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Lithium and Palladium mediated cyclization reactions towards the stereocontrolled synthesis of (hetero)benzo-fused indolizidines

MEMORIA PRESENTADA POR

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A Marcus

A Ama y a Aita

"Strive not to be a success, but
rather to be of value"

Albert Einstein

Desearía expresar mi más sincero agradecimiento a las Dras. Esther Lete y Nuria Sotomayor, directoras de este trabajo, por darme la oportunidad de realizar esta Tesis Doctoral bajo su supervisión y por su dedicación para que la realización de ésta haya sido posible.

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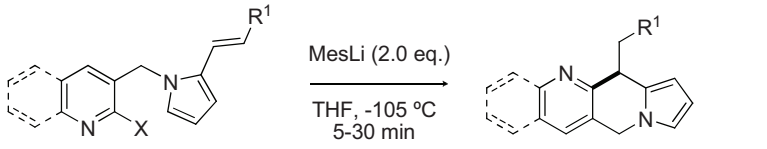
A mi Familia y a mis Amigos, Gracias.

Resumen

El trabajo de investigación que se recoge en la presente memoria se centra en el desarrollo de nuevos métodos sintéticos basados en el empleo de compuestos organolíticos y catálisis con paladio para la formación de enlaces carbono-carbono, orientados a la preparación de heterociclos nitrogenados, tales como pirroloisoquinolinas, naftiridinas y pirrolicinas.

Tal y como se describe en el segundo capítulo y en conexión con los trabajos de nuestro grupo de investigación, se ha extendido la reacción de carbolitiación intramolecular tipo Parham a heteroaril-litios deficientes de electrones, tales como piridinil- y quinolinil-litios derivados de *N*-(*o*-haloheteroarilmetil)pirroles, obteniendo las correspondientes dihidropirrolo[1,2-*g*][1,6]naftiridinas y dihidrobenzo[*b*]pirrolo[1,2-*g*][1,6]naftiridinas con rendimientos de bajos a moderados. El alqueno que actúa como electrófilo interno debe estar activado con grupos electroatractores de electrones, en nuestro caso ésteres y amidas, y se ha comprobado que el empleo de MesLi como agente metalante es crucial para evitar reacciones competitivas de adición conjugada (Esquema 1).

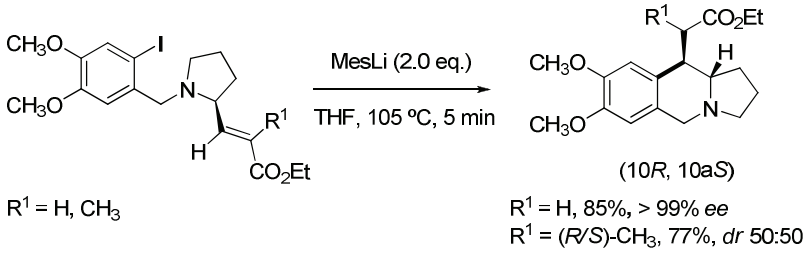


X = Br, I
R^1 = CO_2Et, $CONEt_2$

piridina, R^1 = CO_2Et, 49%
piridina, R^1 = $CONEt_2$, 56%
quinolina, R^1 = CO_2Et, 30%
quinolina, R^1 = $CONEt_2$, 28%

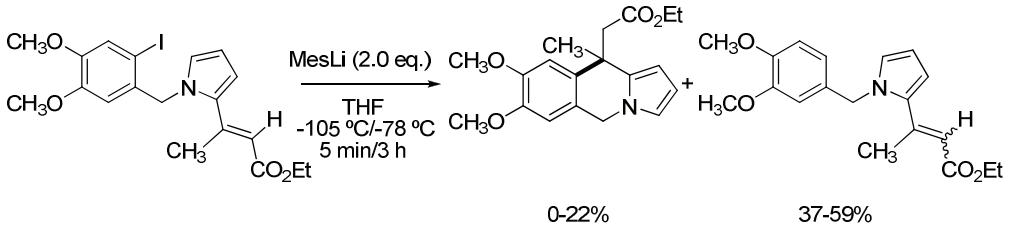
Esquema 1

Por otro lado, se ha logrado sintetizar (10*R*,10a*S*)-hexahidropirrolo[1,2-*b*]isoquinolinas enantioméricamente puras partiendo de *N*-(*o*-yodobencil)pirrolidinilacrilatos derivados de L-prolina, mediante una reacción de carbolitiación intramolecular que resultó ser totalmente diastereoselectiva, cuando el alqueno estaba disustituído, generando eficientemente el centro estereogénico terciario (Esquema 2). Sin embargo, si el alqueno presentaba un grupo metilo en posición α al éster, se obtenía una mezcla de diastereoisómeros, cuya relación dependía de las condiciones empleadas. Si bien la carbolitiación intramolecular parece ser diastereoselectiva, la protonación del intermedio litiado, en la que se genera el tercer centro estereogénico, no fue selectiva.



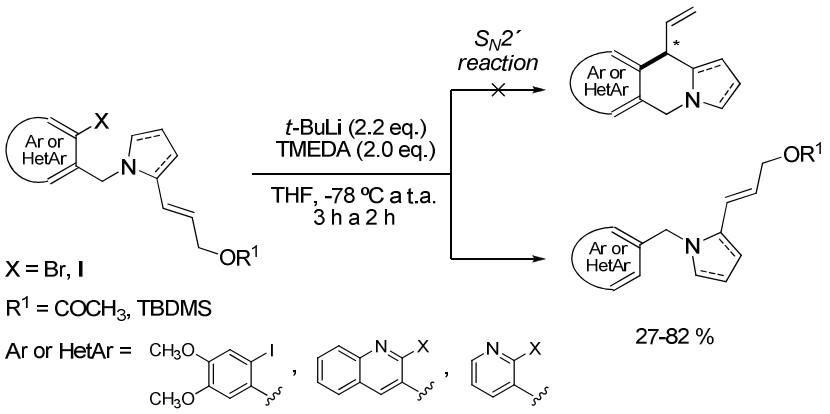
Esquema 2

Por otra parte, la extensión del procedimiento a los correspondientes *N*-(*o*-yodobencil)pirrolilbutenoatos para la formación de un centro cuaternario, no ha proporcionado buenos resultados, aislándose la correspondiente pirroloisoquinolina con bajos rendimientos, siendo el sustrato desyodado el producto mayoritario (Esquema 3).



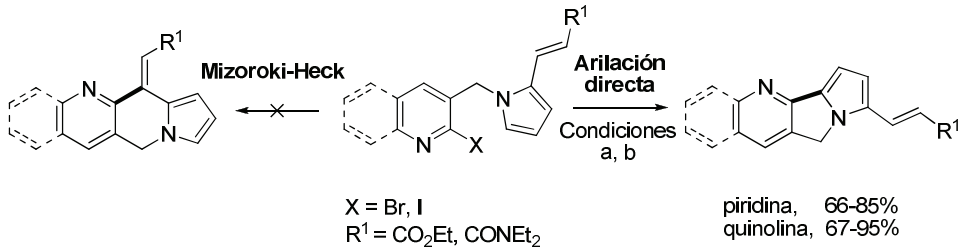
Esquema 3

Asimismo, se ha estudiado la reacción de carbolitiación intramolecular mediante procesos tipo S_N2' sobre *N*-(*o*-yodobencil)pirroles o pirrolidinas alquenil sustituídas, así como sobre las correspondientes halopiridinas y haloquinolinas, en las que el electrófilo interno era un alcohol alílico protegido (R^1 = $COCH_3$, TBDMS). Sin embargo, si bien, en todos los casos, se encontraron las condiciones experimentales para efectuar la metalación, la subsecuente ciclación fallaba, aislándose los sustratos deshalogenados, junto con productos secundarios de adición/sustitución del alquil-litio empleado para efectuar el intercambio halógeno-litio (Esquema 4).



Esquema 4

El tercer capítulo de este trabajo se centra en el estudio de las reacciones intramoleculares tipo Heck catalizadas por paladio. En una primera parte, se ha realizado el estudio de la competencia entre la reacción de Mizoroki-Heck y arilación directa empleando haluros de heteroarilo deficientes en electrones, tales como *o*-bromo- y *o*-yodopiridinas o quinolinas. Se ha investigado la reacción sobre *N*-(*o*-haloheteroaril)pirrolilacrilatos y acrilamidas, tratando de dirigir el ataque hacia el alqueno o hacia el núcleo de pirrol eligiendo el sistema catalítico adecuado. Sin embargo, se ha demostrado que no es posible controlar la quimioselectividad de la reacción. La reacción de arilación directa sobre el C-2 del pirrol está favorecida en todos los casos, incluso empleando sistemas catalíticos basados en $Pd(PPh_3)_4$ que dan lugar a especies catalíticas que pueden favorecer la reacción de Mizoroki-Heck a través de un mecanismo neutro en sustratos relacionados. Así, se ha logrado sintetizar con buenos rendimientos pirido[2,3-*a*]pirrolicinas y pirrolicino[1,2-*b*]quinolinas mediante arilación directa (Esquema 5).

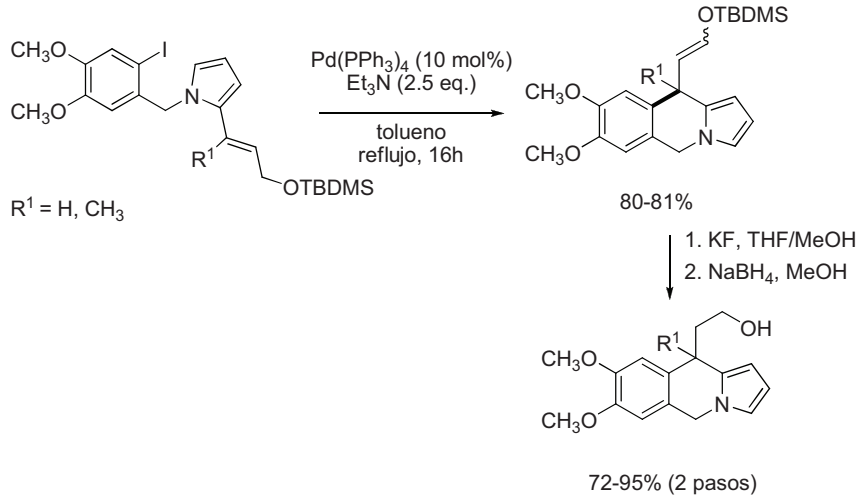


a. $Pd(PPh_3)_4$ (10 mol%), $NaHCO_3$ (2.5 eq.), *n*-Bu_4NCl (1.5 eq.), CH_3CN, reflujo, 48 h
b. $Pd(OAc)_2$ (10 mol%), PPh_3 (10 mol%), *n*-Bu_4NOAc (1.5 eq.), DMF, 110 ºC, 1-2 h

Esquema 5

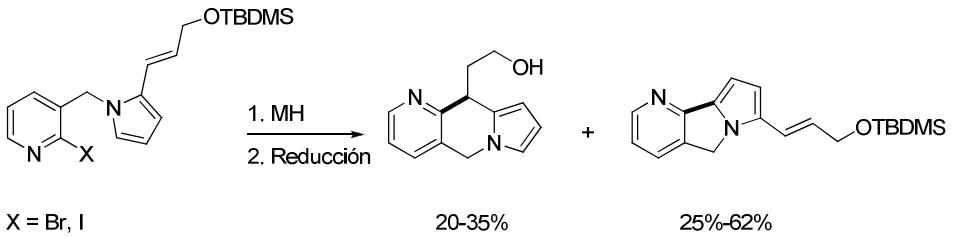
La segunda parte del capítulo se centra en la generación de centros terciarios y cuaternarios en la síntesis de pirroloisoquinolinas y naftiridinas mediante reacción intramolecular de Mizoroki-Heck de diferentes *o*-halo(hetero)arilmetilpirroles, evitando la β-eliminación del hidruro del carbono directamente implicado en la formación del nuevo enlace carbono-carbono, y promoviendo la β´-eliminación de hidruro o de un grupo saliente sobre alcoholes alílicos protegidos.

Por un lado, se ha logrado de manera eficiente la generación de centros cuaternarios y terciarios para la síntesis de pirroloisoquinolinas en versión racémica, partiendo de *N*-(*o*-yodobencil)pirroles en los que se incorporaba una unidad de alcohol protegido con un grupo TBDMS, mediante β´-eliminación selectiva de hidruro (Esquema 6). Dado que en la ciclación se retenía el grupo OTBDMS, el producto se aislaba como una mezcla de diastereoisómeros *E:Z* de silil enol éter, por lo que fue necesaria la desprotección/reducción para obtener la pirroloisoquinolina 10b-hidroxietil sustituída. No obstante, la reacción no es eficiente cuando empleamos fosfinas quirales, lográndose hasta un 18% de *ee* en la generación del centro cuaternario, mediante el empleo de $Pd_2(dba)_3.CHCl_3$ (10 mol%) con (*R*)-BINAP (28 mol%) como ligando, en presencia de Ag_3PO_4 (2.0 eq.) en CH_3CN a reflujo durante 4 h.



Esquema 6

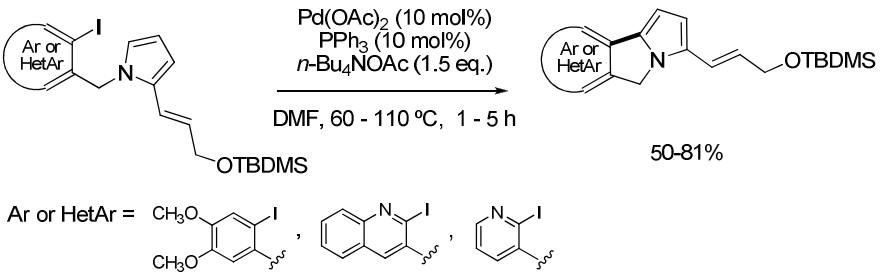
Sin embargo, cuando se trató de extender el procedimiento a las correspondientes *o*-halopiridinas, no pudo controlarse la competencia entre la reacción de Mizoroki-Heck y la arilación directa, obteniendo siempre mezclas de las correspondientes naftiridinas y pirrolicinas, incluso cuando se emplean condiciones que favorecen un mecanismo neutro (Esquema 7). Además, en el caso de *o*-haloquinolinas, únicamente se obtenían productos de arilación directa, sin detectarse el producto de Mizoroki-Heck.



1. $Pd(OAc)_2$ (10 mol%), Et_3N (2.0 eq.), P(*o*-tolyl)$_3$ (10 mol%), CH_3CN:H_2O (10:1), reflujo, 7 h
2. $NaBH_4$ (1.0 eq.), MeOH, t.a., 30 min

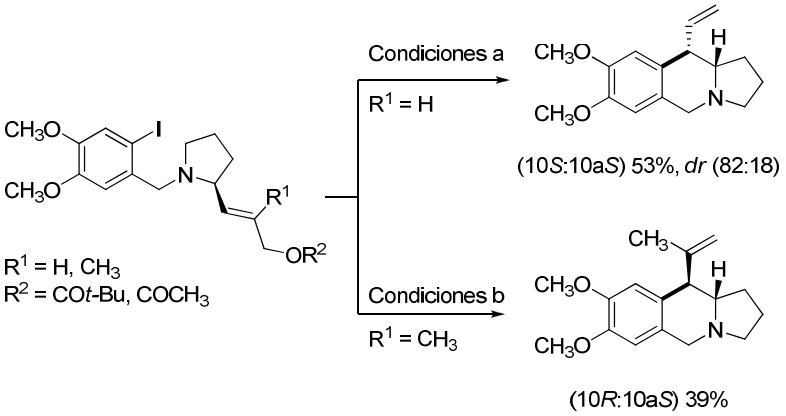
Esquema 7

En vista de estos resultados, se decidió optimizar la reacción de arilación directa sobre *o*-yodo(hetero)arilmetilpirroles que incorporaban un alcohol alílico protegido con un grupo sililo, habiéndose encontrado las condiciones experimentales que promueven la arilación directa sobre el C-2 del pirrol, lo que ha permitido obtener con buenos rendimientos las correspondientes pirrolicinas (hetero)benzo-fusionadas (Esquema 8).



Esquema 8

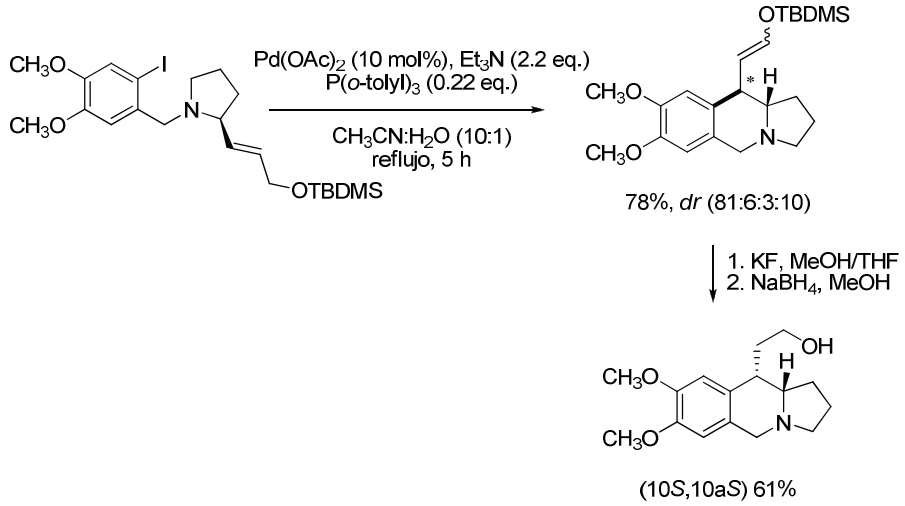
En la última parte del capítulo, se estudió la diastereoselectividad de la reacción de Mizoroki-Heck para la generación de centros terciarios sobre *N*-(*o*-yodobencil)pirrolidinas enantioméricamente puras derivadas de L-prolina. Así, cuando se empleaban pivalatos y acetatos como grupos protectores del alcohol alílico, la ciclación tenía lugar mediante β′-eliminación del grupo carboxilato, obteniéndose 10b-vinil pirroloisoquinolinas con alta diastereoselectividad y rendimientos moderados si el alqueno estaba disustituído (Esquema 9, Condiciones a), si bien los rendimientos eran menores cuando se empleaban alquenos trisustituídos (Condiciones b).



a. $Pd_2(dba)_3.CHCl_3$ (5 mol%), Et_3N (2.0 eq.), P(*o*-tolyl)$_3$ (0.22 eq.), CH_3CN:H_2O (10:1), reflujo, 5 h
b. $Pd_2(dba)_3.CHCl_3$ (10 mol%), Et_3N (2.2 eq.), P(*o*-tolyl)$_3$ (0.44 eq.), DMF, 130 ºC, 4 h

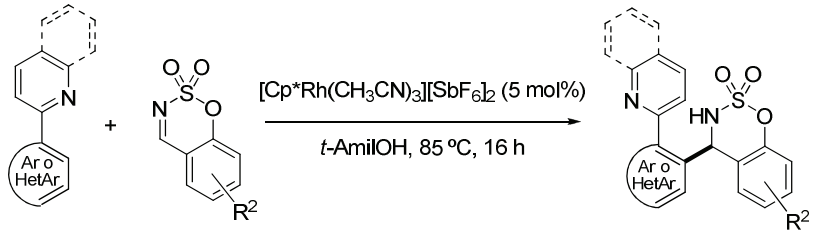
Esquema 9

Por otra parte, cuando el alcohol alílico estaba protegido por un grupo TBDMS, la ciclación tipo Heck tenía lugar mediante β´-eliminación de hidruro, con retención del grupo saliente, de manera diastereoselectiva. La subsecuente desprotección y reducción condujo a la pirroloisoquinolina 10b-hidroxietil sustituída de configuración (10*S*,10a*S*) enantioméricamente pura (Esquema 10).



Esquema 10

Finalmente, en el cuarto capítulo se describe el trabajo desarrollado en el Instituto de Química Orgánica de la RWTH Universidad de Aachen, bajo la supervisión del Prof. Carsten Bolm. Durante la estancia de tres meses en estos laboratorios, se ha estudiado la adición nucleófila de 2-(hetero)arilpiridinas a iminas cíclicas con distintos patrones de sustitución, mediante catálisis con complejos de rodio(III) *vía* activación C-H. Este método, en el cual la piridina actúa como grupo director de la activación C-H, ha permitido la síntesis eficiente de las respectivas aminas en condiciones suaves (Esquema 11).



Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-PhC_6H_4, 3-$OMeC_6H_4$, 4-naftilo
HetAr = 2-tiofenilo
R^2 = H, 4-OMe, 4-F, 4-Cl, 4-Br

Esquema 11

En este contexto, en el grupo de Bolm se había realizado previamente la optimización de las condiciones catalíticas para llevar a cabo la adición nucleofila catalizada por rodio(III) de la 2-fenilpiridina a la [1,2,3]-benzoxatiacina sin sustituir (R^2 = H), *vía* activación del enlace C-H. Mi trabajo ha consistido en la síntesis de sustratos con distintos patrones de sustitución y el empleo de los mismos para estudiar el alcance de la metodología propuesta.

Summary

The research work described in this thesis is focused on the use of lithium and palladium mediated cyclization reactions for the stereocontrolled synthesis of (hetero)benzo-fused indolizidines through carbon-carbon bond formation.

The Parham-type intramolecular carbolithiation *via* conjugate addition and S_N2' reactions of aryl and heteroaryllithiums has been investigated for the construction of the indolizidine core present in different type of heterocycles. On the other hand, the competition between Mizoroki-Heck and direct arylation reaction on alkenyl substituted *o*-halopyridines and *o*-haloquinolines has been studied. Moreover, a procedure for the generation of tertiary and quaternary stereocenters through Heck cyclization *via* β′-hydride or β′-leaving group elimination in different *o*-halo(hetero)arylmethylpyrroles has been developed.

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Chapter VI

EXPERIMENTAL SECTION

Appendix

Abbreviations, acronyms and symbols

Δ	Heat
aq.	Aqueous
ATR	Attenuated Total Reflection
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-Butoxycarbonyl
CH_{arom}	Aromatic carbon
ChiraPhos	Bis(diphenylphosphino) butane
c	Concentration
CI	Chemical Ionization
CDI	Carbonyldiimidazole
CMD	Concerted metalation -deprotonation
COSY	COrrelated SpectroscopY
Cy	Cyclohexyl
δ	Chemical Shift
DavePhos	2-Dicyclohexylphosphino-2′-(*N,N*-dimethylamino) biphenyl
dba	Dibenzylidenacetone
DCC	*N,N'*-dicyclohexyl-carbodiimide
DCE	Dichloroethane
DEPT	Distorsionless Enhancement by Polarization Transfer
DG	Directing group
DIBAL-H	Diisobutylaluminum hydride
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMEDA	*N,N´*-Dimethylethylenediamine
DMF	*N,N*-Dimethylformamide
DMG	Direct Metalation Group
DMSO	Dimethylsulfoxide
D*o*M	Directed *ortho*-Metalation
dppp	1,3-Bis (diphenylphosphino) propane
dr	Diastereomeric ratio
E	Electrophile
Ed(s).	Editor(s)
ee	Enantiomeric excess
EI	Electronic impact
Eq.	Equivalent

ESI	ElectroSpray Ionization
EWG	Electron-Withdrawing Group
FT	Fourier Transform
GC	Gas Chromatography
HetAr	Heteroaryl
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
IR	Infrarred
J	Coupling constant
L	Ligand
Lit.	Literature
LG	Leaving Group
M	Metal
$\mathbf{M^+}$	Molecular Ion (MS)
m.p.	Melting point
MTBE	*Tert*-butyl methyl ether
MS	Mass Spectrometry
MW	Microwave
m/z	Mass to charge ratio
NMR	Nuclear Magnetic Resonance
n.O.e	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement SpectroscopY
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
p.	Page
[Pd]	Palladium source
PCC	Pyridinium Chlorochromate
PG	Protecting Group
Piv	Pivaloyl, *tert*-butylcarbonyl
PMP	1,2,2,6,6-Pentamethylpiperidine
Prod.	Product
Py	Pyridine
QTOF	Quadrupole time-of-flight mass spectrometer
quant.	Quantitative
RCM	Ring Closing Metathesis
r.t.	Room temperature
SEM	2-(Trimethylsilyl)ethoxymethyl
Subs.	Substrate
T	Temperature

t	Time
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
Tf	Triflate, Trifluoromethane-sulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TIPS	Tri(isopropyl)silyl
TLC	Thin layer chromatography
TMBTP	4,4′-Bis(diphenylphosphino)-2,2′,5,5′-tetramethyl-3,3′-bithiophene
TMEDA	*N,N,N′,N′*-Tetramethylethylene-diamine
TMSCl	Trimethylsilyl chloride
tol	Tolyl, 4-methylphenyl
$\mathbf{t_r}$	Retention time
Ts	Tosyl, 4-toluensulfonyl
UPLC	Ultra Performance Liquid Chromatography
UV	Ultraviolet
vs	*versus*

I

Aims and Work Plan

1.1. Group precendents

1.2. Aims and work plan

1.2.1. Intramolecular carbolithiation reaction of 2-alkenyl substituted *N*-(*o*-haloheteroarylmethyl)pyrroles

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1.2.4. Intramolecular Mizoroki-Heck and direct arylation competition study of *N*-(*o*-haloheteroarylmethyl)pyrroles

1.2.5. Generation of quaternary and tertiary centers through intramolecular Mizoroki-Heck reaction

1.2.6. Rhodium(III)-catalyzed nucleophilic addition of 2-(hetero)arylpyridines to cyclic imines

1.1. Group precedents

Organometallic Chemistry has become one of the most interesting fields in Synthetic Organic Chemistry as it affords the possibility to perform a wide number of chemical transformations. In particular, it should be highlighted that organolithium compounds, aryl and heteroaryllithium compounds[1] amongst others, have emerged as versatile intermediates in synthesis, since their reaction with carbon electrophiles allows the introduction of new functionality in a molecule, together with carbon-carbon bond formation. Thus, strategies based on aromatic lithiation have been widely applied in the field of natural products´ synthesis.[2]

[1] a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*, Pergamon Press: New York, 2nd Ed, **1990**. b) Wakefield, B. J. *Organolithium Methods,* Academic Press: London, **1990**. c) Clayden, J. *Organolithiums: Selectivity for Synthesis*, Pergamon Press: New York, 1st Ed, **2002**. d) Rappoport, Z.; Marek, I. Eds., *The Chemistry of Organolithium Compounds, Patai Series: The Chemistry of Functional Groups*, Wiley-VCH: Chichester, **2004**. e) Majewski, M.; Snieckus, V. Eds. In *Science of Synthesis*, *Vol. 8a*, Thieme: Stuttgart, **2006**.

[2] For some selected examples, see: a) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Org. Biomol. Chem.* **2005**, *3*, 2305. b) Moreau, A.; Lorion, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2006**, *71*, 3303. c) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **2007**, *63*, 2664. d) James, C. A.; Snieckus, V. *J. Org. Chem*. **2009**, *74*, 4080. e) Wang, X.; Fu, J.; Snieckus, V. *Helv. Chim. Acta* **2012**, *95*, 2680.

Aromatic lithiation reaction[3] can take place through hydrogen-lithium exchange or halogen-lithium exchange. On the one hand, directed *ortho*-lithiation[4] can be considered as an acid-base reaction in which a strong base such as an alkyllithium reagent causes deprotonation in an *ortho* position to a directing group, leading to an *ortho*-lithiated species, which could further react with electrophiles.

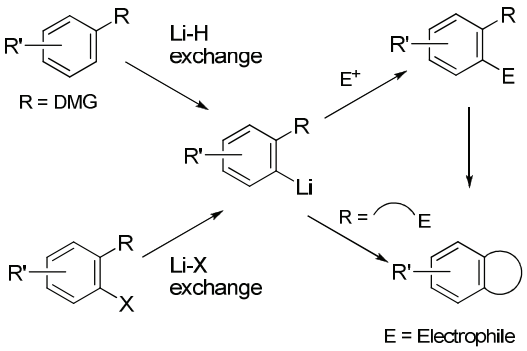
On the other hand, the halogen-lithium exchange procedure allows the possibility to functionalize non-activated positions of an aromatic ring. Moreover, the celerity that characterizes halogen-lithium exchange, even at low temperatures, permits the preparation of aryllithiums in the presence of highly reactive functional groups, such as ketones and imides.

We will focus our attention on the halogen-lithium exchange based lithiation, as it is related to the present research project. Once the halogen-lithium exchange takes place to generate an aryl or heteroaryllithium species, it may react with external or internal electrophiles, resulting in the latter case in cyclization reactions (Scheme 1.1). Intramolecular cyclization reactions that involve an aryllithium intermediate produced by halogen-lithium exchange are termed as Parham cyclizations.[5]

[3] a) Snieckus, V. *Chem. Rev*. **1990**, *90*, 879. b) Snieckus, V. *Pure Appl. Chem*. **1994**, *66*, 2155. c) Gray, M.; Tinkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry II*, *Vol. 11*, Abel, E. W.; Stone, F.G.A.; Wilkinson, G. Eds., Pergamon: Exeter, **1995**, p. 66. d) Schlosser, M. *Eur. J. Org. Chem*. **2001**, 3975. e) Clayden, J. In *The Chemistry of Organolithium Compounds*, *Patai Series: The Chemistry of Functional Groups,* Rappoport, Z.; Marek, I. Eds., Wiley-VCH: Chichester, **2004**, p. 495.

[4] a) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109. b) Wittig, G.; Furhmann, G. *Chem. Ber*. **1940**, *73*, 1197.

[5] a) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1975**, *40*, 2394. b) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.



