34 (dt, J = 4.7, 1.4 Hz, 1H) ppm;^{13}C NMR (75.5 MHz, $CDCl_3$): δ 122.4, 122.7, 123.4, 126.9, 129.7, 130.2, 136.6, 137.2, 142.9, 146.1, 149.3, 149.8, 150.7, 191.7 ppm; MS (ESI): *m/z* (rel intensity): 311 (MH^+, 100), 274(1); HRMS (ESI-TOF): calcd. for $C_{16}H_{11}N_2O_3S$ [MH^+]: 311.0490; found: 311.0500.

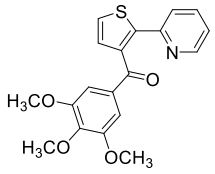


(3,5-Dimethoxyphenyl)[2-(pyridin-2-yl)thiophen-3-yl]methanone (11ai). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 3,5-dimethoxybenzaldehyde **2i** (166.1 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2)

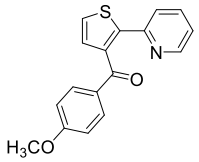


afforded **11ai** as a yellow oil (140.7 mg, 86%): IR (ATR): 3060, 2942, 1743, 1658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 6H), 6.57 (t, J = 2.3 Hz, 1H), 6.97 (d, J = 2.3 Hz, 2H), 7.07 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 7.22 (d, J = 5.2 Hz, 1H), 7.37 (dt, J = 8.0, 1.1 Hz, 1H), 7.41 (d, J = 5.2 Hz, 1H), 7.49 (ddd, J = 8.0, 7.5, 1.8 Hz, 1H), 8.48 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.5, 105.9, 107.6, 122.4, 122.5, 126.5,129.9, 136.4, 137.7, 139.4, 145.8, 149.4, 151.4, 160.6, 193.2 ppm; MS (ESI): *m/z* (rel intensity): 327 (MH^+, 100), 296 (1), 274 (1); HRMS (ESI-TOF): calcd. for $C_{18}H_{16}NO_3S$ [MH^+]: 326.0845; found: 326.0865.

[2-(Pyridin-2-yl)thiophen-3-yl](3,4,5-trimethoxyphenyl)methanone (11aj). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1mmol), PivOH (38.8 mg, 0.38 mmol), 3,4,5-trimethoxybenzaldehyde **2j**(196.2 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **11aj** as a white solid (135.3 mg; 78%): m.p. (CH_2Cl_2): 142-144 °C; IR (ATR): 16478 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 6H), 3.86 (s, 3H), 7.03– 7.14 (m, 3H), 7.25 (d, J = 5.2 Hz, 1H), 7.31 (dt, J = 8.0, 1.1 Hz, 1H), 7.40–7.54 (m, 2H), 8.50 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.2, 60.9, 107.5, 122.5, 122.8, 126.7, 130.0, 132.4, 136.3, 137.5, 142.6, 145.8, 149.5, 151.5, 152.9, 192.3 ppm; MS (EI): *m/z* (rel intensity): 355 (M^+, 88), 326 (100), 280 (29), 188 (51). HRMS (ESI-TOF): calcd. for $C_{19}H_{18}NO_4S$ [MH^+]: 356.0957; found: 356.0962.



(4-Methoxyphenyl)[2-(pyridin-2-yl)thiophen-3-yl]methanone (11ap). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-methoxybenzaldehyde **2p** (0.12 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 20 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **11ap** as a white solid (70.2 mg, 48%): m.p. (CH_2Cl_2): 112-114 °C; IR (ATR): 3006, 2967, 2839, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.82–6.85 (m, 2H), 7.07 (ddd, J = 7.4, 4.9, 1.2 Hz, 1H), 7.18 (d, J = 5.2 Hz, 1H), 7.36 (dt, J = 8.0, 1.1 Hz, 1H), 7.42 (d, J = 5.2 Hz, 1H), 7.47 (ddd, J = 8.1, 7.4, 1.8 Hz, 1H), 7.76–7.88 (m, 2H), 8.49 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.5, 113.7, 122.2, 122.3, 126.7, 129.7, 130.3,



132.3, 136.4, 138.1, 144.9, 149.4, 151.4, 163.8, 192.7 ppm; MS (ESI): *m/z* (rel intensity): 297 (MH^+, 15), 296 (100), 188 (6). HRMS (ESI-TOF): calcd. for $C_{17}H_{14}NO_2S$ [MH^+]: 296.0745; found: 296.0750.

1-Methylpyrrol-3-yl)[2-(pyridin-2-yl)thiophen-3-yl]methanone (11as). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 1-methyl-1*H*-pyrrole-3-carbaldehyde **2s** (0.11 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 20 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **11as** as an amber oil (99.6 mg, 74%): IR (ATR): 3102, 3056, 2946, 1712, 1622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 3H), 6.01 (dd, *J* = 4.1, 2.4 Hz, 1H), 6.58 (dd, *J* = 4.1, 1.8 Hz, 1H), 6.85–6.87 (m, 1H), 7.09 (ddd, *J* = 6.7, 4.9, 1.7 Hz, 1H), 7.22 (d, *J* = 5.2 Hz, 1H), 7.36 (d, *J* = 5.2 Hz, 1H), 7.58–7.47 (m, 2H), 8.54 (ddd, *J* = 4.9, 1.6, 1.1 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 37.5, 108.5, 122.1, 122.2, 123.5, 126.1, 130.0, 131.4, 132.0, 136.4, 139.1, 144.5, 149.4, 151.8, 183.1 ppm; MS (ESI): *m/z* (rel intensity): 269 (MH^+, 47), 189 (9), 188 (100); HRMS (ESI-TOF): calcd. for $C_{15}H_{13}N_2OS$ [MH^+]: 269.0749; found: 269.0751.

Furan-3-yl[2-(pyridin-2-yl)thiophen-3-yl]methanone (11at) Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (16.8 mg, 0.075 mmol), PivOH (38.8 mg, 0.38 mmol), furan-3-carbaldehyde **2t** (0.09 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **3at** as an orange solid (65.7 mg, 51%): m.p. (CH_2Cl_2): 73-76 °C; IR (ATR): 3123, 3006, 2981, 1732, 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.15 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1H), 7.27 (d, *J* = 5.2 Hz, 1H), 7.39 (dd, *J* = 1.9, 1.4 Hz, 1H), 7.42 (d, *J* = 5.2 Hz, 1H), 7.48 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.58 (ddd, *J* = 8.0, 7.4, 1.8 Hz, 1H), 7.71 (dd, *J* = 1.5, 0.8 Hz, 1H), 8.55 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 109.3, 122.6, 122.7, 126.9, 128.2, 129.4, 136.5, 138.4, 144.2, 145.7, 149.5, 149.8, 151.3, 186.7 ppm; MS (ESI): *m/z* (rel intensity): 256 (MH^+, 100), 188 (2); HRMS (ESI-TOF): calcd. for $C_{14}H_{10}NO_2S$ [MH^+]: 256.0432; found: 256.0433.

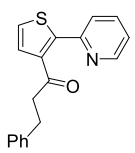
Cyclopentyl[2-(pyridin-2-yl)thiophen-3-yl]methanone (11au). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1mmol), PivOH (38.8 mg, 0.75 mmol), cyclopentanecarbaldehyde **2u** (0.11 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 20 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11au** as an orange solid (58.6 mg, 45%): m.p. (CH_2Cl_2) 78-80 ºC; IR (ATR): 3052, 2952, 2868, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40–1.95 (m, 8H), 3.10–3.32 (m, 1H), 7.13 (ddd, J = 7.3, 4.9, 1.3 Hz, 1H), 7.21 (d, J = 5.3 Hz, 1H), 7.26 (d, J = 5.3 Hz, 1H), 7.54 (dt, J = 8.0, 1.2 Hz, 1H), 7.57–7.64 (m, 1H), 8.52 (ddd, J = 4.9, 1.7, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.2, 29.9, 50.9, 122.7, 123.1, 126.3, 128.9, 136.4, 139.1, 146.3, 149.3, 151.9, 202.8 ppm; MS (ESI): *m/z* (rel intensity): 258 (MH^+, 100), 240 (2); HRMS (ESI-TOF): calcd. for $C_{15}H_{16}NOS$ [MH^+]: 258.0953; found: 258.0960.

Cyclohex-1-en-1-yl[2-(pyridin-2-yl)thiophen-3-yl]methanone (11av). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1mmol), PivOH (38.8 mg, 0.75 mmol), cyclohex-1-ene-1-carbaldehyde **2v** (0.11 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11av** as an orange solid (97.6 mg, 72%): m.p. (CH_2Cl_2): 113-116 °C; IR (ATR): 2939, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45–1.57 (m, 2H), 1.56 – 1.67 (m, 2H), 1.94–2.06 (m, 2H), 2.32–2.43 (m, 2H), 6.55 (dt, J = 4.0, 2.2 Hz, 1H), 7.10 (d, J = 5.1 Hz, 1H), 7.14 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H), 7.39–7.28 (m, 2H), 7.61 (td, J = 7.8, 1.8 Hz, 1H), 8.55 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.5, 21.8, 23.3, 26.2, 122.0, 122.2, 126.4, 129.4, 136.4, 138.6, 140.1, 143.8, 145.5, 149.4, 151.8, 195.8 ppm; MS (EI): *m/z* (rel intensity): 269 (18, M^+), 241 (37), 212 (100), 188 (64); HRMS (ESI-TOF): calcd. for $C_{16}H_{16}NOS$ [MH^+]: 270.0953; found: 270.0959.

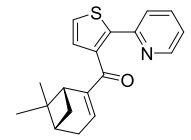
1-{4-[2-(Pyridin-2-yl)thiophene-3-carbonyl]phenyl}ethan-1-one (11aw). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (16.8 mg, 0.075 mmol), PivOH (38.8 mg, 0.38 mmol), 4-acetylbenzaldehyde **2w** (148.1 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 20 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **11aw** as

grey solid (81.5 mg, 53%): m.p. (CH_2Cl_2): 78-80 °C; IR (ATR): 3101, 3006, 1682, 1658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3H), 7.04 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 7.24 (d, J = 5.2 Hz, 1H), 7.37 (dt, J = 8.0, 1.1 Hz, 1H), 7.42–7.54 (m, 2H), 7.80–7.93 (m, 4H), 8.38 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H,) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.7, 122.4, 122.5, 126.7, 128.1, 129.7, 129.8, 136.4, 137.5, 139.8, 141.1, 146.0, 149.4, 151.0, 192.8, 197.5 ppm; MS (ESI): *m/z* (rel intensity): 308 (MH^+, 100); HRMS (ESI-TOF): calcd. for $C_{18}H_{14}NO_2S$ [MH^+]: 308.0745; found: 308.0754.

3-Phenyl-1-[2-(pyridin-2-yl)thiophen-3-yl]propan-1-one (11ax). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05mmol), PivOH (38.8 mg, 0.38 mmol), hydrocinnamaldehyde **2x** (0.12 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11ax** as an yellow oil (94.5 mg, 64%): IR (ATR): 3003, 2984, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.97–3.16 (m, 4H), 7.13–7.36 (m, 8H), 7.58 (d, J = 7.8 Hz, 1H), 7.65 (td, J = 7.7, 1.8 Hz, 1H), 8.60 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 30.3, 44.5, 122.9, 123.4, 126.1, 126.4, 128.5, 128.8, 136.5, 138.7, 141.0, 146.8, 149.4, 151.8, 198.4 ppm; MS (ESI): *m/z* (rel intensity): 294 (MH^+, 100), 278(2), 239(2), 178 (7); HRMS (ESI-TOF): calcd. for $C_{18}H_{16}NOS$ [MH^+]: 294.0953; found: 294.0961.



[(1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl][2-(pyridin-2-yl)thiophen-3-yl]methanone (11ay). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), (1*R*)-(−)-myrtenal **2y** (0.15 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11ay** as an white solid (91.5 mg, 59%): m.p. (CH_2Cl_2): 83-86 °C; IR (ATR): 2981, 2939, 2882, 1739, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (s, 3H) , 0.93 (d, J = 9.1 Hz, 1H), 1.35 (s, 3H), 1.97–2.12 (m, 1H), 2.28–2.30 (m, 2H), 2.46 (dt, J = 9.1, 5.7 Hz, 1H), 3.10 (td, J = 5.7, 1.6 Hz, 1H), 6.40 (dt, J = 3.3, 1.8 Hz, 1H), 7.04–7.19 (m, 2H), 7.31–7.40 (m, 2H), 7.52–7.64 (m, 1H), 8.55 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.9, 25.8, 31.0, 32.7, 37.6, 39.9, 40.3, 122.1, 122.2, 126.5, 129.4, 136.5, 138.3, 142.7,

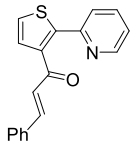


143.6, 149.5, 150.0, 151.7, 193.3 ppm; MS (ESI): *m/z* (rel intensity): 310 (MH^+, 100), 299 (<1), 292 (<1); HRMS (ESI-TOF): calcd. for $C_{19}H_{20}NOS$ [MH^+]: 310.1266; found: 310.1267.

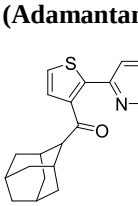
(*S*)-[4-(Prop-1-en-2-yl)cyclohex-1-en-1-yl][2-(pyridin-2-yl)thiophen-3-yl]methanone (11az). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), (*S*)-(−)-perillaldehyde **2z** (0.16 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11az** as a yellow oil (101.9 mg, 66%): IR (ATR): 3073, 3049, 2974, 2931, 1739, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (dtd, *J* = 13.2, 10.9, 5.4 Hz, 1H), 1.61 (t, *J* = 1.0 Hz, 3H), 1.76– 1.93 (m, 2H), 1.94– 2.14 (m, 2H), 2.16–2.33 (m, 1H), 2.52-2.68 (m, 1H), 4.52 (dt, *J* = 1.6, 1.0 Hz, 1H), 4.63 (t, *J* = 1.6 Hz, 1H), 6.48 (tq, *J* = 3.5, 2.1, 1.6 Hz, 1H), 7.02 (d, *J* = 5.2 Hz, 1H), 7.07 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 7.18–7.36 (m, 2H), 7.54 (td, *J* = 7.8, 1.8 Hz, 1H), 8.48 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7, 23.6, 26.7, 31.4, 40.0, 109.3, 121.9, 122.2, 126.4, 129.4, 136.4, 138.6, 139.9, 143.8, 144.6, 148.5, 149.5, 151.8, 195.5 ppm; MS (ESI): *m/z* (rel intensity): 310 (MH^+, 100), 292 (1), 188 (<1); HRMS (ESI-TOF): calcd. for $C_{19}H_{20}NOS$ [MH^+]: 310.1266; found: 310.1272.

1-[2-(Pyridin-2-yl)thiophen-3-yl]octan-1-one (11aaa). Following the general procedure, **10a** (322.4 mg, 2 mmol) was treated with $Pd(OAc)_2$ (45.0 mg, 0.2 mmol), PivOH (153.0 mg, 1.50 mmol), octanal **2aa** (0.64 mL, 4 mmol) and TBHP (5.5 M in decane, 1.44 mL, 8 mmol). After 15 min at 80°C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11aaa** as a yellow oil (335.7 mg, 58 %): IR (ATR): 3052, 2960, 2854.13, 1736, 1683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78–0.91 (m, 3H), 1.19–1.28 (m, 8H), 1.64 (quint., *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 7.20-7.25 (m, 1H), 7.28–7.36 (m, 2H), 7.57–7.78 (m, 2H), 8.60 (d, *J* = 4.7 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 22.6, 24.3, 29.1, 29.2, 31.7, 42.8, 122.9,123.5, 126.3,128.9, 136.6, 138.9, 146.4, 149.2, 151.8, 199.6 ppm; MS (ESI): *m/z* (rel intensity): 288 (MH^+, 100), 260 (<1), 178 (<1); HRMS (ESI-TOF): calcd. for $C_{17}H_{22}NOS$ [MH^+]: 288.1422; found: 288.1426.

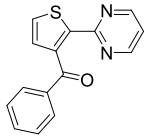
(*E*)-3-Phenyl-1-[2-(pyridin-2-yl)thiophen-3-yl]prop-2-en-1-one (11aab). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (16.9 mg, 0.075mmol), PivOH (38.8 mg, 0.38 mmol), *trans*-cinnamaldehyde **2ab** (0.12 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11aab** as an orange oil (33.5 mg, 23%): IR (ATR): 3087, 3056, 2984, 1729, 1658, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (d, J = 16.0 Hz, 1H), 7.11 (ddd, J = 6.8, 4.9, 1.5 Hz, 1H), 7.20–7.37 (m, 7H), 7.42–7.61 (m, 3H), 8.54 (d, J = 4.7 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 122.8, 123.4, 126.5, 126.7, 128.4, 128.9, 129.5, 130.6, 134.6, 136.5, 139.0, 144.9, 146.3, 149.6, 151.7, 190.5 ppm; MS (ESI): *m/z* (rel intensity): 292 (MH^+, 100), 188 (7); HRMS (ESI-TOF): calcd. for $C_{18}H_{14}NOS$ [MH^+]: 292.0796; found: 292.0801.



(Adamantan-1-yl)[2-(pyridin-2-yl)thiophen-3-yl)]methanone (11aac). Following the general procedure, **10a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1mmol), PivOH (38.8 mg, 0.75 mmol), adamantane-1-carbaldehyde **2ac** (164.3 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 15 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 10/1) afforded **11aac** as a white solid (36.9 mg, 23%): m.p. (CH_2Cl_2): 126-128 °C ; IR (ATR): 2903, 2850, 1746, 1683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56–1.77 (m, 6H), 1.90 (d, J = 3.0 Hz, 6H), 1.98–2.03 (m, 3H), 6.96 (d, J = 5.1 Hz, 1H), 7.16 (ddd, J = 7.7, 4.8, 1.1 Hz, 1H), 7.37 (d, J = 5.1 Hz, 1H), 7.43–7.51 (m, 1H), 7.66 (td, J = 7.7, 1.8 Hz, 1H), 8.56 (dt, J = 4.8, 1.4 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.0, 36.5, 38.5, 47.5, 120.7, 122.2, 126.3, 127.1, 136.7, 139.4, 140.2, 149.3, 151.7, 212.2 ppm; MS (ESI): *m/z* (rel intensity): 324 (MH^+, 100), 318 (<1), 200 (<1).); HRMS (ESI-TOF): calcd. for $C_{20}H_{22}NOS$ [MH^+]: 324.1422; found: 324.1430.