Scheme 1.1

The application of this methodology using different internal electrophiles, such as alkyl halides, epoxides, alkenes, alkynes, ketones, imines, amides or carbamates, which remain passive during the halogen-lithium exchange process, but are reactive enough to participate in the posterior ring-closure process, provides a successful strategy to regioselectively synthesize carbocycles and heterocycles.[6]

In the last years, our group has developed a variety of synthetic methodologies based on Parham cyclization allowing the synthesis of diverse nitrogen heterocycles.[7] In particular, the use of imides[8] as internal electrophiles is especially attractive as they are much more reactive towards nucleophiles than primary

[6] Sotomayor, N.; Lete, E. *Curr. Org. Chem*. **2003**, *7,* 275.
[7] For selected reviews, see: a) Ardeo, A.; Collado, M.I.; Osante, I.; Ruiz, J.; Sotomayor, N.; Lete, E. In *Targets in Heterocyclic Systems, Vol. 15*, Attanasi, O.; Spinelli, D. Eds., Italian Society of Chemistry: Rome, **2001**, p. 393. b) Arrasate, S.; Sotomayor, N.; Lete, E. In *New methods for the asymmetric synthesis of nitrogen heterocycles,* Vicario, J. L.; Badía, D.; Carrillo, L. Eds., Research Signpost: India, **2005**, p. 223. c) Martínez-Estíbalez, U.; Gómez-SanJuan, A.; García-Calvo, O.; Aranzamendi, E.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem*. **2011**, 3610.
[8] For a review, see: a) Ref. 7c. For some representative examples, see: b) Lete, E.; Eguiarte, A.; Sotomayor, N.; Vicente, T.; Villa, M. J. *Synlett* **1993**, 41. c) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M. J.; Lete, E. *J. Org. Chem.* **1997**, *62*, 2080. d) Osante, I.; Lete, E.; Sotomayor, N. *Tetrahedron Lett*. **2004**, *45*, 1253.

amides. In this sense, in a direct lithiation process (X = H), the organolithium reagents undergo preferentially addition to the carbonyl group of the imide providing α-hydroxylactam intermediates that are immediate precursors of *N*-acyliminium ions (Scheme 1.2). Subsequently, these *N*-acyliminium intermediates are prone to cyclize with the aromatic ring *via* an intramolecular α-amidoalkylation reaction. On the other hand, taking advantage of the fast rates in halogen-lithium exchange, a Parham cyclization can be conducted for iodinated aryl substrates (X = I), which contain an imide as internal electrophile, to afford bicyclic α-hydroxylactams. These lactams are precursors of bicyclic *N*-acyliminium ions, which may react with external nucleophiles *via* intermolecular α-amidoalkylation reaction.[7c]

These two synthetic methodologies have resulted diastereocomplementary and have permitted the stereocontrolled synthesis of different nitrogenated heterocycles.[9] Furthermore, these cyclizations have been carried out in an asymmetric fashion with the aid of chiral auxiliaries under Lewis acid catalysis[10] or with chiral Brönsted acids as catalysts.[11] The combination of α-amidoalkylation and Parham cyclization reactions with intramolecular metathesis reactions (RCM) or conjugated addition has permitted our group to achieve the synthesis of a variety of alkaloid cores (Scheme 1.2).[12]

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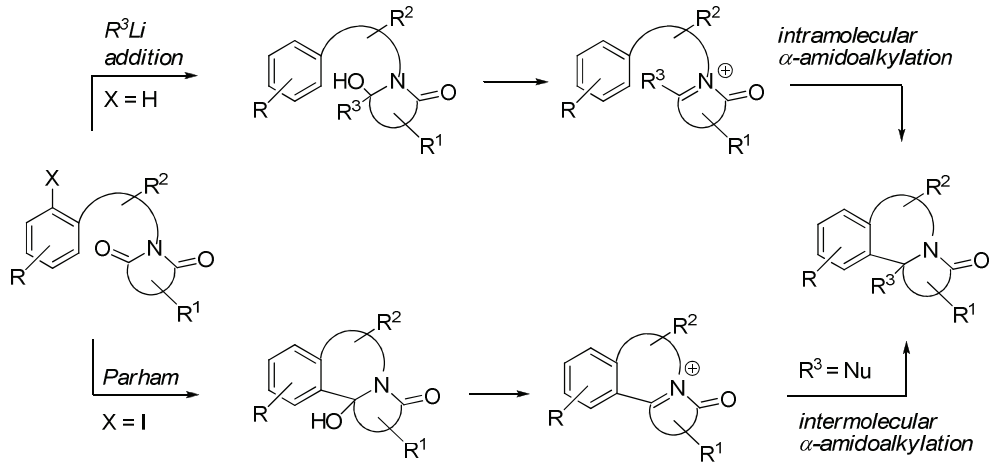
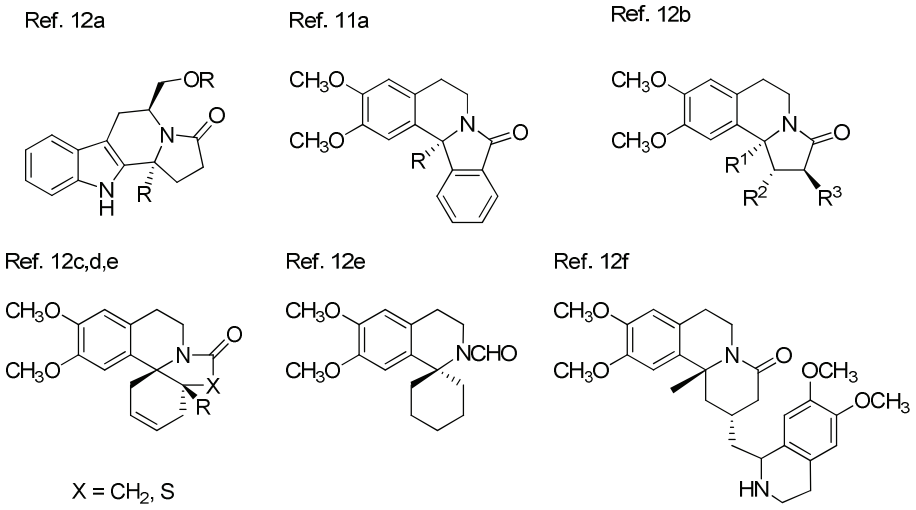
[9] For some representative examples, see: a) Osante, I.; Collado, M. I.; Lete, E.; Sotomayor, N. *Synlett* **2000**, 101. b) Osante, I.; Collado, M. I.; Sotomayor, N.; Lete, E. *Eur. J. Org. Chem*. **2001**, 1267. c) García. E.; Arrasate, S.; Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2001**, *42*, 1511. d) García, E.; Arrasate S.; Lete, E.; Sotomayor, N. *J. Org. Chem*. **2005**, *70*, 10368.

[10] a) González-Temprano, I.; Lete, E.; Sotomayor, N. *Synlett* **2002**, 593. b) González-Temprano, I.; Osante, I.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2004**, *69*, 3875.

[11] a) Aranzamendi, E.; Sotomayor, N.; Lete, E. *J. Org. Chem.* **2012**, *77*, 2986. b) Gómez-SanJuan, A.; Sotomayor, N.; Lete, E. *Tetrahedron Lett.* **2012**, 2157.

[12] a) Ardeo, A.; García, E.; Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron Lett*. **2003**, *44*, 8445. b) Camarero, C.; González-Temprano, I.; Gómez-SanJuan, A.; Arrasate, S.; Lete, E.; Sotomayor, N.

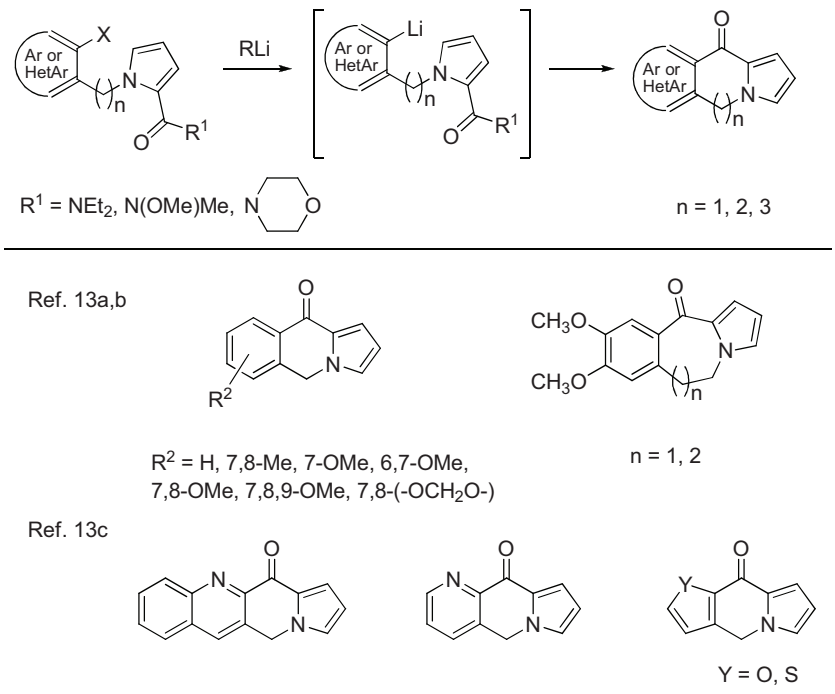




Scheme 1.2

Tetrahedron **2009**, *65*, 5787. c) Osante, I.; Sotomayor, N.; Lete, E. *Lett. Org. Chem.* **2004**, *1*, 323. d) Osante, I.; Abdullah, M. N.; Arrasate, S.; Sotomayor, N.; Lete, E. *Arkivoc* **2007**, *4*, 206. e) Abdullah, M. N.; Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron* **2008**, *64*, 1323. f) García, E.; Lete, E.; Sotomayor, N. *J. Org. Chem*. **2006**, *71*, 6776.

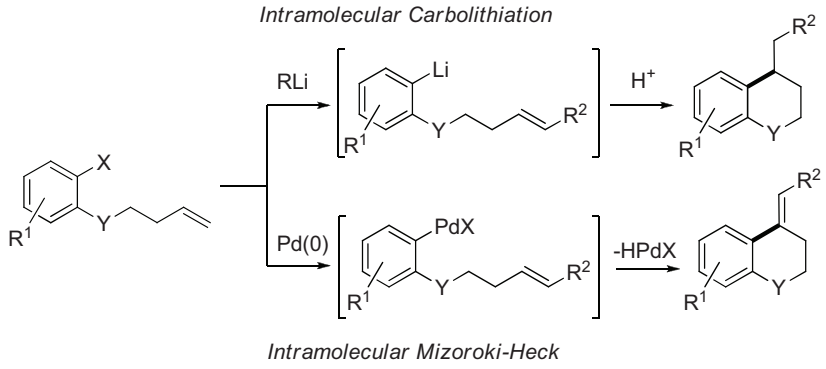
In parallel, our group has studied the generation of six-, seven- or eight-membered rings through Parham cyclization of aryl and heteroaryllithiums with an amide moiety as internal electrophile.[13] This methodology has allowed us the synthesis of benzo- and hetero-fused indolizine type systems, as well as benzazepine and benzazocine skeletons (Scheme 1.3). In this case, the aromatic metalation-cyclization sequence may be considered as an anionic Friedel-Crafts equivalent, with the advantages that it can be performed under milder conditions and it lacks the electronic requirements of the classical reaction.



Scheme 1.3

[13] a) Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* **2003**, *5*, 1115. b) Ruiz, J.; Ardeo, Ignacio, R.; Sotomayor, N; Lete, E. *Tetrahedron* **2005**, *61*, 3311. c) Ruiz, J.; Lete, E.; Sotomayor, N. *Tetrahedron* **2006**, *62*, 6182.

When an alkene is used as an internal electrophile, the carbolithiation would take place in an intramolecular fashion. Our group has also been involved in the study of these cyclization reactions to promote the construction of heterocyclic six-membered rings. In parallel, we have investigated the Mizoroki-Heck reaction as an alternative strategy for the synthesis of this type of heterocycles, as both reactions share common substrates. In this context, making use of both independent methodologies we have conducted the synthesis of quinoline derivatives (Scheme 1.4), since they represent important building blocks in the total synthesis of natural products,[14] as well as they often show biological activity interesting for pharmaceutical and agrochemical industries.[15]



Scheme 1.4

[14] For selected reviews, see: a) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245. b) Solomon, V. R.; Lee, H. *Curr. Med. Chem.* **2011**, *18*, 1488. c) Montalban, A. G. In *Heterocycles in Natural Products Synthesis*, Majumbar, K. C.; Chattopadhyay, S. K. Eds., Wiley: Weinheim, **2011**, p. 299. d) Sridharan, V.; Suryavanshi, P. A.; Menendez, J. C. *Chem. Rev.* **2011**, *111*, 7157.

[15] For selected examples, see: a) Pryor, W. A.; Strickland, T.; Church, D. F. *J. Am. Chem. Soc.* **1988**, *110*, 2224. b) De Koning, A. J. *Int. J. Food Prop.* **2002**, *5*, 451. c) Blaszczyck, A.; Skolimowski, J. *Chem. –Biol. Interact.* **2006**, *162*, 70. d) Kouznetsov, V. V.; Gomez, C. M. M.; Derita, M. G.; Svetaz, L.; Olmo, E. D.; Zacchino, S. A. *Bioorg. Med. Chem.* **2012**, *20*, 6506. e) Kouznetsov, V. V.; Ruiz, F. A.; Vargas, L. Y.; Gupta, M. P. *Lett. Drug Des. Discov.* **2012**, *9*, 680 and references cited therein.

The chemistry of intramolecular carbolithiation reaction[16] will be discussed in detail in Chapter 2, while the palladium-catalyzed Mizoroki-Heck reaction[17] will be studied separately in Chapter 3 of this manuscript. However, we will show selected examples for the synthesis of already mentioned quinoline skeletons.

On the one hand, the synthesis of tetrahydroquinoline system through 6-*exo* intramolecular carbolithiation reaction has been reached from *N*-butenyl substituted 2-iodoanilines bearing different electron-withdrawing substituents on the alkene and in α position to the nitrogen atom.[18] Thus, 2,4-disubstituted tetrahydroquinolines were obtained with moderate diastereoselectivities depending on the nature of the organolithium reagent used, the solvent, and the presence of additives (Figure 1.1a).

[16] For reviews on carbolithiation reactions: a) Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535. b) Clayden, J. *Organolithiums: Selectivity for Synthesis*, Pergamon Press: Oxford, **2002**, p. 273. c) Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59. d) Normant, J. F. *Top. Organomet. Chem*. **2003**, 287. e) Fañañás, F. J.; Sanz, R. In *The Chemistry of Organolithium Compounds, Patai Series: The Chemistry of Functional Groups*, Rappoport, Z.; Marek, I. Eds., Wiley: Chinchester, **2006**, p. 295. f) Hogan, A. M. L.; O´Shea, D. F. *Chem. Commun*. **2008**, 3839. g) Sanz, R. In *Targets in Heterocyclic Systems*, Attanasi, O.; Spinelli, D. Eds., Italian Society of Chemistry: Rome, **2008**, vol. 12, p. 349. h) Martínez-Estíbalez, U.; Gómez-SanJuan, A.; García-Calvo, O.; Arrasate, S.; Sotomayor, N.; Lete, E. In *Targets in Heterocyclic Systems*, Attanasi, O.; Spinelli, D. Eds., Italian Society of Chemistry: Rome, **2010**, vol. 14, p. 124. i) Lete. E.; Sotomayor, N. In *Science of Synthesis*, Vol. 8a update [*Compounds of Group 1 (Li…Cs)*], Yus, M. Ed., Thieme: Stuggart, **2012**, p. 191. i) Minko, Y.; Marek, I. In *Lithium Compounds in Organic Synthesis*, Luisi, R.; Capriati, V. Eds., Wiley: Weinheim, **2014**, p. 329.

[17] For selected reviews, see: a) Heck, R. F. *Org. React.* **1982**, *27*, 345. b) Heck, R. F. In *Comprehensive Organic Synthesis*, *Vol. 4,* Trost, B. M.; Fleming, I. Eds., Pergamon Press: Oxford, **1991**, p. 833. c) Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 2379. d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000**, *100*, 3009. e) Hegedus, L. S. In *Organometallics in Synthesis: A Manual*, Schlosser. M. Ed., Wiley-VCH: Chichester, 2nd Ed, **2002**, p. 1123. f) Oestreich, M. Ed. *The Mizoroki-Heck Reaction*, Wiley-VCH: Chichester, **2009**. g) Larhed, M. Ed. *Science of Synthesis. Cross-Coupling and Heck-type reactions, Vol. 3,* Thieme: Stuttgart, **2013**.

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

In view of these results, we decided to study this 6-*exo* ring-closure over chiral non-racemic 2-iodoanilines derived from glyceraldehyde.[18b] The reaction took place with complete diastereoselectivity to afford the tetrahydroisoquinoline as a single (2*R*,4*S*)-*cis* isomer (Figure 1.1b). The enantioselective version of this reaction was also studied and we were pleased to find that when performing the cyclization of racemic *N*-substituted 2-iodoanilines in the presence of a chiral bidentated ligand, such as (–)-sparteine, the reaction led to the tetrahydroquinolines in moderate diastereoselectivity (in favor of the 2,4-*trans* isomer) and with excellent *ee* for both diastereomers (Figure 1.1c).[18a] In this case, the incorporation of a phenyl group in α position to the nitrogen atom and the substitution pattern in the olefin (Weinreb amide) were crucial to achieve good enantioselection.

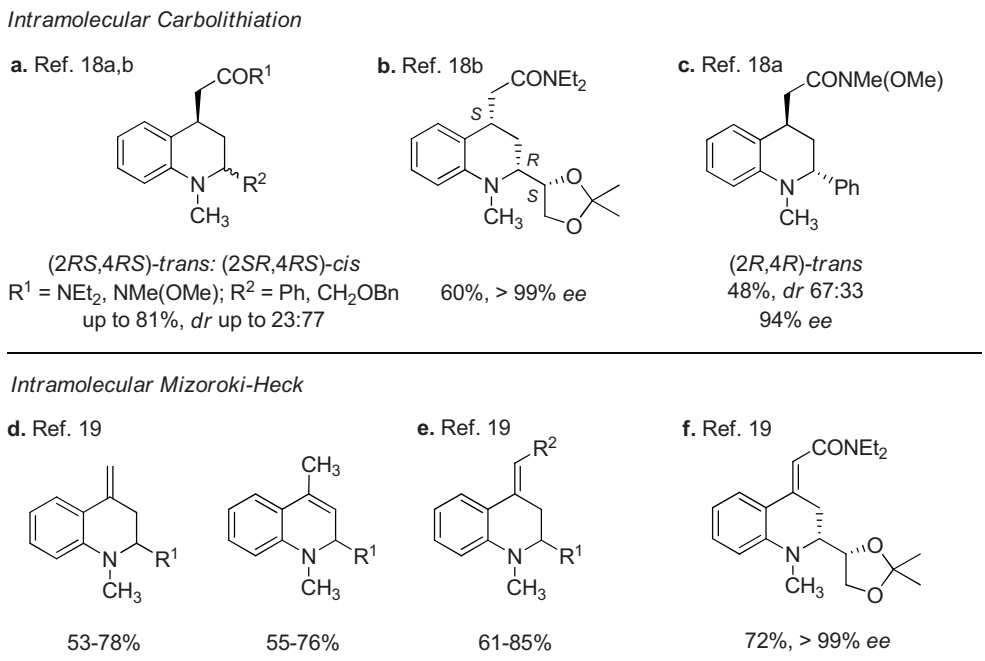
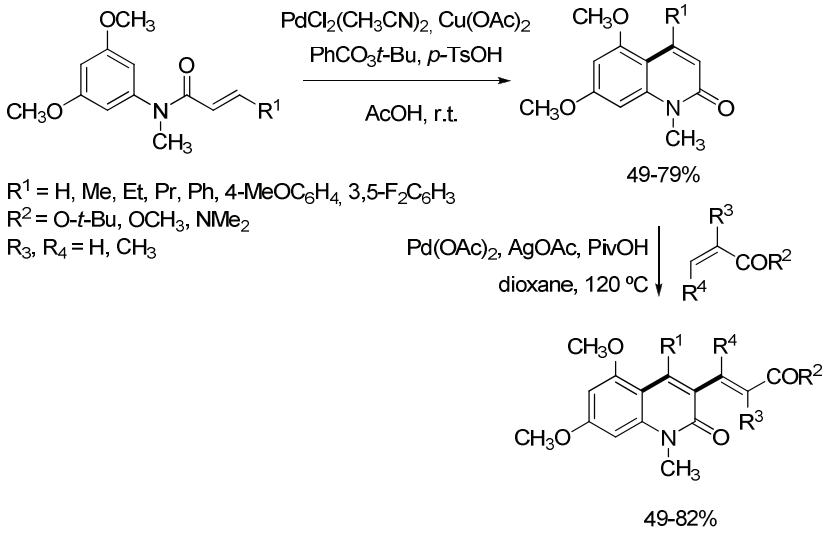


Figure 1.1

The Mizoroki-Heck reaction has also been applied to the synthesis of tetrahydroquinoline derivatives using similar *N*-alkenyl substituted 2-haloanilines as substrates.[19] Concerning these studies, we can outline that cyclization always proceeded in a 6-*exo*-*trig* manner, with high functional group tolerance. Additionally, when using non-substituted alkenes, isomerization and oxidation could be controlled by using adequate catalytic systems and experimental conditions to achieve the regioselective preparation of quinolines with the double bond in an *exo* or *endo* position (Figure 1.1d). When conjugated alkenes were used, the same methodologies afforded selectively the tetrahydroquinoline product with its exocyclic double bond of *E* geometry (Figure 1.1e). The use of chiral substrates also allowed the synthesis of enantiomerically pure tetrahydroquinolines (Figure 1.1f).[19]

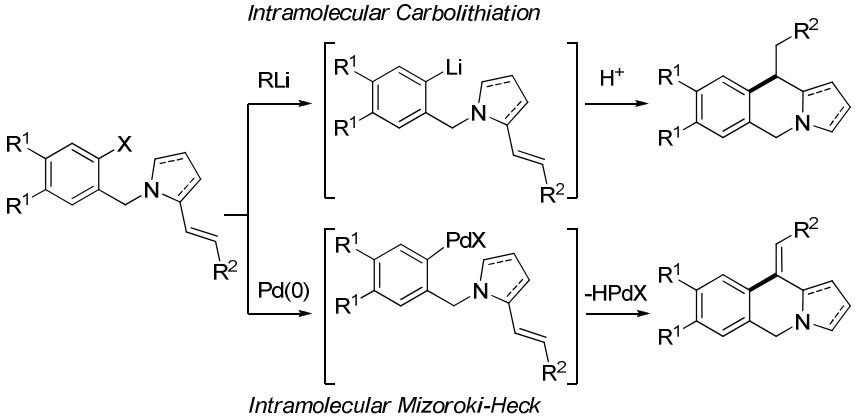
As an alternative to the Mizoroki-Heck reaction, our group has investigated the palladium(II)-catalyzed C-H alkenylation known as Fujiwara-Moritani reaction, which does not require prefunctionalization of substrates. Therefore, we have recently reported an efficient and atom-economical strategy to achieve the regioselective synthesis of 4-substituted quinolones through 6-*endo* intramolecular C-H alkenylation reaction of *N*-phenylacrylamides. A second intermolecular C-H activation reaction led to further functionalization at C-3 position (Scheme 1.5).[20]

[19] Martínez-Estíbalez, U.; García-Calvo, O.; Ortiz-de-Elguea, V.; Sotomayor, N.; Lete, E. *Eur. J. Org. Chem*. **2013**, 3013.
[20] Ortiz-de-Elguea, V.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal*. **2015**, *357*, 463.



Scheme 1.5

We were also interested in the synthesis of pyrroloisoquinolines starting from 2-alkenyl *N*-(*o*-iodobenzyl)pyrroles and pyrrolidines through Parham cyclization and/or Mizoroki-Heck cyclization processes (Scheme 1.6).



Scheme 1.6

In this case, the use of mesityllithium to promote Parham cyclization over 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles allowed the regioselective synthesis of pyrrolo[1,2-*b*]isoquinoline systems, when olefins activated with electron-withdrawing groups were used (Figure 1.2a).[21] The same methodology could be applied for the construction of seven- and eight-membered rings, opening new routes to access benzazepine and benzazocine cores (Figure 1.2b,c).[22]

In addition, we have reported the diastereoselective intramolecular carbolithiation of racemic *N*-(*o*-iodobenzyl)pyrrolidines to obtain *trans*-(10*RS*,10a*SR*)-hexahydropyrrolo[1,2-*b*]isoquinolines as single diastereomers (Figure 1.2d).[23] When chiral non-racemic *N*-(*o*-iodobenzyl)pyrrolidines derived from L-prolinal were used, the 6-*exo*-*trig* cyclization took place with the same degree of diastereoselectivity providing a single *trans*-(10*R*,10a*S*) diastereomer in enantiomerically pure form (Figure 1.2e).[22]

[21] Lage, S.; Villaluenga, I.; Sotomayor, N.; Lete, E. *Synlett* **2008**, 3188.
[22] García-Calvo, O.; Coya, E.; Lage, S.; Coldham, I.; Sotomayor, N.; Lete, E. *Eur. J. Org. Chem.* **2013**, 1460.
[23] a) García-Calvo, O.; Sotomayor, N.; Lete, E.; Coldham, I. *Arkivoc* **2011** (v), 57. b) García-Calvo, O. Ph.D Thesis, University of the Basque Country, **2011**.

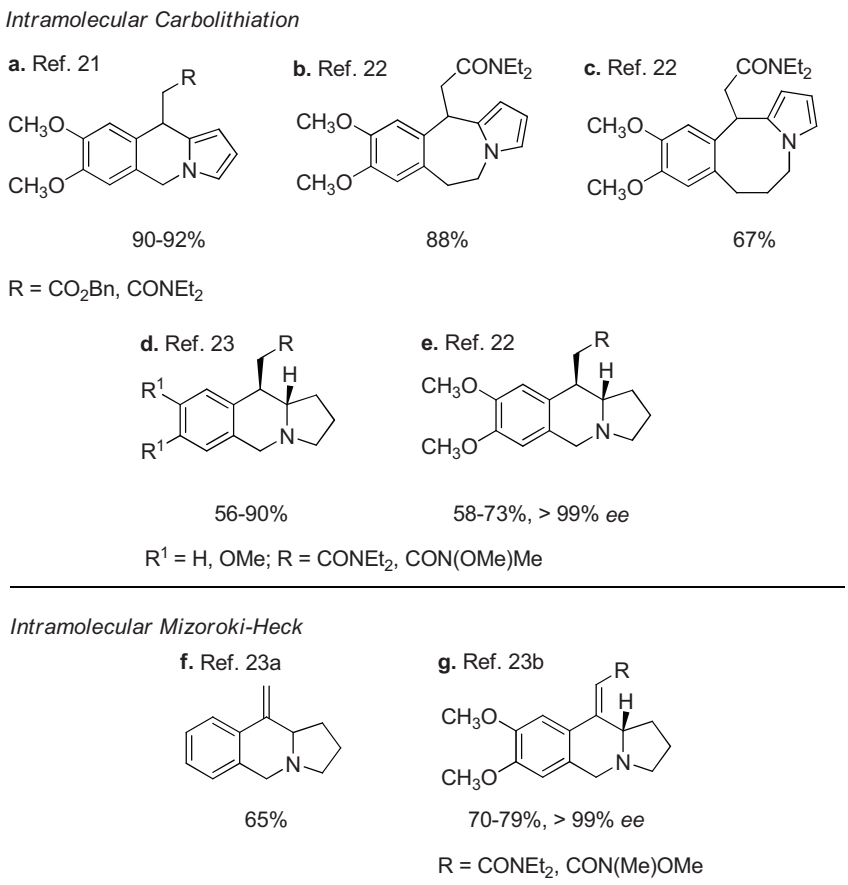
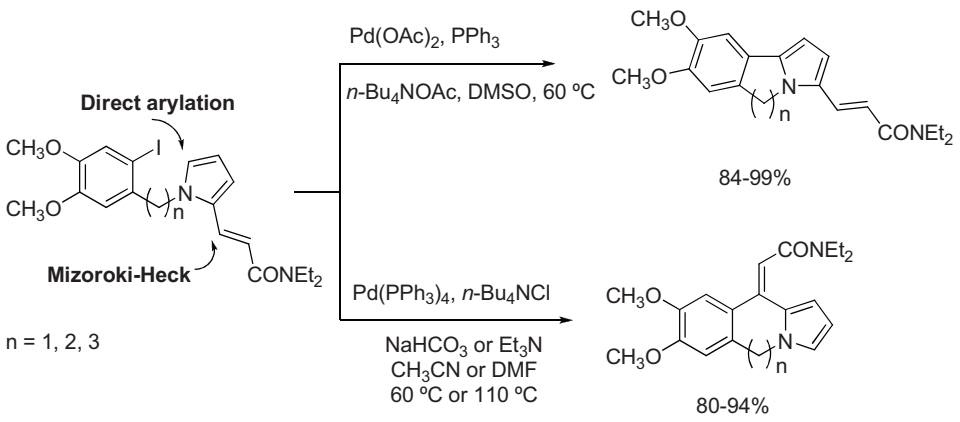


Figure 1.2

Regarding palladium-catalyzed ring-closures, we have described the 6-*exo* Heck cyclization over 2-alkenyl *N*-(*o*-iodobenzyl)pyrrolidines in the synthesis of hexahydropyrrolo[1,2-*b*]isoquinolines (Figure 1.2f), a methodology which can also be applied to the corresponding chiral non-racemic substrates affording enantipure cyclized products (Figure 1.2g).[23]

Furthermore, when 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles are used as substrates in palladium-catalyzed reactions, a competition between Mizoroki-Heck reaction and direct arylation reaction can be established. Hence, it has been possible to control the chemoselectivity of the reaction by applying specific conditions to direct the cyclization towards the olefin or the pyrrole nucleus, affording the regioselective synthesis of pyrroloisoquinolines or pyrroloisoindoles, respectively.[24] This methodology has been extended for the construction of medium size rings (Scheme 1.7).[25]



Scheme 1.7

[24] Lage, S.; Martínez-Estibalez, Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2009**, *351*, 2460 (Highlighted in *Synfacts* **2010**, 0023).
[25] Coya, E.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal*. **2014**, *356*, 1853.

Moreover, we centered our attention in the use of heteroaromatic halides, such as thiophenyl halides, in order to promote cyclizations mediated by lithium and palladium. Regarding carbolithiation reactions, thiophenyllithiums could be prepared by halogen-lithium exchange with MesLi at low temperature, but the 6-*exo* and 7-*exo* ring-closure did not proceed with the same degree of regiochemical efficiency than that one achieved in the reactions with the corresponding aryllithiums. However, this methodology allowed the synthesis of pyrrolo[1,2-*a*]thieno[2,3-*d*]azepine and thieno[3,2-*f*]indolizine in moderate yields (Figure 1.3a).[26]

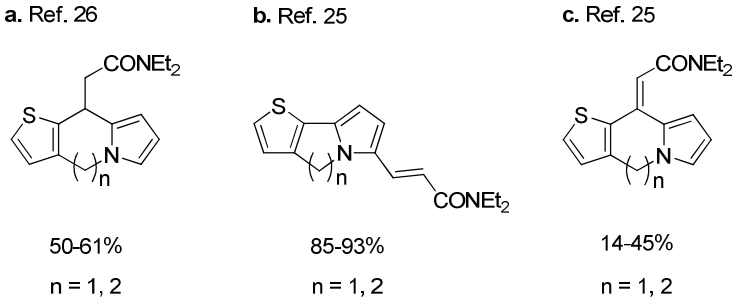
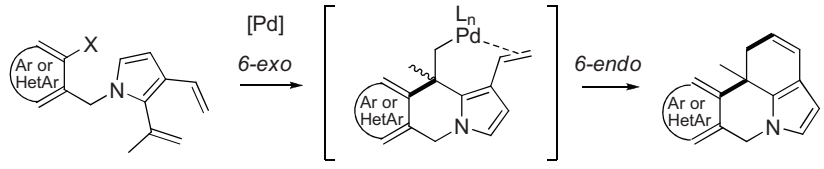


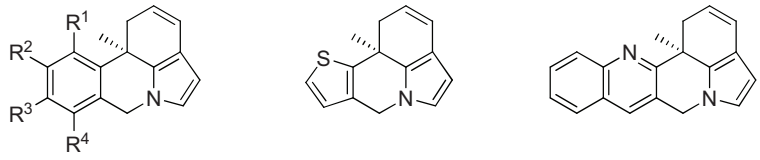
Figure 1.3

The competition between Heck cyclization and direct arylation reaction over thiophenyl halides caused difficulties to control the chemoselectivity of the reaction. In this case, the attack to the pyrrole nucleus was favored (Figure 1.3b), so the Heck-reaction products were always isolated in low to moderate yields (Figure 1.3c).[25]

[26] Coya, E. Ph.D Thesis, University of the Basque Country, **2013**.

Furthermore, we recently showed that quaternary stereocenters can be generated using chiral phosphane ligands through a polyene cyclization. Thus, our group has described the asymmetric palladium-based 6-*exo*/6-*endo* cascade reaction over 2,3-dialkenyl-*N*-(*o*-iodobenzyl)pyrroles in the presence of (*R*)-BINAP ligand to achieve the synthesis of enantioenriched (11*bR*)-substituted pyrrolophenanthridines, which present the tetracyclic framework of the Lycorane core (Scheme 1.8).[27] This polyene cyclization can be further extended to other heteroaromatic rings and tolerates different substitution patterns in the aromatic ring.





up to 75%, up to 72% *ee* 46%, 66% *ee* 11%, 99% *ee*

$R^1 = R^4 = H, OCH_3$
$R^2 = H, OCH_3, OBn$
$R^3 = H, OCH_3, OBn, F, OCH_2(3\text{-}NO_2C_6H_4)$
$R^2, R^3 = -OCH_2O-$

Scheme 1.8

[27] Coya, E.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2015**, *357*, 3206 (Highlighted in *Synfacts* **2016**, *12*, 67).

1.2. Aims and work plan

The overall goal of this research work consists in the development of new methodologies for the synthesis of nitrogenated heterocycles by formation of carbon-carbon bonds through intramolecular carbolithiation and/or palladium-catalyzed Mizoroki-Heck type coupling reactions.

In view of the previously described group precedents, an extension of the Parham cyclization reaction to electron-deficient heteroaryllithiums, derived from *o*-halopyridines and *o*-haloquinolines, will be studied in order to synthesize (benzo)pyrrolonaphthyridines.

On the other hand, an extension of the diastereoselective version of intramolecular carbolithiation reaction will be conducted with alkenyl substituted *N*-(*o*-iodobenzyl)pyrrolidinylacrylates. Additionally, the generation of a quaternary center will be studied by Parham cyclization over a properly designed substrate. Furthermore, an extension of intramolecular carbolithiation methodologies to substrates, where different leaving groups in the allylic chain would be introduced to promote ring closure *via* S_N2' reaction, will be studied.

In parallel, the competition between direct arylation and Mizoroki-Heck reaction over substituted 2-alkenyl *N*-(*o*-haloheteroaryl)pyrroles will be investigated in order to control the chemoselectivity of the reaction for the synthesis of naphthyridine and pyrrolizine frameworks.

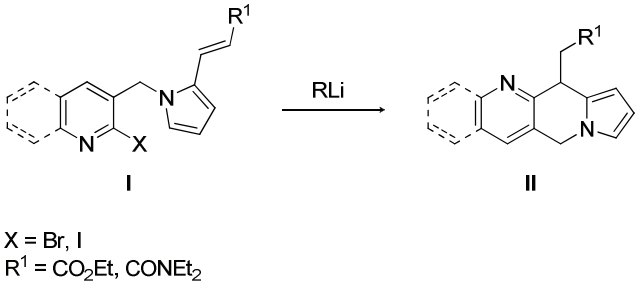
Besides, generation of tertiary and quaternary stereocenters through Heck cyclization over protected allylic alcohols will be studied in order to promote a β´-leaving group or β´-hydride elimination. These reactions will be carried out in the presence of chiral phosphane ligands in order to study the enantioselective variant. The diastereoselectivity of the reaction will also be investigated on chiral non-racemic *N*-(*o*-iodobenzyl)pyrrolidines for the synthesis of pyrroloisoquinolines.

Finally, during a predoctoral stay in the laboratories of Prof. C. Bolm in the RWTH Aachen University, a strategy to perform rhodium(III)-catalyzed nucleophilic addition of 2-(hetero)arylpyridines to cyclic imines *via ortho* C-H bond activation for the synthesis of amines under mild conditions will be studied.

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

1.2.1. Intramolecular carbolithiation reaction of 2-alkenyl substituted *N*-(*o*-haloheteroarylmethyl)pyrroles

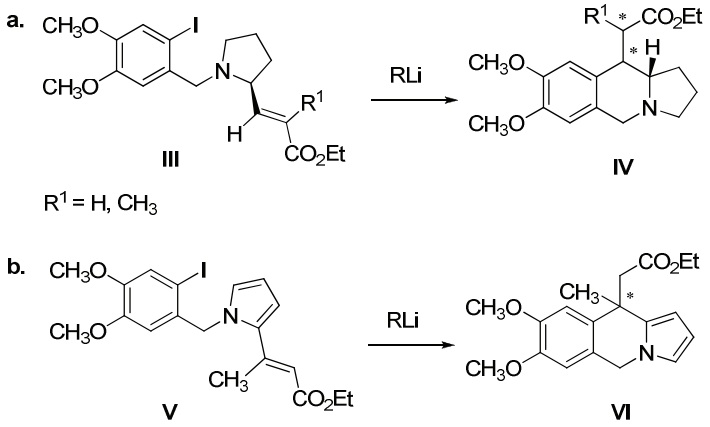
The intramolecular carbolithiation reaction over 2-alkenyl substituted *N*-(*o*-haloheteroarylmethyl)pyrroles **I** will be studied using 2-halo-pyridinyl and quinolinyl derivatives as precursors for the heteroaryllithiums, to open new routes for the synthesis of dihydropyrrolo[1,2-*g*][1,6]naphthyridine and dihydrobenzo[*b*]pyrrolo[1,2-*g*][1,6]naphthyridine skeletons **II** (Scheme 1.9). In view of the group precedents, olefins activated with electron-withdrawing groups will be used.



Scheme 1.9

1.2.2. Intramolecular carbolithiation reaction of *N*-(*o*-halobenzyl)pyrrolidines and pyrroles for generation of tertiary and quaternary centers

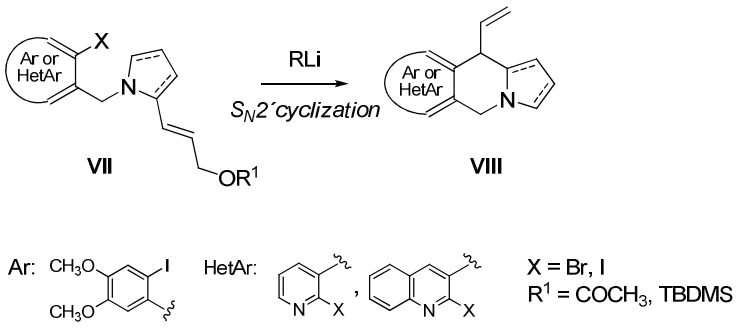
Firstly, an extension of the diastereoselective Parham cyclization previously applied to alkenyl *N*-(o-iodobenzyl)pyrrolidinyl acrylamides, this time over the corresponding acrylates **III** will be studied in order to achieve diastereoselectively tetrahydropyrroloisoquinolines **IV** by the generation of a tertiary stereocenter (Scheme 1.10a). Moreover, an intramolecular carbolithiation over a properly substituted alkenyl *N*-(o-iodobenzyl)pyrrole **V** will be investigated to obtain pyrroloisoquinoline **VI** with generation of a quaternary center (Scheme 1.10b).



Scheme 1.10

1.2.3. Intramolecular carbolithiation reaction of *N-(o*-iodobenzyl) and *N-(o*-haloheteroarylmethyl)pyrrolyl and pyrrolidinyl allylic alcohol derivatives

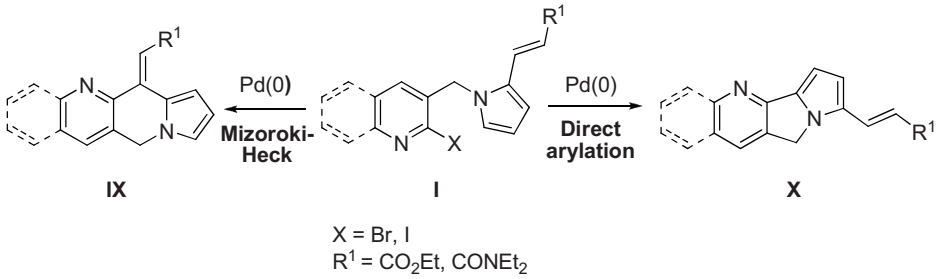
An extension of intramolecular carbolithiation methodologies to substrates **VII**, where different leaving groups in the allylic chain will be introduced to promote ring closure *via* S_N2' reaction, will be studied. Different aryl and heteroaryl halides will be tried (Scheme 1.11).



Scheme 1.11

1.2.4. Intramolecular Mizoroki-Heck and direct arylation competition study on *N-(o*-haloheteroarylmethyl)pyrroles

An extension of the methodologies previously reported for the control in the chemoselectivity to direct palladium-catalyzed reactions towards a Mizoroki-Heck (MH) cyclization or a direct arylation reaction will be studied over electron-deficient heteroaryl halides, such as pyridine and quinoline derivatives **I**. In this sense, an access to naphthyridine **IX** and pyrrolizine **X** cores will be tried (Scheme 1.12).

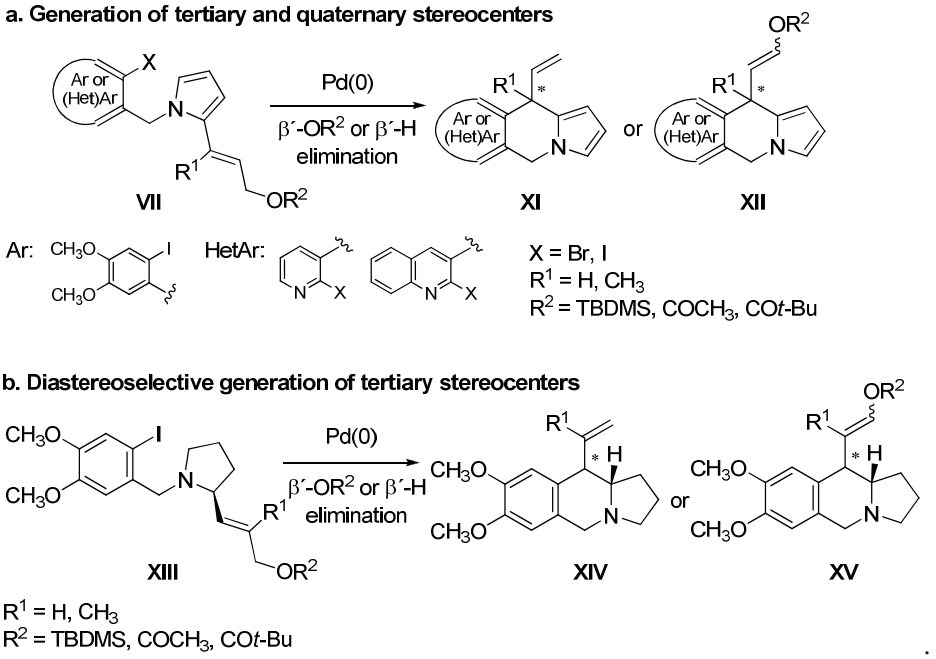


Scheme 1.12

1.2.5. Generation of quaternary and tertiary centers through intramolecular Mizoroki-Heck reaction

The possibility to generate quaternary and tertiary centers will be studied by applying Heck cyclization over different *o*-halo(hetero)arylmethylpyrroles **VII** that will be properly designed incorporating a protected allylic alcohol moiety, in order to avoid β-hydride elimination on the carbon atom directly involved in the new formed bond. In some of the cases, an enantioselective study will be conducted evaluating different parameters such as catalysts, chiral ligands, solvents, additives, etc. (Scheme 1.13a).

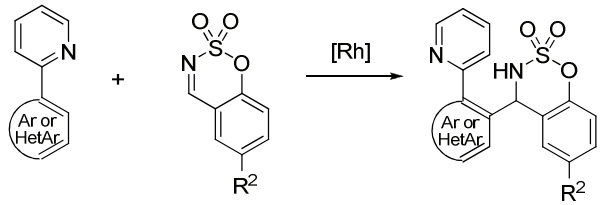
In a similar way, we will subject enantiopure *N*-(*o*-iodobenzyl)pyrrolidines **XIII** to Heck cyclization conditions in order to study the diastereoselectivity of the reaction. We will value the incorporation of different leaving groups in the allylic alcohol to generate a tertiary stereocenter *via* β´-hydride or β´-leaving group elimination (Scheme 1.13b).



Scheme 1.13

1.2.6. Rhodium(III)-catalyzed nucleophilic addition of 2-(hetero)arylpyridines to cyclic imines

During the realization of this PhD, a three-month stay in the RWTH Aachen University (Germany) was carried out to develop a project related to the transition-metal catalyzed nucleophilic addition of *ortho* C-H bonds to unsaturated polar bonds. In this field of research, the rhodium(III)-catalyzed addition of 2-aryl and 2-heteroarylpyridines **XVI** to differently substituted cyclic imines **XVII** will be studied *via* C-H activation (Scheme 1.14). In this context, the synthesis of a variety of coupling partners, which bear different substitution patterns, in order to evaluate the scope of the methodology that had been already studied in the group, will be developed.



XVI **XVII** **XVIII**

Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-PhC_6H_4, 3-$OMeC_6H_4$, 4-naphthyl
HetAr = 2-thiophenyl
R^2 = H, OMe, Cl, Br, F, -OCH_2O-

Scheme 1.14

This part of the work has been carried out under the supervision of Prof. Carsten Bolm.

II

Intramolecular Carbolithiation Reaction

*2.3.4.2. Intramolecular carbolithiation reaction of N-(o-iodobenzyl)pyrrolyl **44a**, **44b** and N-(o-iodobenzyl)pyrrolidinyl allylic alcohol derivatives **46**.*

2.3.4.2.1. Synthesis of *N*-(*o*-iodobenzyl)pyrroles **44a**, **44b** and pyrrolidine **46**.

2.3.4.2.2. Attempts of intramolecular carbolithiation of *N*-(*o*-iodobenzyl)pyrroles **44a**, **44b** and pyrrolidine **46** *via* S_N2' reaction.

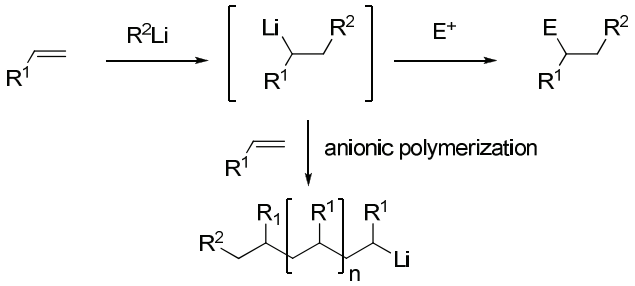
2.1. Introduction

The term carbolithiation is defined as the addition of alkyl, vinyl and (hetero)aryllithiums to the unactivated π bond contained in an olefinic or alkyne system. These reactions, which belong to a wider family of carbometalation transformations, are highly valuable in Synthetic Organic Chemistry, due to their ability to construct not only carbon-carbon bonds in a regio- and stereoselective manner, but also new organolithium species.[1] The newly generated organolithium species may be used for further *in situ* transformations with different electrophiles that would offer the possibility of introducing additional functionality in the molecule.

As pointed above, carbolithiation is generally applied to unactivated alkenes, but sometimes the introduction of substituents in the π double bond is required to favor the stabilization of the resulting organolithium for its posterior addition to the electrophile.

[1] For reviews in carbolithiation reactions: a) Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535. b) Clayden, J. *Organolithiums: Selectivity for Synthesis*, Pergamon Press: Oxford, **2002**, p. 273. c) Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59. d) Fañanás, F. J.; Sanz, R. In *The Chemistry of Organolithium Compounds, Patai Series: The Chemistry of Functional Groups*, Rappoport, Z.; Marek, I. Eds., Wiley: Chinchester, **2006**, p. 295. e) Hogan, A. M. L.; O´Shea, D. F. *Chem. Commun*. **2008**, 3839. f) Sanz, R. In *Targets in Heterocyclic Systems*, Attanasi, O.; Spinelli, D. Eds., Italian Society of Chemistry: Rome, **2008**, vol. 12, p. 349. g) Martínez-Estíbalez, U.; Gómez-SanJuan, A.; García-Calvo, O.; Arrasate, S.; Sotomayor, N.; Lete, E. In *Targets in Heterocyclic Systems*, Attanasi, O.; Spinelli, D. Eds., Italian Society of Chemistry: Rome, **2010**, vol. 14, p. 124. h) Lete. E.; Sotomayor, N. In *Science of Synthesis*, Vol. 8a update [*Compounds of Group 1 (Li…Cs)*], Yus, M. Ed., Thieme: Stuggart, **2012**, p. 191. i) Minko, Y.; Marek, I. In *Lithium Compounds in Organic Synthesis*, Luisi, R.; Capriati, V. Eds., Wiley: Weinheim, **2014**, p. 329.

Carbolithiation reactions can be carried out in both inter- and intramolecular fashion. In the intermolecular carbolithiation reaction (Scheme 2.1), the main drawback emerges as a consequence of the reactivity shown by the new generated organolithium towards the unsaturated substrate. When the organolithium reacts with a second molecule of the alkene, anionic polymerization may take place, which should be avoided to allow the formation of the target molecule.



Scheme 2.1

The challenge to successfully perform carbolithiation reactions implies the suppression of the anionic polymerization process in favor of the formation of a carbolithiated monomer intermediate and addition to the electrophile. This goal was first reached by Bartlett *et al.* for the simplest unactivated C=C bond in ethene (R^1 = H), in which the carbolithiation reaction was controlled by the use of secondary (R^2 = *s*-Bu) and tertiary alkyllithiums (R^2 = *t*-Bu).[2] The main reason for this behavior is that the rate of carbolithiation is faster for the bulkier R^2 alkyl groups. Moreover, polymerization processes can also be circumvented by the introduction of substituents on the double bond that stabilize the organolithium

[2] Bartlett, P.D.; Friedman, S.; Stiles, M. *J. Am. Chem. Soc.* **1953**, *75*, 1771.

intermediate. For instance, successfully controlled carbolithiation reactions of α and β-alkyl substituted styrenes and stilbenes have been reported.[3]

Carbolithiation reaction over acetylenic systems has also been investigated, but not so deeply developed as those over olefinic systems. The addition of the organolithium reagent to the carbon-carbon triple bond is useful for the synthesis of stereochemically defined tri- and tetrasubstituted alkenes, but often the regioselectivity of the process becomes an obstacle. The abstraction of acetylenic or propargylic protons usually predominates over the addition of the organolithium reagent to the unsaturated triple bond.[4] This side reaction can be overcome when the addition is accelerated by the introduction of an electron-withdrawing group or a heteroatom directing group in the propargylic position.[5] Thus, carbolithiation of alkynes might have a limited synthetic application, not only because it is restricted to the use of some kind of alkynes, but also because obtained vinyllithium intermediates are prone to suffer isomerization.[1b]

In contrast, the intramolecular carbolithiation of alkenes and alkynes has become a powerful tool for the highly regio- and stereoselective construction of carbocyclic and heterocyclic systems.[1] In these reactions, the formation of the lithiated species has to be carried out in the presence of an internal alkene or alkyne. Different

[3] a) Wei, X.; Taylor, R. J. K. *Chem. Commun*. **1996**, 187. b) Wei, X.; Johnson, P.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1109. c) Landgrebe, J. A.; Shoemaker, J. D. *J. Am. Chem. Soc*. **1967**, *89*, 4465. d) Coleman, C. M.; O´Shea, D. F. *J. Am. Chem. Soc.* **2003**, *125*, 4054. e) Kessler, A.; Coleman, C. M.; Charoenying, P.; O´Shea D. F. *J. Org. Chem*. **2004**, *69*, 7836. f) Tang, S.; Han, J.; He, J.; Zheng, J.; He, Y.; Pan, X.; She, X. *Tetrahedron Lett.* **2008**, *49*, 1348. g) Cottineau, B.; Gillaizeau, I.; Farard, J.; Auclair, M.; Coudert, G. *Synlett* **2007**, 1925. h) Hogan, A. L.; O´Shea, D. F. *Org. Lett*. **2006**, *8*, 3769. i) Hogan, A. L.; O´Shea, D. F. *Org. Lett*. **2007**, *72*, 9557.
[4] Knochel, P. In *Comprehensive Organic Synthesis*, Vol. 4, Trost. B. M.; Flemming, I.; Semmelhack, M. F. Eds., Pergamon Press: Oxford, **1991**, p. 865.
[5] Igawa, K.; Tomooka, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 232.

approaches to generate the organolithium have been described, such as deprotonation,[6] halogen-lithium exchange, tin-lithium exchange,[7] selenium-lithium exchange[8] or reductive lithiation.[9]

In this context, the intramolecular carbolithiation reactions with alkenes may be exemplified by the cyclization of 1-hex-5-enyllithium to generate cyclopentylmethyllithium (Scheme 2.2). The 5-*exo*-*trig* cyclization might occur through a rigid chair-like transition state, where substituents preferentially occupy pseudo-equatorial positions and the lithium atom is coordinated to the C-5–C-6 π bond.[10] Mechanistical outcome suggest that retention of configuration in the C-1 is possible, due to *syn* addition to the π bond giving as a result a total stereo and regioselectivity.[11]

[6] a) Funk, R. L.; Bolton, G. L.; Brummond, K. M.; Ellestad, K. E.; Stallman, J. B. *J. Am. Chem. Soc*. **1993**, *115*, 7023. b) Oestreich, M.; Fröhlich, R.; Hoppe, D. *Tetrahedron Lett.* **1998**, *39*, 1745. c) Oestreich, M.; Fröhlich, R.; Hoppe, D. *J. Org. Chem*. **1999**, *64*, 8616. d) Hoppe, D.; Woltering, M. J.; Oestreich, M.; Fröhlich, R. *Helv. Chim. Acta* **1999**, *82*, 1860. e) Velasco, R.; Feberero, C.; Roberto, S. *Org. Lett*. **2015**, *17*, 4416.

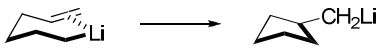
[7] a) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336. b) Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322. c) Coldham, I.; Lang-Anderson, M. M. S.; Rathmell, R.E.; Snowden, D. J. *Tetrahedron Lett.* **1997**, *38*, 7621. d) Coldham, I.; Fernàndez, J.-C.; Price, K. N.; Snowden, D. J. *J. Org. Chem.* **2000**, *65*, 3788. e) Gralla, G.; Wibbeling, B.; Hoppe, D. *Org. Lett.* **2002**, *4*, 2193. f) Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomol. Chem*. **2003**, *1*, 2111. g) Guido, C.; Stratmann, C.; Coldham, I.; Hoppe, D. *Org. Lett*. **2006**, *8*, 4469.

[8] Krief, A.; Kenda, B.; Maertens, C.; Remacle, B. *Tetrahedron* **1996**, *52*, 7465.

[9] a) La Cruz, T. E.; Rychnovsky, S. D. *Chem. Commun*. **2004**, 168. b) La Cruz, T. E.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 1068.

[10] Bailey, W. F.; Kahnolkar, A. D.; Gavascar, K.; Ovasca, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 5720. For a review, see: Bailey, W. F.; Ovasca, T.V. In *Advances in Detailed Reaction Mechanism,* Coxon, J. M. Ed., JAI Press: Greenwich, CT, **1994**, vol. 3, Mechanisms of Importance in Synthesis, p. 251. Intramolecular coordination of the lithium atom with the π bond in the transition state has been experimentally confirmed: Rölle, T.; Hoffmann, R. W. *J. Chem. Soc.*, *Perkin Trans*. *2* **1995**, 1953.

[11] a) Woltering, M. J.; Fröhlich, R.; Hoppe, D. *Angew. Chem. Int. Ed.* **1997**, *36*, 1764. b) Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett*. **1997**, *38*, 8939.



Scheme 2.2

Alkyl[12] and alkenyllithium[13] species have not been the only intermediates used in intramolecular carbolithiation reactions, the cycloisomerization of aryl and heteroaryllithiums has been also described. Although these reactions can be carried out with alkenes and alkynes,[14] in this section, we will focus on the cyclization of aryl and heteroaryllithiums, formed by halogen-lithium exchange with alkenes. This particular reaction could be considered as a Parham-type metalation-cyclization process.[15]

---

[12] For examples of alkyllithium addition to alkenes or alkynes, see: a) Ref. 1h and references cited therein. b) Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc*. **2012**, *134*, 9078. c) Gati, W.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Beilstein J. Org. Chem*. **2012**, *8*, 2214. d) Luderer, M. R.; Mealy, M. J.; Bailey, W. F. *J. Org. Chem.* **2014**, *79*, 10722. e) Ryu, I.; Yamamura, G.-H.; Minakata, S.; Komatsu, M.; Kubo, H.; Ueda, M. *Synlett* **2015**, *26*, 2413.

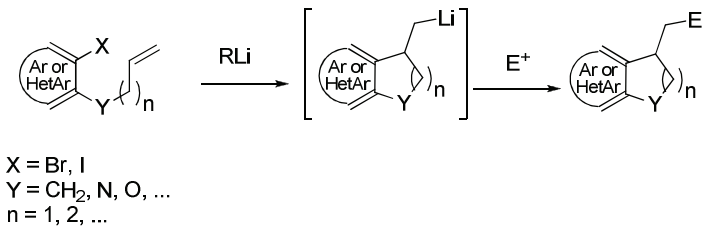
[13] For examples of alkenyllithium addition to alkenes or alkynes, see: a) Ref. 1h and references cited therein. b) Bailey, W. F.; Bakonyi, J. M. *J. Org. Chem*. **2013**, *78*, 3493. c) Bailey, W. F.; Fair, J. D. *Beilstein J. Org. Chem*. **2013**, *9,* 537.

[14] For selected examples of intramolecular carbolithiations using aryllithiums with alkynes, see: a) Wu, G.; Cederbaum, F. E.; Negishi, E. *Tetrahedron Lett*. **1990**, *31*, 493. b) Bailey, W.F.; Wachter-Jurcsak, N. M.; Pineau, M. R., Ovaska, T. V.; Warren, R. R.; Lewis, C. E. *J. Org. Chem.* **1996**, *61*, 8216. c) Le Strat, F.; Maddaluno, J. *Org. Lett.* **2002**, *4*, 2791. d) Le Strat, F.; Harrowven, D. C.; Maddaluno, J. *J. Org. Chem.* **2005**, *70*, 489. e) Fressigné, C.; Girard, A.-L.; Durandetti, M.; Maddaluno, J. *Chem. Eur. J*. **2008**, *14*, 5159. f) Fressigné, C.; Girard, A.-L.; Durandetti, M.; Maddaluno, J. *Eur. J. Org. Chem*. **2009**, 721. g) Girard, A.-L.; Lhermet, R.; Fressigné, C.; Silvi, B.; Durandetti, M.; Maddaluno, J. *Eur. J. Org. Chem.* **2012**, 2895. h) Fressigné, C.; Lhermet, R.; Girard, A. -L.; Durandetti, M.; Maddaluno, J. *J. Org. Chem*. **2013**, *78*, 9659. i) Lhermet, R.; Ahmad, M.; Fressigné, C.; Durandetti, M.; Maddaluno, J. *Chem. Eur. J*. **2014**, *20*, 10249. j) Lhermet, R.; Ahmad, M.; Hauduc, C.; Fressigné, C.; Durandetti, M.; Maddaluno, J. *Chem. Eur. J*. **2015**, *21*, 8105.

[15] a) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1975**, *40*, 2394. For reviews, see: b) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300. c) Gray, M.; Tynkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry II*, Abel, E. W.; Stone, F. G. A.; Wilkinson, G. Eds., Pergamon Press: Exeter, **1995**, vol. 11, p. 66. d) Ardeo, A.; Collado, M. I.; Osante, I.; Ruiz, J.; Sotomayor, N.; Lete E. In *Targets In Heterocyclic Systems*, Attanassi, O.; Spinelli, D. Eds., Italian Society of Chemistry: Rome, **2001**, vol. 5, p. 393. e) Sotomayor, N.; Lete, E. *Curr. Org. Chem*. **2003**, 7, 275. f) Gribble, G. W. In *Name Reactions for Homologations*; Li, J. J. Ed., Wiley, Chinschester, **2009**, Part. 2, p. 749.

2.2. Synthetic applications of the intramolecular carbolithiation reaction of (hetero)aryllithiums with alkenes

The Parham cyclization using alkenes as internal electrophiles followed by treatment of the generated lithiated species with diverse external electrophiles, allows the possibility of introducing different functionalization on the cyclized molecule, opening new routes for the regio- and diastereoselective construction of benzo- or hetero-fused carbocycles and heteretocycles (Scheme 2.3).



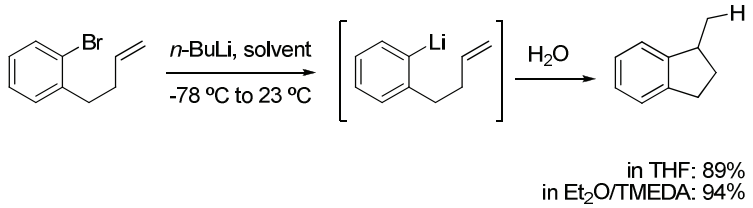
Scheme 2.3

This anionic cyclization has allowed the formation of five-membered rings through 5-*exo*-*trig* ring-closure with high levels of regio- and stereocontrol. However, generation of six-membered rings is not so general, as there are only a few examples described and it is not clear that the cyclization would take place with the same degree of regio- and stereochemical efficiency.

To give a general overview on the concept of intramolecular carbolithiation with aryl and heteroaryllithiums, formed by halogen-lithium exchange, some synthetic applications classified by the size of the resulting ring will be presented. Additionally, enantioselective examples of the reaction will also be disclosed.