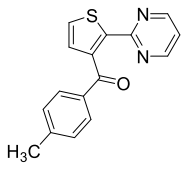


Phenyl[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11ba). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), benzaldehyde **2a** (0.10 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **11ba** as a white solid (97.7 mg, 74%): m.p. (CH_2Cl_2): 143-144

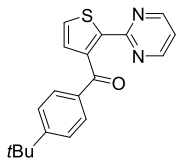


°C; IR (ATR): 3098, 3041, 1739, 1669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (t, J = 4.9 Hz, 1H), 7.07 (d, J = 5.1 Hz, 1H), 7.22–7.30 (m, 2H), 7.34–7.42 (m, 1H), 7.43 (d, J = 5.1 Hz, 1H), 7.70–7.78 (m, 2H), 8.36 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 118.5, 128.3, 129.0, 129.3, 129.4, 132.9, 137.7, 140.9, 141.9, 156.8, 160.5, 194.7 ppm; MS (ESI): *m/z* (rel intensity): 267 (MH^+, 100), 227 (2), 149 (1); HRMS (ESI-TOF): calcd. for $C_{15}H_{11}N_2OS$ [MH^+]: 267.0592; found: 267.0605.

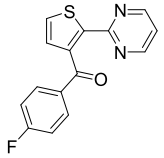
[2-(Pyrimidin-2-yl)thiophen-3-yl](*p*-tolyl)methanone (11bb). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-methylbenzaldehyde **2b** (0.12 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtO_2 8/2) afforded **11bb** as a white solid (115.4 mg, 82%): m.p. (CH_2Cl_2): 153-155 °C; IR (ATR): 3045, 2977, 2924, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 6.95 (t, J = 4.9 Hz, 1H), 7.19–7.12 (m, 3H), 7.52 (d, J = 5.1 Hz, 1H), 7.69–7.82 (m, 2H), 8.47 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.7, 118.4, 128.9, 129.1, 129.3, 129.5, 135.2, 140.6, 142.2, 143.7, 156.9, 160.5, 194.4 ppm; MS (ESI): *m/z* (rel intensity): 281 (MH^+, 100), 189 (3); HRMS (ESI-TOF): calcd. for $C_{16}H_{13}N_2OS$ [MH^+]: 281.0749; found: 281.0762.



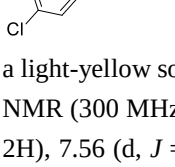
4-(*tert*-Butyl)phenyl][2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11bc). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-*tert*-butylbenzaldehyde **2c** (0.17 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **11bc** as a brown solid (126.7 mg, 79%): m.p. (CH_2Cl_2): 150-152 °C; IR (ATR): 3037, 2963, 2867, 1665, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9H) , 6.96 (t, J = 4.9 Hz, 1H), 7.14 (d, J = 5.1 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 5.1 Hz, 1H), 7.727–7.872 (m, 2H), 8.49 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 31.1, 35.1, 118.4, 125.3, 128.9, 129.2, 129.4, 135.0, 140.6, 142.2, 156.7, 156.9, 160.6, 194.4 ppm; MS (ESI): *m/z* (rel intensity): 323 (MH^+, 100), 189 (1); HRMS (ESI-TOF): calcd. for $C_{19}H_{19}N_2OS$ [MH^+]: 323.1218; found: 323.1224.



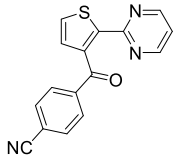
(4-Fluorophenyl)[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11bd). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-fluorobenzaldehyde **2d** (0.11 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **11bd** as a light-brown solid (112.7 mg, 79%): m.p. (CH_2Cl_2): 120-122°C; IR (ATR): 3045, 2988, 1739, 1669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (t, J = 4.9 Hz, 1H), 6.99–7.07 (m, 2H), 7.16 (d, J = 5.1 Hz, 1H), 7.53 (d, J = 5.1 Hz, 1H), 7.81–7.90 (m, 2H), 8.46 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 115.4 (d, J = 21.9 Hz), 118.5, 128.8, 129.5, 131.9 (d, J = 9.0 Hz), 134.3 (d, J = 3.3 Hz), 140.9, 141.5, 156.9, 160.4, 165.6 (d, J = 255.0 Hz), 193.1 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -105.49 (tt, J = 8.6, 5.4 Hz) ppm; MS (ESI): *m/z* (rel intensity): 250 (MH^+, 100), 105 (1); HRMS (ESI-TOF): calcd. for $C_{15}H_{10}FN_2OS$ $[MH^+]$: 285.0498; found: 285.0504.



(4-Chlorophenyl)[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11be). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-chlorobenzaldehyde **2e** (140.6 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11be** as a light-yellow solid (119.7 mg, 80 %): m.p. (CH_2Cl_2): 155-158 °C; IR (ATR): 1661 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (t, J = 4.9 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 7.30–7.40 (m, 2H), 7.56 (d, J = 5.1 Hz, 1H), 7.74–7.85 (m, 2H), 8.49 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 118.5, 128.6, 128.8, 129.6, 130.6, 136.2, 139.2, 141.3, 156.9, 160.6, 163.5, 193.4 ppm; MS (EI): *m/z* (rel intensity): 302 (M^{+2}, 18) 300 (M^+, 43), 271 (100), 189 (51), 135 (25), 111 (41), 75 (29); HRMS (ESI-TOF):calcd. for $C_{15}H_{10}ClN_2OS$ $[MH^+]$: 301.0202; found: 301.0204.

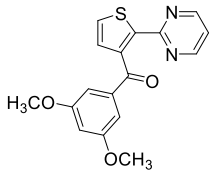


4-[2-(Pyrimidin-2-yl)thiophene-3-carbonyl]benzonitrile (11bg). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-formylbenzonitrile **2g** (131.1 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **11bg** as an amber solid (120.6 mg,



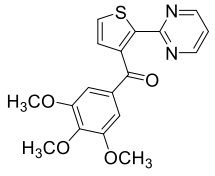
83%): m.p. (CH_2Cl_2): 164-166°C; IR (ATR): 2227, 1672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (t, J = 4.9 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 7.56 (d, J = 5.1 Hz, 1H), 7.60–7.70 (m, 2H,), 7.82 – 7.92 (m, 2H), 8.41 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 115.7, 118.1, 118.7, 128.9, 129.3, 130.0, 132.2, 140.5, 141.1, 141.7, 156.8, 160.0, 192.9 ppm; MS (ESI): *m/z* (rel intensity): 292 (MH^+, 100), 259 (1), 246 (1); HRMS (ESI-TOF): calcd. for $C_{16}H_{10}N_3OS$ [MH^+]: 292.0545; found: 292.0556.

(3,5-Dimethoxyphenyl)[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11bi). Following



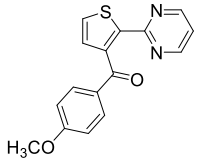
the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.75 mmol), 3,5-dimethoxybenzaldehyde **2i** (166.2 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 35 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **11bi** as a white solid (150.8 mg, 92%): m.p. (CH_2Cl_2): 125-126 °C; IR (ATR): 3091, 3005, 2941, 2835, 1669, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 6H), 6.60 (t, J = 2.3 Hz, 1H), 6.93– 7.04 (m, 3H), 7.16 (d, J = 5.1 Hz, 1H), 7.52 (d, J = 5.1 Hz, 1H), 8.51 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.5, 105.4, 107.2, 118.5, 128.9, 129.3, 139.7, 140.9, 141.7, 156.8, 160.5, 160.6, 194.2 ppm; MS (ESI): *m/z* (rel intensity): 327 (MH^+, 100), 296 (1), 274 (1); HRMS (ESI-TOF): calcd. for $C_{17}H_{15}N_2O_3S$ [MH^+]: 327.0803; found: 327.0806.

[2-(Pyrimidin-2-yl)thiophen-3-yl](3,4,5-trimethoxyphenyl)methanone (11bj). Following

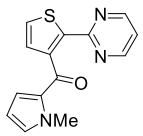


the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 3,4,5-trimethoxybenzaldehyde **2j** (196.2 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtO_2 7/3) afforded **11bj** as a yellow solid (140.0 mg, 79%): m.p. (CH_2Cl_2): 161-163 °C; IR (ATR): 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 6H), 3.87 (s, 3H), 6.98 (t, J = 4.9 Hz, 1H), 7.10 (s, 2H), 7.17 (d, J = 5.1 Hz, 1H), 7.53 (d, J = 5.1 Hz, 1H), 8.51 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.2, 60.9, 106.9, 118.5, 129.0, 129.2, 132.9, 141.1, 141.5, 142.4, 152.9, 156.9, 160.6, 193.2 ppm; MS (EI): *m/z* (rel intensity): 356 (M^+, 100), 327 (52) 189 (54); HRMS (ESI-TOF): calcd. for $C_{18}H_{17}N_2O_4S$ [MH^+]: 357.0909; found: 357.0909.

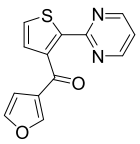
(4-Methoxyphenyl)[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11bp). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-methoxybenzaldehyde **2p** (0.12 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **11bp** as a white solid (94.5 mg, 64%): m.p. (CH_2Cl_2): 159-161 °C; IR (ATR): 3094, 3034, 2963, 2840, 1661 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.77–6.88 (m, 2H), 6.95 (t, J = 4.9 Hz, 1H), 7.13 (d, J = 5.1 Hz, 1H), 7.51 (d, J = 5.1 Hz, 1H), 7.73–7.88 (m, 2H), 8.48 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.4, 113.6, 118.4, 128.9, 129.2, 130.8, 131.7, 140.4, 142.2, 156.9, 160.6, 163.4, 193.4 ppm;; MS (ESI): *m/z* (rel intensity): 297 (MH^+, 100), 190 (2), 189 (30); HRMS (ESI-TOF): calcd. for $C_{16}H_{13}N_2O_2S$ [MH^+]: 297.0698; found: 297.0701.



(1-Methyl-1*H*-pyrrol-2-yl)[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11bs). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 1-methyl-1*H*-pyrrole-2-carbaldehyde **2s** (0.11 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **11bs** as a light-grey solid (84.2 mg, 63%): m.p. (CH_2Cl_2): 104-106°C; IR (ATR): 3098, 2984, 2949, 1629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (s, 3H), 5.98 (dd, J = 4.1, 2.3 Hz, 1H), 6.42 (dd, J = 4.1, 1.7 Hz, 1H), 6.84 (t, J = 2.3 Hz, 1H), 6.98 (t, J = 4.9 Hz, 1H), 7.20 (d, J = 5.1 Hz, 1H), 7.45 (d, J = 5.1 Hz, 1H), 8.56 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 37.3, 108.1, 118.3, 121.9, 128.5, 129.3, 131.2, 131.9, 140.6, 143.0, 156.9, 160.9, 183.8 ppm; MS (ESI): *m/z* (rel intensity): 270 (MH^+, 13), 190 (8), 189 (100); HRMS (ESI-TOF): calcd. for $C_{14}H_{12}N_3OS$ [MH^+]: 270.0701; found: 270.0703.



Furan-3-yl[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11bt). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), furan-3-carbaldehyde **2t** (0.09 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **11bt** as a light-brown solid (61.6 mg, 48%): m.p. (CH_2Cl_2): 1117-119°C; IR (ATR): 3123, 3045, 1661, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.89–6.80



(m, 1H), 7.04 (t, *J* = 4.9 Hz, 1H), 7.19 (d, *J* = 5.1 Hz, 1H), 7.40 (t, *J* = 1.7 Hz, 1H), 7.50 (d, *J* = 5.1 Hz, 1H), 7.60–7.67 (m, 1H), 8.58 (d, *J* = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 109.0, 118.6, 128.7, 128.9, 129.2, 141.1, 142.3, 144.2, 149.1, 157.0, 160.6, 187.9 ppm; MS (ESI): *m/z* (rel intensity): 257 (MH^+, 100), 189 (11); HRMS (ESI-TOF): calcd. for $C_{13}H_9N_2O_2S$ [MH^+]: 257.0385; found: 257.0388.

Cyclopentyl[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11bu) Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), cyclopentanecarbaldehyde **2u** (0.11 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 20 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11bu** as a yellow oil (65,3 mg, 51%): IR (ATR): 2952, 2868, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46–1.62 (m, 2H), 1.66–1.89 (m, 4H), 1.89–2.05 (m, 2H), 3.36 (quint, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 5.1 Hz, 1H), 7.11 (t, *J* = 4.9 Hz, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 8.67 (d, *J* = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.2, 29.8, 52.6, 118.6,128.0, 129.2, 139.6, 144.9, 157.0, 160.8, 207.2 ppm; MS (ESI): *m/z* (rel intensity): 259 (MH^+, 100), 241 (7); HRMS (ESI-TOF): calcd. for $C_{14}H_{15}N_2OS$ [MH^+]: 259.0905; found: 259.0911.

Cyclohex-1-en-1-yl[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11bv). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), cyclohex-1-ene-1-carbaldehyde **2v** (0.11 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **11bv** as a brown solid (85.9 mg, 64%): m.p. (CH_2Cl_2): 129-132°C; IR (ATR): 3034, 2935, 2860, 1650, 1637 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.60 (m, 2H), 1.59–1.73 (m, 2H), 1.92–2.13 (m, 2H), 2.43–2.54 (m, 2H), 6.32–6.46 (m, 1H), 6.97–7.11 (m, 2H ·), 7.44 (d, *J* = 5.1 Hz, 1H), 8.61 (d, *J* = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.7, 21.9, 23.3, 26.0, 118.4, 128.8, 128.9, 140.1, 141.0, 142.6, 142.8, 156.8, 160.7, 196.3 ppm; MS (ESI): *m/z* (rel intensity): 271 (MH^+, 100), 253 (4); HRMS (ESI-TOF): calcd. for $C_{15}H_{15}N_2OS$ [MH^+]: 271.0905; found: 271.0912.

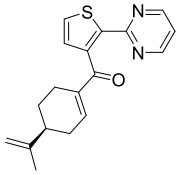
1-{4-[2-(Pyrimidin-2-yl)thiophene-3-carbonyl]phenyl}ethan-1-one (11bw). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 4-acetylbenzaldehyde **2w** (148.1 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2 to 6:4) afforded **11bw** as a yellow solid (70.3 mg, 46%): m.p. (CH_2Cl_2): 108-110 °C; IR (ATR): 3098, 3013, 1679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3H), 6.95 (t, J = 4.9 Hz, 1H), 7.20 (d, J = 5.1 Hz, 1H), 7.56 (d, J = 5.1 Hz, 1H), 7.84–8.04 (m, 4H), 8.43 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.9, 118.6, 128.2, 128.9, 129.3, 129.7, 139.8, 141.2, 141.2, 141.4, 156.8, 160.2, 193.9, 197.6 ppm; MS (ESI): *m/z* (rel intensity): 309 (MH^+, 100), 246 (1), 207 (1); HRMS (ESI-TOF): calcd. for $C_{17}H_{13}N_2O_2S$ [MH^+]: 309.0698; found: 309.0704.

3-Phenyl-1-[2-(pyrimidin-2-yl)thiophen-3-yl]propan-1-one (11bx). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), hydrocinnamaldehyde **2x** (0.12 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 35 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11bx** as a white solid (70.8 mg, 48%): m.p. (CH_2Cl_2): 69-71°C; IR (ATR): 3023, 1697cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.43–2.69 (m, 4H), 7.05 (d, J = 5.1 Hz, 1H), 7.10 (t, J = 4.9 Hz, 1H), 7.17–7.33 (m, 5H), 7.43 (d, J = 5.1 Hz, 1H), 8.60 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 30.3, 45.5, 118.7, 126.0, 127.9, 128.5, 128.6, 129.5, 139.9, 141.3, 144.2, 157.1, 160.7, 203.2 ppm; MS (ESI): *m/z* (rel intensity): 295 (MH^+, 100), 293 (2), 279 (1), 277 (1), 229 (3), 179 (4), 103 (1); HRMS (ESI-TOF): calcd. for $C_{17}H_{15}N_2OS$ [MH^+]: 295.0905; found: 295.0910.

[(1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl][2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11by). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), (1*R*)-(−)-myrtenal **2y** (0.15 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11by** as a white solid (84.2 mg, 54%): m.p. (CH_2Cl_2): 123-125°C; IR (ATR): 2984, 2878, 1650, 1616

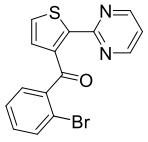
cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.05 (d, J = 9.0 Hz, 1H), 1.39 (s, 3H), 2.09–2.15 (m, 1H), 2.31–2.37 (m, 2H), 2.52 (dt, J = 9.0, 5.7 Hz, 1H), 3.21 (td, J = 5.7, 1.7 Hz, 1H), 6.29 (dt, J = 3.4, 1.7 Hz, 1H), 6.97–7.24 (m, 2H), 7.46 (d, J = 5.1 Hz, 1H), 8.61 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.1, 25.9, 31.2, 32.5, 37.7, 39.7, 40.5, 118.3, 128.9, 128.9, 139.8, 140.5, 142.6, 150.6, 156.9, 160.8, 193.8 ppm; MS (ESI): *m/z* (rel intensity): 311 (MH^+, 100), 309 (2), 189 (1); HRMS (ESI-TOF): calcd. for $C_{18}H_{19}N_2OS$ [MH^+]: 311.1218; found: 311.1223.

(*S*)-[4-(Prop-1-en-2-yl)cyclohex-1-en-1-yl][2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11bz). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with



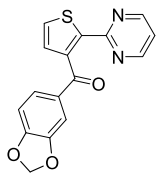
$Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), (*S*)-(−)-perillaldehyde **2z** (0.16 mL, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **11bz** as a white solid (61.4 mg, 40%): m.p. (CH_2Cl_2): 147-150°C; IR (ATR): 3009, 2931, 1654, 1637, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38–1.56 (m, 1H), 1.71 (s, 3H), 1.87–2.28 (m, 4H), 2.31–2.51 (m, 1H), 2.65–2.82 (m, 1H), 4.60–4.67 (m, 1H), 4.71 (t, J = 1.6 Hz, 1H), 6.49–6.38 (m, 1H), 6.94–7.13 (m, 2H), 7.46 (d, J = 5.1 Hz, 1H), 8.63 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.8, 23.5, 26.9, 31.3, 40.2, 109.2, 118.4, 128.8, 128.9, 140.1, 140.7, 141.9, 142.7, 148.7, 156.9,160.7, 196.0 ppm; MS (ESI): *m/z* (rel intensity): 311 (MH^+, 100), 309 (9), 293 (2), 189 (2); HRMS (ESI-TOF): calcd. for $C_{18}H_{19}N_2OS$ [MH^+]: 311.1218; found: 311.1220.