2.2.1. Formation of five-membered rings through intramolecular carbolithiation reactions

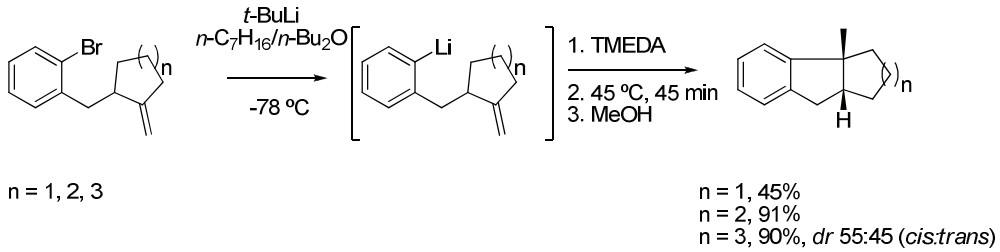
Woolsey *et al.* reported in 1985 for the first time the anionic cyclization of 2-(3-butenyl)phenyllithium, obtained by bromine-lithium exchange using *n*-BuLi at -78 ºC, for the construction of indane nucleus (Scheme 2.4).[16] The cyclization was favored by an increase in solvent polarity or by addition of additives such as TMEDA, as it is known to reduce aggregation of the organolithiums.[17]



Scheme 2.4

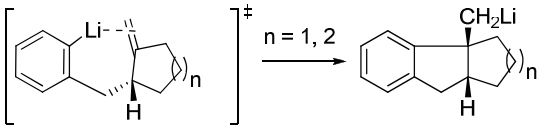
Regarding the high diastereoselectivity involved in the intramolecular carbolithiation reactions, Bailey *et al*. have studied the cyclization of aryllithiums tethered to methylencycloalkanes, obtained through bromine-lithium exchange. This cyclization has been shown to be a kinetically slow, but thermodynamically favored process.[18] As can be seen in Scheme 2.5, the 5-*exo* cyclization appears to take place with higher diastereoselectivity when the methylencycloalkane is a 5- and 6-membered ring, resulting in an exclusive *cis*-configuration of products, while a mixture of diastereomers was obtained when a 7-membered ring is used.

[16] Ross, G. A.; Koppang, M. D.; Bartak, D. E.; Woolsey, N. F. *J. Am. Chem. Soc.* **1985**, *107*, 6742.
[17] Eberhardt, G. G.; Butte, W. A. *J. Org. Chem.* **1964**, *29*, 2928.
[18] Bailey, W. F.; Daskapan, T.; Rampalli, S. *J. Org. Chem*. **2003**, *68*, 1334.



Scheme 2.5

This fact can be explained by the formation of a transition state where the lithium atom is coordinated to the exocylic π bond for cyclopentane or cyclohexane rings, while for cycloheptane rings the conformation of the transition state is more flexible (Scheme 2.6).[10,11] Additionally, the reaction allows the synthesis of 4α-substituted *cis*-hexahydrofluorenes in a diastereoselective fashion using different electrophiles for quenching the reaction.

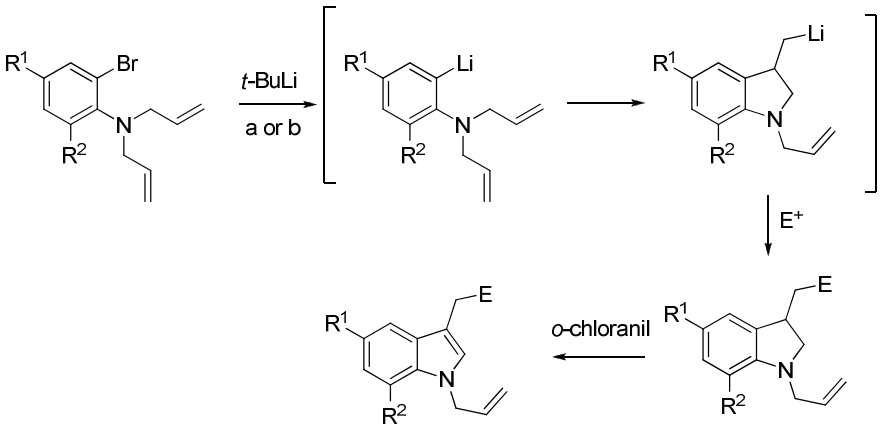


Scheme 2.6

Regarding the obtention of nitrogen containing heterocycles, in 1996 Liebeskind[19] and Bailey[20] published simultaneous but independently, a simple strategy for the construction of *N*-allylindolines and their oxidized counterparts, *N*-allylindoles, bearing a variety of functionalities at the C-3 position, starting from readily

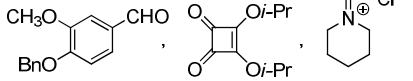
[19] Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594.
[20] Bailey, W. F.; Liang, X.-L. *J. Org. Chem.* **1996**, *61*, 2596.

available 2-bromo-*N,N*-diallylanilines through a Parham cyclization process (Scheme 2.7). Therefore, the treatment of anilines with *t*-BuLi provided lithio-metalated species, which upon protonation or electrophile trapping would lead to a diversity of 3-methylindolines, susceptible of oxidation to the corresponding 3-methylindoles with *o*-chloranil reagent. It should be remarked that the use of TMEDA as additive in the 5-*exo* cyclization of the aryllithium is not required but recommended to prevent loss of yield.[20]



Method a: (Ref. 19)
1. *t*-BuLi, *t*-BuOMe, -78 ºC to r.t.
2. E^+

Method b: (Ref. 20)
1. *t*-BuLi, *n*-C_5H_{12}/Et_2O, -78 ºC
2. TMEDA, -78 ºC to 0 ºC
3. E^+

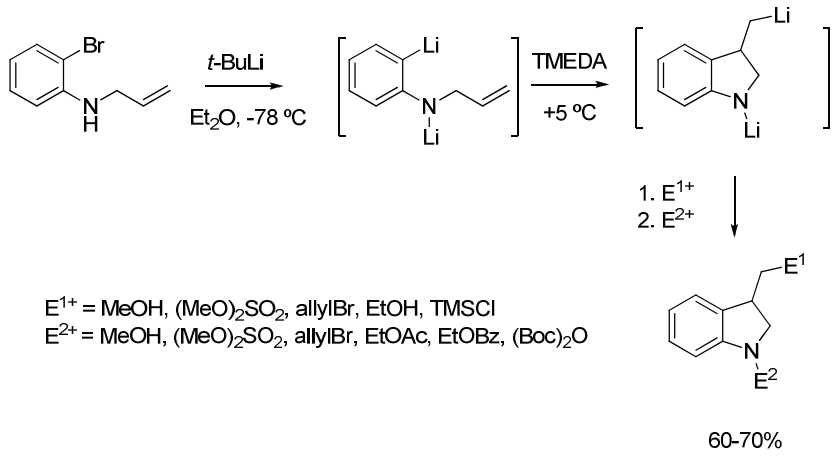
R^1 = H, Me, OMe, N(allyl)$_2$
R^2 = H, OMe
E^+ = H_2O, 

R^1 = H, Me
R^2 = H
E^+ = MeOH, MeOD, TMSCl, Bu_3SnCl, Me_2NCHO, *t*-BuCHO, $ClCO_2Et$

Scheme 2.7

Taking into account the previous methodology, Bailey reported later a more general synthetic route that would allow the formation of selectively functionalized

1,3-disubstituted indolines through the cyclization of (1-lithio-3-indolinyl)methyllithium intermediate, followed by subsequent addition of electrophiles.[21] Accordingly, the dilithio species generated by treatment of *N*-allyl-2-bromoaniline with *t*-BuLi at -78 ºC, was cyclized by the addition of TMEDA and subsequent warming up to +5 ºC. Different functionalization of the resulting cyclized dilithium intermediate was accomplished in high overall yields by sequential addition of different external electrophiles ($E^1 \neq E^2$) (Scheme 2.8).

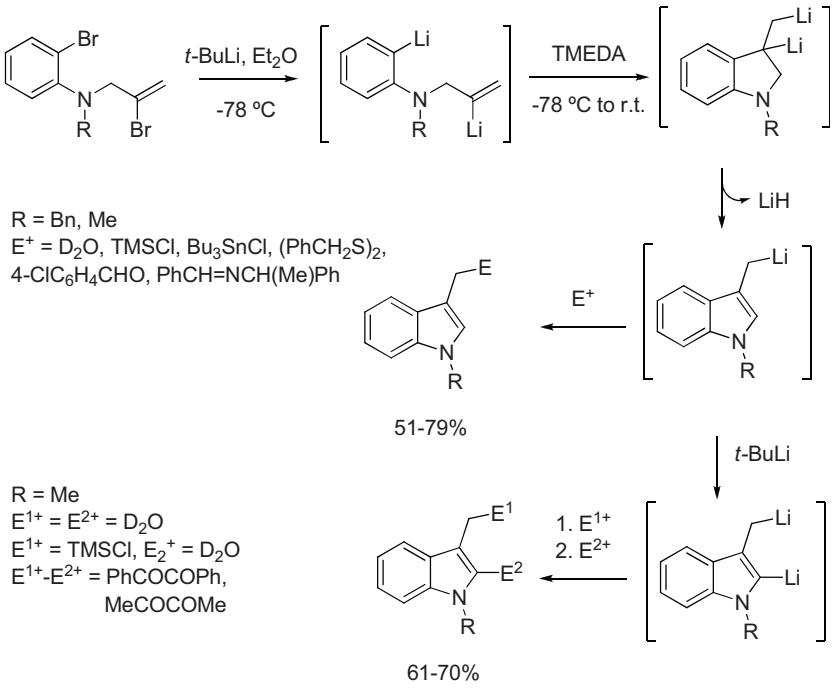


Scheme 2.8

In a similar way, Barluenga described the intramolecular carbometalation of 2-bromo-*N*-(2-bromoallyl)anilines with *t*-BuLi/TMEDA at low temperature.[22] Tertiary amines afforded a dianion, by bromine-lithium exchange, which was susceptible to form the dilithiated indoline by attack of the aryllithium to the vinyllithium moiety. The subsequent elimination of lithium hydride afforded 3-

[21] Bailey, W. F.; Luderer, M. R.; Mealy, M. J. *Tetrahedron Lett*. **2003**, *44*, 5303.
[22] a) Barluenga, J.; Sanz, R.; Granados, A.; Fañanás, J. *J. Am. Chem. Soc.* **1998**, *120*, 4865. b) Fañanás, J.; Granados, A.; Sanz, R.; Ignacio, J. M.; Barluenga, J. *Chem. Eur. J.* **2001**, *7*, 2896.

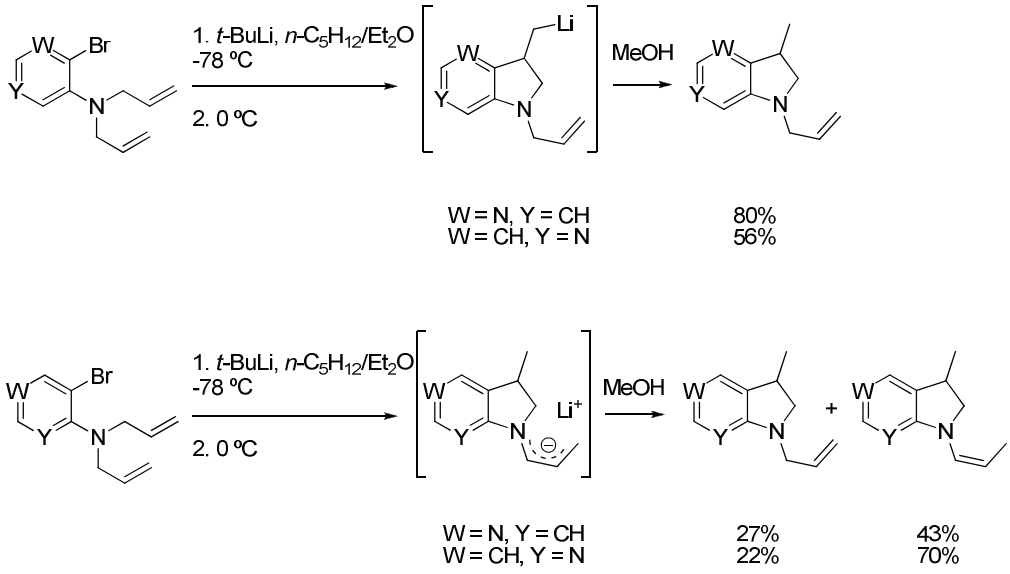
lithiomethylindoles that could be trapped by different electrophiles leading to functionalized indole derivatives (Scheme 2.9). Performing the reaction with an excess of *t*-BuLi, the 2-position of the lithiated indole nucleus may be attacked leading a dianionic species, which sequentially could be functionalized by different electrophiles.



Scheme 2.9

Closely related to this procedure, intramolecular carbolithiation of heteroaryllithiums derived from (*N,N*-diallylamino)bromopyridines afforded 3-substituted 4-, 5-, 6-, and 7-azaindolines *via* one pot, 3-step sequence (Scheme

2.10).[23] The generation of 4- and 6-azaindolines, through anionic cyclization of 2-bromo-3-(*N,N*-diallylamino)pyridine and 4-bromo-3-(*N,N*-diallylamino)pyridine respectively, proceed as expected. However, ring closure to give 5- and 7-azaindolines was found to follow an unexpected pathway, as 3-methyl-*N*-allyl anions are formed. In this case, two isomeric azaindolines were isolated: the expected 1-allyl-azaindolines were the minor products, while *Z*-isomer of the corresponding enamines, were the major products.

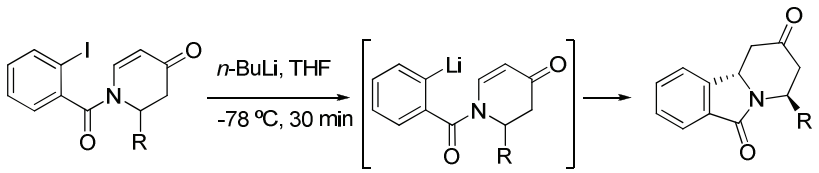


Scheme 2.10

This type of intramolecular carbolithiation reaction can also be performed in a diastereoselective fashion. Thus, Comins et *al*. reported the intramolecular 1,4-addition of the aryllithium, obtained by iodine-lithium exchange, to *N*-acyl- and *N*-

[23] Bailey, W. F.; Salgaonkar, P. D.; Brubaker, J. D.; Sharma, V. *Org. Lett.* **2008**, *10*, 1071.

alkylenaminones in a diastereoselective manner.[24] The presence of an electron-withdrawing group in the alkene accelerated the cyclization reaction that occurred at -78 ºC in just 30 min to afford the *trans*-diastereomer of dihydropyrido[1,2-*a*]isoindolodiones with high sterocontrol (Scheme 2.11).



R = Ph, Cy, vinyl, HC≡C-, BuC≡C-

86-91%
dr > 95:5

Scheme 2.11

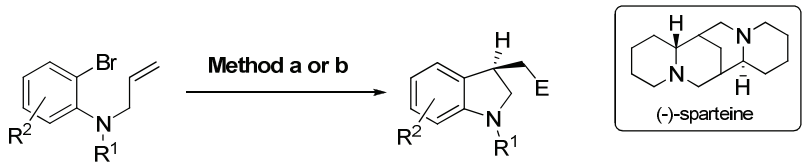
On the other hand, the enantioselective version of intramolecular carbolithiation reaction has also been developed. As has been stated previously, anionic cyclization reactions take place through a rigid transition state adopted by the lithiated intermediate, where the lithium atom may be coordinated to the π double bond in a chair-like conformation.[10] Taking into account that this coordinated organolithium might have two additional sites suitable for ligation, the carbolithiation could be carried out enantioselectively, if performed in the presence of a chiral bidentate ligand such as (–)-sparteine.[25] Thus, it has been possible to

[24] Comins, D. L.; Zhang, Y.-M. *J. Am. Chem. Soc*. **1996**, *118*, 12248.

[25] For reviews on the use of (–)-sparteine as chiral ligand, see: a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. b) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 2282. c) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, 33, 715. d) Hoppe, D.; Christoph, G. In *The Chemistry of Organolithium Compounds*, Rappoport, Z.; Marek, I. Eds., Wiley & Sons: New York, **2004**, Chapter 17, p. 1055.

perform asymmetric carbolithiation reactions, starting from achiral substrates by promoting facial selectivity of the double bond.[26]

The first reports related to enantioselective intramolecular carbolithiation reaction for the synthesis of 3-substituted indolines, using aryllithiums generated *via* halogen-lithium exchange, were simultaneously published in 2000 by Bailey and Groth. Bailey and coworkers[27] reported a 5-*exo* enantioselective cyclization of differently substituted (*N*-allylamino)-2-bromoanilines by treatment with *t*-BuLi at low temperature in the presence of (–)-sparteine ligand in *n*-C_5H_{12}/Et_2O. The choice of the solvent was crucial to achieve a high degree of enantioselection (Scheme 2.12, Method a).



Method a: (Ref. 27)
1. *t*-BuLi, *n*-C_5H_{12}/Et_2O, -78 ºC
2. (-)-sparteine
3. -40 ºC
4. MeOH

R^1 = Me, allyl; R^2 = H; E = H
69-88%, 70-86% *ee*

Method b: (Ref. 28)
1. *t*-BuLi, (-)-sparteine, toluene, -90 ºC
2. MeOH or $Br(CH_2)_2Br$

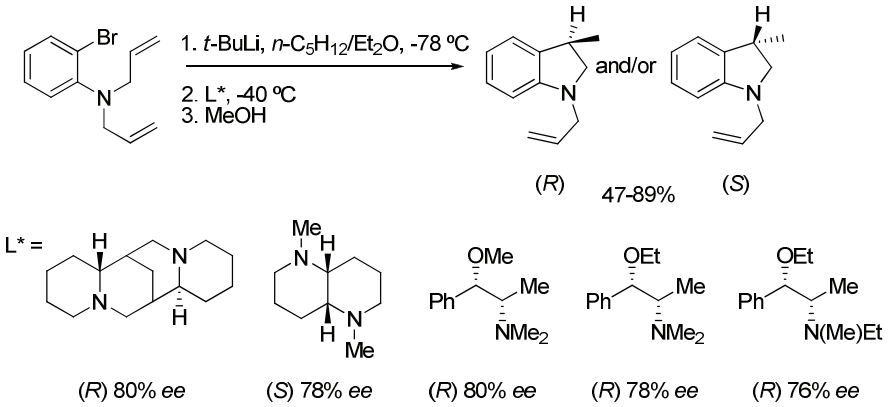
R^1 = Bn; R^2 = H, 4-OBn, 5-OBn, 4-Me, 4-F; E = H, Br
65-90%, 82-90% *ee*

Scheme 2.12

[26] For reviews on enantioselective carbolithiation reaction, see: a) Normant, J. F. *Top. Organomet. Chem*. **2003**, 287. b) Gómez-SanJuan, A.; Sotomayor, N.; Lete, E. *Beilstein J. Org. Chem*. **2013**, *9*, 313, and references cited therein.
[27] Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787.

Groth and coworkers[28] described an analogous methodology for asymmetric anionic cyclization of *N*-allyl-*N*-benzyl-2-bromoaniline with *t*-BuLi and (–)-sparteine in toluene, a solvent that also favored coordination of the ligand with lithium (Scheme 2.12, Method b).

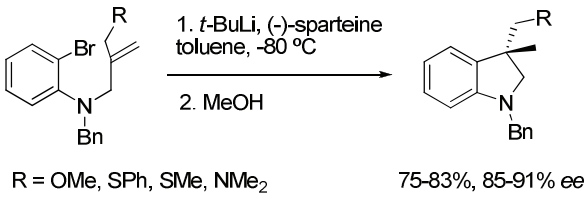
Progressing with their studies in asymmetric intramolecular carbolithiation reactions, Bailey *et al.* studied the ability of a large and chemically diverse set of thirty chiral ligands to promote enantioselection in the 5-*exo* cyclization of *N,N*-diallyl-2-bromoanilines for the synthesis of 3-methyl indolines.[29] None of the ligands examined improved the enantioselection observed for the formerly studied (–)-sparteine ligand, but many of them effectively matched the same results (Scheme 2.13).



Scheme 2.13

[28] Gil, G. S.; Groth, U. M. *J. Am. Chem. Soc.* **2000**, *122*, 6789.
[29] Mealy, M. J.; Luderer, M. R.; Bailey, W. F.; Sommer, M. B. *J. Org. Chem.* **2004**, *69*, 6042.

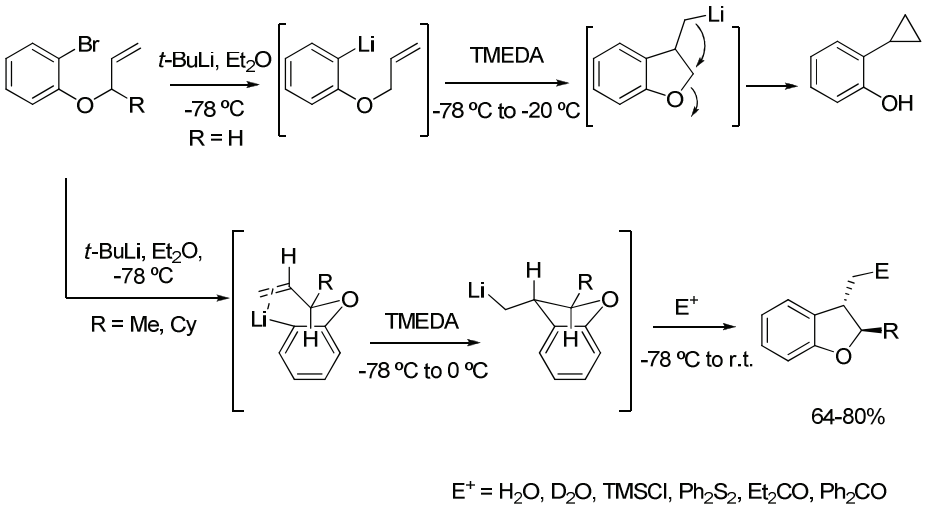
In addition, Groth and coworkers published the enantioselective synthesis of 3,3-disubstituted indolines through a 5-*exo* anionic cyclization of *N*-benzyl-protected bromoanilines with different substitution patterns in the allyl moiety, using *t*-BuLi and (–)-sparteine.[30] Oxygen-, nitrogen- and sulfur-substituted anilines showed a chelating effect, which may promote a higher enantioselection in the course of the cyclization (Scheme 2.14).



Scheme 2.14

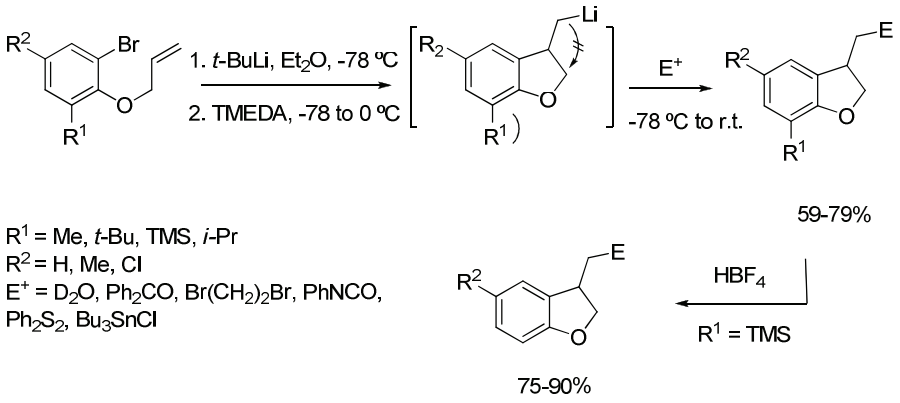
This anionic cyclization reaction is also effective for the benzo-fused furan synthesis. In this sense, Barluenga and coworkers reported readily access to dihydrobenzofuran derivatives *via* Parham cyclization of 2-bromophenyl ethers with *t*-BuLi as metalating agent (Scheme 2.15).[31] The presence of a substituent in α to the oxygen atom was necessary to avoid γ-elimination reaction.[32] The reaction led to *trans*-2,3-dihydrobenzofurans isomers with a complete diastereoselectivity, due to the chair-like configuration adopted by the aryllithium intermediate, in which the substituent occupies a pseudoequatorial position.[10]

[30] Groth, U.; Köttgen, P.; Langenbach, P.; Lindenmaier, A.; Schütz, T.; Wiegand, M. *Synlett* **2008**, 1301.
[31] Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C. *Chem. Eur. J.* **2005**, *11*, 5397.
[32] Bailey, W. F.; Punzalan, E. R. *Tetrahedron Lett.* **1996**, *37*, 5435.



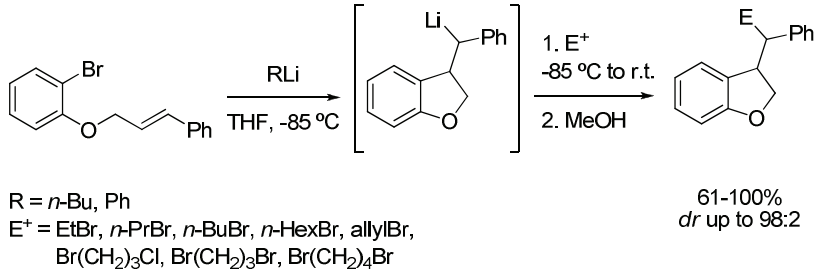
Scheme 2.15

Substitution at the C-6 position of the aryl moiety was also found out to avoid the isomerization on the lithiated intermediate due to stereoelectronic effects. Thus, functionalized 2,3-dihydrobenzofurans could be synthesized under the same conditions, starting from simple 2-propenyl ethers. The easily removal of the TMS group, would provide benzofuran derivatives with no substitution at 2- and 7-positions (Scheme 2.16).[31]



Scheme 2.16

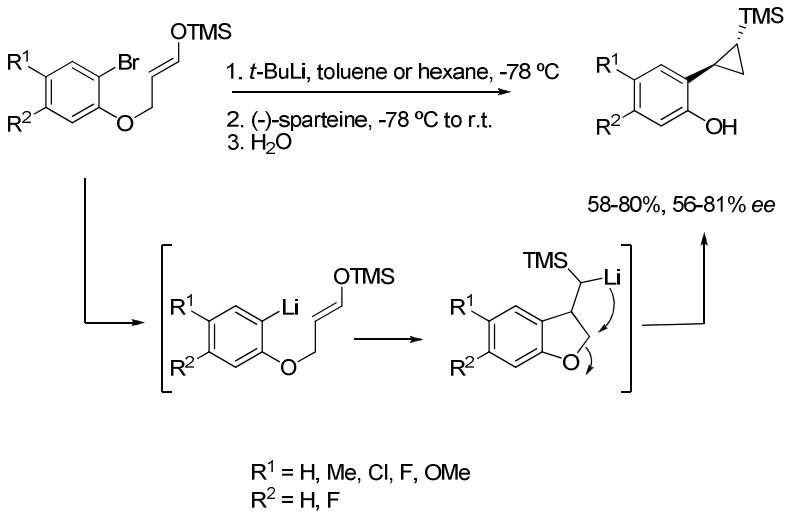
More recently, Nudelman and coworkers applied this methodology to phenyl substituted alkenes. Hence, intramolecular carbolithiation of 2-bromophenyl-3-phenylprop-2-enyl ether afforded the corresponding 3-substituted-2,3-dihydrobenzofurans in a diastereoselective manner, although stereochemistry was not determined, *via* bromine-lithium exchange and followed by trapping of the cyclic lithiated intermediate by different electrophiles (Scheme 2.17). [33]



Scheme 2.17

[33] Rodriguez, C.; Nudelman, N. S. *Synth. Commun*. **2014**, *44*, 772.

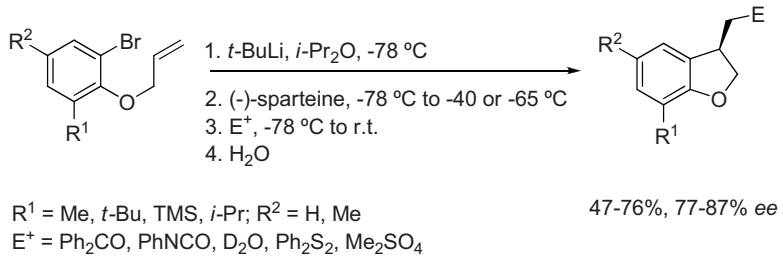
Barluenga and coworkers made use of previously stated 5-*exo* cyclization and γ-elimination competitive pathways[31] to develop the enantioselective version of the reactions. Firstly, they described the intramolecular carbolithiation reaction-γ elimination tandem sequence of achiral allyl *o*-bromoarylether with *t*-BuLi/(–)-sparteine in toluene or hexane, which resulted in the diastereoselective synthesis of the corresponding *trans*-cyclopropanes with moderate to good *ee* (Scheme 2.18).[34]



Scheme 2.18

With regard to 5-*exo* ring-closure, 3-functionalized-2,3-dihydrobenzofurans were obtained with high enantioselectivities applying the procedure to C-6 substituted derivatives (Scheme 2.19).[31]

[34] Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C. *Org. Lett.* **2002***, 4*, 2225.



Scheme 2.19

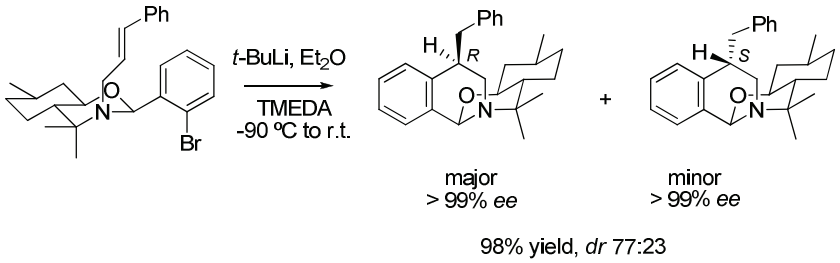
2.2.2. Formation of six-membered rings through intramolecular carbolithiation reactions

As it has been stated previously, anionic cyclization of aryl and heteroaryllithiums with unsaturated double bonds has been generally applied for the synthesis of five-membered rings, but generation of six-membered rings has not been so deeply studied. There are a few precedents describing intramolecular carbolithiation through alkyl and alkenyllithiums in the formation of six-membered rings,[35] since 6-*exo* cyclization is slower than 5-*exo* cyclization. In some cases, the activation of the double bond by electron-withdrawing groups is required to form a stabilized lithiated intermediate that favors the cyclization.[36]

In this context, Pedrosa and coworkers[37] described the first diastereoselective synthesis of enantiomerically pure 4-substituted tetrahydroisoquinolines by 6-*exo* cyclization. Aryllithiums were formed by the treatment of chiral 2-(*o*-

[35] a) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442. b) Chamberlin, A. R.; Bloom, S. H.; Cevini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788. c) Ashweek, N. J.; Coldham, I.; Snowden, D. J.; Venall, G. P. *Chem. Eur. J.* **2002**, *8*, 195.
[36] a) Rychnovhky, S. C.; Takaoka, L. R. *Angew. Chem. Int. Ed.* **2003**, *42*, 818. b) Coldham, I.; Venall, C. P. *Chem. Commun.* **2000**, 1569.
[37] Pedrosa, R.; Andrés, C.; Iglesias, J. M.; Pérez-Encabo, A. *J. Am. Chem. Soc*. **2001**, *123*, 1817.

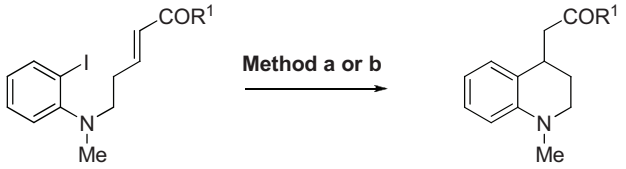
bromophenyl)-substituted perhydro-1,3-benzoxazines with *t*-BuLi at -90 ºC in the presence of TMEDA, through a bromine-lithium exchange. The subsequent addition of the aryllithium to the internal unsaturated bond provided tetrahydroisoquinolines. As depicted in Scheme 2.20, the intramolecular 6-*exo* carbolithiation reaction was viable when a stabilizing phenyl group was attached to the terminal alkene moiety.



Scheme 2.20

In connection to this research, our group has described the intramolecular carbolithiation reaction of *N*-substituted *o*-iodoanilines using *n*-BuLi as metalating agent for the synthesis of tetrahydroquinoline derivatives.[38] The cyclization was effective as long as the double bond was activated with an electron-withdrawing moiety. Intramolecular carbolithiation reactions are fast even in the absence of TMEDA as additive. Moreover, suppression of side reactions, such as addition of organolithium reagent to the enamide group, might be possible using MesLi as reagent (Scheme 2.21).

[38] García-Calvo, O.; Martínez-Estíbalez, U.; Lete, E.; Sotomayor, N. *Heterocycles* **2014**, *88*, 425.



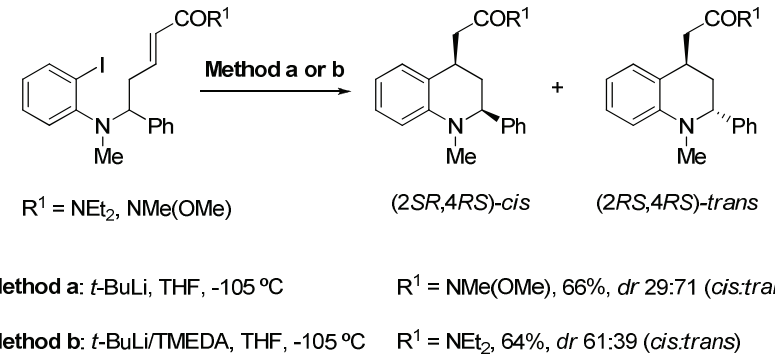
Method a: *n*-BuLi/TMEDA, THF, -105 ºC $R^1 = NEt_2$, NMe(OMe), 53-78%

Method b: MesLi, THF, -78 ºC $R^1 = NEt_2$, NMe(OMe), 71-85%

Scheme 2.21

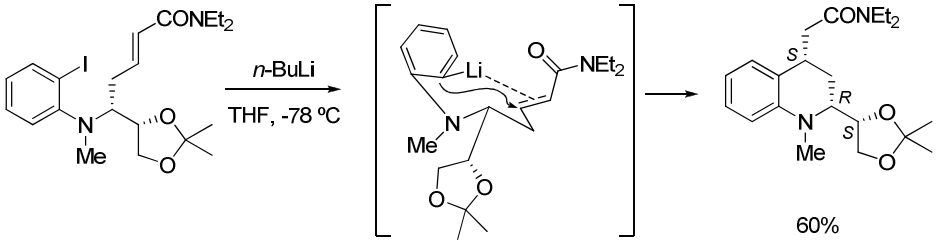
Moreover, we were pleased to find out that 2-iodoanilines, bearing a phenyl group in α to the nitrogen atom, subjected to Parham cyclization, always with electron-deficient double bonds, were prone to give 4-substituted 2-phenyltetrahydroquinolines.[39] The diastereoselectivity of the reaction was influenced by the substitution pattern of the alkene, the type of alkyllithium or the presence of additives (Scheme 2.22). In this sense, treatment with *t*-BuLi in THF at -105 ºC of 2-iodoanilines with alkenes activated by a Weinreb amide, provided the *trans*-diastereomer as the major product (Scheme 2.22, Method a). When this methodology was applied to the same type of substrates in combination with the addition of TMEDA, 2,4-disubstituted tetrahydroquinolines were obtained with moderate diastereoselectivity, in favor of the *cis*-isomer (Scheme 2.22, Method b).

[39] Martínez-Estíbalez, U.; Sotomayor, N.; Lete, E. *Org. Lett.* **2009**, *11*, 1237.



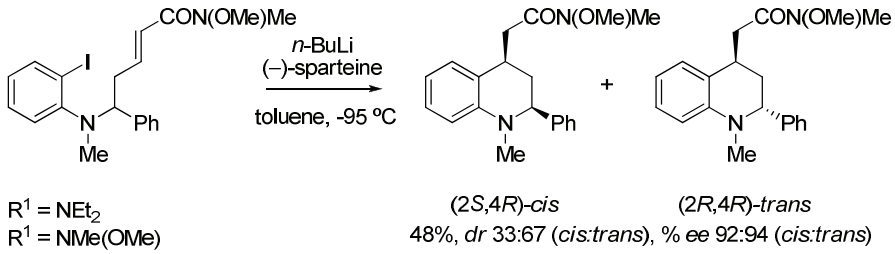
Scheme 2.22

The scope of this reaction may be enlarged, by incorporating a dimethyl-1,3-dioxolanyl substituent in α to the nitrogen atom. Thus, the diastereoselective cyclization of enantiopure 2-iodoanilines, derived from glyceraldehyde, led to the disubstituted tetrahydroquinoline as a single diastereomer (Scheme 2.23).[38] Cyclization of the aryllithium would follow a rigid pseudo-chair transition state, involving the coordination of the lithium atom to the π bond with location of both substituents in pseudo-equatorial positions and subsequent attack to the *Re*-face of the alkene. In this case, the complete diastereoselectivity could be understood by the presence of the bulky dioxolanyl substituent, which afforded the (2*R*,4*S*)-*cis* diastereomer. Diastereoselectivity observed is in agreement with the results obtained with a benzyloxymethyl substituent at C-2, which resulted in a 61:39 mixture, in favor of the *cis*-diastereomer, in 59% yield when using *n*-BuLi in THF.[38]



Scheme 2.23

On the other hand, our group also performed the synthesis of 2-phenyl 4-substituted tetrahydroquinolines from *N*-alkenyl substituted 2-iodoanilines with moderate diastereoselectivities and high enantiomeric excess by using (–)-sparteine as chiral ligand, when the alkene moiety was substituted by a Weinreb amide (Scheme 2.24).[39]

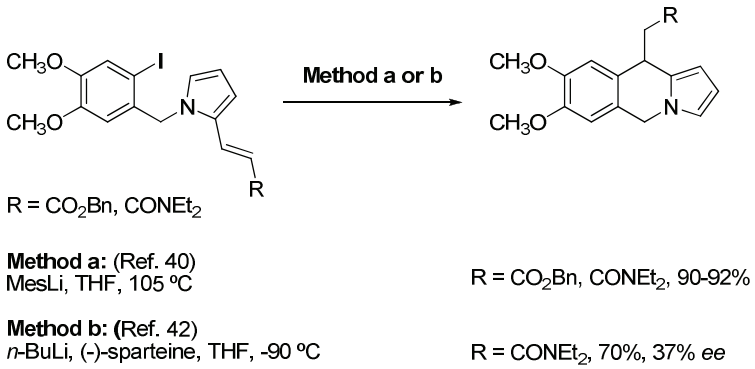


Scheme 2.24

In addition, our group has studied the 6-*exo* cyclization on alkenyl substituted *o*-iodobenzylpyrroles as a way to obtain pyrroloisoquinoline frameworks.[40] In this work, it could be shown that substitution of the double bond by an electron-withdrawing group (ester or amide) was also required to perform cyclization. The use of *t*-BuLi as reagent at low temperature and in the presence of TMEDA, led to

[40] Lage, S.; Villaluenga, I.; Sotomayor, N.; Lete, E. *Synlett* **2008**, *20*, 3188.

low yields of the pyrroloisoquinolines due to undesired 1,2- and 1,4-addition reactions of the alkyllithium to both the alkene and ester or amide moieties. To overcome this competitive reactions, the use of MesLi, a bulkier and non-nucleophilic organolithium reagent,[41] was necessary (Scheme 2.25, Method a).

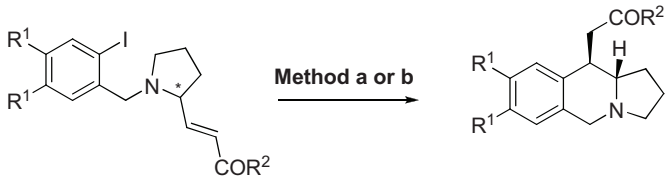


Scheme 2.25

Paying special attention to a possible asymmetric variant, we tried to perform the enantioselective version of the reaction using (–)-sparteine as chiral bidentate ligand (Scheme 2.25, Method b). However, the pyrroloisoquinoline was obtained in moderate yield and low *ee* (up to 37%). Although several attemps were tried to improve the enantioselectivity by varying temperatures of the reaction or the order of additives in the addition, no improvements in enantioselectivity were achieved.[42]

[41] a) Mhaske, S. B. *Synlett* **2005**, 184. For a example in an halogen-lithium exchange reaction, see: b) Kondo, Y.; Asai, M.; Miura, T.; Uchiyama, M.; Sakamoto, T. *Org. Lett*. **2001**, *3*, 13.
[42] García-Calvo, O.; Coya, E.; Lage, S.; Coldham, I.; Sotomayor, N.; Lete, E. *Eur. J. Org. Chem.* **2013**, 1460.

In view of these results, we decided to study the diastereoselective variant of this intramolecular carbolithiation on 2-alkenyl substituted *N*-*o*-iodobenzylpyrrolidines that allowed the synthesis of hexahydropyrrolo[1,2-*b*]isoquinolines in a total diastereoselective fashion.[42,43] The *6-exo-trig* cyclization reaction took place with a complete diastereoselectivity and no 1,4-addition reaction to the enamide moiety was observed when treatment with *t*-BuLi or *n*-BuLi was performed in the presence of TMEDA at low temperature (Scheme 2.26, Method a).



Method a: (Ref. 43, racemic substrate)
n-BuLi or *t*-BuLi, TMEDA, THF, -78 ºC to r.t.

R^1 = H, R^2 = NEt_2, 79-90%

Method b: (Ref. 42, enantiopure substrate)
n-BuLi, TMEDA, THF, -78 ºC

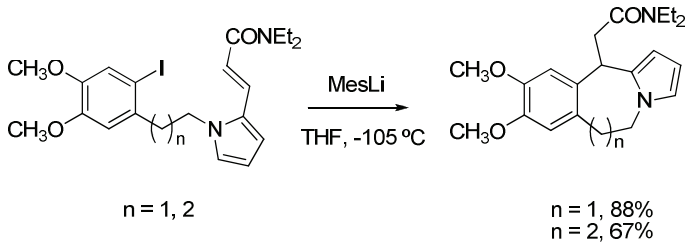
R^1 = OCH_3, R^2 = NEt_2, N(OMe)Me,
58-60%, > 99% *ee*

Scheme 2.26

Further studies in this research topic allowed our group to report the asymmetric synthesis of enantiopure (10*R*,10a*S*)-pyrroloisoquinolines, starting from enantiomerically pure *N*-(*o*-iodobenzyl)pyrrolidines, prepared from commercially available L-prolinal (Scheme 2.26, Method b).[42]

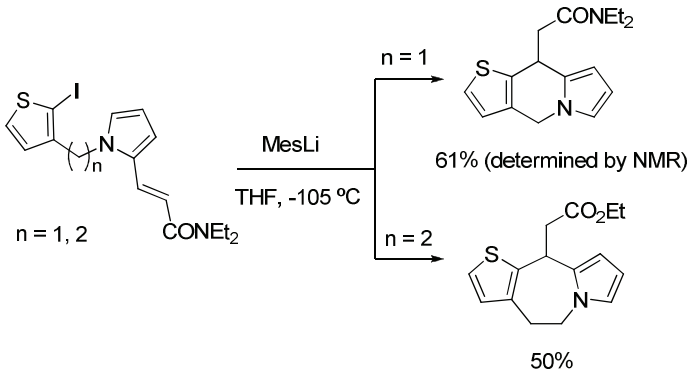
Furthermore, the use of MesLi as reagent at low temperatures permitted the generation of medium-sized rings, such as benzazepines and benzazocines through 7-*exo* and 8-*exo* cyclizations, as depicted in Scheme 2.27.[42]

[43] García-Calvo, O.; Sotomayor, N.; Lete, E.; Coldham, I. *Arkivoc* **2011** (v), 57.



Scheme 2.27

In addition, our group studied the intramolecular carbolithiation reaction of electron-rich heteroaryllithiums, such as thiophenyllithiums, by 6-*exo* and 7-*exo* cyclizations, respectively.[44] The use of MesLi at low temperature promoted fast metalation by iodine-lithium exchange, but the subsequent cyclization required longer reaction times and higher temperatures, which resulted in lower yields due to competitive side reactions and decomposition. Thus, the pyrrolo[1,2-*a*]thieno[2,3-*d*]azepine was obtained in moderate yield, while thieno[3,2-*f*]indolizine could not be purified by chromatographic methods (Scheme 2.28).



Scheme 2.28

[44] Coya, E. Ph.D Thesis, University of the Basque Country, **2013**.

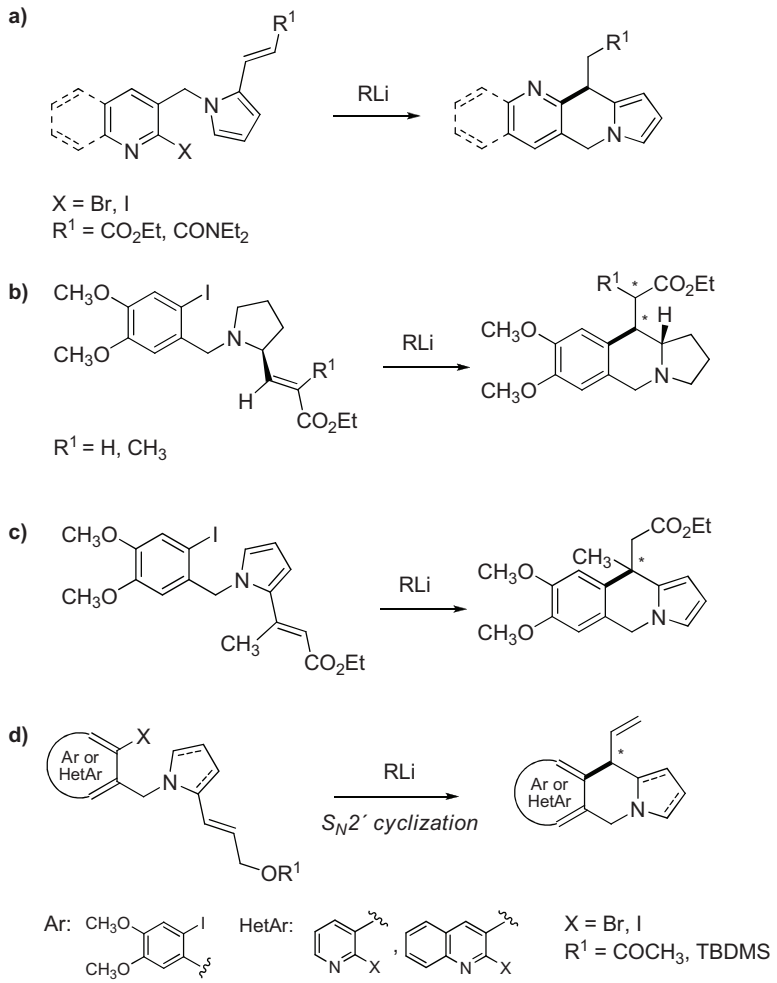
2.3. Results and discussion

As has been shown in the previous section, our group has developed an efficient intramolecular carbolithiation reaction of 2-alkenyl substituted *o*-iodobenzylpyrroles to access to pyrrolo[1,2-*b*]isoquinolines by using electron-withdrawing groups (ester and amide) to activate the alkene moiety.[40,42] Besides, the use of electron-rich heteroaryllithiums as thiophenyllithiums has been investigated, although it proved to be less efficient and selective for the obtention of hetero-fused indolizines and azepines.[44]

Thus, the first objective of this work was to study the scope of this Parham-type cyclization by using electron-poor heteroaryllithiums derived from *o*-halopyridines and *o*-haloquinolines. This methodology would provide access to interesting heterocycles, such as dihydropyrrolo[1,2-*g*][1,6]naphthyridines and the corresponding benzo-fused derivatives (Scheme 2.29a).

On the other hand, we have previously conducted studies on the diastereoselective version of the Parham cyclization using enantiomerically pure 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrrolidines to synthesize hexahydropyrrolo[1,2-*b*]isoquinolines.[42] Therefore, the second aim of this work was to study the possibility to perform this reaction by using different substitution patterns on the alkene (Scheme 2.29b). Next, intramolecular carbolithiation reaction of 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles to generate a quaternary stereocenter was planned by introducing a methyl group in the olefinic carbon atom that is directly involved in the carbon-carbon bond formation (Scheme 2.29c).

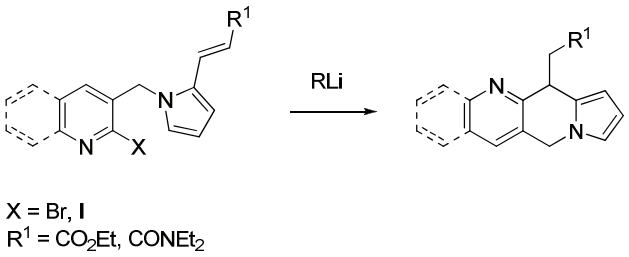
Finally, an extension of intramolecular carbolithiation methodologies to substrates, where different leaving groups in the allylic chain would be introduced to promote ring closure *via* S_N2' reaction, was studied. Different aryl and heteroaryl halides would be tried (Scheme 2.29d).



Scheme 2.29

2.3.1. Intramolecular carbolithiation reaction *via* conjugate addition on *N*-(*o*-haloheteroarylmethyl)pyrrolylacrylates and acrylamides

We firstly centered our attention in the first objective, which involved the development of intramolecular carbolithiation reactions on electron-deficient heteroaryl halides (Scheme 2.30).



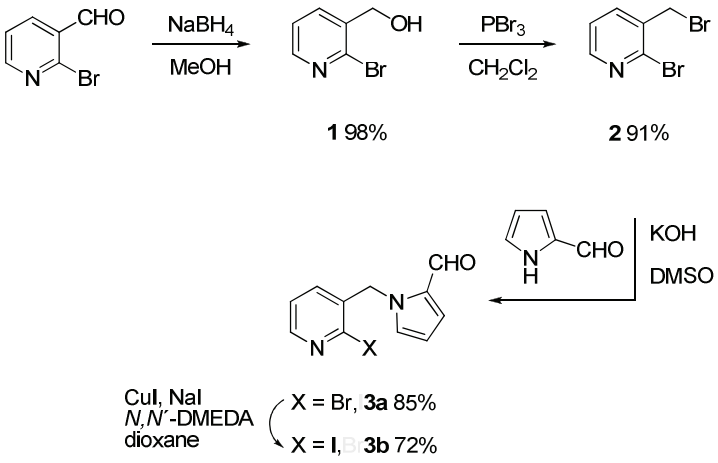
Scheme 2.30

*2.3.1.1. Synthesis of o-halopyridines **5a-5d** and o-haloquinolines **9a-9d**.*

In this section, the preparation of the required *o*-halopyridines **5a-5d** and *o*-haloquinolines **9a-9d** is presented. Both the brominated and iodinated heteroaryl derivatives, bearing an olefin moiety substituted with electron-deficient groups, such as an ester or an amide, have been synthesized.

Firstly, the synthesis of *o*-halopyridines **5a-5d** was carried out, starting from commercially available 2-bromopyridine-3-carboxaldehyde, whose reduction with $NaBH_4$ in MeOH led to the corresponding primary alcohol, 2-bromo-3-hydroxymethylpyridine (**1**). A subsequent conversion of the alcohol into bromide by reaction with PBr_3 in CH_2Cl_2 at room temperature resulted in the generation of

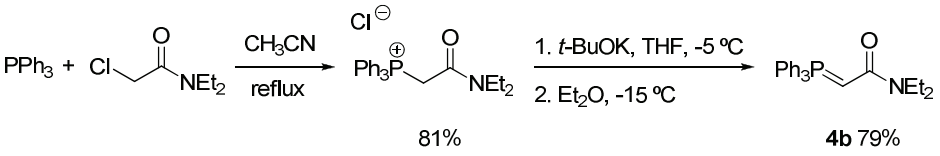
the dibromopyridine **2** in excellent yield (89% yield over two steps)[45] (Scheme 2.31). Alkylation reaction of readily synthesized 2-bromo-3-bromomethylpyridine (**2**) with commercially available pyrrole-2-carboxaldehyde using KOH as base in DMSO as solvent enabled the preparation of (*o*-bromopyridinylmethyl)pyrrole carbaldehyde **3a** in good yield. The corresponding iodinated derivative **3b** was prepared by treatment of the bromo derivative **3a** with NaI/CuI in dioxane.[46]



Scheme 2.31

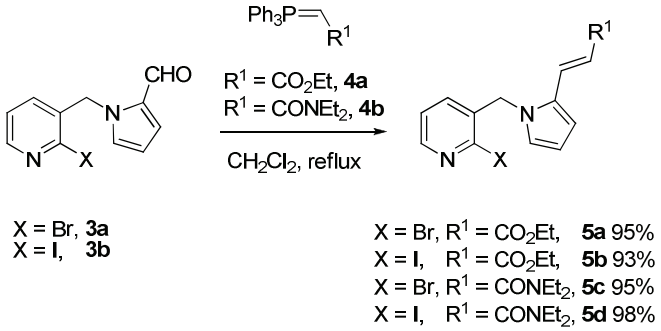
To perform the next olefination step, it was necessary to prepare ylide **4b**, while ethyl (triphenylphosphoranylidene)acetate (**4a**) was commercially available. The synthesis was performed as depicted in the Scheme 2.32[47] in a two step sequence beginning with the generation of the phosphonium salt to follow with the formation of ylide, which was stored under argon at low temperature to prevent decomposition.

[45] Ruiz, J.; Lete, E.; Sotomayor, N. *Tetrahedron* **2006**, *62*, 6182.
[46] Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844.
[47] Cardillo, G.; Gentilucci, L.; De Matteis, V. *J. Org. Chem*. **2002**, *67*, 5957.



Scheme 2.32

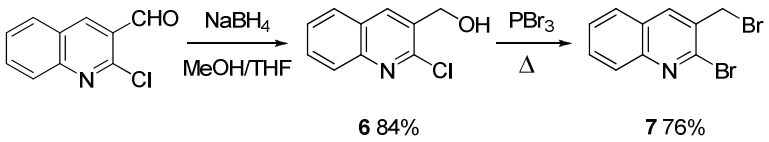
Finally, the introduction of the olefin moiety took place through Wittig olefination of both (*o*-halopyridinylmethyl)pyrroles **3a** and **3b** with ylide **4a** in CH_2Cl_2 at reflux, affording (*E*)-acrylates **5a** and **5b** in excellent yields (Scheme 2.33). In the same way, the corresponding acrylamides **5c** and **5d** were obtained in excellent yields as single diastereomers of (*E*)-configuration, by treatment of previous aldehydes **3a** and **3b** with the synthesized ylide **4b**.



Scheme 2.33

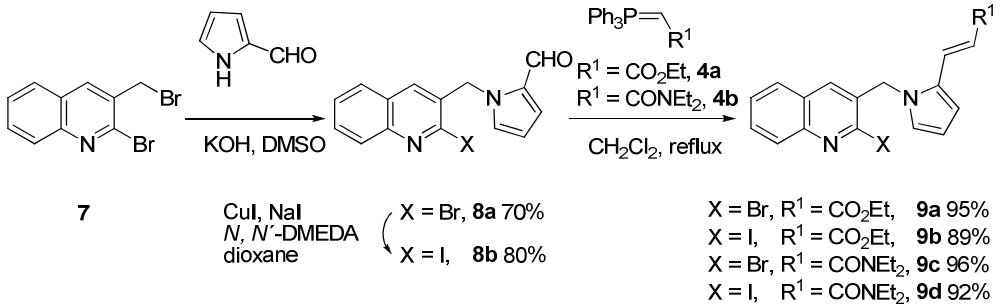
In parallel, *o*-haloquinolines **9a**-**9d** were prepared starting with the formation of 2-bromo-3-bromomethylquinoline (**7**) from commercially available 2-chloro-3-formylquinoline (Scheme 2.34). The reduction of the aldehyde to primary alcohol, by using $NaBH_4$ as reducting agent in a 1:1 mixture of MeOH:THF, led to 2-

chloro-3-hydroxymethylquinoline (**6**), which was converted into 2-bromo-3-bromomethylquinoline (**7**) by treatment with PBr_3 under heating.[45]



Scheme 2.34

Alkylation of the bromomethylquinoline **7** with pyrrole-2-carboxaldehyde resulted in the formation of (*o*-bromoquinolinylmethyl)pyrrole carbaldehyde **8a** in a 70% yield. As previously described for pyridines, we were able to synthesize the iodo derivative **8b.** The subsequent Wittig olefination afforded the acrylates and acrylamides **9a-9d** in excellent yields (89-95%) as single diastereomers of (*E*)-configuration (Scheme 2.35).

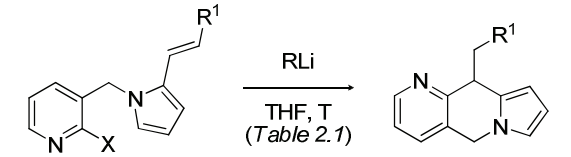


Scheme 2.35

*2.3.1.2. Intramolecular carbolithiation reaction of o-halopyridines **5a-5d**. Synthesis of 5,10-dihydropyrrolo[1,2-g][1,6]naphthyridines **10a**, **10b**.*

Once the substrates had been synthesized, we started studying the cyclization of *o*-halopyridines **5a-5d** in order to obtain dihydropyrrolonaphthyridines **10a**, **10b**.

We first tested the reaction using *n*-BuLi as metalating agent, as it had given the best results in related Parham cyclizations carried out in our group.[45] However, when acrylamides **5c** and **5d** were treated with *n*-BuLi in dry THF at -90 ºC, as expected, dehalogenated pyrrolylmethylpyridine **11**, derived from addition of the alkyllithium to the double bond (Figure 2.1), was obtained as the major product, together with the desired naphthyridine **10b** in low yields (Scheme 2.36, Table 2.1, Entries 1-2).



X = Br, R^1 = CO_2Et, **5a**
X = I, R^1 = CO_2Et, **5b**
X = Br, R^1 = $CONEt_2$, **5c**
X = I, R^1 = $CONEt_2$, **5d**

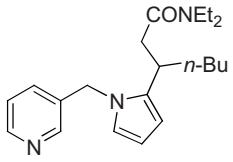
R^1 = CO_2Et, **10a**
R^1 = $CONEt_2$, **10b**

Scheme 2.36

*Table 2.1. Carbolithiation reactions of o-halopyridines **5a**-**5d**.*

Entry	Substrate	RLi	T (ºC)	Time (min)	Product	Yield (%)[a]
1	**5c**	*n*-BuLi[b]	-90	5	**10b**[d]	9
2	**5d**	*n*-BuLi[b]	-90	5	**10b**[e]	9
3	**5c**	MesLi[c]	-105	5	**10b**	27[f]
4	**5c**	MesLi[c]	-105	10	**10b**	55
5	**5d**	MesLi[c]	-105	10	**10b**	56
6	**5a**	MesLi[c]	-105	5	**10a**	47
7	**5b**	MesLi[c]	-105	5	**10a**	49

[a] Isolated yield. [b] 2.2 eq. [c] 2.0 eq. [d] Addition product **11** (45%) was also isolated. [e] Addition product **11** (44%) was also isolated. [f] Conversion 86%.

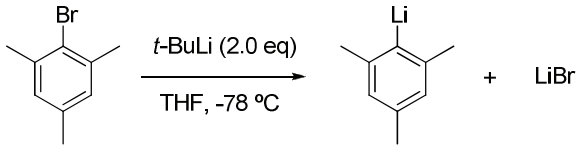


11

Figure 2.1

Therefore, we decided to choose MesLi as the metalating agent, as it is known to avoid competitive 1,2- and 1,4-addition reactions of the alkyllithium reagent to the alkene moiety.[40] As mentioned before, MesLi is a non-nucleophilic and strongly basic bulky reagent, which has to be prepared *in situ* as is not stable enough to be

stored. The preparation of MesLi involves lithiation of 2-bromomesitylene with an excess of *t*-BuLi at low temperature under inert atmosphere (Scheme 2.37).[48]



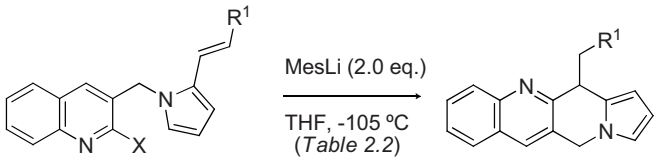
Scheme 2.37

We took the conditions optimized by our group for the carbolithiation of *N*-(*o*-iodobenzyl)pyrroles[40] as a starting point (MesLi in THF, from -90 ºC to -105 ºC). Low temperatures and very short reaction times were required for the formation of this type of heteroaryllithiums.[45] Thus, first attempts were conducted by treating *o*-bromopyridine **5c** with MesLi in dry THF at -105 ºC, which provided pyrrolonaphthyridine **10b** in only a 27% yield (Table 2.1, Entry 3), but starting material was recovered (86% conversion). Longer reaction times were required to obtain **10b** in moderate yield (55%) (Entry 4). When this procedure was applied to *o*-iodopyridine derivative **5d**, naphthyridine **10b** was obtained in a similar 56% yield (Entry 5). The procedure could be also applied to the corresponding acrylates **5a** and **5b**, obtaining pyrrolonaphthyridine **10a** in just 5 min in moderate yields (Entries 6-7).

[48] a) Seebach, D.; Neumann, H. *Chem. Ber*. **1974**, *107*, 847. b) Yoshifuji, M.; Nakamura, T.; Inamoto, N. *Tetrahedron Lett.* **1987**, *28*, 6325. c) Rathman, T. L.; Woltermann, C. J. *PharmaChem*. **2003**, *2*, 6.

*2.3.1.3. Intramolecular carbolithiation reaction of o-haloquinolines **9a-9d**. Synthesis of 5,12-dihydrobenzo[b]pyrrolo[1,2-g][1,6]naphthyridines **12a, 12b**.*

A similar methodology was applied to *o*-haloquinolines **9a-9b**, affording this time dihydrobenzopyrrolonaphthyridines **12a**, **12b** (Scheme 2.38).