(2-Bromophenyl)[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11bae). Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 2-bromobenzaldehyde **2ae** (183.0 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 25 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **11bae** as a light-brown solid (130.6 mg, 76%): m.p. (CH_2Cl_2): 102-105°C; IR (ATR): 3034, 1675 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (t, J = 4.9 Hz, 1H), 7.09–7.20 (m, 2H), 7.32–7.42 (m, 2H), 7.50 (d, J = 5.1 Hz, 1H), 7.56–7.61 (m, 1H), 8.51 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 118.6, 121.8, 126.5, 128.8, 130.2, 131.0, 131.8, 134.1, 139.8, 141.8, 143.0, 156.7, 160.1, 192.5 ppm; MS (ESI): *m/z* (rel intensity): 347 (MH^+ +2, 100), 345 (MH^+, 97), 274 (1), 265



(1), 189 (1); HRMS (ESI-TOF): calcd. for $C_{15}H_{10}BrN_2OS$ [MH^+]: 344.9697; found: 344.9704.

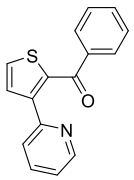
Benzo[*d*][1,3]dioxol-5-yl[2-(pyrimidin-2-yl)thiophen-3-yl]methanone (11baf).



Following the general procedure, **10b** (81.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), piperonal **2af** (150.1 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 30 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **11baf** as a white solid (119.2 mg, 77%); m.p (CH_2Cl_2): 178-181 °C; IR (ATR): 3048, 2907, 1658, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (s, 2H), 6.72 (d, J = 8.1 Hz, 1H), 6.99 (t, J = 4.9 Hz, 1H), 7.14 (d, J = 5.1 Hz, 1H), 7.32 (dd, J = 8.1, 1.7 Hz, 1H), 7.44 (d, J = 1.7 Hz, 1H), 7.52 (d, J = 5.1 Hz, 1H), 8.52 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 101.8, 107.7, 108.6, 118.4, 126.4, 128.9, 129.3, 132.7, 140.5, 142.0, 148.1, 151.8, 156.9, 160.5, 193.0 ppm; MS (ESI): *m/z* (rel intensity): 311 (MH^+, 100), 189 (12); HRMS (ESI-TOF): calcd. for $C_{16}H_{11}N_2O_3S$ [MH^+]: 311.0490; found: 311.0496.

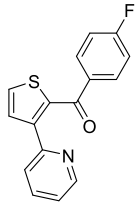
6.2.2.3. C-2 acylation of thiophene and furan **12a,b** rings under thermal conditions

Phenyl(3-(pyridin-2-yl)thiophen-2-yl)methanone (13aa). Following the general procedure

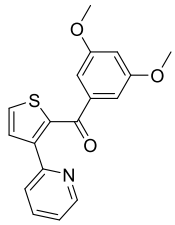


for the synthesis of ketones **3**, **12a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1 mmol), PivOH (38.8 mg, 0.38 mmol), benzaldehyde **2a** (0.10 mL, 1 mmol) and TBHP (5.5 M, 0.36 mL, 2 mmol). After 16 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **13aa** as white solid (59.7 mg, 45 %): m.p. (CH_2Cl_2): 80-81°C; IR (ATR): 3052, 3012, 1641, 1587, 1526, 1451, 1433 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.01 (ddd, J = 7.7, 4.9, 1.2 Hz, 1H), 7.27 – 7.12 (m, 3H), 7.39 – 7.31 (m, 1H), 7.43 (td, J = 7.7, 1.8 Hz, 1H), 7.48 (d, J = 5.1 Hz, 1H), 7.71 – 7.60 (m, 3H), 8.41 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 122.1, 124.2, 127.9, 129.6, 129.6, 129.9, 132.3, 135.8, 137.9, 138.9, 145.1, 149.3, 153.4, 190.2 ppm; EM (ESI^+): *m/z* (rel intensity): 266 (MH^+, 100); HRMS (ESI^+): calcd. for $C_{16}H_{11}NOS$ [MH^+]: 266.0640; found: 266.0635.

(4-fluorophenyl)(3-(pyridin-2-yl)thiophen-2-yl)methanone (**13ad)**. Following the general procedure for ketones **3**, **12a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1 mmol), PivOH (38.8 mg, 0.38 mmol), 4-fluorobenzaldehyde **2d** (0.11 mL, 1 mmol) and TBHP (5.5 M, 0.36 mL, 2 mmol). After 16 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 9/1) afforded **13ad** as white solid (58.7 mg, 41 %): m.p. (CH_2Cl_2): 62-63 °C; IR (ATR): 3009, 2984, 1745, 1637, 1594 cm^{1-}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.72 – 6.97 (m, 2H), 7.04 (ddd, J = 7.7, 4.9, 1.1 Hz, 1H), 7.24 (dt, J = 7.7, 1.1 Hz, 1H), 7.40 – 7.51 (m, 2H), 7.64 (d, J = 5.1 Hz, 1H), 7.66 – 7.72 (m, 2H, H_{2Ph},H_{6Ph}), 8.41 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H, $H_{6'}$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 115.1 (d, J = 20.7 Hz, C_{3Ph},C_{5Ph}), 122.2, 124.0, 129.5, 129.9, 132.1 (d, J = 9.2 Hz, C_{2Ph}, C_{6Ph}), 134.3 (d, J = 3.1 Hz, C_{1Ph}), 135.9, 138.7, 144.9, 149.4, 153.3, 165.1 (d, J = 256.1 Hz), 188.8 ppm; EM (ESI^+): *m/z* (rel intensity): 285 (MH^{+1+}, 14), 284 (MH^+, 100), 123 (<1); HRMS (ESI^+): calcd. for $C_{16}H_{10}FNOS$ [MH^+]: 284.0556; found: 284.0545.



(3,5-dimethoxyphenyl)(3-(pyridin-2-yl)thiophen-2-yl)methanone (13ai). Following the general procedure for ketones **3**, **12a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1 mmol), PivOH (38.8 mg, 0.38 mmol), 3,5-dimethoxybenzaldehyde **2i** (166.2 mg, 1 mmol) and TBHP (5.5 M, 0.36 mL, 2 mmol). After 16 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **13ai** as yellow oil (87.6 mg, 54 %): IR (ATR): 3006, 2991, 2970, 1739, 1641, 1591 cm^{1-};^1H NMR (300 MHz, $CDCl_3$): δ = 3.69 (s, 6H), 6.46 (t, J = 2.3 Hz, 1H), 6.83 (d, J = 2.3 Hz, 2H), 7.07 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 7.20–7.31 (m, 1H), 7.40–7.53 (m, 2H), 7.64 (d, J = 5.1 Hz, 1H), 8.46 (ddd, J = 4.9, 1.6, 1.1Hz,1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.5, 105.6, 107.2, 122.2, 124.1, 129.8, 130.1, 135.8, 138.7, 139.8, 145.2, 149.3, 153.6, 160.3, 189.6 ppm; EM (ESI^+): *m/z* (rel intensity): 326 (MH^+, 100), 304 (<1), 288 (<1), 213 (<1), 165 (<1); HRMS (ESI^+): calcd. for $C_{18}H_{15}NO_3S$ [MH^+]: 326.0851; found: 326.0855.



(4-methoxyphenyl)(3-(pyridin-2-yl)thiophen-2-yl)methanone (13ap). Following the general procedure for ketones **3**, **12a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1 mmol), PivOH (38.8 mg, 0.38 mmol), 4-methoxybenzaldehyde **2p** (0.12 mL, 1 mmol) and TBHP (5.5 M, 0.36 mL, 2 mmol). After 16 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 8/2) **13ap** as yellow solid (57.9 mg, 39 %): m.p. (CH_2Cl_2): 122-124 °C; IR (ATR): 3002, 2973, 1741, 1637, 1590, 1462 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H), 6.75 – 6.67 (m, 2H), 7.04 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.24 (dt, J = 7.9, 1.0 Hz, 1H), 7.44 (td, J = 7.6, 1.8 Hz, 1H), 7.49 (d, J = 5.1 Hz, 1H), 7.59 (d, J = 5.1 Hz, 1H), 7.69 (d, J = 8.9 Hz, 2H), 8.46 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.4, 113.3, 122.0, 124.2, 129.0, 129.4, 130.6, 132.1, 135.9, 138.9, 144.2, 149.3, 153.5, 163.2, 189.0 ppm; EM (ESI^+): *m/z* (rel intensity): 296 (MH^+, 100), 288 (<1), 274 (<1), 269 (1), 188 (3); HRMS (ESI^+): calcd. for $C_{17}H_{13}NO_2S$ $[MH]^+$: 296.0757; found: 296.0745.

(3-(benzyloxy)phenyl)(3-(pyridin-2-yl)thiophen-2-yl)methanone (13aq). Following the general procedure for ketones **3**, **12a** (80.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1 mmol), PivOH (38.8 mg, 0.38 mmol), 3-(benzyloxy)benzaldehyde **2q** (202.2 mg, 1 mmol) and TBHP (5.5 M, 0.36 mL, 2 mmol). After 16 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **13aq** as yellow solid (88.2 mg, 47 %): m.p. (CH_2Cl_2): 92-94 °C; IR (ATR, cm^{1-}): 3037, 3009, 1741, 1637, 1583, 1437 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.99 (s, 2H), 6.93–7.07 (m, 2H), 7.11 (t, J = 7.9 Hz, 1H), 7.21 – 7.28 (m, 2H), 7.31 – 7.45 (m, 7H), 7.49 (d, J = 5.1 Hz, 1H), 7.64 (d, J = 5.1 Hz, 1H), 8.42 (dd, J = 4.5, 1.4 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 70.0, 114.6, 120.0, 122.1, 122.7, 124.1, 127.6, 128.1, 128.6, 129.0, 129.6, 130.0, 135.9, 136.6, 138.8, 139.3, 145.1, 149.2, 153.4, 158.4, 189.9 ppm; EM (ESI^+): m/z (rel intensity): 373 (MH^{+1+}, 21), 372 (MH^+, <1), 372(1), 372 (100); HRMS (ESI^+): calcd. for $C_{23}H_{17}NO_2S$ $[MH^+]$: 372.1058; found: 372.1047.

Phenyl(3-(pyridin-2-yl)furan-2-yl)methanone (13ba). Following the general procedure for ketones **3**, **12b** (72.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1 mmol), PivOH (38.8 mg, 0.38 mmol), benzaldehyde **2a** (0.10 mL, 1 mmol) and TBHP (5.5 M, 0.36 mL, 2 mmol). After 16 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 8/2) afforded **13ba** as yellow oil (43.6 mg, 35 %): IR (ATR): 3006, 2980, 2926, 1645, 1591, 1566, 1494 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, J = 1.8 Hz, 1H, H_4), 7.23 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 7.43 (td, J = 7.5, 1.5 Hz, 2H), 7.59 – 7.51 (m, 1H), 7.73 – 7.61 (m, 2H),7.99 – 7.83 (m, 3H), 8.75 – 8.39 (m, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 114.5, 122.9, 125.0, 128.2, 129.7, 132.6, 134.7, 136.1, 137.7, 144.9, 147.8, 149.4, 150.9, 184.4 ppm; EM (ESI^+): *m/z* (rel intensity): 250 (MH^+, 100), 237 (<1), 105 (<1); HRMS (ESI^+): calcd. for $C_{16}H_{11}NO_2$ [MH^+]: 250.0868; found: 250.0880.

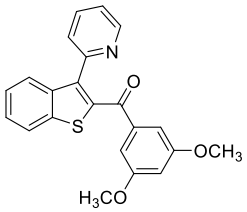
(3,5-dimethoxyphenyl)(3-(pyridin-2-yl)furan-2-yl)methanone (13bi). Following the general procedure for ketones **3, 12b** (72.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1 mmol), PivOH (38.8 mg, 0.38 mmol), 3,5-dimethoxybenzaldehyde **2i** (166.2 mg, 1 mmol) and TBHP (5.5 M, 0.36 mL, 2 mmol). After 16 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **13bi** as orange solid (33.5 mg, 22 %): m.p. (CH_2Cl_2): 79-81 °C; IR (ATR): 3009, 2977, 1649, 1595, 1462 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 6H), 6.62 (t, J = 2.4 Hz, 1H), 7.04 (d, J = 2.4 Hz, 2H), 7.09 (d, J = 1.8 Hz, 1H), 7.23 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.59 – 7.71 (m, 2H), 7.85 (dt, J = 8.0, 1.1 Hz, 1H), 8.65 (ddd, J = 4.9, 1.9, 1.0 Hz, 1H), ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 183.9, 160.5, 151.0, 149.4, 147.6, 145.1, 139.3, 136.0, 134.8, 125.0, 122.9, 114.5, 107.5, 105.4, 55.6 ppm; EM (ESI^+): *m/z* (rel intensity): 310 (MH^+, 100), 309 (1), 288 (<1), 269 (<1), 237 (<1), 165 (<1); HRMS (ESI^+): calcd. for $C_{18}H_{15}NO_4$ [MH^+]: 310.1079; found: 310.1082;

(4-methoxyphenyl)(3-(pyridin-2-yl)furan-2-yl)methanone (**13bp).** Following the general procedure for ketones **3**, **12b** (72.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.1 mmol), PivOH (38.8 mg, 0.38 mmol), 4-methoxybenzaldehyde **2p** (0.12 mL, 1 mmol) and TBHP (5.5 M, 0.36 mL, 2 mmol). After 16 h at 120 °C, purification by column chromatography (silica gel, petroleum ether/AcOEt 7/3) afforded **13bp** as orange solid (39.9

mg, 29 %): m.p. (CH_2Cl_2): 49-51 °C; IR (ATR): 3006, 2980, 1741, 1645, 1595, 1462 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 3H), 6.80 – 6.98 (m, 2H), 7.10 (d, J = 1.7 Hz, 1H), 7.21 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.60 – 7.69 (m, 2H), 7.90 – 7.96 (m, 3H), 8.60 – 8.67 (m, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.5, 113.5, 114.3, 122.7, 125.0, 130.2, 132.3, 133.9, 136.1, 144.4, 148.1, 149.4, 151.1, 163.3, 183.0 ppm; EM (ESI^+): *m/z* (rel intensity): 280 (MH^+, 100), 269 (<1), 172 (1); HRMS (ESI^+): calcd. for $C_{17}H_{13}NO_3$ [MH^+]: 280.0974; found: 280.0976.

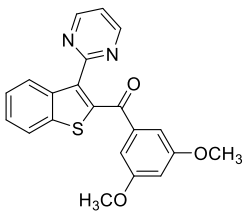
6.2.2.4. C-2 acylation of benzothiophene **14a,b** with 5-dimethoxybenzaldehyde **2i**

(3,5-Dimethoxyphenyl)[3-(pyridin-2-yl)benzo[*b*]thiophen-2-yl]methanone (15ai).



Following the general procedure for ketones **11**, **14a** (105.6 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (16.8 mg, 0.075mmol), PivOH (38.8 mg, 0.38 mmol), 3,5-dimethoxybenzaldehyde **2i** (166.2 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 40 min at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **15ai** as an orange solid (106.9 mg, 57%) m.p. (CH_2Cl_2): 94-96 °C;IR (ATR): 3056, 3009, 2960, 2836, 1640, 1591 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 6H), 6.45 (t, J = 2.3 Hz, 1H), 6.84 (d, J = 2.3 Hz, 2H), 7.15 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.24–7.33 (m, 1H), 7.46 (ddd, J = 8.3, 7.0, 1.4 Hz, 1H), 7.47–7.59 (m, 2H), 7.94-8.00 (m, 2H), 8.64 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.5, 105.8, 107.2, 122.5, 122.6, 125.3, 125.4, 125.9, 127.0, 135.9, 138.7, 139.5, 139.5, 140.1, 140.8, 149.6, 153.5, 160.2, 190.6 ppm; MS (ESI): *m/z* (rel intensity): 376 (MH^+, 100), 226 (1); HRMS (ESI-TOF): calcd. for $C_{22}H_{18}NO_3S$ [MH^+]: 376.1007; found: 376.1011.

(3,5-Dimethoxyphenyl)[3-(pyrimidin-2-yl)benzo[*b*]thiophen-2-yl]methanone (15bi).



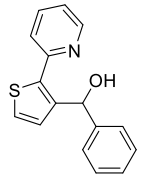
Following the general procedure for ketones **11**, **14b** (106.1 mg, 0.5 mmol) was treated with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PivOH (38.8 mg, 0.38 mmol), 3,5-dimethoxybenzaldehyde **2i** (166.1 mg, 1 mmol) and TBHP (5.5 M in decane, 0.36 mL, 2 mmol). After 40 min at 80 °C, purification by column chromatography (silica gel,

petroleum ether/EtOAc 7/3) afforded **15bi** as a light-yellow solid (20.4 mg, 15%): m.p. (CH_2Cl_2): 158-160 °C; IR (ATR): 2938, 1650, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 6H), 6.51 (t, J = 2.3 Hz, 1H), 6.93 (d, J = 2.3 Hz, 2H), 7.06 (t, J = 4.9 Hz, 1H), 7.47–7.58 (m, 2H), 7.89– 8.03 (m, 1H), 8.56–8.74 (m, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.6, 105.7, 106.8, 118.8,122.5, 125.5, 125.8, 126.4, 135.9, 137.4, 139.8, 140.2, 143.2, 156.6, 160.5, 162.0, 190.8 ppm; MS (ESI): *m/z* (rel intensity): 377 (MH^+, 100), 295 (1); HRMS (ESI-TOF): calcd. for $C_{21}H_{17}N_2O_3S$ [MH^+]: 377.0960; found: 377.0962.

6.2.2.5. Diversification of 3-acylthiophenes

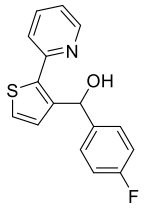
Carbonyl group reduction. General procedure. A solution of corresponding ketone **11aa-ax** (1 mmol) in methanol (6 mL) was cooled at 0°C. Then, sodium borohydride (2 mmol) was added portion wise. The mixture was stirred for 1.5-3 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution, extracted with EtOAc (3 × 15mL) dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography affording corresponding alcohols **16aa-ax**.