X = Br, R^1 = CO_2Et, **9a**
X = I, R^1 = CO_2Et, **9b**
X = Br, R^1 = $CONEt_2$, **9c**
X = I, R^1 = $CONEt_2$, **9d**

R^1 = CO_2Et, **12a**
R^1 = $CONEt_2$, **12b**

Scheme 2.38

All essays are collected in Table 2.2, but unfortunately low yields of the corresponding benzonaphthyridines **12a**, **12b** were always obtained. Carbolithiation carried out on acrylates **9a**, **9b** resulted in 29-30% yield of the benzonaphthyridine **12a** (Entries 1-2). Acrylamides **9c**, **9d** needed longer times for the reaction to reach completion, but the yields were not improved (Entries 3-5). In all cases, the reaction afforded a complex mixture of products, from which benzonaphthyridines **12a**, **12b** were difficult to isolate.

*Table 2.2. Carbolithiation reactions of o-haloquinolines **9a-9d**.*

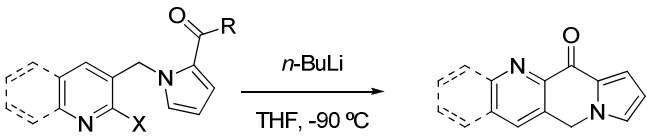
Entry	Substrate	Time (min)	Product	Yield (%)[a]
1	**9a**	5	**12a**	29
2	**9b**	10	**12a**	30
3	**9c**	10	**12b**	20[b]
4	**9c**	30	**12b**	25
5	**9d**	30	**12b**	28

[a] Isolated yield. [b] Conversion 86%.

In summary, it has been possible to perform intramolecular carbolithiation reaction with electron-deficient heteroaryllithiums, such as pyridinyllithiums, to obtain 5,10-dihydropyrrolo[1,2-*g*][1,6]naphthyridines **10a-10b** in moderate yields. However, the use of the corresponding quinolinyllithium derivatives provided the corresponding 5,12-dihydrobenzo[*b*]pyrrolo[1,2-*g*][1,6]naphthyridines **12a-12b** in lower yields. No difference in reactivity was observed between bromo and iodo derivatives for the formation of heteroaryllithiums and subsequent cyclizations.

These results contrast with the more efficient Parham cyclization reaction of *o*-halobenzylpyrroles for the synthesis of pyrrolo[1,2-*a*]isoquinolines when using activated alkenes as internal electrophiles[40] (see Scheme 2.25). On another hand, when using amides as internal electrophiles, we have reported that pyridinyl and quinolinyllithiums could be efficiently generated by treatment with *n*-BuLi followed by fast cyclization at -90 ºC, leading to pyrrolo[1,2-*b*]acridinones and pyrrolo[1,2-*g*]quinolones in good yields (Scheme 2.39).[45] However, in the case presented in this work, it was necessary to use MesLi to avoid 1,2- and 1,4-competitive addition reactions. Besides, the reactions required longer reaction

times to reach completion, which probably led to decomposition of the substrates/products. Similar results were observed when electron-rich heteroaryllithiums were used in carbolithiation reactions (see Scheme 2.28).[44]



X = Br, I
R = NEt_2, N(OMe)Me

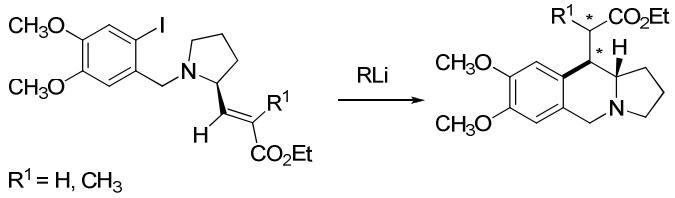
61-85%

Scheme 2.39

2.3.2. Intramolecular carbolithiation reaction *via* conjugate addition on *N*-(*o*-iodobenzyl)pyrrolidinylacrylates

As summarized in the introduction of this chapter, our group had described the intramolecular carbolithiation of chiral non-racemic *N*-(*o*-iodobenzyl)pyrrolidinylacrylamides derived from L-prolinal, which took place with complete diastereoselectivity.[42] In order to expand the scope of this methodology, we decided to investigate the effect of the substitution pattern in the alkene on the carbolithiation reaction of related substrates.

For this purpose, we chose enantiomerically pure 2-alkenyl *N-(o*-iodobenzyl)pyrrolidines, where the alkene was substituted by an ester group, with or without substituents in the α-position of the acrylate moiety (Scheme 2.40).

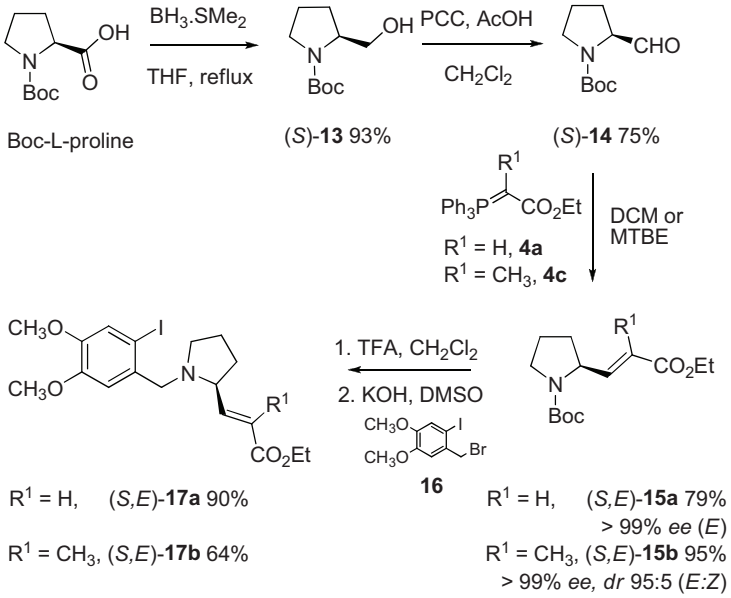


Scheme 2.40

*2.3.2.1. Synthesis of N-(o-iodobenzyl)pyrrolidines **17a**, **17b**.*

The synthesis of enantiopure *N*-(*o*-iodobenzyl)pyrrolidines (*S,E*)**-17a** and (*S,E*)-**17b** was performed starting from commercially available Boc-L-proline (Scheme 2.41). Thus, Boc-L-prolinal (**14**) was prepared by reduction of the carboxylate group of Boc-L-proline to the alcohol **13** by treatment with the borane adduct $BH_3.SMe_2$[49] and subsequent oxidation to an aldehyde moiety with PCC.[50] Wittig olefination with commercially available ylides **4a**, **4c** resulted in the formation of acrylates **15a**, **15b** as single diastereomers of (*E*)-configuration without epimerization at the stereogenic centre (> 99% *ee*). The enantiomeric purity was determined by chiral stationary phase HPLC using Chiralcel IC column in a hexane/*i*-PrOH (95:5) mobile phase and by comparison with data obtained from racemic samples of the acrylates **15a**, **15b**, which were prepared by following the same procedures starting from racemic proline (See Experimental Section). These acrylates were deprotected with TFA and *N*-alkylated with benzyl bromide **16**,[51] to give *N*-(*o*-iodobenzyl)pyrrolidines **17a** and **17b**.

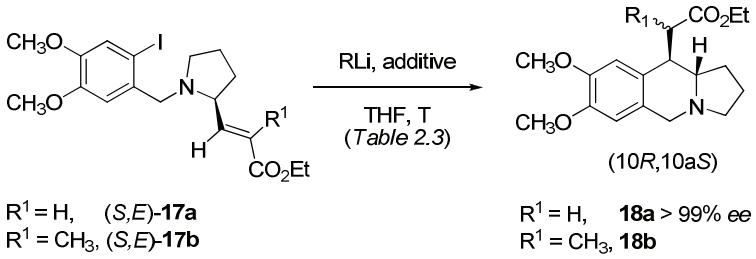
[49] Reed, P.E.; Katzenellenbogen, J.A. *J. Org. Chem.* **1991**, *56*, 2624.
[50] Trybulski, E.J.; Kramss, R.H.; Mangano, R.M.; Rusinko, A. *J. Med. Chem.* **1990**, *33*, 3190.
[51] The synthesis of benzylbromide **16** was performed by iodination of commercially available 3,4-dimethoxybenzyl alcohol with I_2 and CF_3COOAg in $CHCl_3$ as solvent (91%), followed by treatment with PBr_3 to provide 1-(bromomethyl)-2-iodo-4,5-dimethoxybenzene (**16**) in 89% yield. See: Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311.



Scheme 2.41

*2.3.2.2. Intramolecular carbolithiation reaction of N-(o-iodobenzyl)pyrrolidines **17a, 17b**. Synthesis of hexahydropyrrolo[1,2-b]isoquinolines **18a, 18b**.*

Based on the precedents already mentioned, we started the study of intramolecular carbolithiation of pyrrolidines (*S,E*)-**17a** and (*S,E*)-**17b** as depicted Scheme 2.42 and Table 2.3. We first carried out the reaction using MesLi as metalating agent to avoid competitive addition reactions. Thus, treatment of pyrrolidinylacrylate *(S,E)*-**17a** with MesLi in dry THF at -105 ºC led to (10*R*,10a*S*)-hexahydropyrrolo[1,2-*b*]isoquinoline **18a** as a single diastereomer in excellent yield (85%) (Entry 1). Therefore, the cyclization took place with total diastereoselectivity in agreement with our previous results on the corresponding acrylamides.[42,43]



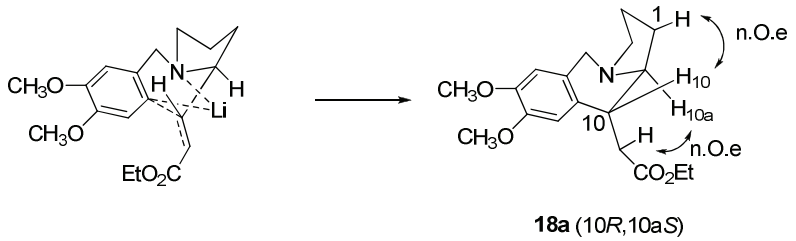
Scheme 2.42

*Table 2.3. Carbolithiation reactions of N-(o-iodobenzyl)pyrrolidines **17a, 17b**.*

Entry	Subs.	RLi	Additive	T (ºC)	Time (min)	Prod.	Yield (%)[a] (*dr*)[b]
1	(*S,E*)-**17a**	MesLi[c]	-	-105	5	**18a**	85
2	(*S,E*)-**17b**	MesLi[c]	-	-105	5	**18b**	77 (50:50)
3	(*S,E*)-**17b**	*n*-BuLi[d]	TMEDA[d]	-78	10	**18b**[f]	40 (69:31)
4	(*S,E*)-**17b**	*n*-BuLi[d]	TMEDA[d]	-78	40	**18b**[g]	48 (59:41)
5	(*S,E*)-**17b**	*n*-BuLi[d]	(–)-sparteine[d][e]	-90	10	**18b**[h]	36 (38:62)
6	(*S,E*)-**17b**	*n*-BuLi[d]	(–)-sparteine[d][e]	-90	60	**18b**[i]	45 (38:62)

[a] Isolated yield. [b] Diastereomer ratio determined by ^{1}H NMR spectroscopy. [c] 2.0 eq. [d] 2.2 eq. [e] Toluene as solvent. [f] Addition product **19** (21%) was also isolated. [g] Addition product **19** (8%) was also isolated. [h] Addition product **19** (23%) was also isolated. [i] Addition product **19** (22%) was also isolated.

We could confirm the (10*R*,10a*S*)-*trans* configuration in the indolizidine system by 2D NOESY experiments, which showed an enhancement between H-10 and H-1, and between H-10a and a methylenic proton of the substituent at C-10 (Figure 2.2). The stereochemical outcome of the reaction could be explained by attack of the intermediate aryllithium as shown in Figure 2.2. This model allows possible nitrogen-lithium chelation and subsequent cyclization.



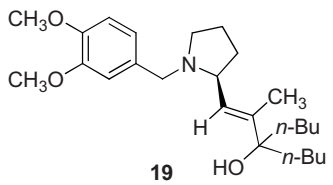
18a (10*R*,10a*S*)

Figure 2.2

In view of these results, we submitted the pyrrolidinylacrylate (*S,E*)-**17b** to the same reaction conditions. In this case, a 1:1 mixture of diastereomers **18b** was obtained (Table 2.3, Entry 2), which could not be separated by chromatographic methods. The NMR studies carried out on the mixture seem to indicate that the cyclization was diastereoselective, but the protonation of the final lithiated intermediate was non-selective. However, the stereochemistry could not be unambiguously determined due to overlapping of the signals.

The change to *n*-BuLi as organolithium reagent in the presence of TMEDA at -78 ºC provided the mixture of the same diastereomers in different ratio (69:31) in moderate yield (40%) (Entry 3), together with byproduct **19** (21%), derived from a double addition of *n*-BuLi to the ester moiety as represented in Figure 2.3. Longer reaction times improved slightly the yield (48%), but with a drop in diastereoselectivity (Entry 4). The use of *n*-BuLi in the presence of a chiral bidentate ligand, such as (–)-sparteine, in toluene at lower temperatures, generated the hexahydropyrrolo[1,2-*b*]isoquinoline **18b** in moderate yields but with an inversion in the stereochemical outcome (Entries 5-6). A reversal of

diastereoselection has been previously reported when (–)-sparteine was used instead of TMEDA in related processes.[52]



19

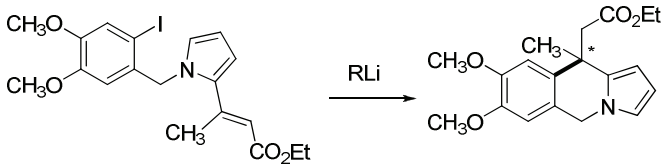
Figure 2.3

To sum up, the intramolecular conjugate addition of the aryllithium intermediate to the acrylate moiety of pyrrolidine (*S,E*)-**17a** takes place diastereoselectively to obtain the hexahydropyrrolo[1,2-*b*]isoquinoline **18a** with a (10*R*,10a*S*)-configuration. However, in the case of acrylate **17b**, the protonation is non-selective, obtaining **18b** as an epimeric mixture, in a different ratio depending on the reaction conditions.

2.3.3. Intramolecular carbolithiation reaction *via* conjugate addition on *N*-(*o*-iodobenzyl)pyrrolylbutenoate

According to our objectives, our next task was to study the possibility of generating a quaternary stereocenter by intramolecular carbolithiation on *N*-(*o*-iodobenzyl)pyrrolylbutenoate **26** (Scheme 2.43).

[52] a) See Ref. 39. b) Arrasate, S.; Sotomayor, N.; Lete, E. *Tetrahedron: Asymmetry* **2002**, *13*, 311.



26

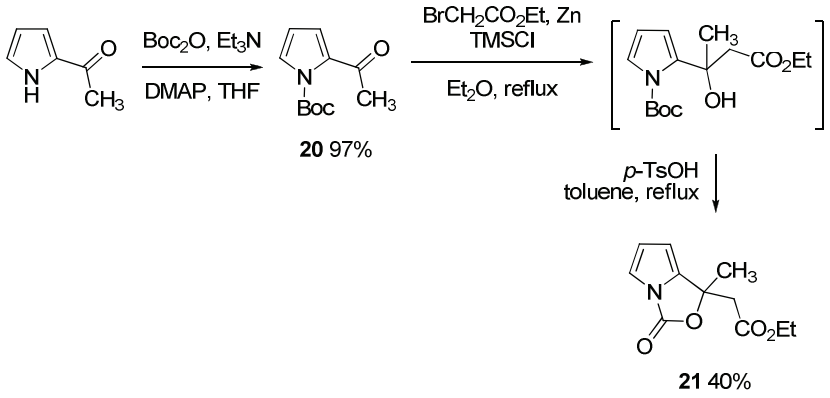
Scheme 2.43

*2.3.3.1. Synthesis of N-(o-iodobenzyl)pyrrole **26**.*

We first focused on the synthesis of *N*-(*o*-iodobenzyl)pyrrolylbut-2-enoate **26**. Different approaches were tried to introduce a methyl group in the β position of the α,β-unsaturated ester moiety of the pyrrole.

The first strategy planned started with Boc-protection of commercially available 2-acetylpyrrole to afford **20**.[53] However, all attempts to perform Wittig olefination reactions over Boc-acetylpyrrole **20** failed, probably due to the lower reactivity of ketones compared to aldehydes. Therefore, we chose the Reformatsky reaction,[54] followed by dehydration, as an alternative pathway to synthesize this α,β-unsaturated ester. However, when **20** was reacted with $BrCH_2CO_2Et$ in the presence of Zn, oxazolone **21** was obtained in 40% yield, after treatment with *p*-TsOH in dry toluene, as depicted in Scheme 2.44. The formation of this oxazolone could be explained by intramolecular reaction of the hydroxyl group of the β-hydroxy ester intermediate with the Boc group catalyzed by *p*-TsOH.

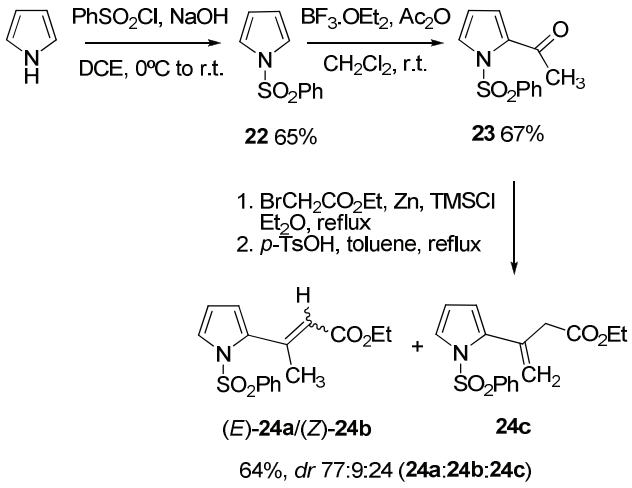
[53] Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 1046.
[54] a) Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796. b) Thakur, V.V.; Nikalje, M.D.; Sudalai, A. *Tetrahedron: Asymmetry* **2003**, *14*, 581.



Scheme 2.44

Observing this outcome of the Reformatsky reaction, we decided to introduce an alternative protecting group on the pyrrole nitrogen, the phenylsulfonyl group, which would remain unchanged during that step. Thus, treatment of commercially available pyrrole with phenylsulfonyl chloride, followed by acetylation (Ac_2O, $BF_3.OEt_2$ in CH_2Cl_2) at C-2 position[55] led to **23**. When *N*-phenylsulfonylpyrrole **23** was submitted to Reformatsky reaction conditions, a mixture of three isomers (whose ratio was determined by GC-MS) was obtained (Scheme 2.45). This mixture was difficult to separate and only (*E*)-**24a** was isolated and completely characterized. Besides, all attemps to deprotect the sulphonyl group of (*E*)-**24a** failed.

[55] Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.



Scheme 2.45

The configuration of the isomer (*E*)-**24a** was determined by NOE difference experiments, which showed an enhancement between the olefinic proton and H-3 of the pyrrole, and between the same olefinic proton and the aromatic protons of the phenyl group. Enhancements between the alkene methyl group, and both pyrrole H-3 and aromatic protons were also observed. Therefore, the alkene is likely to be coplanar with the pyrrole, giving two preferred conformations (Figure 2.4). Equilibrium between the two conformations would be fast on the chemical shift timescale.

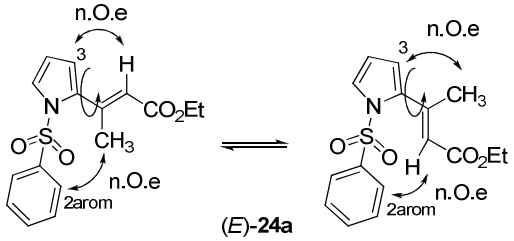
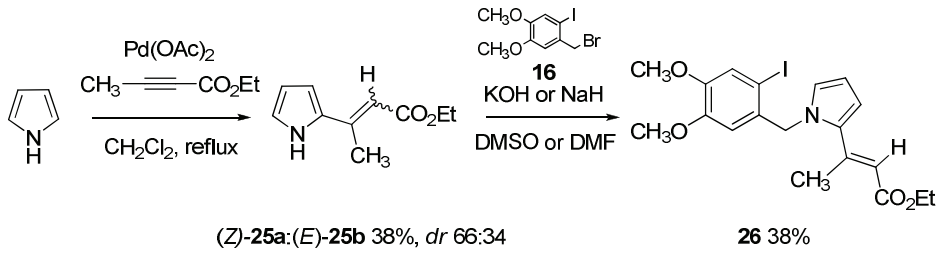


Figure 2.4

On the other hand, it has been reported that palladium-catalyzed cross-coupling reaction *via* C-H bond activation of simple heteroarenes, such as pyrroles and indoles, with alkynes, affords *cis*-heteroarylalkenes in most cases.[56] Therefore, an alternative strategy was planned. Commercially available ethyl 2-butynoate was reacted with pyrrole in the presence of $Pd(OAc)_2$, to provide 2-ethyl 3-(1*H*-pyrrol-2-yl)but-2-enoate (**25**) as a 66:34 mixture of *Z*:*E* diastereomers in low yield (38%) (Scheme 2.46).



Scheme 2.46

Both diastereomers could be separated, characterized and their stereochemistry assigned on the basis of 2D NOESY experiments (Figure 2.5). As in the case of *N*-phenylsulfonylpyrrole (*E*)-**24a**, enhancements between olefinic proton, pyrrole H-3 and N-H, together with enhancements between methyl group and pyrrole H-3, were observed for (*E*)-**25b**. Therefore, an equilibrium between the two conformers, shown in Figure 2.5, is established. On the other hand, the enhancements between the methyl group, pyrrole H-3 and olefinic proton were observed for (*Z*)-**25a**. Additionally, in the last case, no NOE between the olefinic proton and pyrrole H-3 could be detected.

[56] Lu, W.; Jia, C.; Kitamura, T.; Fujiwara. Y. *Org. Lett.* **2000**, *2*, 2927.

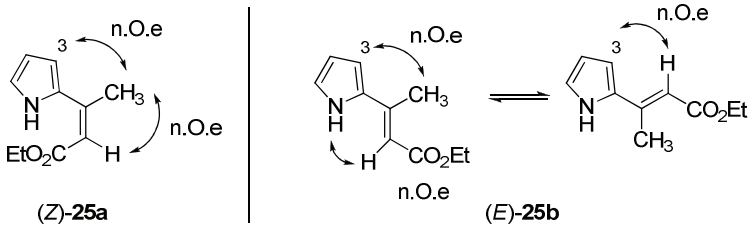
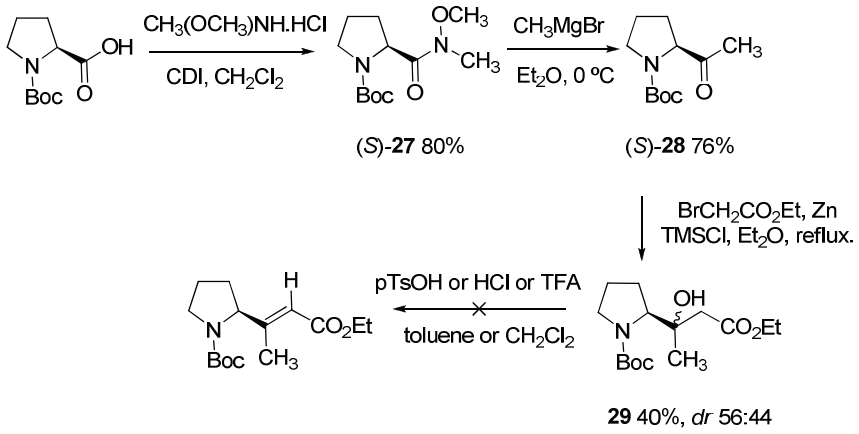


Figure 2.5

Although the reaction proved inefficient due to the presence of byproducts derived from the coupling in C-3 position of the pyrrole nucleus, *N*-alkylation of both 2-ethyl 3-(1*H*-pyrrol-2-yl)but-2-enoate diastereomers **25** with benzyl bromide **16** was performed independently under different conditions, obtaining in all cases the desired *N*-(*o*-iodobenzyl)pyrroles **26** as a single diastereomer of (*E*)-configuration in yields up to 38% (Scheme 2.46).

Synthesis of analogous pyrrolidine derivative was also tried starting from commercial enantiopure Boc-L-proline (Scheme 2.47). The preparation of Weinreb amide derivative (*S*)-**27** was accomplished by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and CDI in CH_2Cl_2.[57] The amide was further transformed to a ketone moiety by reaction with methylmagnesium bromide, thus obtaining *N*-Boc protected 2-acetylpyrrolidine (*S*)-**28**.[57,58] The subsequent Reformatsky reaction[54] afforded **29** as a 54:46 mixture of diastereomers (40% yield). All attempts to dehydrate this β-hydroxyester with *p*-TsOH, HCl or TFA failed, so we decided to give up the synthesis of this intermediate.

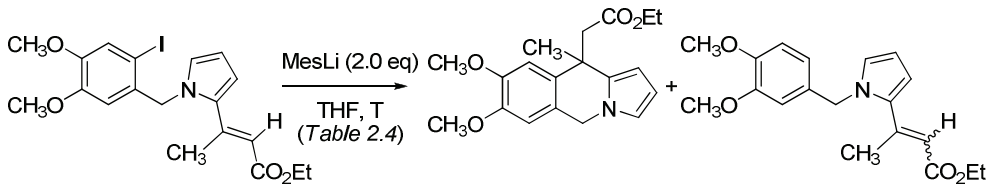
[57] Kong, C.; Jana, N.; Driver, T. G. *Org.Lett.* **2013**, *15*, 824.
[58] Barluenga, J.; Escribano, M.; Aznar, F.; Valdés, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6856.



Scheme 2.47

*2.3.3.2. Intramolecular carbolithiation of N-(o-iodobenzyl)pyrrole **26**. Synthesis of 5,10-dihydropyrrolo[1,2-b]isoquinoline **30**.*

Based on our previous experience, we started the study of intramolecular carbolithiation reaction of pyrrole **26** with MesLi (Scheme 2.48). Treatment of *N*-(*o*-iodobenzyl)pyrrole **26** with MesLi in THF at -105 ºC afforded 10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline **30** in low yield (22%), together with deiodinated pyrrole **31** as a 25:75 mixture of diastereomers (*Z:E*) in a 52% yield (Table 2.4, Entry 1). Longer reaction times and different temperatures were tried, but the results could not be improved, isolating in all cases deiodinated benzylpyrrole **31** as major product (Entries 2-3). When the reaction was allowed to warm up to room temperature overnight only (*E*)-diastereomer of **31** was isolated (Entry 4).



26 **30** **31**

Scheme 2.48

*Table 2.4. Carbolithiation reactions of N-(o-iodobenzyl)pyrrole **26**.*

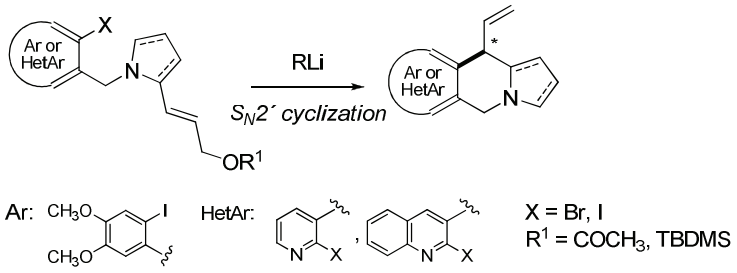
Entry	T (ºC)	Time (min)	Yield (%)	
			30	**31**[b]
1	-105	5	22	52[c]
2	-105	45	-[a]	59[d]
3	-78	180	-[a]	45[c][e]
4	-78 → r.t.	180 → 16 h	-	37[f][g]

[a] Traces of **30** were observed. [b] Ratio of (*Z:E*) diastereomers determined by GC-MS. [c] (*Z:E,* 25:75). [d] (*Z:E,* 47:53). [e] Conversion 76%. [f] Only (*E*)-diastereomer was obtained. [g] Conversion 61%.

In view of these results, we decided not to carry out the asymmetric version of the carbolithiation reaction on this substrate.

2.3.4. Intramolecular carbolithiation reactions *via* S_N2' reaction

According to the aims proposed in section 2.3, we decided to study the intramolecular carbolithiation reaction on allyl substituted pyrroles and pyrrolidines *via* S_N2'process (Scheme 2.49).



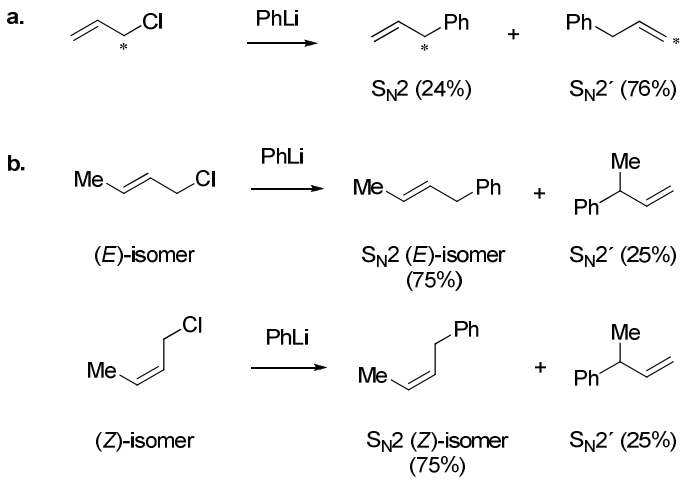
Scheme 2.49

For that purpose, we are going to present a brief overview of the reactions of organolithium reagents with allylic derivatives. Allylic compounds may undergo competitive displacement reactions using organometallic reagents, which involve carbon-carbon bond formation at the α- or γ-position of the allyl moiety. The development of methods to control this regioselectivity has emerged as an important goal in the last years. We will focus on nucleophilic substitution at an allylic carbon taking place through S_N2' mechanism when organolithium compounds are used.

In the 1960´s, Magid and Welch[59] reported that treatment of allyl chloride, ^2H or ^{14}C- labeled at the α-position, with PhLi afforded a 1:3 mixture of α-coupled and γ-

[59] a) Magid, R. M.; Welch, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 5681. b) Magid, R. M.; Welch, J. G. *J. Am. Chem. Soc*. **1968**, *90*, 5211.

coupled instead of a 1:1 mixture (Scheme 2.50a). When using *cis*- and *trans*-γ-methylallyl chloride under the same conditions, the same mixture of compounds was obtained with retention of the stereochemistry in the double bond (Scheme 2.50b).[60] These evidences claimed for concerted S_N2 and S_N2'mechanism, rejecting a mechanism that involved a resonance stabilized allylic cation intermediate (S_N1 or S_N1'mechanisms).

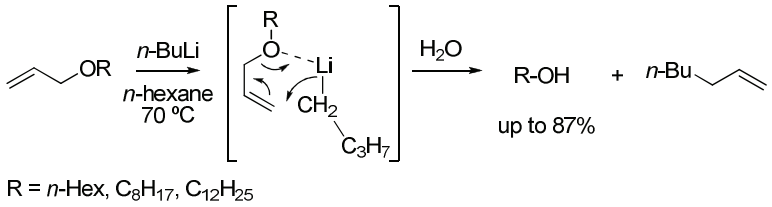


Scheme 2.50

Both S_N2 and S_N2' mechanisms take place under same nucleophilic conditions. However, different factors can affect the reaction outcome. For example, a S_N2' process may be favored in those substrates where α-position is sterically hindered, or by increasing the size of the nucleophile. In addition, the nature of the leaving group might also affect the competition.

[60] Magid, R. M.; Gandour, R. D. *J. Org. Chem*. **1970**, *35*, 269. b) Magid, R. M.; Nieh, E. C.; Gandour, R. D. *J. Org. Chem*. **1971**, *36*, 2069.

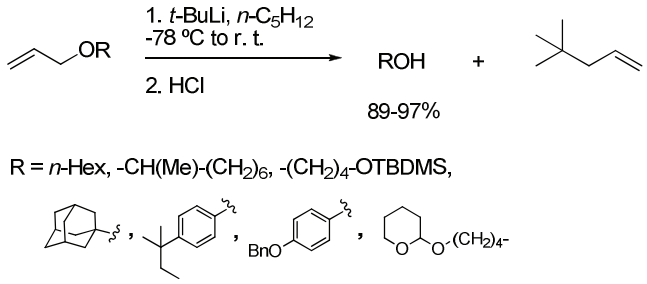
A pioneer study was also carried out by Broaddus[61] in 1965, where the cleavage of several alkyl allyl ethers occurred upon treatment with *n*-BuLi in a hydrocarbon solution at 70 ºC, affording the corresponding alcohols and *n*-heptene. In fact, nucleophilic S_N2' displacement process was proposed to take place *via* a cyclic 6-membered transtition state, where the lithium atom was coordinated to the oxygen atom (Scheme 2.51).



Scheme 2.51

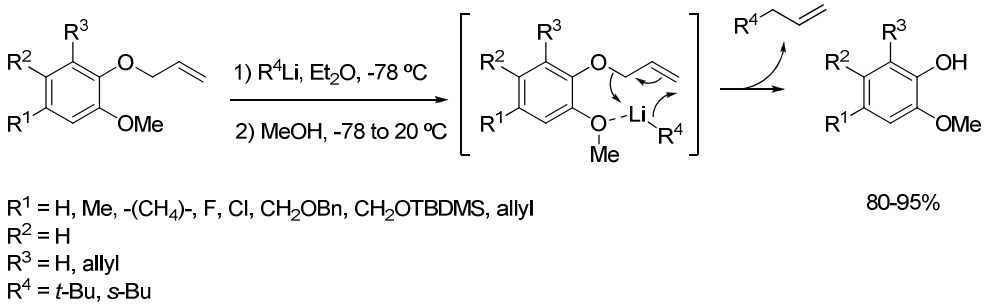
Based in these precedents, more recently Bailey and coworkers published an efficient methodology to perform *O*-deallylation of allyl ethers as a strategy for alcohol deprotection, when using allyl units as robust protecting groups.[62] In this case, differently substituted allylic ethers led to their corresponding alcohols and 4,4-dimethyl-1-pentene using *t*-BuLi in pentane solution at -78 ºC and allowing to warm up the reaction mixture to room temperature (Scheme 2.52). This methodology provides a convenient strategy for the selective removal of an allyl protecting group, even in presence of an acetal or a silyl groups.

[61] Broaddus, C. D. *J. Org. Chem*. **1965**, *30*, 4131.
[62] Bailey, W. F.; England, M. D.; Mealey, M. J. Thongsornkleeb, C.; Teng, L. *Org. Lett*. **2000**, *2*, 489.



Scheme 2.52

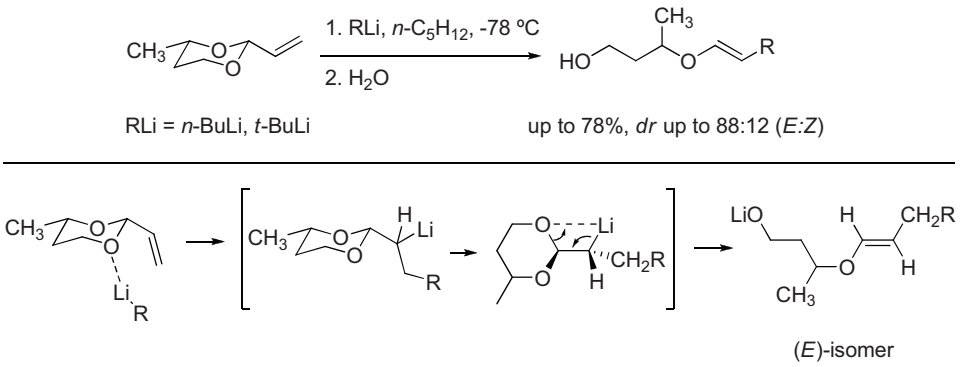
In the same context, Fañanás and coworkers[63] reported a selective method for easy deallylation of *o*-allyloxyanisoles by using *s*-BuLi or *t*-BuLi at low temperature. The coordination of the methoxy group with the organolithium reagent, favored a S_N2' attack to the double bond and thus, allyl ethers derived from *o*-methoxyphenols and naphthols were cleanly cleaved to obtain the corresponding phenols or naphthols in excellent yields (Scheme 2.53).



Scheme 2.53

[63] Sanz, R.; Martínez, A.; Marcos, C.; Fañanás, F. J. *Synlett* **2008**, 1957.

In this context, Bailey and coworkers[64] have also reported the regioselective ring opening of *cis*-4-methyl-2-vinyl-1,3-dioxane. Preferential cleavage of the C–O bond, remote from the 4-methyl substituent occurred, which resulted in the formation of *E*-enol ether shown on Scheme 2.54 as the major product. However, in this case, a two-step mechanism, which differs from the simple one step-S_N2' process, involving addition of alkyllithium and subsequent *syn*-elimination of lithium alkoxide was suggested.

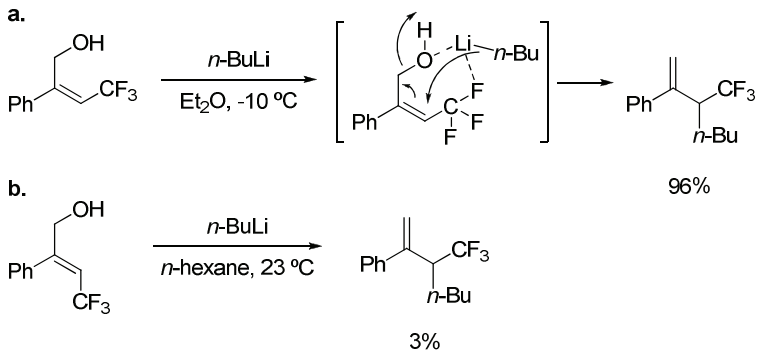


Scheme 2.54

Sodeoka and coworkers[65a] described the release of a poor leaving group, such as hydroxyl group, through S_N2' reaction, when (*Z)*-trifluoromethylated 2-phenyl allylic alcohol was treated with *n*-BuLi in Et_2O at -10 ºC (Scheme 2.55a). Posterior mechanistical studies confirmed that hydroxyl group plays the role of leaving group and of directing group.[65b] In addition, trifluoromethyl moiety favors the reactivity towards the S_N2' process, not only by its electron-withdrawing

[64] Bailey, W. F.; Zarcone, L. M. J. *Chirality*, **2002**, 14, 163.
[65] a) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4577. b) Egami, H.; Usui, Y.; Kawamura, S.; Shimizu, R.; Nagashima, S.; Sodeoka, M. *J. Fluorine Chem.* **2015**, *179*, 121.

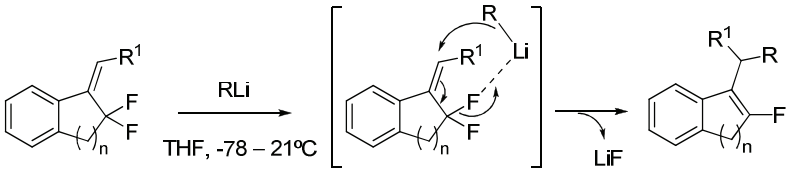
properties, but also by chelation of the lithium alkoxide, which fixes the conformation of the substrate. In this case, the (*Z*)-isomer allows geometrically more favorable chelation, compared to the (*E*)-isomer, which only afforded a 3% of product (Scheme 2.55b).[65b] In addition, the aryl group also plays a crucial role in controlling the regioselectivity and reactivity of the process.



Scheme 2.55

In the same context, Paquin *et al*.[66] reported the carbolithiation *via* S_N2' displacement of a fluoride group located in an allylic system. In this case, the cleavage of carbon-fluoride bonds on 3,3-difluoropropene derivatives with various alkyllithiums was achieved, thus obtaining monofluoroalkenes. Although fluoride group is thought to be a poor leaving group, in this example, its nucleofuge ability may increase due to a C–F···Li chelation. Hence, fluorine-lithium coordination has been proposed to activate carbon-fluorine bond, so LiF would be released acting as a driving force to promote S_N2' process (Scheme 2.56).

[66] Bergeron, M.; Johnson, T.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2011**, *50*, 11112.

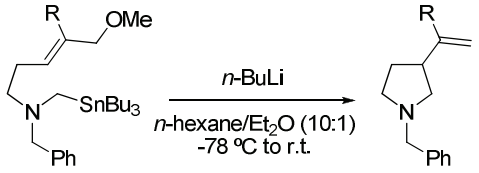


n = 1, 2, 3
R^1 = H, Me, Ph
RLi = MeLi, *s*-BuLi, *n*-BuLi, *t*-BuLi, PhLi

Scheme 2.56

However, best results in this type of S_N2' processes with organolithium compounds have been obtained using transition-metal catalysts such as copper salts,[67] which involve a transmetallation process to form organocuprate intermediates that are the reactive species in the addition to allylic systems.

The carbolithiation reactions *via* a S_N2' process can also be carried out in an intramolecular fashion. In this context, Coldham and coworkers[7f] reported the anionic cyclization of α-amino-organolithium species, formed by tin-lithium exchange, onto allylic ethers to obtain the corresponding pyrrolidines (Scheme 2.57).



R = H, Me

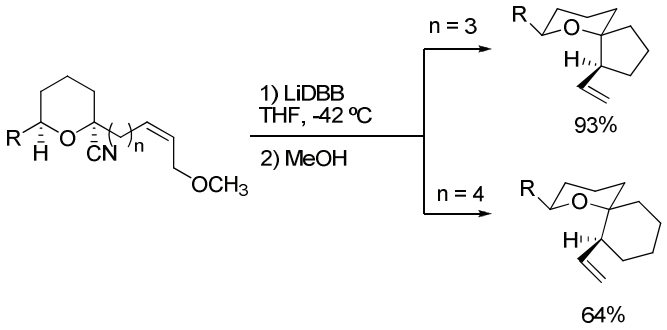
64-81%

Scheme 2.57

[67] For some representative examples, see: a) Yus, M.; Ortiz, R. *Eur. J. Org. Chem.* **2004**, 3833. b) Kiyotsuka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **2008**, *49*, 7256. c) Pérez, M.; Fañanás-Mastral, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. *Nat. Chem.* **2011***, 3,* 377. d) Konno, T.; Ikemoto, A.; Ishihara, T. *Org. Biomol. Chem.* **2012**, *10*, 8154.

A similar methodology was applied by Krief[68] for the synthesis of cyclopentanes, but in this case, a selenium-lithium exchange provided benzyllithium intermediates, which cyclized over the allyl ether through S_N2' reaction.

In addition, alkyllithiums formed by reductive lithiation of a nitrile have also proved to undergo intramolecular carbolithiation reactions *via* S_N2' pathway.[9] In this context, Takaoka[36a] has reported the formation of five- and six-membered rings by cyclization of an alkyllithium over an allylic ether moiety by displacement of an alkoxide (Scheme 2.58).

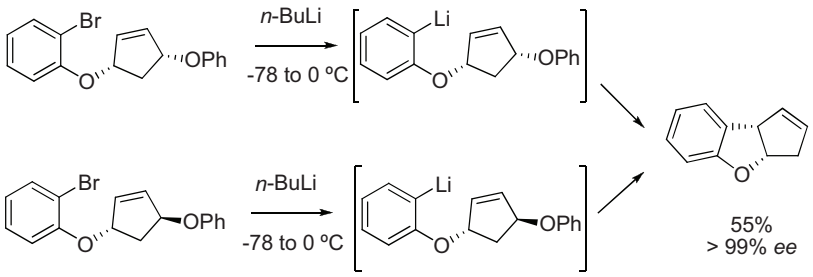


Scheme 2.58

In relation to our work, we are interested on intramolecular carbolithiation reactions of aryl and heteroaryllithiums, generated by halogen-lithium exchange, over allylic systems bearing leaving groups in α-position to promote S_N2' reactions.

[68] Krief, A.; Remacle, B.; Mercier, J. *Synlett* **2000**, 1443.

To our knowledge, very few precedents are found in literature. Thus, Nishiyama and coworkers[69] described the synthesis of optically pure cyclopenta[*b*]benzofuran derivatives *via* a S_N2' intramolecular carbolithiation, starting from enantiomerically pure aryl ethers. Regardless of the C-4 configuration in the starting cyclopentyl eter (Scheme 2.59), the reaction took place with a total diastereoselectivity, affording cyclopenta[*b*]benzofuran as a single *cis*-isomer in enantiomerically pure form.

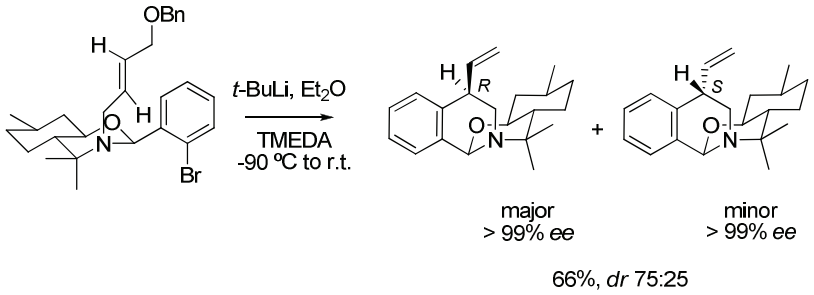


Scheme 2.59

The same group had previously investigated the asymmetric induction promoted by several chiral lithium alkoxides in the bis-phenyllithium intermediate, in the anionic cyclization of enantiopure *cis*-1,4-bis(2-bromophenoxy)cyclopent-2-ene by a S_N2' process.[70]

On the other hand, Pedrosa and coworkers[37] described the intramolecular 6-*exo* carbolithiation reaction of chiral 2-(*o*-bromophenyl)perhydro-1,3-benzoxazines with an allylic moiety following an S_N2' reaction, affording the corresponding tetrahydroisoquinoline in enantiomerically pure form as a 75:25 mixture of diastereomers in 66% yield (Scheme 2.60).

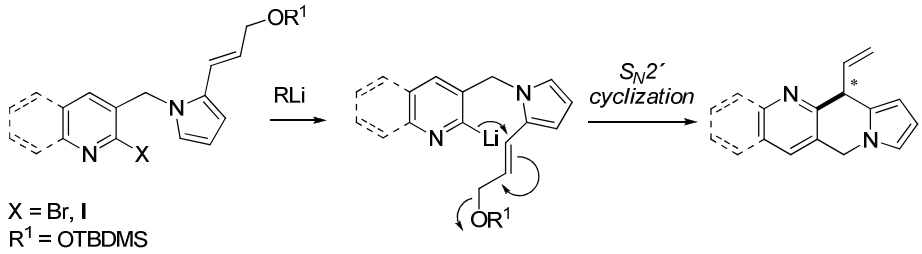
[69] Nishiyama, H.; Sugimoto, H.; Wakita, H.; Nagase, H. *Synlett* **1998**, 930.
[70] Nishiyama, H.; Sakata, N.; Motoyama, Y.; Wakita, H.; Nagase, H. *Synlett* **1997**, 1147.



Scheme 2.60

2.3.4.1. Intramolecular carbolithiation reaction of N-(o-halopyridinylmethyl) ***34a****,* ***34b*** *and N-(o-haloquinolinylmethyl)pyrrolyl allylic alcohol derivatives* ***35a****,* ***35b****.*

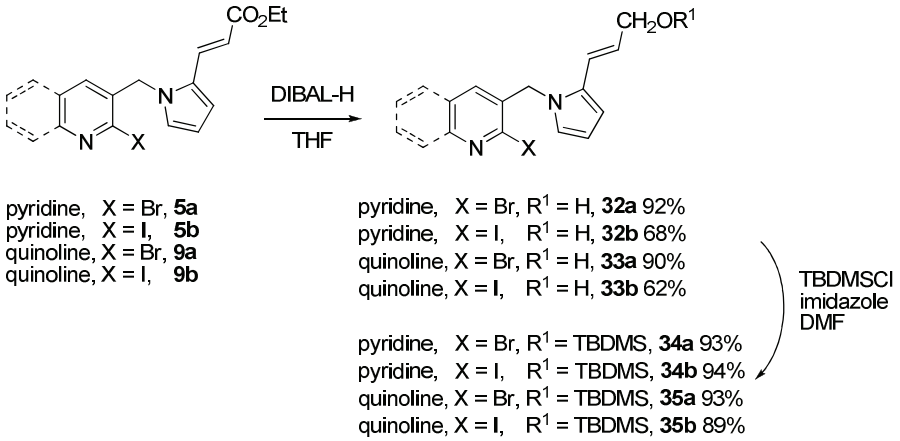
As previously stated, we first began to study the cyclization *via* S_N2' reaction of *N*-(*o*-halopyridinylmethyl) and *N*-(*o*-quinolinylmethyl)pyrrolyl allylic alcohol derivatives to afford (benzo)naphthyridine cores (Scheme 2.61).



Scheme 2.61

2.3.4.1.1. Synthesis of *o*-halopyridines **34a**, **34b** and *o*-haloquinolines **35a**, **35b**.

We performed the synthesis of *o*-halopyridines **34a**, **34b** and *o*-haloquinolines **35a**, **35b** by using a standard methodology. Firstly, previously synthesized pyridinyl **5a**, **5b** and quinolinylacrylates **9a**, **9b** were reduced with diisobutylaluminum hydride in THF[71] to the corresponding allylic alcohols giving pyridines **32a**, **32b** and quinolines **33a**, **33b**, respectively in excellent yields. The reduction step was followed by protection of the alcohol moiety as a silyloxy group (R^1 = TBDMS) by treatment with *t*-butyldimethylsilyl chloride and imidazole in DMF[72] to afford the corresponding silyl protected allylic alcohols **34a**, **34b**, **35a**, **35b**, as depicted in Scheme 2.62.

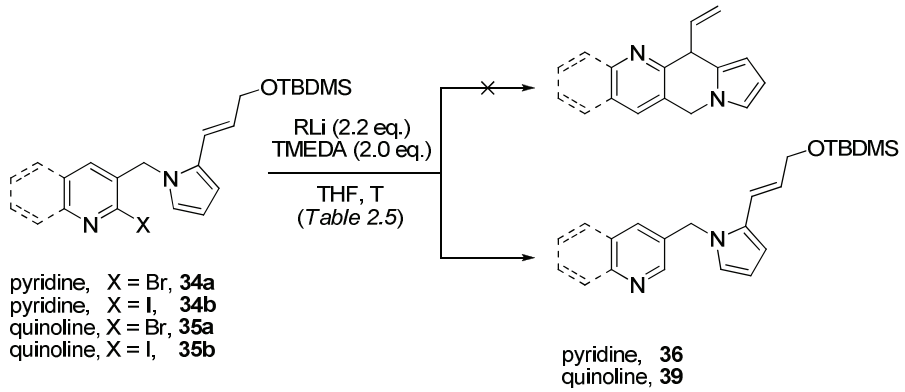


Scheme 2.62

[71] Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc*. **2006**, *128*, 1424.
[72] Gritsch, P. J.; Stempel, E.; Gaich, T. *Org. Lett*. **2013**, *15*, 5472.

2.3.4.1.2. Attemps of intramolecular carbolithiation of *o*-halopyridines **34a**, **34b** and *o*-haloquinolines **35a**, **35b** *via* S_N2'reaction.

The research started with the treatment of *o*-halopyridines **34a**, **34b** with *n*-BuLi in the presence of TMEDA as additive, in dry THF at -90 ºC (Scheme 2.63, Table 2.5, Entries 1-2). After 50 min, no cyclization was observed to occur, however products **36** and **37** (Figure 2.6), which come from dehalogenation of the heteroaromatic ring, were isolated. Treatment of *o*-halopyridines **34a**, **34b** with *t*-BuLi in the presence of TMEDA in dry THF at -78 ºC for 3 h and allowing the reaction mixture to reach room temperature for 2 h also led to the formation of dehalogenated products **36** (40-42%) and **38** (8-16%) (Figure 2.6), instead of the expected cyclization products (Entries 3-4). Therefore, although metalation took place, the subsequent cyclization failed.

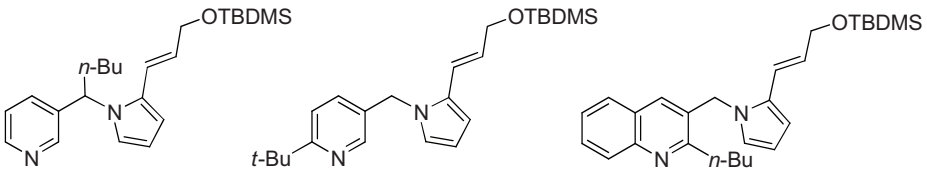


Scheme 2.63

*Table 2.5. Carbolithiation reactions of o-halopyridines **34a**, **34b** and o-haloquinolines **35a**, **35b**.*

Entry	Subs.	RLi (2.2 eq.)	T (ºC)	Time (min)	Product	Yield (%)
1	**34a**	*n*-BuLi	-90	50	**36**[a]	63
2	**34b**	*n*-BuLi	-90	50	**36**[b]	53
3	**34a**	*t*-BuLi	-78 → r.t.	3 h → 2 h	**36**[c]	40
4	**34b**	*t*-BuLi	-78 → r.t.	3 h → 2 h	**36**[d]	42
5	**35a**	*n*-BuLi	-90	50	**39**[e]	8
6	**35b**	*n*-BuLi	-90	50	**39**[f]	11
7	**35a**	*t*-BuLi	-78 → r.t.	3 h → 2 h	**39**	27
8	**35b**	*t*-BuLi	-78 → r.t.	3 h → 2 h	**39**	37

[a] Byproduct **37** (11%) was also obtained. [b] Byproduct **37** (22%) was also obtained. [c] Byproduct **38** (8%) was also obtained. [d] Byproduct **38** (16%) was also obtained. [e] Product **40** (21%) was also obtained. [f] Product **40** (40%) was also obtained.



37 **38** **40**

Figure 2.6

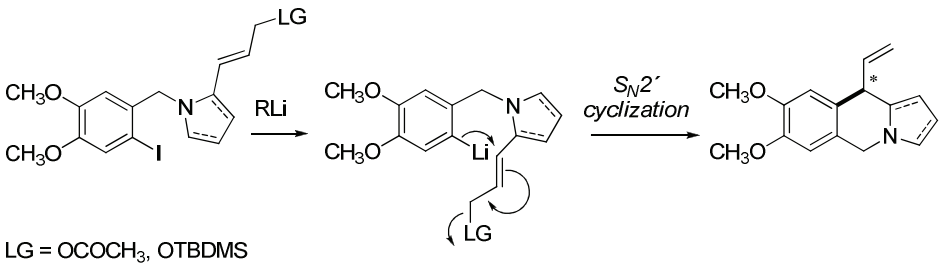
When *o*-haloquinolines **35a**, **35b** were treated under the same conditions, similar results were obtained, with no visible evidence for the desired S_N2' reaction (Scheme 2.63). Table 2.5 also shows the results obtained in the attempts of intramolecular carbolithiation of *o*-haloquinolines **35a**, **35b**. The use of *n*-BuLi and

TMEDA in THF at -90 ºC gave products **39** (8-11%) and **40** (21-40%) (Figure 2.6) (Entries 5-6). Using *t*-BuLi as metalating agent, the formation of dehalogenated product **39** was isolated (27-37%) (Entries 7-8).

In view of these results, we may conclude that in all cases the halogen-lithium exchange took place at low temperature, but the alkene moiety does not seem to be electrophilic enough to prompt the cyclization even when reaction was allowed to reach room temperature. Therefore, we were not able to achieve the cyclization *via* S_N2' reaction using heteroaryllithiums derived from electron-poor heterocycles.

*2.3.4.2. Intramolecular carbolithiation reaction of N-(o-iodobenzyl)pyrrolyl **44a**, **44b** and N-(o-iodobenzyl)pyrrolidinyl allylic alcohol derivatives **46**.*

In order to complete the investigations on the Parham cyclization *via* S_N2' reaction pathway, we chose electron-rich aryllithiums to promote ring-closure through S_N2' displacement (Scheme 2.64).

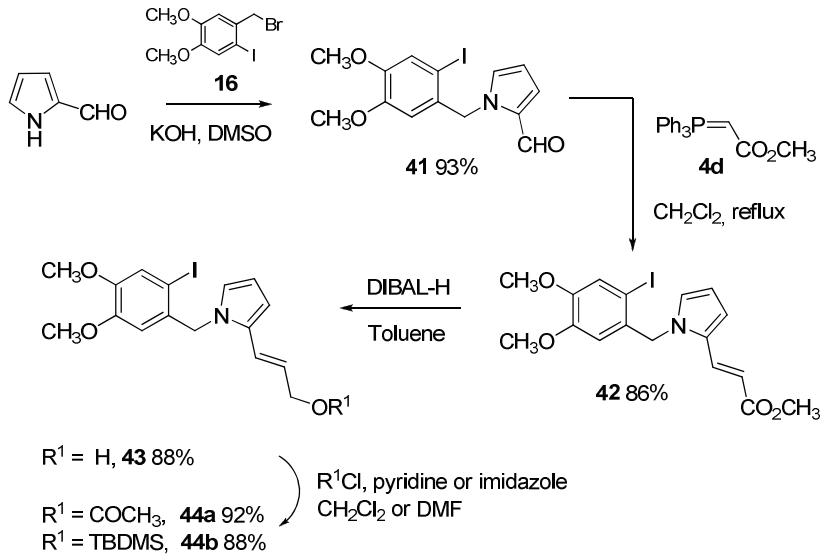


Scheme 2.64

2.3.4.2.1. Synthesis of *N*-(*o*-iodobenzyl)pyrroles **44a**, **44b** and pyrrolidine **46**.

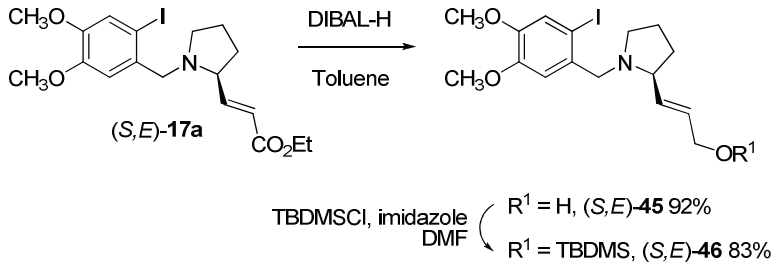
The synthetic route designed for *N*-(*o*-iodobenzyl)pyrroles **44a**, **44b**, illustrated in Scheme 2.65, is analogous to that one described for *o*-halopyridines **34a, 34b** and *o*-haloquinolines **35a, 35d**. The route began with the *N*-alkylation of pyrrole-2-carboxaldehyde with benzyl bromide **16**[51] to obtain *N*-benzylpyrrole **41** (93%). Wittig olefination of pyrrole **41** with ylidene **4d** provided acrylate **42** as a single diastereomer of (*E*)-configuration in a 86% yield. Reduction with DIBAL-H in dry toluene under inert atmosphere[71] afforded allylic alcohol **43** (88%). At this point, the introduction of different groups in the allylic alcohol was attempted, in order to synthesize allylic derivatives for the S_N2'reaction. All attempts to transform the allylic alcohol into a mesylate group (Scheme 2.64, LG = OMs: MsCl, Et_3N in CH_2Cl_2 at 0 ºC),[73] tosylate group (LG = OTs: *p*-TsCl, Et_3N in CH_2Cl_2 at 0 ºC), silane group (LG = $SiMe_3$: $(SiMe_3)_2$, $[Pd(BF_4)_2(CH_3CN)_4]$ as catalyst in MeOH/DMSO at 50 ºC),[74] bromide (LG = Br: PBr_3 in CH_2Cl_2 at r.t.), chloride (LG = Cl: $SOCl_2$, benzotriazole in CH_2Cl_2 at r.t.)[75] or carbonate group (LG = OCO_2CH_3: CH_3OCOCl, pyridine in CH_2Cl_2 at r.t.) failed, and complex mixtures of products were obtained in all cases. However, allylic alcohol **43** could be acylated and silylated[72] to obtain the acetoxy **44a** (92%) and silyloxy **44b** (88%) derivatives respectively, in excellent yields.

[73] Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062.
[74] Selander, N.; Paasch, J. R.; Szabó, K. J. *J. Am. Chem. Soc.* **2011**, *133*, 409.
[75] a) Bandgar, B.P.; Bettigeri, S. V. *Monatsh. Chem.* **2004**, *135*, 1251. b) Pavlakos, E.; Georgiou, T.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2009**, *11*, 4556.



Scheme 2.65

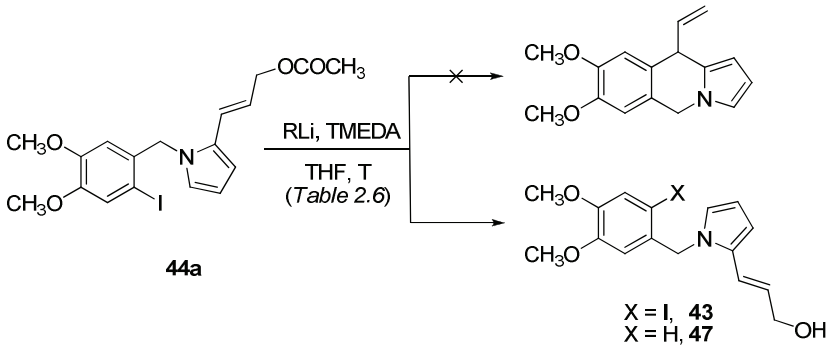
The synthesis of the enantiomerically pure *o*-iodobenzylpyrrolidine **46** could also be readily achieved by reduction[71] of previously prepared acrylate **17a** to provide the allylic alcohol (*S,E*)-**45** (92%), followed by silylation to the enantiopure sililoxymethyl derivative (*S,E*)-**46** in excellent yield (Scheme 2.66).