Phenyl[2-(pyridin-2-yl)thiophen-3-yl]methanol (16aa). Following the general procedure, **11aa** (79.6 mg, 0.3 mmol) was treated with $NaBH_4$ (22.7 mg, 0.6 mmol). After 1.5 h at room temperature, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **16aa** as a colourless oil whose data are coincidental to those reported[30] (66.7 mg, 83%): IR (ATR): 3314, 3059, 2984, 1587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (s, 1H), 6.73 (d, J = 5.2 Hz, 1H), 7.17–7.37 (m, 5H), 7.43–7.49 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.69–7.78 (m, 2H), 8.58 (d, J = 4.9 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): 70.3, 121.8, 122.7, 125.1, 126.5, 126.9, 128.0, 131.1, 137.7, 138.1, 143.3, 146.0, 148.2, 152.6 ppm; MS (ES^+): *m/z* (rel intensity): 290 (MNa^+, 3), 250 (100), 157 (1); HRMS (ESI-TOF): calcd. for $C_{16}H_{13}NNaOS$ [MNa^+]: 290.0616; found: 290.0617.

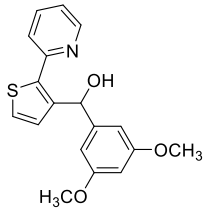


[30] Wang, C.; Zhou, B.; Hu, Y. Manganese-Catalyzed Direct Nucleophilic C(sp^2)-H Addition to Aldehydes and Nitriles. *Angew.Chem. Int. Ed.* **2015**, *54*,13659-13663.

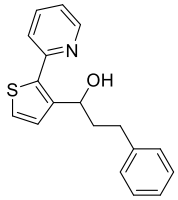
(4-Fluorophenyl)[2-(pyridin-2-yl)thiophen-3-yl]methanol (16ad). Following the general procedure, **11ad** (85.0 mg, 0.3 mmol) was treated with $NaBH_4$ (22.7 mg, 0.6 mmol). After 1.5 h at room temperature, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **16ad** as a yellow oil (63.7 mg, 74%): IR (ATR): 3275 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (s, 1H), 6.71 (d, J = 5.2 Hz, 1H), 6.96–7.06 (m, 2H), 7.15–7.27 (m, 2H), 7.41 (dd, J = 8.4, 5.6 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.70–7.84 (m, 2H), 8.57 (d, J = 4.3 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 69.8, 114.8 (d, J = 21.0 Hz), 121.9, 122.7, 125.2, 128.0 (d, J = 7.7 Hz), 130.9, 137.8, 138.1, 139.1 (d, J = 3.0 Hz), 145.8, 148.2, 152.5, 162.0 (d, J = 245 Hz) ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -116.20 (tt, J = 8.9, 4.4 Hz) ppm; MS (EI): *m/z* (rel intensity): 269 (15), 268 (100); HRMS (ESI-TOF): calcd. for $C_{16}H_{12}FNNaOS$ [MNa^+]: 308.0521; found: 308.0525.



(3,5-Dimethoxyphenyl)[2-(pyridin-2-yl)thiophen-3-yl]methanol (16ai). Following the general procedure, **11ai** (97.6 mg, 0.3 mmol) was treated with $NaBH_4$ (22.7 mg, 0.6 mmol). After 1.5 h at room temperature, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **16ai** as a yellow oil (90.5 mg, 92%): IR (ATR): 3300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 6H), 5.94 (s, 1H), 6.36 (t, J = 2.2 Hz, 1H), 6.63 (d, J = 2.2 Hz, 2H), 6.76 (d, J = 5.2 Hz, 1H), 7.17–7.24 (m, 2H), 7.63 (d, J = 7.9 Hz, 1H), 7.74 (td, J = 7.9, 1.7 Hz, 1H), 8.58 (d, J = 4.3 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.3, 70.3, 99.3, 104.5, 121.9, 122.8, 125.1, 131.1,137.8, 138.0, 145.8, 145.8, 148.2, 152.6, 160.6 ppm; MS (ESI): *m/z* (rel intensity): 311 (19), 310 (100); HRMS (ESI-TOF): calcd. for $C_{18}H_{17}NNaO_3S$ [MNa^+]: 350.0827; found: 350.0824.



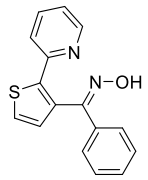
3-Phenyl-1-[2-(pyridin-2-yl)thiophen-3-yl]propan-1-ol (16ax). Following the general procedure, **11ax** (88.0 mg, 0.3 mmol) was treated with $NaBH_4$ (22.7 mg, 0.6 mmol). After 1.5 h at room temperature, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **16ax** as a colourless oil (73.5 mg, 83 %): IR (ATR): 3388 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.04–2.39 (m, 2H), 2.99–2.67 (m, 2H), 4.86 (dd, J = 8.7, 5.4 Hz, 1H), 7.13 (d, J = 5.1 Hz, 1H), 7.17–7.36 (m, 7H), 7.63 (d, J = 7.9 Hz, 1H), 7.75 (td, J = 7.9, 1.8 Hz, 1H), 8.60 (d, J = 4.9 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 32.9,



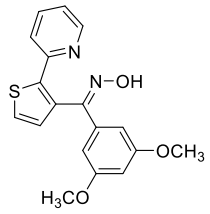
38.3, 68.5, 121.8, 122.7, 125.6, 125.7, 128.3, 128.5, 129.7, 137.7, 137.8, 142.3, 145.9, 148.3, 152.9 ppm; MS (EI): *m/z* (rel intensity): 279(16), 278 (100); HRMS (ESI-TOF): calcd. for $C_{18}H_{17}NNaOS$ [MNa^+]: 318.0929; found: 318.0938.

Oxime formation. General procedure. To a solution of $NH_2OH{\cdot}HCl$ (2 mmol) and corresponding ketone **11aa,ai** (1 mmol) in EtOH (5 mL), a solution of NaOAc (1 mmol.) in H_2O (2 mL) was added and the mixture was refluxed for 5 h. The mixture was cooled down to r.t, the solvent was removed under vacuum and the residue was dissolved in H_2O and extracted with Et_2O (3 × 15 mL). The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography afforded oximes **17aa,ai**.

(*E*)-Phenyl[2-(pyridin-2-yl)thiophen-3-yl]methanone oxime (17aa). Following the general procedure, **11aa** (106.1 mg, 0.4 mmol) was treated with NH_2OH-HCl (55.9 mg, 0.8 mmol). After 5 h under reflux, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded oxime **17aa** as a white solid (83.6 mg, 77%): m.p. (CH_2Cl_2): 156-158 °C; IR (ATR): 3006, 1587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03–7.13 (m, 2H), 7.24–7.34 (m, 3H), 7.46–7.57 (m, 5H), 8.56 (d, J = 4.8 Hz, 1H), 9.50 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 120.4, 122.2, 127.0, 127.2, 128.5, 129.5, 129.8, 129.8, 134.7, 136.8, 142.6, 149.3, 151.7, 155.0 ppm; MS (ESI): *m/z* (rel intensity): 281 (MH^+, 78), 264 (14), 263 (100); HRMS (ESI-TOF): calcd. for $C_{16}H_{13}N_2OS$ [MH^+]: 281.0749; found: 281.0752.



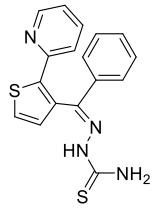
(*E*)-(3,5-Dimethoxyphenyl)[2-(pyridin-2-yl)thiophen-3-yl]methanone oxime (17ai). Following the general procedure, **11ai** (130.2 mg, 0.4 mmol) was treated with NH_2OH-HCl (55.9 mg, 0.8 mmol). After 5 h under reflux, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded oxime **17ai** as an orange solid (101.0 mg, 74%): m.p. (CH_2Cl_2): 145-147 °C; IR (ATR): 3006, 1587 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 6H), 6.45 (t, J = 2.2 Hz, 1H), 6.72 (d, J = 2.2 Hz, 2H), 7.00 (d, J = 5.1 Hz, 1H), 7.08–7.12 (m, 1H), 7.48–7.53 (m, 3H), 8.56 (d, J = 4.8 Hz, 1H), 8.96 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.4, 102.0, 105.3, 120.3, 122.2, 127.1, 129.5, 129.6, 136.7, 136.8, 142.5, 149.3, 151.8, 155.0, 160.7 ppm; MS (ESI): *m/z* (rel



intensity): 341 (MH^+, 100), 324 (10), 323 (63); HRMS (ESI-TOF): calcd. for $C_{18}H_{16}N_2NaO_3S$ [MNa^+]: 363.0779; found: 363.0780.

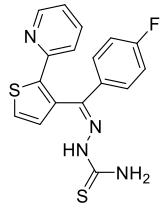
Synthesis of thiosemicarbazones 18. General procedure. Thiosemicarbazide (1 mmol) was added to a solution of corresponding ketone **11a** (1 mmol) in EtOH (25 mL). 4Å molecular sieve and 3 drops of conc. HCl were added and the mixture was stirred and under reflux for 24 hours. The mixture was cooled down to r.t, filtered under vacuum and the solvent was removed under reduced pressure. The residue was purified by column chromatography affording corresponding thiosemicarbazones **18**.

(*Z*)-2-(Phenyl[2-(pyridin-2-yl)thiophen-3-yl)methylene]hydrazine-1-carbothioamide (18aa). Following the general procedure, **11aa** (212.3 mg, 0.8 mmol) was reacted with



thiosemicarbazide (72.9 mg, 0.8 mmol). After 24 h under reflux, purification by column chromatography (silica gel, petroleum ether/EtOAc 6/4) afforded **18aa** as a white solid (229.2 mg, 85%): m.p. (CH_2Cl_2): 185-188 °C; IR (ATR): 3427, 3331, 3253 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J = 5.1 Hz, 1H), 7.04 (dd, J = 7.0, 4.8 Hz, 1H), 7.20 (s, 1H), 7.24–7.33 (m, 4H), 7.41–7.52 (m, 2H), 7.57 (m, 3H), 8.48 (d, J = 4.8 Hz, 1H), 8.76 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 119.8, 122.9, 127.3, 127.5, 128.7, 128.9, 129.4, 130.4, 135.4, 137.1, 144.4, 147.5, 149.7, 150.4, 178.8 ppm; MS (EI): *m/z* (rel intensity): 339 (MH^+, 55), 322 (100), 264 (3); HRMS (ESI-TOF): calcd. for $C_{17}H_{15}N_4S_2$ [MH^+]: 339.0738; found: 339.0739.

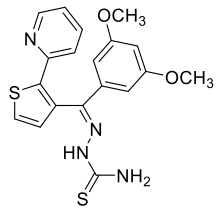
(*Z*)-2-{(4-Fluorophenyl)[2-(pyridin-2-yl)thiophen-3-yl]methylene}hydrazine-1-carbothioamide (18ad). Following the general procedure, **11ad** (226.6 mg, 0.8 mmol) was



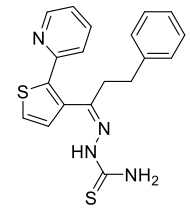
reacted with thiosemicarbazide (73.0 mg, 0.80 mmol). After 24 h under reflux, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **18ad** as a yellow solid (213.7 mg, 75%): m.p. (CH_2Cl_2): 190-192°C; IR (ATR): 3487, 3423, 3328, 3261, 3147, 3056, 2988, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H); 6.93–7.03 (m, 3H), 7.11 (ddd, J = 7.6, 4.9, 1.0 Hz, 1H), 7.24–7.32 (m, 1H), 7.43 (s, 1H), 7.50–7.59 (m, 3H), 7.63 (d, J = 5.1 Hz, 1H), 8.51 (dt, J = 4.8, 1.3 Hz, 1H), 8.75 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 115.8 (d, J = 21.9 Hz), 119.9, 122.9, 127.3, 128.7, 129.3 (d, J = 8.5 Hz), 129.5, 131.7 (d, J = 3.3 Hz), 137.0, 144.5, 146.7, 149.8, 150.3, 164.2 (d, J =

251.8 Hz), 178.9 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -109.66 – -109.56 (m) ppm; MS (ESI): *m/z* (rel intensity): 357 (MH^+,59), 340 (100), 284 (2), 282 (2), 281 (2), 274 (1); HRMS (ESI-TOF): calcd. for $C_{17}H_{14}FN_4S_2$ [MH^+]: 357.0644; found: 357.0649.

(*Z*)-2-{(3,5-Dimethoxyphenyl)[2-(pyridin-2-yl)thiophen-3-yl]methylene}hydrazine-1-carbothioamide (18ai). Following the general procedure, **11ai** (260.3 mg, 0.8 mmol) was reacted with thiosemicarbazide (72.9 mg, 0.8 mmol). After 24 h under reflux, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **18ai** as a white solid (257.8 mg, 81%): m.p. (CH_2Cl_2): 206-208 °C; IR (ATR): 3388, 3310, 3261 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 6H), 6.40–6.58 (m, 2H), 6.74 (d, *J* = 2.3 Hz, 2H), 6.96 (d, *J* = 5.1 Hz, 1H), 7.13 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H), 7.29–7.33 (m, 1H), 7.40 (s, 1H), 7.54 (td, *J* = 7.8, 1.8 Hz, 1H), 7.62 (d, *J* = 5.1 Hz, 1H), 8.63–8.49 (m, 1H), 8.74 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, DMSO-*d*^{6}): δ 55.5, 102.0, 105.7, 119.8, 122.9, 127.3, 128.9, 129.3, 137.0,137.4, 144.5, 147.4, 149.8, 150.5, 160.9, 179.1 ppm; MS (ESI): *m/z* (rel intensity): 399 (MH^+, 100), 384 (4), 382 (53); HRMS (ESI-TOF): calcd. for $C_{19}H_{19}N_4O_2S_2$ [MH^+]: 399.0949; found: 399.0950. [The stereochemistry of **18ai** was determined by 2D-experiments (NOESY)].



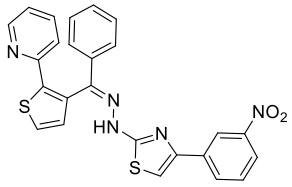
(*Z*)-2-{3-Phenyl-1-[2-(pyridin-2-yl)thiophen-3-yl]propylidene}hydrazine-1-carbothioamide (18ax). Following the general procedure, **11ax** (196.3 mg, 0.67 mmol) was reacted with thiosemicarbazide (61.1 mg, 0.67 mmol). After 24 h under reflux, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **18ax** as a light-brown solid (170.2 mg, 69%): m.p. (CH_2Cl_2): 190-191°C; IR (ATR): 3388, 3267, 3168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82–2.97 (m, 4H), 6.31 (s, 1H), 6.89 (d, *J* = 5.2 Hz, 1H), 7.11–7.35 (m, 8H), 7.53 (d, *J* = 5.2 Hz, 1H), 7.64 (td, *J* = 7.8, 1.6 Hz, 1H), 8.44–8.73 (m, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 32.2, 38.8, 120.3, 122.8, 126.2, 127.7, 128.3, 128.5, 128.8, 130.0, 137.1, 140.7, 142.6, 149.8, 150.7, 151.4, 178.9 ppm; MS (EI): *m/z* (rel intensity): 367 (MH^+, 88), 350 (100), 351 (17); HRMS (ESI-TOF): calcd. for $C_{19}H_{19}N_4S_2$ [MH^+]: 367.1051; found: 367.1055.



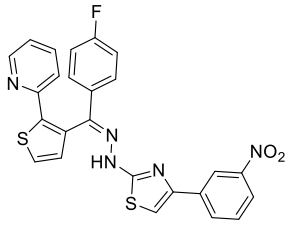
Synthesis of thiazoles 19. General procedure. A solution of 2-bromo-3´-nitroacetophenone (2 mmol) and corresponding thiosemicarbazone **18a** (1 mmol) in EtOH (30 mL) was stirred

at room temperature for 24 h. Then, the solvent was removed under vacuum, the residue was dissolved in dichloromethane and the resulting solution was washed with water (2 × 15mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography afforded thiazoles **19a**.

(*Z*)-4-(3-nitrophenyl)-2-{{2-{phenyl[2-(pyridin-2-yl)thiophen-3-yl]methylene}hydrazineyl}}thiazole (19aa). Following the general procedure, **18aa** (101.5 mg, 0.3 mmol) was treated 2-bromo-3´-nitroacetophenone (146.4 mg, 0.6 mmol). After 24 hours at room temperature, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1 to 6:4) afforded **19aa** as an orange solid (123.8 mg, 85%): m.p. (CH_2Cl_2): 206-208°C; IR (ATR): 3006, 2992, 2971, 1739, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, J = 5.2 Hz, 1H), 7.06–7.13 (m, 2H), 7.33–7.42 (m, 4H), 7.51 (t, J = 7.8 Hz, 2H), 7.62–7.74 (m, 3H), 8.05 (dt, J = 7.8, 1.4 Hz, 1H), 8.10 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 8.61–8.52 (m, 2H), 8.88 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 106.2, 119.5, 120.7, 122.2, 122.7, 126.7, 128.1, 128.7, 129.0, 129.3, 129.5, 129.6, 131.5, 135.8, 136.3, 137.1, 144.1, 145.7, 148.6, 149.2, 149.6, 150.7, 168.4 ppm; MS (ESI): *m/z* (rel intensity): 484 (MH^+, 100), 249 (<1); HRMS (ESI-TOF): calcd. for $C_{25}H_{18}N_5O_2S_2$ [MH^+]: 484.0902; found: 484.0903.

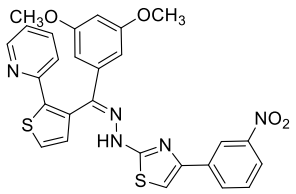


(*Z*)-2-{{2-{(4-Fluorophenyl)[2-(pyridin-2-yl)thiophen-3-yl]methylene}hydrazineyl}}-4-(3-nitrophenyl)thiazole (19ad). Following the general procedure, **18ad** (106.9 mg, 0.3 mmol) was treated 2-bromo-3´-nitroacetophenone (146.4 mg, 0.6 mmol). After 24 hours at room temperature, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **19ad** as a dark-orange solid (130.6 mg, 87%): m.p. (CH_2Cl_2): 203-206; IR (ATR): 3310, 3113, 3052, 2992, 1605, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J = 5.2 Hz, 1H), 6.98–7.13 (m, 4H), 7.36 (dt, J = 8.0, 1.1 Hz, 1H), 7.41–7.52 (m, 2H,), 7.55–7.70 (m, 3H), 7.95–8.08 (m, 2H), 8.42–8.61 (m, 2H), 9.05 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 106.1, 115.70 (d, J = 21.9 Hz), 119.5, 120.7, 122.1, 122.8, 127.9, 128.5, 128.6, 128.8, 129.4 (d, J = 4.7 Hz), 131.5, 132.0 (d, J = 3.2 Hz), 136.2, 137.1, 144.1, 144.8, 148.6, 149.2, 149.7, 150.6, 163.6 (d, J = 250.3 Hz), 168.3 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -111.06 (tt, J = 8.8, 4.3 Hz) ppm; MS (ES^+): *m/z* (rel intensity): 502 (MH^+, 100), 472 (1), 320

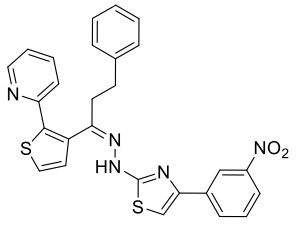


(<1), 267 (<1), 228 (<1); HRMS (ESI-TOF): calcd. for $C_{25}H_{17}FN_5O_2S_2$ [MH^+]: 502.0808; found: 502.0799.

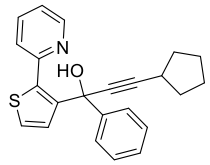
(*Z*)-2-{{2-{(3,5-Dimethoxyphenyl)[2-(pyridin-2-yl)thiophen-3-yl]methylene}hydrazineyl}}-4-(3-nitrophenyl)thiazole (19ai). Following the general procedure, **18ai** (119.5 mg, 0.3 mmol) was treated 2-bromo-3´-nitroacetophenone (146.4 mg, 0.6 mmol). After 24 hours at room temperature, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded **19ai** as an orange solid (127.9 mg, 78%): m.p. (CH_2Cl_2): 192-195 °C; IR (ATR): 3006 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 6H), 6.48 (s, 1H), 6.86 (d, J = 2.1 Hz, 2H), 6.97 (d, J = 5.1 Hz, 1H), 7.05–7.14 (m, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.44 –7.54 (m, 2H), 7.62 (d, J = 5.1 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 8.08 (dd, J = 8.4, 1.6 Hz, 1H), 8.55–8.58 (m, 2H), 8.90 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.4, 101.5, 105.0, 106.1, 119.5, 120.7, 122.2, 122.8, 127.9, 129.1, 129.3, 129.5, 131.6, 136.3, 137.2, 137.8, 144.1, 145.4, 148.6, 149.3, 149.7, 150.7, 160.9, 168.2 ppm; MS (ESI): *m/z* (rel intensity): 545 (25), 544 (MH^+, 100); HRMS (ESI-TOF): calcd. for $C_{27}H_{22}N_5O_4S_2$ [MH^+]: 544.1113; found: 544.1117.



(*Z*)-4-(3-Nitrophenyl)-2-{{2-{3-phenyl-1-[2-(pyridin-2-yl)thiophen-3-yl]propylidene}hydrazineyl}}thiazole (19ax). Following the general procedure, **18ax** (110.0 mg, 0.3 mmol) was treated 2-bromo-3´-nitroacetophenone (146.4 mg, 0.6 mmol). After 24 hours at room temperature, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1 to 9:1) afforded **19ax** as a brown solid (109.2 mg, 71 %): m.p. (CH_2Cl_2): 69-72°C; IR (ATR): 3314 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.94 (t, J = 7.5 Hz, 2H), 3.04 (t, J = 7.5 Hz, 2H), 6.92 (d, J = 5.1 Hz, 1H), 7.03 (s, 1H), 7.16 (dd, J = 7.4, 4.9 Hz, 1H), 7.22–7.33 (m, 6H), 7.48–7.56 (m, 2H)*, 7.52 (d, d, J = 5.1 Hz, 1H)* 8.04–8.10 (m, 2H), 8.53–8.59 (m, 2H), 8.73 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 32.0, 38.8, 105.6, 119.8, 120.7, 122.1, 122.7, 126.1, 127.8, 128.4, 128.7, 128.9, 129.5, 130.7, 131.5, 136.4, 137.1, 141.1, 142.4, 148.6, 149.0, 149.7, 150.8, 168.8 ppm; MS (ESI): *m/z* (rel intensity): 513 (28), 512 (MH^+, 100); HRMS (ESI-TOF): calcd. for $C_{27}H_{22}N_5O_2S_2$ [MH^+]: 512.1215; found: 512.1224. (* partially overlapped signals).

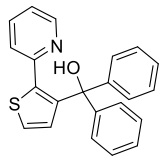


3-Cyclopentyl-1-phenyl-1-[2-(pyridin-2-yl)thiophen-3-yl]prop-2-yn-1-ol (20aa). Under



Argon atmosphere, a well-stirred solution of cyclopentylacetylene (0.11 mL mmol, 0.99 mmol) in anhydrous THF (6 mL) was cooled down to –78 °C. Then, *n*-BuLi (1.6 M solution in hexanes, 1.09 mmol) was added dropwise and the solution was stirred at –78 °C for 2.5 h. Then, a solution of **11aa** (238.8 mg, 0.9 mmol) in anhydrous THF (3 mL) was added dropwise at –78 °C. The mixture was allowed to reach slowly room temperature and stirred for an additional 2 h. The reaction was quenched with a saturated NH_4Cl solution (20 mL) and the mixture was extracted with EtOAc (2 × 15 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc 9/1) to afford **20aa** as a white solid (199.9 mg, 62%): m.p. (CH_2Cl_2): 112-114 °C; IR (ATR): 3087, 3052, 2960, 2868, 2231, 1587, 1474 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22–1.62 (m, 6H), 1.62 –1.78 (m, 2H), 2.51 (quint, J = 7.3 Hz, 1H), 6.73 (d, J = 5.2 Hz, 1H), 7.06–7.38 (m, 5H), 7.57 (d, J = 8.0 Hz, 1H), 7.65–7.74 (m, 3H), 8.54 (dd, J = 5.1, 1.8 Hz, 1H), 9.58 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.9, 24.9, 30.1, 33.6, 33.6, 70.8, 83.5, 89.4, 122.0, 123.1, 124.1, 126.5, 127.2, 127.7, 131.5, 137.5, 137.8, 145.5, 147.3, 148.2, 152.7 ppm; MS (ESI): *m/z* (rel intensity): 382 (MNa^+, 3), 343 (18), 342 (100), 308 (1); HRMS (ESI-TOF): calcd. for $C_{23}H_{21}NNaOS$ [MNa^+]: 382.1242; found: 382.1244.

Diphenyl[2-(pyridin-2-yl)thiophen-3-yl]methanol (20ab). Under Argon atmosphere,



phenylmagnesium bromide (1 M in THF, 1.13 mmol) was added dropwise to a solution of **11aa** (199.0 mg, 0.75 mmol) in dry THF (2.3 mL) at 0 °C. The solution was allowed to reach room temperature and stirred for 5 hours. The reaction was quenched with a saturated NH_4Cl solution (20 mL) and extracted with EtOAc (2 × 15 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc 8/2) to afford **20ab** as a white solid (192.1 mg, 75%): m.p. (CH_2Cl_2): 160-163 °C; IR (ATR): 3084, 3056, 2840, 1587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, J = 5.2 Hz, 1H), 6.99 (ddd, J = 6.8, 5.0, 1.6 Hz, 1H), 7.12–7.29 (m, 7H,), 7.34–7.44 (m, 4H), 7.51–7.65 (m, 2H), 8.26 (dd, J = 5.0, 1.4 Hz, 1H), 9.78 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 78.7, 121.5, 123.0, 123.8, 126.6, 127.4, 127.5, 133.3, 137.6, 137.8, 147.1, 147.9, 150.0, 152.5 ppm; MS (ESI): *m/z* (rel intensity):

366 (MNa^+, 2), 326 (100), 320 (1), 318 (1); HRMS (ESI-TOF): calcd. for $C_{22}H_{17}NNaOS$ [MNa^+]: 366.0929; found: 366.0939.

1-Phenyl-1-[2-(pyridin-2-yl)thiophen-3-yl]propan-1-ol (20ac). Following the previous procedure, **11aa** (199.0 mg, 0.75 mmol) was treated with an ethylmagnesium bromide solution (1 M in THF, 1.13 mmol). After 5 h at room temperature, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **20ac** as a white solid (88.2 mg, 40%): m.p. (CH2Cl2): 67-69 °C; IR (ATR): 3056, 3016, 2974, 2935, 2871, 1591 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ, 0.93 (t, J = 7.3 Hz, 3H), 2.10–2.26 (m, 1H), 2.29–2.48 (m, 1H), 6.94–7.14 (m, 4H), 7.22–7.31 (m, 2H), 7.29–7.39 (m, 2H), 7.41 (dt, J = 8.1, 1.1 Hz, 1H), 7.55 (td, J = 8.0, 1.8 Hz, 1H), 8.41 (ddd, J = 5.0, 1.9, 1.0 Hz, 1H), 9.09 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 8.5, 36.6, 75.9, 121.5, 123.1, 124.6, 125.8, 126.1, 126.9, 130.1, 137.5, 137.9, 147.0, 147.6, 149.9, 152.6 ppm; MS (ESI): *m/z* (rel intensity): 296 (MH^+, 1), 278 (100); HRMS (ESI-TOF): calcd. for $C_{18}H_{18}NOS$ [MH^+]: 296.1104; found: 296.1118.

Synthesis of 4*H*-thieno[2,3-*a*]indolizin-5-ium salts 21. General procedure. Under argon atmosphere, trifluoromethanesulfonic acid (0.25 mmol) was added to a solution of corresponding tertiary alcohol **20** (0.25 mmol) in dry toluene/MeOH (10:1, *v/v*, 2.53 mL). The mixture was stirred at 80 °C for 3 h. The reaction mixture was filtered through a Celite pad washing with MeOH. The filtrate was concentrated, and the crude product was purified using column chromatography on silica gel to obtain **21a-c.**

4-(Cyclopentylethynyl)-4-phenyl-*4H*-thieno[2,3-*a*]indolizin-5-ium trifluoromethanesulfonate (21aa). Following the general procedure, **20aa** (89.9 mg, 0.25 mmol) was treated with trifluoromethanesulfonic acid (22 µL, 0.25 mmol). After 3 h at 80 °C, purification by column chromatography (silica gel, DCM/MeOH 25/1) afforded **21aa** as a white solid (107.3 mg, 87%): m.p. (CH_2Cl_2): 172-174°C; IR (ATR): 3081, , 2971, 2871, 2238, 1739, 1623 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.55–1.86 (m, 6H), 1.95–2.12 (m, 2H), 2.78–3.06 (m, 1H), 7.28 (d, J = 5.0 Hz, 1H), 7.44–7.57 (m, 5H), 7.84 (ddd, J = 7.6, 6.4, 1.3 Hz, 1H), 8.24 (d, J = 5.0 Hz, 1H), 8.42 (dt, J = 8.3, 1.0 Hz, 1H), 8.63 (td, J = 7.9, 1.2 Hz,

1H), 9.02 (dt, J = 6.4, 1.1 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, CD_3OD): δ 24.7, 29.8, 33.0, 71.4, 76.3, 97.7, 120.4, 120.5 (q, J = 317.5 Hz), 121.1, 124.3, 126.3, 129.6, 130.7, 132.0, 134.4, 140.5, 141.0, 147.6, 148.7, 155.6 ppm; MS (ESI): *m/z* (rel intensity): 342 (M^+, 100); HRMS (ESI-TOF): calcd. for $C_{23}H_{20}NS$ [M^+]: 342.1311; found: 342.1324.

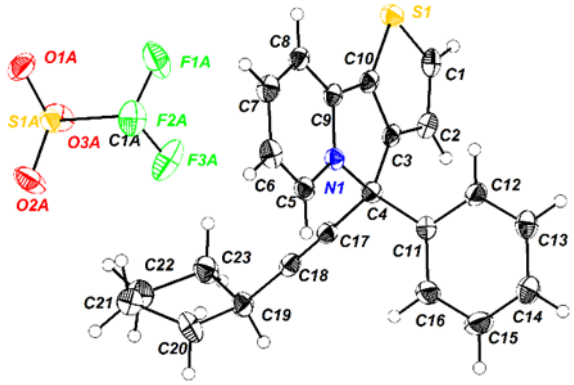
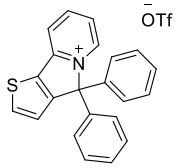


Figure 6.1. R-ray Difraction of **21aa**. ORTEP plot of compound **21aa** with thermal ellipsoids at the 50% probability level with the atomic nomenclature used.

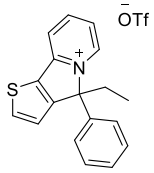
4,4-Diphenyl-4*H*-thieno[2,3-*a*]indolizin-5-ium trifluoromethanesulfonate (21ab).



Following the general procedure, **20ab** (85.9 mg, 0.25 mmol) was treated with trifluoromethanesulfonic acid (22 µL, 0.25 mmol). After 3 h at 80 °C, purification by column chromatography (silica gel, DCM/MeOH 25/1) afforded **21ab** as a light-brown solid (92.7 mg, 78%): m.p. (CH_2Cl_2): 164-167°C; IR (ATR): 3084, 3009, 2988, 1739,1627 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.14–7.30 (m, 4H), 7.43 (d, J = 5.0 Hz, 1H), 7.42–7.52 (m, 6H), 7.81– 7.92 (m, 1H), 8.21 (d, J = 5.0 Hz, 1H), 8.48 (d, J = 8.3 Hz, 1H), 8.57–8.71 (m, 1H), 9.08 (d, J = 6.4 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, CD_3OD): δ 86.5, 120.5 (q, J = 317.7 Hz), 120.7, 122.2, 123.6, 127.4, 129.6, 130.0, 131.3, 137.0, 140.7, 141.7, 147.2, 149.6, 158.2 ppm; MS (ESI): *m/z* (rel intensity):

326 (M^+, 100), 209 (1); HRMS (ESI-TOF): calcd. for $C_{22}H_{16}NS$ [M^+]: 326.1003; found: 326.1006

4-Ethyl-4-phenyl-4*H*-thieno[2,3-*a*]indolizin-5-ium trifluoromethanesulfonate (21ac).



Following the general procedure, **20ac** (51.0 mg, 0.17 mmol) was treated with trifluoromethanesulfonic acid (15 µL, 0.17 mmol). After 3 h at 80 °C, purification by column chromatography (silica gel, DCM/MeOH 20/1) afforded **21ac** as a colourless oil (21.9 mg, 30%): IR (ATR): 3081, 3009, 2984, 1627, 1496 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (t, J = 7.2 Hz, 3H), 2.88 (dq, J = 14.5, 7.2 Hz, 1H), 3.03 (dq, J = 14.5, 7.2 Hz, 1H), 7.15 (d, J = 4.9 Hz, 1H), 7.30–7.37 (m, 2H), 7.39–7.44 (m, 3H), 7.85 (ddd, J = 7.6, 6.3, 1.3 Hz, 1H), 8.04 (d, J = 4.9 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 8.43–8.59 (m, 1H), 9.02 (d, J = 6.3 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.8, 30.6, 84.2, 119.8, 120.7 (q, J = 319.8 Hz), 121.9, 124.5, 126.7, 130.1, 130.8, 132.4, 134.4, 139.8, 141.2, 146.6, 148.7, 156.9 ppm; MS (ESI): *m/z* (rel intensity): 278 (M^+, 100), 215 (1); HRMS (ESI-TOF): calcd. for $C_{18}H_{16}NS$ [M^+]: 278.1003; found: 278.1007.

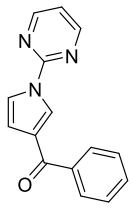
6.3. COBATL(III)-CATALYZED C-H ACYLATION AND AMINOCARBONYLATION OF HETEROAROMATICS

6.3.1. C-H acylation of pyrroles catalyzed by Co(III)

6.3.1.1. Cobalt(III)-catalyzed acylation of **1a**

Cobalt(III)-catalyzed acylation of 1a with phenylglyoxylic acid 22a. Under argon atmosphere, a 20 mL reaction tube equipped with a stirring bar was charged with **1a** (58.2 mg, 0.4 mmol), Cp*CoI_2(CO) (13.6 mg, 0.04 mmol), $AgSbF_6$ (68.7 mg, 0.2 mmol), Ag_2CO_3 (358.5 mg, 1.2 mmol) and phenylglicoxylic acid 22a (180.2 mg, 1.2 mmol). Dry α,α,α-trifluorotoluene was added (4 mL). Then, the reaction tuve was sealed and the reaction mixture was stirred at 140 °C for 24 h. After cooling to room temperature, the reaction mixture was filtered through silica gel and the filtrate was concentrated under vacuum. The residue was purified by column chromatography affording **3aa** (3.4 mg, 3%) and **23aa** as colourless oil (24.9 mg, 25%).

phenyl(1-(pyrimidin-2-yl)-1H-pyrrol-3-yl)methanone (23aa). IR (ATR): 1748, 1632, 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (dd, J = 3.3, 1.8 Hz, 1H), 7.09 (t, J = 4.8 Hz, 1H), 7.34 – 7.55 (m, 3H), 7.78 (dd, J = 3.3, 2.0 Hz, 1H), 7.80 – 7.86 (m, 2H), 8.23 (t, J = 1.8 Hz, 1H), 8.59 (d, J = 4.8 Hz, 2H). ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 112.8, 118.4, 120.4, 125.6, 127.1, 128.3, 129.0, 131.7, 139.5, 155.7, 158.61, 190.83 ppm; MS (ESI^+): *m/z* (rel intensity): 250 (MH^+, 100), 105 (2). HRMS (ESI-TOF): calcd. for $C_{15}H_{12}N_3O$ [MH^+]: 250.0980; found: 250.0983.

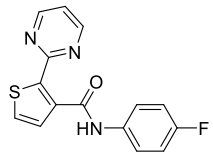


6.3.2. Cobalt(III)-catalyzed C-H aminocarbonylation of thiophenes

6.3.2.1. Aminocarbonylation of **10b** with isocyanates

Aminocarbonylation of 10b with isocyanates. General procedure:[31] Under argon atmosphere, a 20 mL vial equipped with a stirring bar was charged with **10b** (0.5 mmol), Cp*CoI_2(CO) (0.025 mmol), $AgSbF_6$ (0.05 mmol), NaOPiv·H_2O (0.05 mmol) and corresponding icocyanate **24a–g** (1 mmol). DCE was added (2 mL). Then, the vial was sealed and the reaction mixture was stirred at 80 °C for 24 h. After cooling to room temperature, the reaction mixture was filtered through silica gel and the filtrate was concentrated under vacuum. The residue was purified by column chromatography affording **25ba-bg.**

***N*-(4-fluorophenyl)-2-(pyrimidin-2-yl)thiophene-3-carboxamide (25ba).** Following the general procedure, 10b (81.1 mg, 0,5 mmol) was treated with Cp*CoI_2(CO) (8.5 mg, 0.025 mmol), $AgSbF_6$ (17.2 mg, 0.05 mmol), NaOPiv·H_2O (7.1 mg , 0.05 mmol) and 4-fluorophenyl isocyanate (0.11 mL, 1 mmol) After 24 h at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc/DCM 7/2/1) afforded **25ba** as a white solid (135.8 mg, 91%): m.p. (CH_2Cl_2): 172-174°C IR (ATR): 3285, 3003, 2868, 2840, 1672, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (t, J = 8.7 Hz, 1H), 7.30 (t, J = 4.8 Hz, 1H), 7.46 (d, J = 5.4 Hz, 1H), 7.59 – 7.81 (m, 1H), 7.94 (d, J = 5.4 Hz, 0H), 8.82 (d, J = 4.9 Hz, 2H). ppm; ^{13}C



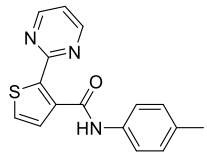
[31] Li, J.; Ackermann, L. Cobalt(III)-Catalyzed Aryland Alkenyl C-H Aminocarbonylation with Isocyanates and Acyl Azides. *Angew. Chem. Int. Ed.* **2015**, *54*, 8551-8554.

NMR (75.5 MHz, $CDCl_3$): δ 115.6 (d, J = 22.3 Hz), 119.2, 121.8 (d, J = 7.8 Hz), 128.6, 134.9, 135.1 (d, J = 2.64 Hz), 138.2, 140.5, 156.6, 159.2 (d, J = 243.1 Hz), 160.54, 160.80 ppm; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -118.47 ppm; MS (ESI): *m/z* (rel intensity): 302 (MH^{++2},1), 301 (MH^{++}, 5), 300 (MH^+, 37), 249 (2), 189 (100); HRMS (ESI-TOF): calcd. for $C_{15}H_{11}FN_3OS$ [MH^+]: 300.0607; found: 300.0611.

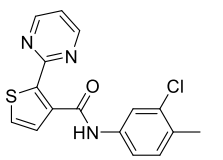
***N*-(4-chlorophenyl)-2-(pyrimidin-2-yl)thiophene-3-carboxamide (25bb).** Following the general procedure, **10b** (81.1 mg, 0,5 mmol) was treated with Cp*CoI_2(CO) (8.5 mg, 0.025 mmol), $AgSbF_6$ (17.2 mg, 0.05 mmol), NaOPiv·H_2O (7.1 mg , 0.05 mmol) and 4-chlorophenyl isocyanate **24b** (153.6 mg, 1 mmol) After 24 h at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc/DCM 7/2/1) afforded **25bb** as a grey solid (107.8 mg, 68%): m.p. (CH_2Cl_2): 202-204°C; IR (ATR): 3002, 2793, 1665, 1622 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d^6) δ 7.33 – 7.46 (m, 4H), 7.68 – 7.75 (m, 2H), 7.81 (d, J = 5.1 Hz, 1H), 8.80 (d, J = 4.9 Hz, 2H), 11.04 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, DMSO-d^6): δ 120.1, 121.7, 127.4, 129.1, 130.3, 130.7, 138.8, 139.1, 140.3, 158.0, 160.4, 163.9 ppm; MS (ESI): *m/z* (rel intensity): 318 (M^{++2}, 8), 317 (MH^{++}, 3), 316 (MH^+, 26), 191 (3), 190 (7), 189 (100); HRMS (ESI-TOF): calcd. for $C_{15}H_{11}ClN_3OS$ [MH^+]: 316.0311; found: 316.0311.

***N*-phenyl-2-(pyrimidin-2-yl)thiophene-3-carboxamide (25bc).** Following the general procedure, **10b** (81.1 mg, 0,5 mmol) was treated with Cp*CoI_2(CO) (8.5 mg, 0.025 mmol), $AgSbF_6$ (17.2 mg, 0.05 mmol), NaOPiv·H_2O (7.1 mg , 0.05 mmol) and phenyl isocyanate **24c** (0.10 mL, 1 mmol) After 24 h at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc/DCM 8/1/1) afforded **25bc** as a light-brown solid (76.7 mg, 55%): m.p. (CH_2Cl_2): 160-162 °C; IR (ATR): 3030, 2860, 2822, 1665, 1629 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 – 7.18 (m, 1H), 7.25 (t, J = 4.9 Hz, 1H), 7.37 (t, J = 7.9 Hz, 2H), 7.44 (d, J = 5.4 Hz, 1H), 7.66 – 7.81 (m, 2H), 7.94 (d, J = 5.4 Hz, 1H), 8.78 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): 119.1, 120.2, 124.0, 128.5, 129.0, 134.9, 138.4, 139.1, 140.5, 156.6, 160.6, 160.7. ppm; MS (ESI): *m/z* (rel intensity): 282 (MH^+, 25), 191 (3), 190 (8), 189 (100); HRMS (ESI-TOF): calcd. for $C_{15}H_{12}N_3OS$ [MH^+]: 282.0701; found: 282.0703.

2-(pyrimidin-2-yl)-*N*-(*p*-tolyl)thiophene-3-carboxamide (25bd). Following the general procedure, **10b** (81.1 mg, 0,5 mmol) was treated with Cp*CoI_2(CO) (8.5 mg, 0.025 mmol), $AgSbF_6$ (17.2 mg, 0.05 mmol), NaOPiv·H_2O (7.1 mg , 0.05 mmol) and *p*-tolyl isocyanate **24d** (0.13 mL, 1 mmol) After 24 h at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc/DCM 7/2/1) afforded **25bd** as a white solid (73.0 mg, 49%): m.p. (CH_2Cl_2): 165-167 °C; IR (ATR): 3006, 2854, 1665, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 7.16 (d, J = 8.2 Hz, 2H), 7.24 (t, J = 4.9 Hz, 1H), 7.43 (d, J = 5.4 Hz, 1H), 7.54 – 7.74 (m, 2H), 7.94 (d, J = 5.4 Hz, 1H), 8.77 (d, J = 4.9 Hz, 2H), 13.35 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.0, 119.1, 120.2, 128.4, 129.5, 133.5, 134.9, 136.5, 138.5, 140.4, 156.6, 160.4, 160.7 ppm; MS (ESI): *m/z* (rel intensity): 296.0858 (MH^+, 36), 191 (3), 189 (100); HRMS (ESI-TOF): calcd. for $C_{16}H_{14}N_3OS$ [MH^+]: 296.0858; found: 296.0855.



***N*-(3-chloro-4-methylphenyl)-2-(pyrimidin-2-yl)thiophene-3-carboxamide (25be).** Following the general procedure, **10b** (81.1 mg, 0,5 mmol) was treated with Cp*CoI_2(CO) (8.5 mg, 0.025 mmol), $AgSbF_6$ (17.2 mg, 0.05 mmol), NaOPiv·H_2O (7.1 mg , 0.05 mmol) and 3-chloro-4-methylphenyl isocyanate **24e** (167.6 mg, 1 mmol) After 24 h at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc 6/4) afforded **25be** as white solid (151.1 mg, 92%): m.p. (CH_2Cl_2): 193-196 °C; IR (ATR): 3070, 3009, 2779, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 7.20 (d, J = 8.2 Hz, 1H), 7.27 – 7.36 (m, 1H), 7.47 (d, J = 5.4 Hz, 1H), 7.53 (dd, J = 8.2, 2.2 Hz, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.95 (d, J = 5.4 Hz, 1H), 8.84 (d, J = 4.9 Hz, 2H), 13.54 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.5, 118.4, 119.2, 120.7, 128.6, 131.0, 131.3, 134.5, 135.0, 137.9, 138.2, 140.5, 156.6, 160.5, 160.8 ppm; MS (ESI): *m/z* (rel intensity): 332 (MH^{++2},11), 331 (MH^{++}, 4), 330 (MH^+, 33), 191 (3), 190 (7), 189 (100); HRMS (ESI-TOF): calcd. for $C_{16}H_{13}ClN_3OS$ [MH^+]: 330.0468; found: 330.0471.



***N*-(4-methoxyphenyl)-2-(pyrimidin-2-yl)thiophene-3-carboxamide (25bf).** Following the general procedure, **10b** (81.1 mg, 0,5 mmol) was treated with Cp*CoI_2(CO) (8.5 mg, 0.025 mmol), $AgSbF_6$ (17.2 mg, 0.05 mmol), NaOPiv·H_2O (7.1 mg , 0.05 mmol) and 4-methoxyphenyl isocyanate **24f** (0.12 mL, 1 mmol) After 24 h at 80 °C, purification by column

chromatography (silica gel, petroleum ether/EtOAc/DCM 8/1/1) afforded **25bf** as a yellow solid (75.6 mg, 49%): m.p. (CH_2Cl_2): 176-178 °C; IR (ATR): 3083, 2832, 1658, 1622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.85 – 6.96 (m, 2H), 7.26 (t, J = 5.2 Hz, 1H), 7.45 (d, J = 5.4 Hz, 1H), 7.63 – 7.72 (m, 2H), 7.95 (d, J = 5.4 Hz, 1H), 8.80 (d, J = 4.9 Hz, 2H), 13.30 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.5, 114.2, 119.1, 121.7, 128.5, 132.3, 134.9, 138.6, 140.2, 156.1, 156.6, 160.3, 160.8 ppm; MS (ESI): *m/z* (rel intensity): 312 (MH^+, 44), 191 (3), 190 (8), 189 (100); HRMS (ESI-TOF): calcd. for $C_{16}H_{14}N_3O_2S$ [MH^+]: 312.0807; found: 312.0804.

***N*-(4-acetylphenyl)-2-(pyrimidin-2-yl)thiophene-3-carboxamide (25bg).** Following the general procedure, **10b** (81.1 mg, 0,5 mmol) was treated with Cp*CoI_2(CO) (8.5 mg, 0.025 mmol), $AgSbF_6$ (17.2 mg, 0.05 mmol), NaOPiv·H_2O (7.1 mg , 0.05 mmol) and 4-acetylphenyl isocyanate **24g** (161.2 mg, 1 mmol) After 24 h at 80 °C, purification by column chromatography (silica gel, petroleum ether/EtOAc/DCM 7/2/1 to petroleum ether/EtOAc 1/1) afforded **25bg** as a white solid (38.8 mg, 24%): m.p. (CH_2Cl_2): 172-175 °C IR (ATR): 3083, 3013, 2857, 1669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3H), 7.32 (t, J = 4.9 Hz, 1H), 7.46 (d, J = 5.4 Hz, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.90 – 8.01 (m, 3H), 8.84 (d, J = 4.9 Hz, 2H), 13.84 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.4, 119.3, 119.4, 128.8, 129.8, 132.5, 134.9, 137.8, 141.0, 143.5, 156.6, 160.6, 160.8, 197.0 ppm; MS (ESI): *m/z* (rel intensity): 324 (MH^+, 38), 191 (3), 190 (7), 189 (100); HRMS (ESI-TOF): calcd. for $C_{17}H_{14}N_3O_2S$ [MH^+]: 324.0807; found: 324.0807.

6.4. DUAL LIGAND-ENABLED LATE-STAGE FUJIWARA-MORITANI REACTION

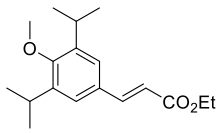
6.4.1. Late-stage nondirected Fujiwara-Moritani reaction of complex bioactive arenes and acrylates with dual-ligand-based palladium catalysts

6.4.1.1. Pd(II)-catalyzed olefination of arenes **26**

General procedure for the olefination of arenes 26: An oven dried 10 mL Schlenk tube was charged with $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 10 mol %), **L1** (9.4 mg, 0.040 mmol, 20

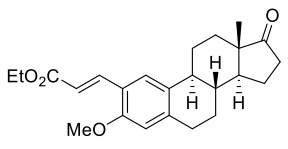
mol %), *N*-acetyl-glycine (7.0 mg, 0.060 mmol, 30 mol %), AgOAc (100.2 mg, 0.6000 mmol, 3 equiv.), arene **26** (0.200 mmol, 1 equiv.) and HFIP (2 mL). The reaction was stirred at room temperature for 2 min. Ethyl acrylate (0.600 mmol, 3 equiv.) was added and the reaction vessel was tightly sealed and placed into an aluminum block at 90 °C with a tightly fitting recess on a magnetic stirrer. The reaction mixture was stirred at this temperature for 24 h. The reaction mixture was allowed to cool to room temperature, filtered through silica, transferred into 100 mL round-bottom flask, and concentrated under reduced pressure. The product was purified by silica gel column chromatography. The conditions for the purification are indicated for the individual experiments below.

(*E*)-ethyl 3-(3,5-diisopropyl-4-methoxyphenyl)acrylate (27a): Following the general procedure and using 1,3-diisopropyl-2-methoxybenzene **26a** (38.5 mg, 0.200 mmol, 1 equiv.) as the arene, afforded compound **27a** as colorless solid (35.5 mg, 61%). The product was purified by silica gel column chromatography using pentane/ethyl acetate 80/1 to 60/1 as the eluent: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 16.0 Hz, 1H), 7.20 (s, 2H), 6.29 (d, J = 16.0 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.67 (s, 3H), 3.25 (hept, J = 6.9 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.17 (d, J = 6.9 Hz, 12H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 156.7, 144.9, 142.4, 130.7, 124.3, 116.8, 62.3, 60.4, 26.5, 23.9, 14.4 ppm; HRMS (ESI$^+$) m/z: calcd for $C_{18}H_{26}NaO_3^+$ 313.1780; found: 313.1771.

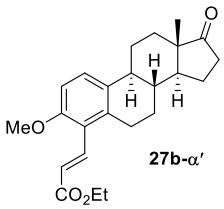


27a

(*E*)-ethyl 3-((8*R*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta*[a]*phenanthren-2-yl)acrylate (27b-α): Following the general procedure and using estrone 3-methyl ether **26b** (56.9 mg, 0.200 mmol, 1 equiv.) as the arene, afforded compound **27b-α** and **27b-α´** as colorless solid (21.1 mg, 28%; α:α´= 91:9). The product was purified by silica gel column chromatography using pentane/ethyl acetate 80/1 to 60/1 as the eluent. The spectroscopic data of this compound were identical to the ones reported in literature:[32] ^{1}H-NMR (600 MHz,



27b-α

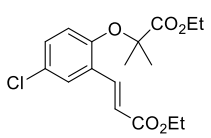


27b-α′

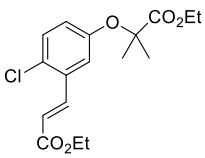
[32] Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X. ; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. Ligand-accelerated non-directed C–H functionalization of arenes. *Nature* **2017**, *551*, 489-493.

$CDCl_3$): δ 7.93 (d, J = 16.1 Hz, 1H$^{\alpha}$), 7.86 (d, J = 16.1 Hz, 1H$^{\alpha'}$), 7.42 (s, 1H$^{\alpha}$), 7.29 (d, J = 8.7 Hz, 1H$^{\alpha'}$), 6.79 (d, J = 8.7 Hz, 1H$^{\alpha'}$), 6.64–6.58 (m, 1H$^{\alpha}$+1H$^{\alpha'}$), 6.50 (d, J = 16.1 Hz, 1H$^{\alpha}$), 4.25 (q, J = 7.1 Hz, 2H$^{\alpha}$+2H$^{\alpha'}$), 3.85 (s, 3H$^{\alpha}$+3H$^{\alpha'}$), 2.97–2.87 (m, 2H$^{\alpha}$+2H$^{\alpha'}$), 2.54–2.47 (m, 1H$^{\alpha}$+1H$^{\alpha'}$), 2.46–2.39 (m, 1H$^{\alpha}$+1H$^{\alpha'}$), 2.28–2.21 (m, 1H$^{\alpha}$+1H$^{\alpha'}$), 2.18–2.11 (m, 1H$^{\alpha}$+1H$^{\alpha'}$), 2.09–1.95 (m, 3H$^{\alpha}$+3H$^{\alpha'}$), 1.66–1.43 (m, 6H$^{\alpha}$+6H$^{\alpha'}$), 1.33 (t, J = 7.1 Hz, 3H$^{\alpha}$+3H$^{\alpha'}$), 0.91 (s, 3H$^{\alpha}$+3H$^{\alpha'}$) ppm;^{13}C-NMR (150 MHz, $CDCl_3$): δ 220.7, 220.6, 168.0, 167.7, 156.9, 156.5, 140.5, 140.3, 138.4, 137.6, 132.5, 132.0, 127.4, 126.2, 123.0, 121.0, 117.8, 111.4, 108.7, 60.3, 60.2, 55.4(6), 55.4(5), 50.4, 47.9(3), 47.8(5), 44.3, 43.7, 38.2, 37.5, 35.8(5), 35.8(1), 31.6, 31.5, 29.9, 29.3, 28.0, 26.4, 25.9, 22.7, 21.5(5), 21.5(1), 14.4, 14.1, 13.8 ppm.

(*E*)-ethyl 3-(5-chloro-2-((1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy)phenyl)acrylate (27c-α) and (*E*)-ethyl 3-(2-chloro-5-((1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy)phenyl)acrylate (27c-β): Following the general procedure and using clofibrate **1c** (48.5 mg, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27c-α** and **27c-β** as yellow oil (32.9 mg, 48%, α:β = 53:47). The product was purified by silica gel column chromatography using pentane/ethyl acetate 40/1 to 20/1 as the eluent. The regioselectivity of **27c-α** and **27c-β** was determined by 1D-NOESY experiments: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.98 (d, J = 16.0 Hz, 1H$^{\beta}$), 7.94 (d, J = 16.2 Hz, 1H$^{\alpha}$), 7.48 (d, J = 2.7 Hz, 1H$^{\alpha}$), 7.24 (d, J = 8.5 Hz, 1H$^{\beta}$), 7.16 (dd, J = 8.9, 2.6 Hz, 1H$^{\alpha}$), 7.10 (d, J = 2.9 Hz, 1H$^{\beta}$), 6.78 (dd, J = 8.8, 2.9 Hz, 1H$^{\beta}$), 6.67 (d, J = 8.8 Hz, 1H$^{\alpha}$), 6.43 (d, J = 16.2 Hz, 1H$^{\alpha}$), 6.31 (d, J = 16.0 Hz, 1H$^{\beta}$), 4.28–4.18 (m, 4H$^{\alpha}$+4H$^{\beta}$), 1.61 (s, 3H$^{\alpha}$+3H$^{\beta}$), 1.58 (s, 3H$^{\alpha}$+3H$^{\beta}$), 1.31 (m, 3H$^{\alpha}$+3H$^{\beta}$), 1.22 (m, 3H$^{\alpha}$+3H$^{\beta}$) ppm;^{13}C-NMR (150 MHz, $CDCl_3$): δ 173.7, 173.6, 166.9, 166.3, 154.3, 152.8, 140.2, 138.6, 133.3, 130.5, 130.2, 128.0, 127.8, 127.8, 127.2, 121.9, 121.1, 120.0, 118.5, 118.0, 80.3, 79.7, 61.7, 61.6, 60.7, 60.5, 25.3, 25.3, 14.3, 14.3, 14.1, 14.0 ppm; HRMS (ESI$^+$) *m/z*: calcd for $C_{17}H_{21}ClNaO_5^+$ 363.0970, Found 363.0967.

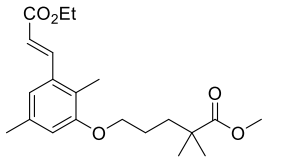


27c-α

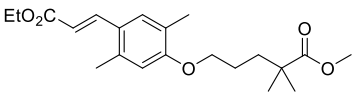


27c-β

(*E*)-methyl 5-(3-(3-ethoxy-3-oxoprop-1-en-1-yl)-2,5-dimethylphenoxy)-2,2-dimethylpentanoate (27d-α) and (*E*)-methyl 5-(4-(3-ethoxy-3-oxoprop-1-en-1-yl)-2,5-dimethylphenoxy)-2,2-dimethylpentanoate (27d-β): Following the general procedure and using 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate **26d** (52.9 mg, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27d-α** and **27d-β** as colorless oil (20.5 mg, 28%, α:β= 60:40). The product was purified by silica gel column chromatography using pentane/ethyl acetate 20/1 as the eluent. The spectroscopic data of this compound were identical to the ones reported in literature.[32]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, J = 15.9 Hz, 1H$^{\alpha}$), 7.91 (d, J = 15.8 Hz, 1H$^{\beta}$), 7.37 (s, 1H$^{\beta}$), 6.97 (d, J = 1.4 Hz, 1H$^{\alpha}$), 6.67–6.63 (m, 1H$^{\alpha}$), 6.58 (s, 1H$^{\beta}$), 6.32 (d, J = 15.9 Hz, 1H$^{\alpha}$), 6.25 (d, J = 15.8 Hz, 1H$^{\beta}$), 4.29–4.23 (m, 2H$^{\alpha}$+2H$^{\beta}$), 3.96–3.90 (m, 2H$^{\alpha}$+2H$^{\beta}$), 3.66 (m, 3H$^{\alpha}$+3H$^{\beta}$), 2.40 (s, 3H$^{\beta}$), 2.31 (s, 3H$^{\alpha}$), 2.26 (s, 3H$^{\alpha}$), 2.18 (s, 3H$^{\beta}$), 1.78–1.67 (m, 4H$^{\alpha}$+4H$^{\beta}$), 1.35–1.32 (m, 3H$^{\alpha}$+3H$^{\beta}$), 1.22–1.21 (m, 6H$^{\alpha}$+6H$^{\beta}$) ppm.;^{13}C NMR (125 MHz, $CDCl_3$): δ 178.3, 167.6, 167.1, 158.7, 157.1, 142.8, 141.9, 137.2, 136.0, 134.3, 128.7, 125.1, 124.8, 123.8, 119.5, 119.1, 116.0, 113.6, 112.8, 68.4, 68.0, 60.4, 60.2, 51.7, 42.1, 42.1, 37.1, 37.0, 25.2, 25.2, 25.1, 21.4, 19.8, 15.8, 14.4, 14.3, 11.2 ppm; HRMS (EI) m/z: Calcd for $C_{21}H_{30}O_5^+$ 362.2088, Found 362.2088.

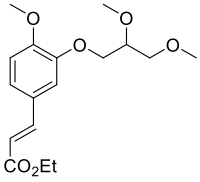


27d-α

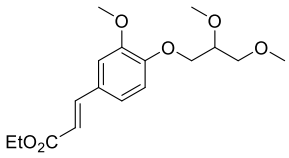


27d-β

(*E*)-ethyl 3-(3-(2,3-dimethoxypropoxy)-4-methoxyphenyl)acrylate (27e-β) and (*E*)-ethyl 3-(4-(2,3-dimethoxypropoxy)-3-methoxyphenyl)acrylate (27e-β´): Following the general procedure and using 1-(2,3-dimethoxypropoxy)-2-methoxybenzene (**26e**) (45.3 mg, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27e-β** and **27e-β´** as colorless oil (33.7 mg, 63%, β:β´ or β`:β = 54:46[33]). The product was purified by silica gel column chromatography using pentane/ethyl acetate 3/1 as the eluent.;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 1H$^{\beta}$+1H$^{\beta'}$), 7.09–6.95 (m, 2H$^{\beta}$+2H$^{\beta'}$), 6.83 (d, J = 8.3 Hz,



27e-β

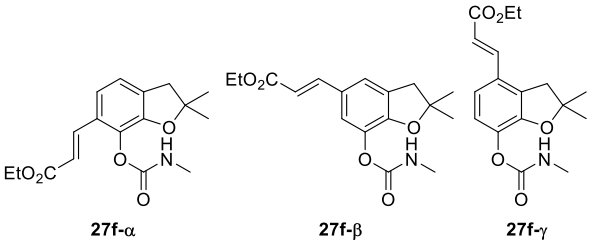


27e-β´

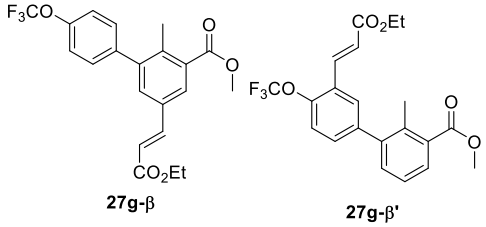
[33] An assignment of β vs. β' could not be achieved. These two regioisomers were obtained in nearly equimolar amounts without the respective α-isomers.

$1H^{\beta/\beta'}$), 6.78 (d, *J* = 8.3 Hz, $1H^{\beta/\beta'}$), 6.23 (m, $1H^{\beta}$+$1H^{\beta'}$), 4.18 (m, $2H^{\beta}$+$2H^{\beta'}$), 4.13–3.98 (m, $2H^{\beta}$+$2H^{\beta'}$), 3.80 (s, $3H^{\beta}$+$3H^{\beta'}$), 3.75–3.66 (m, $1H^{\beta}$+$1H^{\beta'}$), 3.58–3.48 (m, $2H^{\beta}$+$2H^{\beta'}$), 3.46 (m, $3H^{\beta}$+$3H^{\beta'}$), 3.33 (m, $3H^{\beta}$+$3H^{\beta'}$), 1.26 (m, $3H^{\beta}$+$3H^{\beta'}$) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.2, 167.2, 151.7, 150.5, 149.7, 148.6, 144.5, 144.4, 127.9, 127.4, 123.1, 122.4, 116.1, 116.0, 113.2, 112.2, 111.6, 110.4, 78.6, 78.5, 71.9, 71.8, 69.1, 68.8, 60.4, 60.3, 59.4, 58.3, 58.3, 56.0, 14.4 ppm. HRMS (EI) *m/z*: calcd for $C_{17}H_{24}O_6^+$ 324.1567, Found 324.1566.

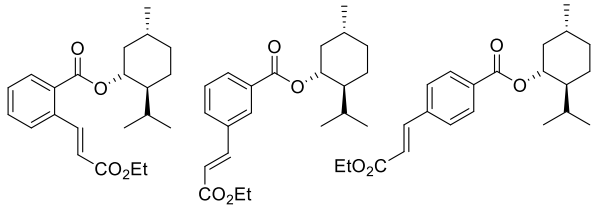
(*E*)-ethyl 3-(2,2-dimethyl-7-((methylcarbamoyl)oxy)-2,3-dihydrobenzofuran-6-yl)acrylate (27f-α), (*E*)-ethyl 3-(2,2-dimethyl-7-((methylcarbamoyl)oxy)-2,3-dihydrobenzofuran-5-yl)acrylate (27f-β) and (*E*)-ethyl 3-(2,2-dimethyl-7-((methylcarbamoyl)oxy)-2,3-dihydrobenzofuran-4-yl)acrylate (27f-γ): Following the general procedure and using 2,2-dimethyl-2,3-dihydrobenzofuran-7-yl methylcarbamate (**26f**) (44.3 mg, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27f-α**, **27f-β** and **27f-γ** as orange solid (41.0 mg, 64%, α:β:γ= 60:30:10). The product was purified by silica gel column chromatography using pentane/ethyl acetate 8/2 to 6/4 as the eluent. The regioselectivity of **27f-α, 27f-β** and **27f-γ** was determined based on the characteristic coupling patterns in ^{1}H-NMR and 1D-NOESY experiments to distinguish between the α- and γ-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 16.1 Hz, $1H^{\alpha}$), 7.61–7.65 (m, $1H^{\beta}$+$1H^{\gamma}$), 7.17 (d, *J* = 1.6 Hz, $1H^{\beta}$), 7.15 (d, *J* = 1.6 Hz, $1H^{\beta}$), 7.07 (d, *J* = 7.8 Hz, $1H^{\alpha}$), 7.03–6.98 (m, $1H^{\alpha}$+$2H^{\gamma}$), 6.39 (d, *J* = 16.1 Hz, $1H^{\alpha}$), 6.30–6.22 (m, $1H^{\beta}$+$1H^{\gamma}$), 5.18–5.04 (m, $1H^{\alpha}$+$1H^{\beta}$), 4.76 (s, $1H^{\gamma}$), 4.26–4.20 (m, $2H^{\alpha}$+$2H^{\beta}$+$2H^{\gamma}$), 3.04–3.03 (m, $2H^{\alpha}$+$2H^{\beta}$+$2H^{\gamma}$), 2.90–2.87 (m, $3H^{\alpha}$+$3H^{\beta}$+$3H^{\gamma}$), 1.51–1.49 (m, $6H^{\alpha}$+$6H^{\beta}$+$6H^{\gamma}$), 1.31 (m, $3H^{\alpha}$+$3H^{\beta}$+$3H^{\gamma}$) ppm.;^{13}C NMR (150 MHz, $CDCl_3$): δ 171.1, 167.3, 167.0, 167.0, 154.3, 153.9, 152.4, 151.6, 144.2, 141.9, 138.8, 136.0, 134.8, 133.6, 131.6, 130.4, 128.0, 127.4, 122.6, 122.5, 122.3, 122.0, 119.8, 119.3, 119.3, 119.0, 115.6, 89.6, 88.9, 88.6, 60.5, 60.4, 60.4, 60.3, 43.2, 42.9, 42.7, 28.3, 28.1, 28.1, 27.9, 21.0, 14.3, 14.3, 14.2 ppm; HRMS (ESI pos) m/z: Calcd for $C_{17}H_{21}NNaO_5^+$ 342.1312, Found 342.1307.



(*E*)-methyl 5-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-methyl-4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-carboxylate (27g-β) and (*E*)-methyl 3'-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-methyl-4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-carboxylate (27g-β'): Following the general procedure and using methyl 2-methyl-4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-carboxylate **(26g)** (62.1 mg, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27g-β, 27g-β'** and minor regioisomers that could not be assigned individually as a colorless oil (44.9 mg, 55%, β:β':others = 64:24:12). The assignment of the major isomers was achieved based on the characteristic aromatic coupling patterns, the β'-isomer was assigned based on the characteristic aromatic coupling patterns and 1D-NOESY data. The product was purified by silica gel column chromatography using pentane/ethyl acetate 40/1 as the eluent: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, J = 2.0 Hz, $1H^{\beta}$), 7.93 (d, J = 16.1 Hz, $1H^{\beta'}$), 7.84–7.81 (m, $1H^{\beta'}$+$1H^{others}$), 7.65 (m, $1H^{\beta}$+$1H^{others}$), 7.57–7.51 (m, $1H^{\beta'}$+$2H^{others}$), 7.47 (d, J = 2.0 Hz, $1H^{\beta}$), 7.36–7.23 (m, $4H^{\beta}$+$4H^{\beta'}$+$3H^{others}$), 6.50–6.38 (m, $1H^{\beta}$+$1H^{\beta'}$+$1H^{others}$), 4.29–4.19 (m, $2H^{\beta}$+$2H^{\beta'}$+$2H^{others}$), 4.01–3.86 (m, $3H^{\beta}$+$3H^{\beta'}$+$3H^{others}$), 2.40–2.39 (m, $3H^{\beta}$+$3H^{\beta'}$), 2.18 (s, $1H^{others}$), 1.31 (m, $3H^{\beta}$+$3H^{\beta'}$+$3H^{others}$) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.5, 168.4(5), 168.2, 168.0, 166.6, 166.34, 166.3, 166.2, 148.6, 148.6, 146.6, 143.1, 142.9, 142.8, 142.3, 141.7, 141.0, 140.8, 140.8, 140.5, 139.4, 139.2, 138.9, 138.1, 137.2, 137.0, 136.5, 135.6, 133.4, 133.0, 132.8, 132.1, 132.0, 131.8, 131.7, 131.3, 131.2, 131.1, 130.6, 130.5, 130.4, 129.9, 129.6, 129.0, 128.8, 128.4, 127.7, 125.5, 125.5, 123.9, 123.4, 121.7, 121.3, 121.1, 121.1, 121.0, 120.8, 120.8, 119.6, 119.1, 117.9, 60.8, 60.7, 60.6, 60.6, 60.5, 52.5, 52.2, 52.2, 52.1, 52.0, 18.6, 18.6, 18.4, 18.1, 17.6, 14.3, 14.2, 14.2, 14.1, 14.0 ppm; HRMS (ESI^{+}) m/z: Calcd for $C_{21}H_{19}F_3NaO_5^{+}$ 431.1077, found 431.1074.



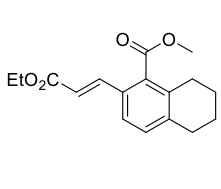
(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)benzoate (27h-*ortho*) , (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 3-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)benzoate (27h-*meta*) and ((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 4-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)benzoate (27h-*para*): Following the general procedure and using (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl benzoate **26h** (52.1 mg, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27h-*ortho***, **27h-*meta*** and **27h-*para*** as colorless oil (29.9 mg, 42%, o:m:p = 16:70:14). The product was purified by silica gel column chromatography using pentane/ethyl acetate 40/1 to 25/1 as the eluent. The regioselectivity of **27h-*ortho***, **27h-*meta*** and **27h-*para*** was determined based on the characteristic aromatic coupling patterns and comparison with the analogous alkynylation products described in literature:[34] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (d, J = 15.9 Hz, 1H^o), 8.18 (s, 1H^m), 8.04 (d, J = 7.8 Hz, 1H^m+2H^p), 7.95 (dd, J = 7.8, 1.4 Hz, 1H^o), 7.76–7.65 (m, 2H^m+1H^p), 7.59–7.54 (m, 1H^o+2H^p), 7.51 (td, J = 7.6, 1.4 Hz, 1H^o), 7.48–7.40 (m, 1H^o+2H^m), 6.50 (d, J = 16.0 Hz, 1H^m+1H^p), 6.27 (d, J = 15.9 Hz, 1H^o), 5.00–4.90 (m, 1H^m+1H^o), 4.30–4.25 (m, 2H^m+2H^o), 2.17–2.07 (m, 1H^m+1H^o), 1.97–1.91 (m, 1H^m+1H^o), 1.76–1.71 (m, 2H^m+2H^o), 1.60–1.52 (m, 2H^m+2H^o), 1.37–1.30 (m, 3H^m+3H^o), 1.19–1.04 (m, 2H^m+2H^o), 1.00–0.83 (m, 7H^m+7H^o), 0.80–0.78 (m, 3H^m+3H^o) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.7, 166.5, 166.5, 166.4, 165.5, 165.4, 144.0, 143.5, 143.2, 138.5, 136.5, 134.8, 132.1, 132.1, 131.9, 131.6, 131.1, 130.6, 130.6, 130.1, 129.3, 129.0, 129.0, 128.0, 127.8, 121.0, 120.5, 119.5, 75.5, 75.2, 75.2, 60.7, 60.6, 60.5, 47.3, 47.2, 47.2, 41.0, 41.0, 34.3, 34.3, 31.5, 31.5, 31.5, 26.5, 26.5, 26.4, 23.7, 23.6, 23.4, 22.0, 20.8, 20.8, 20.8, 16.5, 16.5, 16.3, 14.4, 14.3, 14.3 ppm; HRMS (ESI$^+$) m/z: calcd for $C_{22}H_{30}NaO_4^+$ 381.2036, found 381.2034.



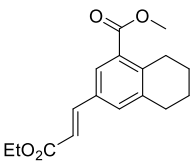
27h-*ortho* 27h-*meta* 27h-*para*

[34] Mondal, A.; Chen, H.; Flämig, L.; Wedi, P.; van Gemmeren, M. Sterically Controlled Late-Stage C–H Alkynylation of Arenes. *J. Am. Chem. Soc.* **2019**, *141*, 18662-18667.

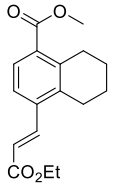
(*E*)-methyl 2-(3-ethoxy-3-oxoprop-1-en-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carboxylate (27i-*α*) ,(*E*)-methyl 3-(3-ethoxy-3-oxoprop-1-en-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carboxylate (27i-β) and (*E*)-methyl 4-(3-ethoxy-3-oxoprop-1-en-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carboxylate (27i-γ): Following the general procedure and using 5,6,7,8-tetrahydronaphthalene-1-carboxylate **26i** (38.0 mg, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27i-β** and **27i-γ+27i-α** as colorless oil (25.8 mg, 45%, β:(α +γ) = 93:7). The product was purified by silica gel column chromatography using pentane/ethyl acetate 15/1 as the eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 15.8 Hz, 1H$^{\gamma/\alpha}$), 7.83 (d, J = 2.3 Hz, 1H$^{\beta}$), 7.64–7.60 (m, 1H$^{\beta}$+1H$^{\gamma+\alpha}$), 7.40–7.33 (m, 1H$^{\beta}$+1H$^{\gamma+\alpha}$), 7.13 (d, J = 8.1 Hz, 1H $^{\gamma/\alpha}$), 6.43 (d, J = 16.0 Hz, 1H$^{\beta}$), 6.34 (d, J = 15.8 Hz, 1H$^{\gamma+\alpha}$), 4.28–4.23 (m, 2H$^{\beta}$+2H$^{\gamma+\alpha}$), 3.94–3.86 (s, 3H$^{\beta}$+3H$^{\gamma+\alpha}$), 3.07–3.04 (m, 2H$^{\beta}$+2H$^{\gamma+\alpha}$), 2.86–2.80 (m, 2H$^{\beta}$+2H$^{\gamma+\alpha}$), 1.80–1.77 (m, 4H$^{\beta}$+4H$^{\gamma+\alpha}$), 1.35–1.31 (m, 3H$^{\beta}$+3H$^{\gamma+\alpha}$) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.9, 166.9, 143.7, 141.1, 139.1, 136.5, 132.2, 131.3, 130.8, 127.6, 127.4, 123.6, 121.5, 118.3, 111.9, 67.9, 60.6, 60.5, 52.0, 37.1, 30.2, 28.2, 27.9, 27.4, 25.2, 22.9, 22.3, 22.3, 14.3 ppm; HRMS (EI) *m/z*: calcd for $C_{17}H_{20}O_4^+$ 288.1356, found 288.1355.



27i-α

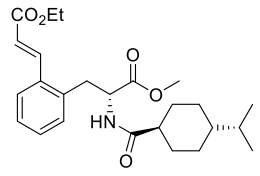


27i-β

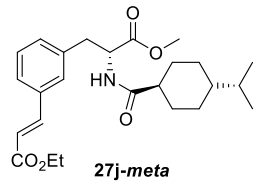


27i-γ

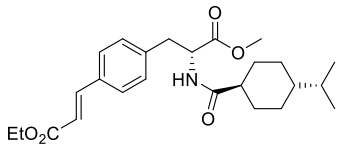
(*E*)-ethyl 3-(2-((*R*)-2-((1*s*,4*S*)-4-isopropyl-cyclohexanecarboxamido) -3- methoxy-3-oxopropyl)phenyl)acrylate (27j-*ortho*), (*E*)-ethyl 3-(3-((*R*)-2-((1*s*,4*S*)-4-isopropylcyclohexanecarboxamido)-3-methoxy-3-oxopropyl)phenyl)acrylate (27j-*meta*) and (*E*)-ethyl 3-(4-((*R*)-2-((1*s*,4*S*)-4-isopropyl-cyclohexanecarboxamido)-3-methoxy-3-oxopropyl)phenyl)acrylate (27j-*para*): Following the general procedure and using (*R*)-methyl 2-((1*S*,4*S*)-4-isopropylcyclohexanecarboxamido)-3-phenylpropanoate **26j** (66.3 mg, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27j-*ortho***, **27j-*meta*** and **27j-*para*** as colourless oil (54.8 mg, 64%, o:m:p = 8:45:47). The product was purified by silica gel column chromatography using pentane:ethyl acetate 4/1 to 3/2 as the eluent. The regioselectivity of **27j-*ortho***, **27j-*meta*** and **27j-*para*** was determined based on the characteristic aromatic coupling patterns and comparison with the analogous alkynylation products described in literature.[34] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, J = 15.7 Hz, 1H^{o}), 7.65–7.59 (m, 1H^{m}+1H^{p}), 7.58 (d, J = 7.8 Hz, 1H^{o}), 7.43 (d, J = 8.1 Hz, 2H^{p}), 7.39 (d, J = 7.8 Hz, 1H^{m}), 7.31-7.28 (m, 1H^{o}+1H^{m}), 7.27–7.23 (m, 1H^{o}), 7.23 (s, 1H^{m}), 7.14 (d, J = 8.5 Hz, 1H^{o}), 7.09 (d, J = 8.1 Hz, 1H^{m}+2H^{p}), 6.42–6.35 (m, 1H^{o} +1H^{m}+1H^{p}), 5.97–5.89 (m, 1H^{o} +1H^{m}+1H^{p}), 4.92–4.84 (m, 1H^{o} +1H^{m}+1H^{p}), 4.29–4.20 (m, 2H^{o} +2H^{m}+2H^{p}), 3.74–3.67 (m, 3H^{o} +3H^{m}+3H^{p}), 3.24–3.15 (m, 1H^{o} +1H^{m}+1H^{p}), 3.12–3.05 (m, 1H^{o} +1H^{m}+1H^{p}), 2.04–1.97 (m, 1H^{o} +1H^{m}+1H^{p}), 1.91–1.81 (m, 2H^{o} +2H^{m}+2H^{p}), 1.80–1.73 (m, 2H^{o} +2H^{m}+2H^{p}), 1.42–1.35 (m, 3H^{o} +3H^{m}+3H^{p}), 1.35–1.30 (m, 3H^{o} +3H^{m}+3H^{p}), 1.07–1.01 (m, 1H^{o} +1H^{m}+1H^{p}), 1.00–0.91 (m, 2H^{o} +2H^{m}+2H^{p}), 0.85–0.81 (m, 6H^{o} +6H^{m}+6H^{p}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 175.6, 172.1, 172.1, 167.0, 166.9, 166.7, 166.6, 144.2, 144.1, 141.4, 140.7, 138.5, 136.8, 135.8, 134.7, 133.8, 133.3, 131.2, 129.9, 129.9, 129.1, 129.0, 128.2, 127.7, 126.9, 126.8, 120.3, 119.5, 118.6, 118.2, 60.7, 60.6, 60.5, 60.5, 52.7, 52.6, 52.6, 52.5, 52.4, 45.5, 45.4, 43.2, 37.8, 37.7, 34.9, 32.8, 29.9, 29.8, 29.6, 29.5, 29.0, 29.0, 28.9, 28.9, 28.9, 19.7, 14.3 ppm; HRMS (ESI^{+}) *m/z*: calcd for $C_{25}H_{35}NNaO_5^{+}$ 452.2407, found 452.2399.



27j-*ortho*

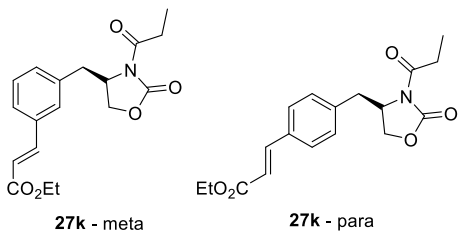


27j-*meta*

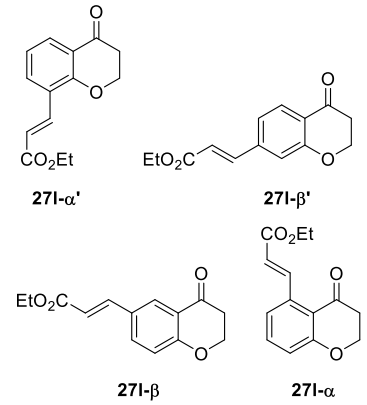


27j-*para*

(*S*,*E*)-ethyl 3-(3-((2-oxo-3-propionyloxazolidin-4-yl)methyl)phenyl)acrylate (27k-meta) and (*S*,*E*)-ethyl 3-(4-((2-oxo-3-propionyloxazolidin-4-yl)methyl)phenyl)acrylate (27k-para): Following the general procedure and using ethyl (*S*)-4-benzyl-3-propionyloxazolidin-2-one **26k** (46.7 mg, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27k-*meta*** and **27k-*para*** as colourless oil (33.7 mg, 51%, m:p = 57:43). The product was purified by silica gel column chromatography using pentane/ethyl acetate 4/1 as the eluent. The regioselectivity of **27k-*meta*** and **27k-*para*** was determined based on the characteristic aromatic coupling patterns and comparison with the analogous alkynylation products described in literature.[34] ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (d, J = 16.0 Hz, 1H^m+1H^p), 7.48 (d, J = 8.1 Hz, 2H^p), 7.43 (d, J = 7.7 Hz, 1H^m), 7.38–7.32 (m, 2H^m), 7.22 (m, 1H^m+2H^p), 6.42 (m, 1H^m+1H^p), 4.67 (m, 1H^m+1H^p), 4.33–4.20 (m, 3H^m+3H^p), 4.14 (m, 1H^m+1H^p), 3.31 (m, 1H^m+1H^p), 3.06–2.85 (m, 2H^m+2H^p), 2.86–2.78 (m, 1H^m+1H^p), 1.33 (m, 3H^m+3H^p), 1.20 (m, 3H^m+3H^p) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$)**:** δ 174.1, 166.9, 166.7, 153.4, 143.8, 143.8, 137.6, 136.2, 135.2, 133.7, 131.1, 129.9, 129.5, 129.0, 128.6, 127.0, 119.0, 118.5, 66.2, 60.6, 60.5, 55.1, 55.0, 37.8, 29.3, 29.2, 14.3, 14.3, 8.3 ppm. HRMS (ESI$^+$) *m/z*: calcd for $C_{18}H_{21}NNaO_5^+$ 354.1312, found 354.1308.

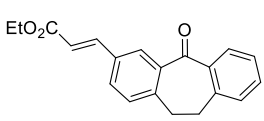


***(E)*-ethyl 3-(4-oxochroman-8-yl)acrylate (27l-α'), (*E*)-ethyl 3-(4-oxochroman-7-yl)acrylate (27l-β'), (*E*)-ethyl 3-(4-oxochroman-6-yl)acrylate (27l- β) and (*E*)-ethyl 3-(4-oxochroman-5-yl)acrylate (27l-*α*):** Following the general procedure and using chroman-4-one (**26l**) (29.6 mg, 0.200 mmol, 1 equiv) as the arene, afforded a mixture of **27l-α'**, **27l-β'**, **27l-β** and **27l-α** as colorless solid (22.6 mg, 46%, α':β':β:α = 68:3:25:4). The product was purified by silica gel column chromatography using pentane:ethyl acetate = 9:1 to 8:2 as the eluent. The regioselectivity was determined in comparison with the literature:[32] ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.55 (d, J = 15.8 Hz, 1H$^{\alpha}$), 8.05 (d, J = 2.3 Hz, 1H$^{\beta}$), 7.94 (dd, J = 7.8, 1.8 Hz, 1H$^{\alpha'}$), 7.91 (m, 1H$^{\alpha'}$+1H$^{\beta'}$), 7.75 (m, 1H$^{\beta'}$), 7.72–7.67 (m, 1H$^{\alpha'}$), 7.66–7.57 (m, 2H$^{\beta}$), 7.43 (t, J = 7.9 Hz, 1H$^{\alpha}$), 7.17 (dd, J =

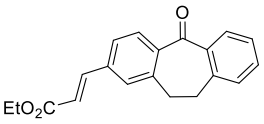


8.3, 1.5 Hz, $1H^{\beta'}$), 7.11–7.06 (m, $1H^{\alpha}$+$1H^{\beta'}$), 7.04 (t, *J* = 7.7 Hz, $1H^{\alpha'}$), 6.99 (d, *J* = 8.7 Hz, $1H^{\beta}$+$1H^{\alpha}$), 6.55 (d, *J* = 16.2 Hz, $1H^{\alpha'}$), 6.48 (d, *J* = 16.0 Hz, $1H^{\beta'}$), 6.37 (d, *J* = 16.0 Hz, $1H^{\beta}$), 6.19 (d, *J* = 15.8 Hz, $1H^{\alpha}$), 4.66–4.61 (m, $2H^{\alpha'}$), 4.60–4.49 (m, $2H^{\beta'}$+$2H^{\beta}$+$2H^{\alpha}$), 4.29–4.23 (m, $2H^{\alpha'}$+$2H^{\beta'}$+$2H^{\beta}$+$2H^{\alpha}$), 2.97–2.66 (m, $2H^{\alpha'}$+$2H^{\beta'}$+$2H^{\beta}$+$2H^{\alpha}$), 1.35–1.31 (m, $3H^{\alpha}$+$3H^{\beta'}$+$3H^{\beta}$+$3H^{\alpha}$) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 191.2, 191.1, 167.0, 166.8, 163.0, 160.2, 145.0, 142.9, 142.8, 138.2, 135.0, 134.8, 134.7, 129.1, 128.0, 127.2, 124.2, 121.9, 121.5, 121.3, 121.2, 120.3, 119.4, 118.7, 117.8, 117.4, 67.3, 67.2, 66.6, 60.6, 60.5, 38.8, 37.7, 37.5, 37.5, 14.3, 14.3 ppm; HRMS (EI) *m/z*: calcd for $C_{14}H_{14}O_4^+$ 246.0887, found 246.0887.

(*E*)-ethyl 3-(5-oxo-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-3-yl)acrylate (27m-β) and (*E*)-ethyl 3-(5-oxo-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-2-yl)acrylate (27m-β´):



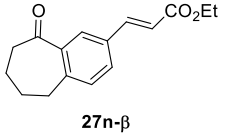
27m-β



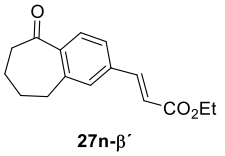
27m-β´

Following the general procedure and using 10,11-dihydro-5H-dibenzo[*a*,*d*][7]annulen-5-one **26m** (41.7 mg, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27m-β** and **27m-β´**as yellow solid (19.2 mg, 31%, β:β´ = 85:15). The product was purified by silica gel column chromatography using pentane/ethyl acetate 4/1 as the eluent. The assignment of regioselectivity was made based on the coupling pattern and the comparison with **27n**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (d, *J* = 1.9 Hz, $1H^{\beta}$), 8.06–7.98 (m, $1H^{\beta}$+$2H^{\beta'}$), 7.73–7.63 (m, $1H^{\beta}$+$1H^{\beta'}$), 7.58 (dd, *J* = 7.8, 2.0 Hz, $1H^{\beta}$), 7.48 (dd, *J* = 8.2, 1.8 Hz, $1H^{\beta'}$), 7.45 (td, *J* = 7.5, 1.5 Hz, $1H^{\beta}$), 7.35 (m, $1H^{\beta}$+$2H^{\beta'}$), 7.28–7.21 (m, $2H^{\beta}$+$2H^{\beta'}$), 6.54–6.46 (m, $1H^{\beta}$+$1H^{\beta'}$), 4.27 (m, $2H^{\beta}$+$2H^{\beta'}$), 3.22 (m, $4H^{\beta}$+$4H^{\beta'}$), 1.34 (m, $3H^{\beta}$+$3H^{\beta'}$) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 194.9, 166.8, 144.0, 143.4, 143.1, 141.9, 141.8, 139.0, 138.3, 133.1, 132.6, 131.4, 131.2, 130.7, 130.7, 130.4, 130.1, 129.3, 129.3, 129.1, 126.8, 126.8, 125.7, 120.4, 118.8, 60.5, 34.9, 34.7, 14.3 ppm; HRMS (ESI^+) m/z: calcd for $C_{20}H_{18}NaO_3^+$ 329.1148, found 329.1145.

(*E*)-ethyl 3-(9-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-yl)acrylate (27n-β) and (*E*)-ethyl 3-(5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-yl)acrylate (27n-β´):



27n-β

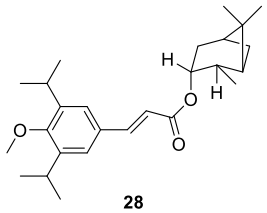


27n-β´

Following the general procedure and using 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one **26n** (30 μL, 0.200 mmol, 1 equiv.) as the arene, afforded a mixture of **27n-β** and **27n-β´**as colorless oil (27.6 mg, 53%, β:β´ = 76:24). The product was purified by silica gel column

chromatography using pentane/ethyl acetate 4/1 as the eluent. The regioselectivity of **27n-β** and **27n-β´** was determined by 2D-NMR (HMBC) experiments: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 (d, J = 2.0 Hz, 1H$^{\beta}$), 7.73 (d, J = 8.0 Hz, 1H$^{\beta'}$), 7.66 (m, 1H$^{\beta}$+1H$^{\beta'}$), 7.55 (dd, J = 7.8, 2.0 Hz, 1H$^{\beta}$), 7.45 (dd, J = 8.0, 1.7 Hz, 1H$^{\beta'}$), 7.34 (d, J = 1.7 Hz, 1H$^{\beta'}$), 7.22 (d, J = 7.8 Hz, 1H$^{\beta}$), 6.52–6.43 (m, 1H$^{\beta}$+1H$^{\beta'}$), 4.31–4.22 (m, 2H$^{\beta}$+2H$^{\beta'}$), 3.01–2.93 (m, 2H$^{\beta}$+2H$^{\beta'}$), 2.78–2.70 (m, 2H$^{\beta}$+2H$^{\beta'}$), 1.95–1.86 (m, 2H$^{\beta}$+2H$^{\beta'}$), 1.84–1.79 (m, 2H$^{\beta}$+2H$^{\beta'}$), 1.33 (m, 3H$^{\beta}$+3H$^{\beta'}$) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 205.4, 205.3, 166.8, 166.6, 143.4, 143.3, 143.3, 141.8, 139.9, 139.3, 137.9, 133.1, 132.2, 131.2, 130.5, 129.5, 129.3, 128.2, 128.2, 126.0, 120.2, 118.8, 60.7, 60.5, 42.1, 40.8, 32.5, 32.4, 25.1, 25.1, 20.9, 20.8, 14.3 ppm; HRMS (EI) *m/z*: calcd for $C_{16}H_{18}O_3^+$ 258.1250, Found 258.1250.

(*E*)-(2*S*,3*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl 3-(3,5-diisopropyl-4-methoxyphenyl)acrylate (28): Following the general procedure and using methyl 3-(3-acetylphenyl)-2,2-dimethylpropanoate **26a** (38.5 mg, 0.200 mmol, 1 equiv.) as the arene and (2*S*,3*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl acrylate (125.0 mg, 0.600 mmol, 3 equiv) as acrylate, afforded **28** as colorless oil (31.0 mg, 39%). The product was purified by silica gel column chromatography using pentane/ethyl acetate 80/1 as the eluent: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 15.9 Hz, 1H), 7.28 (s, 2H), 6.38 (d, J = 15.9 Hz, 1H), 5.21–5.16 (m, 1H), 3.75 (s, 3H), 3.32 (hept, J = 6.9 Hz, 2H), 2.70–2.62 (m, 1H), 2.44–2.38 (m, 1H), 2.25–2.22 (m, 1H), 1.99–1.94 (m, 1H), 1.86 (td, J = 5.8, 2.2 Hz, 1H), 1.79–1.73 (m, 1H), 1.32–1.21 (m, 15H), 1.16–1.13 (m, 4H), 1.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 156.6, 144.6, 142.3, 130.8, 124.2, 117.4, 74.1, 62.3, 47.6, 43.8, 41.4, 38.3, 36.1, 33.6, 27.5, 26.6, 24.0, 23.8, 20.6 ppm; HRMS (ESI$^+$) m/z: Calcd for $C_{26}H_{38}NaO_3^+$ 421.2713, found 421.2708.



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