Scheme 2.66

2.3.4.2.2. Attempts of intramolecular carbolithiation of *N*-(*o*-iodobenzyl)pyrroles **44a**, **44b** and pyrrolidine **46** *via* S_N2' reaction.

In order to promote Parham cyclization of acetylated *N*-(*o*-iodobenzyl)pyrrole **44a**, we decided to use *t*-BuLi in the presence of TMEDA at -78 ºC for 3 h, quenching the reaction with saturated NH_4Cl solution at low temperature. Although no cyclization took place, allylic alcohols **47** (18%) and **43** (63%) were isolated (Scheme 2.67, Table 2.6, Entry 1). Under these conditions, the iodine-lithium exchange was not efficient, and competitive addition to the ester carbonyl ocurred. When the addition of the lithium reagent was performed at -78 ºC and the reaction was allowed to warm up to room temperature for 3 h (Entry 2), only deiodinated allylic alcohol **47** (48%) could be isolated from the reaction mixture. In this case, although I-Li exchange occurred more efficiently, cyclization was not observed. Increasing the reaction time to 16 h (Entry 3), **47** (33%) was also isolated, but in lower yield, probably due to decomposition in the reaction media.



Scheme 2.67

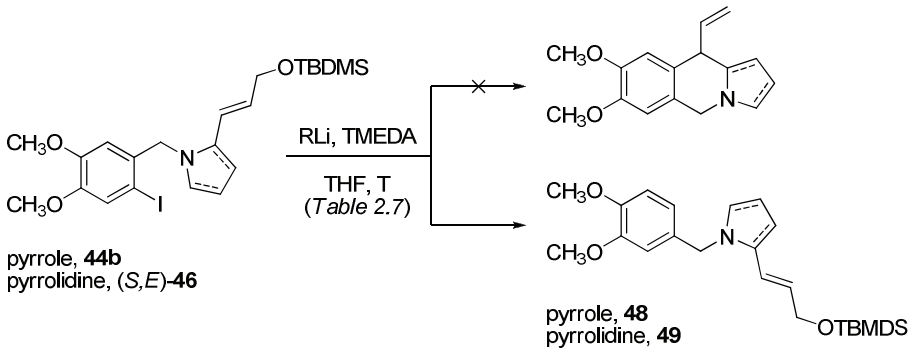
*Table 2.6. Carbolithiation reactions of N-(o-iodobenzyl)pyrrole **44a**.*

Entry	RLi	Additive	T (ºC)	Time (min)	Yield (%) 47
1	*t*-BuLi[a]	TMEDA[a]	-78	3 h	18[e]
2	*t*-BuLi[a]	TMEDA[a]	-78 → r.t.	10 → 3 h	48
3	*t*-BuLi[a]	TMEDA[a]	-78 → r.t.	10 → 16 h	33
4	MesLi[a]	-	-78	3 h	-
5	MesLi[a]	-	-78 → r.t.	10 → 3 h	16
6	*t*-BuLi[b]	-[c] [d]	-78	2 h	17[f]
7	*t*-BuLi[b]	-[c] [d]	-78 → r.t.	2 h → 2 h	7

[a] 2.0 eq. [b] 1.2 eq. [c] CuI (0.1 eq.) and PPh_3 (0.2 eq.) were also added. [d] The reaction was performed in dry CH_2Cl_2. [e] Iodinated allylic alcohol **43** (63%) was obtained as the major product. [f] Iodinated allylic alcohol **43** (5%) was also obtained.

We decided to change the metalating agent to MesLi, but cyclization also failed (Entries 4-5). The attempts to transmetallate the initially formed aryllithium to favor cyclization using *t*-BuLi, CuI and PPh_3 in CH_2Cl_2,[67c] only led to complex mixtures of products (Entries 6-7).

In view of these results, we decided to investigate the carbolithiation reaction of silyl protected allylic alcohols **44b** and (*S,E*)-**46**, in order to access pyrroloisoquinoline structural cores (Scheme 2.68). Treatment of **44b** and (*S,E*)-**46** with *n*-BuLi in the presence of TMEDA in dry THF at -90 ºC for 50 min, resulted in the formation of dehalogenated products **48** (69%) and **49** (100%), respectively (Table 2.7, Entries 1-2). The use of *t*-BuLi as metalating reagent led to similar results.



Scheme 2.68

*Table 2.7. Carbolithiation reactions of N-(o-iodobenzyl)pyrrole **44b** and pyrrolidine **46**.*

Entry	Subs.	RLi (2.2 eq.)	Additive (2.0 eq.)	T (ºC)	Time (min)	Prod.	Yield (%)[a]
1	**44b**	*n*-BuLi	TMEDA	-90	50	**48**	69
2	(*S,E*)-**46**	*n*-BuLi	TMEDA	-90	50	**49**	100
3	**44b**	*t*-BuLi	TMEDA	-90	50	**48**	64
4	**44b**	*t*-BuLi	-	-90	50	**48**	60
5	**44b**	*t*-BuLi	TMEDA	-90 → r.t.	10 → 5 h	**48**	27
6	**44b**	*t*-BuLi	TMEDA	-90 → r.t.	10 → 16 h	**48**	20
7	**44b**	*t*-BuLi	TMEDA	-78 → r.t.	3 h → 2 h	**48**	55
8	(*S,E*)-**46**	*t*-BuLi	TMEDA	-78 → r.t.	3 h → 2 h	**49**	82

[a] Isolated yield.

Thus, treatment of **44b** with *t*-BuLi in the presence of TMEDA resulted in the formation of **48** in a 64% yield (Entry 3). Same conditions conducted in absence of additive gave similar results (Entry 4). This fact indicates that metalation occurred effectively, but not the cyclization. Therefore, an increase of the temperature to 100

favor the carbolithiation *via* S_N2' reaction was tested. Addition of *t*-BuLi at -90 ºC, followed by 10 min of stirring and allowing to warm up to room temperature for longer periods of time, led to decomposition of the initially formed product **48** (20-27%) (Entries 5-6), but there was no evidence of cyclization. Additionally, addition of *t*-BuLi to substrate **44b** or (*S,E*)-**46** at -78 ºC followed by 3 h of stirring and warming up to room temperature for 2 h, afforded again dehalogenated products **48** (55%) and **49** (82%), respectively (Entries 7-8).

Finally, we can conclude that cyclization is not favored when TBDMS or acetyl protected allylic alcohols are used to promote 6-*exo* ring closure of the formed aryllithium through a S_N2' reaction. The use of protecting groups that could be unreactive under the reaction conditions and also offer a better leaving group ability, should be studied as an alternative. Work along these lines is in progress.

III

Intramolecular Mizoroki-Heck Reaction

*3.2.2.1. Intramolecular enantioselective Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrrole **59**. Generation of a quaternary stereocenter.*

*3.2.2.2. Intramolecular Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrroles **44b**, **44c**, o-halopyridines **34a**, **34b** and o-haloquinolines **35a**, **35b**. Generation of a tertiary stereocenter.*

3.2.3. Diastereoselective intramolecular Mizoroki-Heck reaction of *N-(o-*iodobenzyl)pyrrolidinyl allylic alcohol derivatives. Generation of a tertiary stereocenter

3.1. Introduction

Transition metal-catalyzed cross-coupling is nowadays recognized to be one of the most valuable carbon-carbon bond formation processes in organic synthesis.[1] In this context, palladium-mediated transformations[2] occupy an important position, due to their versatility to construct not only carbon-carbon bonds, but also carbon-oxygen, carbon-nitrogen and carbon-sulfur bonds.

Many benefits associated with palladium mediated reactions might be found, particularly the tolerance exhibited by palladium catalysts towards a wide range of functional groups, in this sense, avoiding protecting group chemistry. Additionally, palladium based methodologies generally proceed in excellent yields with a high stereo- and regioselectivity, by the use of catalytic amounts of metal and relatively mild conditions.

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[1] Beller, M.; Bolm, C. Eds. *Transition Metals for Organic Synthesi*s, Wiley-VCH: Weinheim, 2nd Ed, **2004**. b) Diederich, F.; de Meijere, A. Eds. *Metal-Catalyzed Cross-Coupling Reactions,* Wiley-VCH: Weinheim, 2nd Ed, **2004**. c) Schlosser, M. Ed. *Organometallics in Synthesis. Third Manual*, Wiley & Sons: New York, **2013**. d) Meijere, A.; Bräse, S.; Oestreich, M. Eds. *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH: Weinheim, **2014**. e) Lipshutz, B.H. Ed. *Organometallics in Synthesis. Fourth Manual*, Wiley & Sons: New York, **2014**.

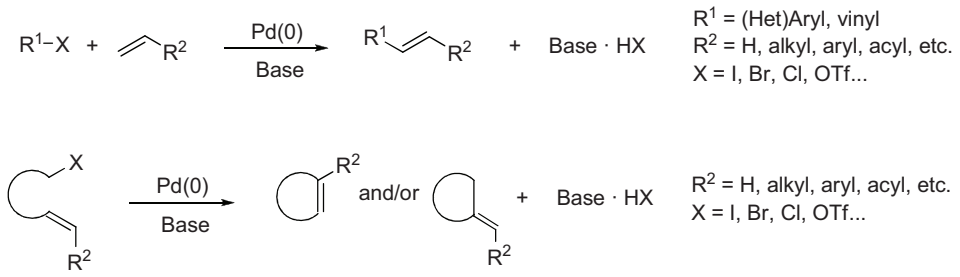
[2] For selected books and reviews, see: a) Tsuji, J. *Palladium Reagents and Catalyst: Innovations in Organic Chemistry*, Wiley & Sons: New York, **1995**. b) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis,* Wiley & Sons: New York, **2002**, Vol. 1 and 2. c) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, Wiley & Sons: New York, **2003**. d) *Palladium in Organic Synthesis*, Tsuji, J. Ed., Springer: Berlin, **2005**. e) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev*. **2006**, *106*, 4622. f) Lindhart, A.T.; Skrydstrup, T. *Chem. Eur. J.* **2008**, *14*, 8756. g) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9047. h) Bolm, C. *J. Org. Chem.* **2012**, *77*, 5221. i) Bräse, E. In *Organometallics in Synthesis. Third Manual*, Schlosser, M. Ed., Wiley & Sons: New York, **2013**, p. 777.

Together with a wide number of well-established palladium-based transformations such as Suzuki-Miyaura,[3] Sonogashira,[4] Stille,[5] Negishi[6] or Kumada[7] reactions, the Mizoroki-Heck[8] reaction has emerged over the last decades as an extremely powerful and useful tool for the preparation of highly functionalized olefins, dienes or other unsaturated compounds. Besides, this reaction is also known to be useful in polymerization chemistry.

The Mizoroki-Heck reaction has been developed significantly from its original concept as the arylation of olefins with aryl mercury compounds.[9] The discovery that aryl mercury compounds could be substituted by aryl iodides, without affecting the oxidation state of the palladium and thus, permiting the use of catalytic amounts in the absence of reoxidants, was independently discovered by Mizoroki[10] and Heck[11] more than 40 years ago.

[3] a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett*. **1979**, *20*, 3437. b) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun*. **1979**, 866.
[4] a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467. b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.
[5] a) Mistein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. b) Mistein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.
[6] a) Negishi, E.; Baba, S. *J. Chem. Soc., Chem. Commun*. **1976**, 596. b) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729.
[7] a) Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, *20*, 1871. b) Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett*. **1980**, *21*, 845.
[8] For selected reviews, see: a) Heck, R. F. *Org. React.* **1982**, *27*, 345. b) Heck, R. F. In *Comprehensive Organic Synthesis*, *Vol. 4,* Trost, B. M.; Fleming, I. Eds., Pergamon Press: Oxford, **1991**, p. 833. c) Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 2379. d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000**, *100*, 3009. e) Hegedus, L. S. In *Organometallics in Synthesis: A Manual*, Schlosser. M. Ed., Wiley-VCH: Chichester, 2nd Ed, **2002**, p. 1123. f) Oestreich, M. Ed. *The Mizoroki-Heck Reaction*, Wiley-VCH: Chichester, **2009**. g) Larhed, M. Ed. *Science of Synthesis. Cross-Coupling and Heck-type reactions, Vol. 3,* Thieme: Stuttgart, **2013.**
[9] a) Heck, R. F. *J. Am. Chem. Soc*. **1968**, *90*, 5531. b) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5535. c) Heck, R. F. *J. Am. Chem. Soc.* **1971**, *93*, 6896.
[10] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
[11] Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

The Mizoroki-Heck reaction can be defined as the Pd(0) mediated cross-coupling reaction of (hetero)aryl and vinyl halides or triflates with alkenes, in both an intermolecular or intramolecular fashion (Scheme 3.1). As stated before, the versatility of this reaction is supported by its great tolerance to different functional groups. Although the use of different types of olefins is possible, it is specially favored with electron-deficient alkenes.



Scheme 3.1

In its intramolecular version, this palladium-catalyzed reaction has been recognized as a simple and useful tool for regio- and stereoselective syntheses of carbo-[12] and heterocyclic[13] compounds. Besides, it has also been widely used in the multi-step syntheses of natural products. Further improvement has been found in the

[12] Machotta, A.; Oestreich, M. In *The Mizoroki-Heck Reaction*, Oestreich, M. Ed., Wiley & Sons: Münster, **2009**, p. 179.

[13] For selected reviews on the application of the Mizoroki-Heck reaction on the synthesis of heterocycles, see: a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. b) Li, J. J.; Gribble, G. W. Eds. *Palladium in Heterocyclic Chemistry,* Elsevier: Amsterdam, **2007**. c) Muller, T.; Bräse, S. In *The Mizoroki-Heck Reaction*, Oestreich M. Ed., Wiley-VCH: Chichester, **2009**, p. 215. d) Majumdar, K. C.; Samanta, S.; Sinha, B. *Synthesis* **2012**, *44*, 817.

development of multiple palladium catalyzed transformations, which are performed in a domino fashion.[14]

A wide variety of different palladium complexes may be used as catalysts in Mizoroki-Heck reaction. Apart from those sources that directly provide Pd(0) in the media, such as $Pd(PPh_3)_4$, $Pd(dba)_2$ and $Pd_2(dba)_3$, other sources of Pd(II) are also used, such as $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$, etc., precatalysts that require a reduction step *in situ* to afford Pd(0) as the active species. The use of ligand free Mizoroki-Heck reactions is interesting from an economical and environmental point of view. However, palladium-stabilizing ligands are often required, which afford reactivity and selectivity to the reaction. The most common ligands used are phosphanes, which are known to keep the catalyst stable at a (0) oxidation state, by forming species like PdL_4 or PdL_2. In addition, other nitrogen, arsine, sulfur or carbene derived ligands have also been developed.

Since the original work of Mizoroki[10] and Heck,[11] many modifications have been proposed in order to improve the selectivity and regioselectivity of the reaction. Among these improvements, the use of tetraalkylammonium salts in the catalytic system (Jeffery protocol),[15] and addition of either silver[16] or thallium[17] salts could be included.

[14] a) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res*. **2005**, *38*, 413. b) Ackermann, L.; Althammer, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1627.
[15] Jeffery, T. *Tetrahedron* **1996**, *52*, 10113 and references cited therein.
[16] Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem*. **1985**, *50*, 3896.
[17] Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett*. **1991**, *32*, 687.

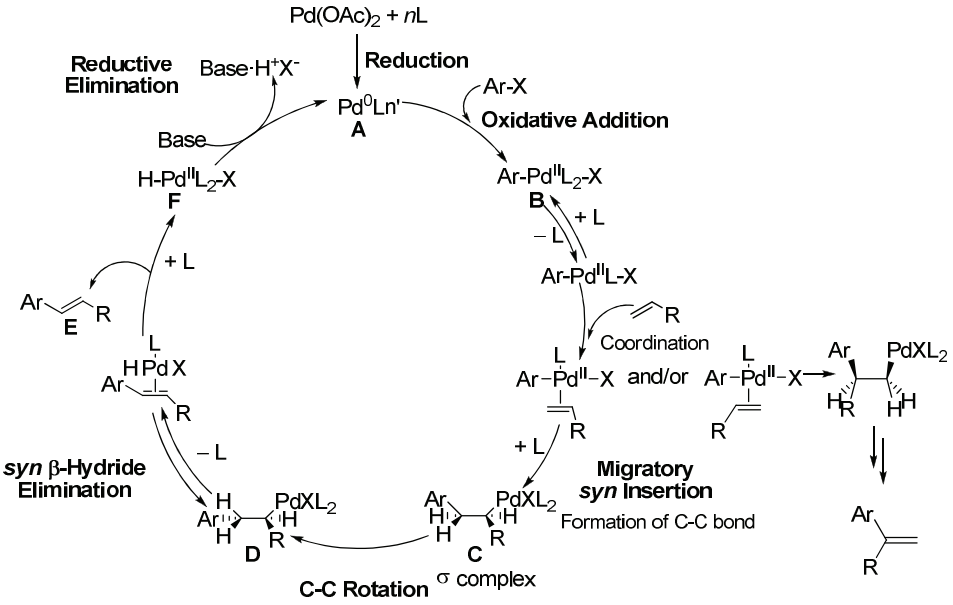
A wide range of solvents can be used in Mizoroki-Heck rections, and elevated temperatures are frequently necessary. Non-protic polar solvents such as DMF, DMA, DMSO, etc. are usually employed. Both organic (trialkylamines) and inorganic bases (NaOAc, $NaHCO_3$, etc.) are required for the regeneration of active palladium(0), although the last ones demand polar solvents to achieve homogeneity in the media.

3.1.1. Mechanistic considerations and competition between Mizoroki-Heck and direct arylation reactions

The mechanism of Mizoroki-Heck reaction has been deeply studied[18] and all current evidence points to be based on a palladium(0/II) cycle. The most widely accepted mechanism was described by Dieck and Heck[19] in 1974, which is illustrated in Scheme 3.2 for the coupling of aryl halides or triflates (Ar-X) with alkenes, using $Pd(OAc)_2$ as precatalyst in combination with monodentate phosphane ligands.

Firstly, the *in situ* generation of the active Pd(0) species is required by reduction of the Pd(II) precursor through an exchange equilibrium of multiple ligands. Once the Pd(0) complex (**A**) is formed, the catalytic cycle starts with the oxidative addition to an aryl halide or triflate (Ar-X) to generate the σ-arylpalladium(II) complex (**B**) which contains 16 electrons.

[18] For reviews on the mechanism of Mizoroki-Heck reaction, see: a) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007***, 5*, 31. b) Jutand, A. In *The Mizoroki-Heck reaction*, Oestreich, M. Ed., Wiley: Chinchester, **2009**, p. 1, and references therein.
[19] Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc*. **1974**, *96*, 1133.



Scheme 3.2

Subsequently, this complex **B**, after dissociation of one phosphane ligand, coordinates to an alkene. Then, migratory *syn* insertion to the double bond generates the σ-(β-aryl)alkylpalladium(II) complex (**C**). The former step can also be termed as a *carbopalladation* process, since a Pd-C and a C-C bonds are formed and is known to be the origin of the regioselectivity in most Mizoroki-Heck reactions. Indeed, two isomeric intermediates might be generated in an α or β arylation of the alkene, to result in branched or linear products respectively.

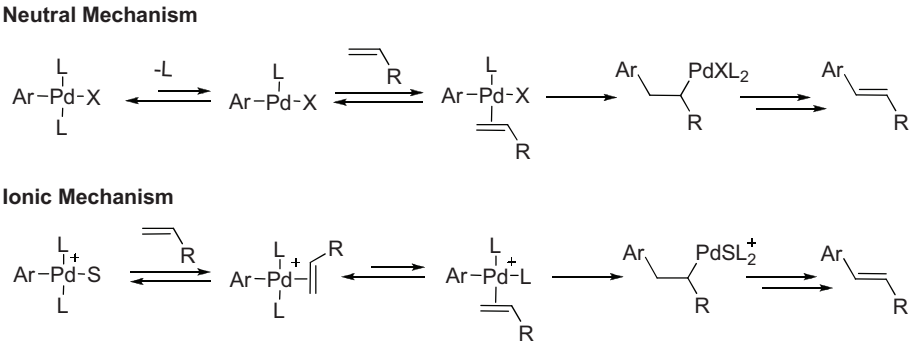
Continuing with the cycle, the intermediate **C** is prone to suffer a C-C bond rotation to give an intermediate **D**, which presents the required *syn* relationship between the β-hydrogen and palladium atom in order to promote the β-elimination. Since the β-hydrogen and the transition metal are located in the same plane, *syn* β-

hydride elimination takes place providing the cross-coupling product (**E**) and a hydropalladium(II) halide complex (**F**). To finish, a reductive elimination of the intermediate **F** takes place to generate the Pd(0) active catalyst, which can enter the catalytic cycle again, associated with the release of HX neutralized by the base present in the media.

As shown, the Heck-type reactivity depends on the ability of Pd(0) species to undergo oxidative addition to C-X bonds of aryl halides and the subsequent addition of thus formed Ar-Pd-X intermediates to unsaturated bonds. Under the same experimental conditions, the reactivity order for aryl halides and triflates in Mizoroki-Heck reactions is: Ar-I >> Ar-OTf > Ar-Br >> Ar-Cl,[20] suggesting that the oxidative addition step is rate determining for the less reactive aryl halides. On the contrary, for the more reactive ones it is thought that the complexation/insertion process to the alkene would be the limiting one.

To account for differences in the regioselectivity derived from the *syn* insertion of the Ar-Pd(II)-X complex to the alkene, two different mechanistic pathways have been proposed, termed as "cationic" and "neutral" depending on the formal charge on the first-formed palladium(II)-alkene complex generated (Scheme 3.3). In the neutral mechanism (non polar route), a neutral palladium species is formed by dissociation of one ligand, while in cationic mechanism (polar route) a loss of the X group leads in the formation of a cationic palladium species which undergoes *syn* addition.

[20] Jutand, A.; Negri, S.; de Vries, J. G. *Eur. J. Inorg. Chem*. **2002**, 1711.



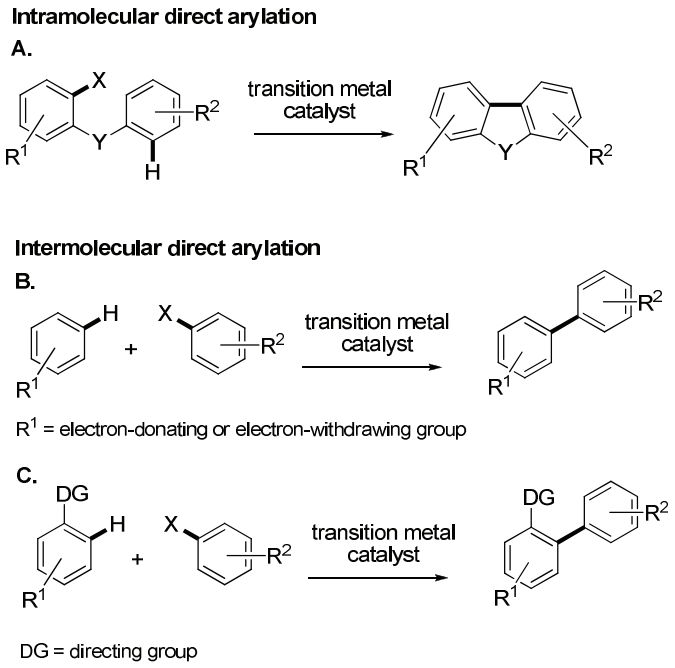
Scheme 3.3

The vinylation of aryl halides promoted by the use of $Pd(PPh_3)_4$ as catalyst, is known to follow a classical "neutral" pathway.[21] However, when $Pd(OAc)_2$ is used in combination with monodentate phosphane ligands $n$$PPh_3$ (n>2), the reaction follows a "cationic" pathway, being ionic species $[ArPd(PPh_3)_2]^+$ favored in polar aprotic solvents and at high temperatures.[22]

Both mechanisms could take place when monodentate phosphanes are employed, while the use of bidentate species, such as dppp, promote the formation of electrophilic palladium(II) species, which follows a polar route due to steric reasons.[23]

[21] a) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009. b) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818. c) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605. d) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 25. e) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.
[22] Amatore, C.; Carré, E.; Jutand, A. *Acta. Chem. Scand*. **1998**, *52*, 100.
[23] Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465.

Analogous electrophilic palladium(II) species have been considered as intermediates in the direct arylation reaction *via* C-H bond cleavage of aromatic and heteroaromatic rings with aryl halides in the presence of palladium catalysts.[24] This direct arylation reaction can take place both in an intermolecular or intramolecular fashion as represented in Scheme 3.4.

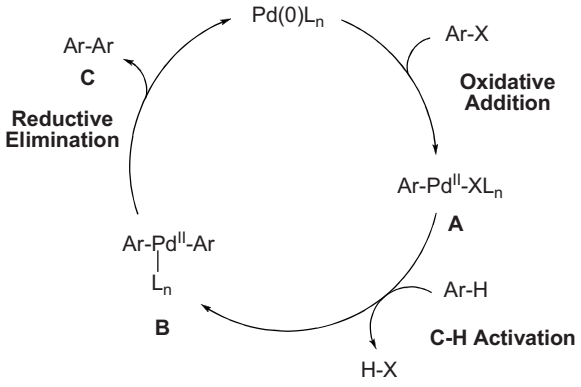


Scheme 3.4

[24] For selected reviews, see: a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev*. **2007**, *107*, 174. b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev*. **2007**, *36*, 1773. c) Miura, M.; Satoh, T. In *Modern Arylation Methods*, Ackermann, L. Ed.; Wiley-VCH: Weinheim, **2009**, p. 335. d) Catellani, M.; Motti, E.; Della Ca, N. *Acc. Chem. Res*. **2008**, *41*, 1512. e) McGlacken, G. P.; Bateman, L. M.; *Chem. Soc. Rev*. **2009**, *38*, 2447. f) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed*. **2009**, *48*, 9742. g) Livendahl, M.; Echavarren, A. M. *Isr. J. Chem*. **2010**, *50*, 360. h) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem.* **2010**, *2*, 20. i) Su, Y.-X.; Sun, L.-P. *Mini-Rev. Org. Chem*. **2012**, *9*, 87. j) Sharma, A.; Vacchani, D.; Van der Eycken, E. *Chem. Eur. J*. **2013**, *19*, 1158.

For intramolecular direct arylation, a higher control of the regioselectivity is possible, since restraints are present to limit the degree of freedom in the system (Scheme 3.4A). On the other hand, in the intermolecular reaction, the existence of a greater degree of freedom difficults the control of regioselectivity. Therefore, the arene should be substituted by groups that influence the stereoelectronics in the ring (Scheme 3.4B) or, more commonly, directing groups are used to direct the arylation to a specific position, generally *ortho* to the directing group (Scheme 3.4C).

The direct arylation of aryl halides with arenes, in an intermolecular fashion, follows the catalytic cycle represented in Scheme 3.5. First, similarly to the Heck-reaction previously discussed, the oxidative addition of Pd(0) species to the aryl halide takes place generating the Ar-Pd(II)-X complex (**A)**. Subsequently, C-H bond activation of an arene occurs, forming the Ar-Pd(II)-Ar complex (**B)** with the release of HX. To conclude, reductive elimination in the intermediate **B** affords the coupled biaryl compound (**C**) by generation of a C-C bond and Pd(0) catalyst, ready to enter the cycle again.



Scheme 3.5

Different mechanisms for the C-H activation step with the electrophilic Ar-Pd(II)-X species, formed after oxidative addition, have been described (Scheme 3.6). In an initial approach, the mechanism was proposed to follow a S_EAr pathway,[25] which would proceed like a Friedel-Crafts type reaction, followed by a rearomatization step to form the diarylpalladium(II) intermediate (path a). On the other hand, the fact that the reactivity has been shown to depend on the acidity of the C-H bond, [26] not on the (hetero)arene nucleophilicity, led to the proposal of the C-H bond functionalization step *via* a concerted metalation-deprotonation process (CMD),[27] which is also supported by theoretical calculations (path b).[28] In this mechanistic hypothesis, $Pd(OAc)_2$ is generally the transition metal precatalyst, and a carboxylate (or carbonate) anion plays a fundamental role in the C-H cleavage,[29]

[25] a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 467. b) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett*. **2003**, *5*, 301. c) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett*. **2003**, *5*, 4835. d) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett*. **2004**, *6*, 1159. e) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. f) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem*. **2008**, *73*, 5529.

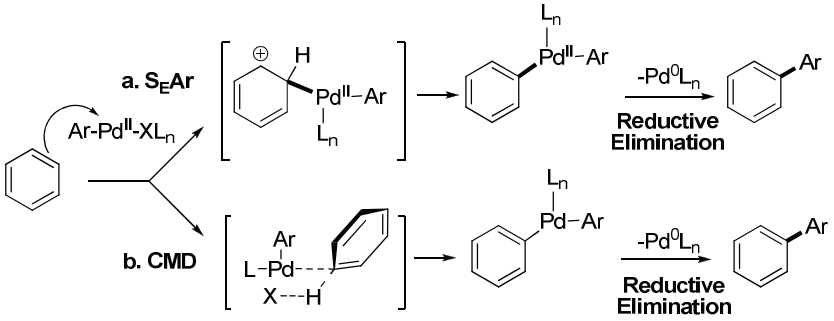
[26] Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc*. **2006**, *128*, 8754.

[27] For selected examples of direct arylation where a CMD pathway has been proposed, see: a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754. b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc*. **2006**, *128*, 16496. c) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. d) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. e) Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021. f) Gorelsky, S.I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. g) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. h) Guihaume, J.; Clot, E.; Einstein, O.; Perutz, R. N. *Dalton Trans.* **2010**, *39*, 10510. i) Liégault, B.; Petrov, I.; Gorelsky, S.I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047. j) Rene, O.; Fagnou, K. *Adv. Synth. Catal.* **2010**, *352*, 2116. k) Lapointe, D.; Markiewicz, T., Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, *76*, 749. l) Carrer, A.; Rousselle, P.; Florent, J.-C.; Bertounesque, E. *Adv. Synth. Catal.* **2012**, *354*, 2751. m) Gorelsky, S.I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658. n) Gorelsky, S.I. *Organometallics* **2012**, *31*, 4631. o) Korenaga, T.; Suzuki, N.; Sueda, M.; Shimada, K. *J. Organomet. Chem.* **2015**, *780*, 63.

[28] Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem*. **2007**, *5*, 2727.

[29] For evidence for the critical role of the base, see, for example: a) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180. b) Si Larbi, K.; Fu, H. Y.; Laidaoui, N.; Beydoun, K.; Miloudi, A.; El Abed, D.; Djabbar, S.; Doucet, H. *ChemCatChem* **2012**, *4*, 815.

which occurs in the rate determining step of this model simultaneously with carbon-palladium bond formation. In the CMD mechanism, the choice of an appropriate base represents an important element of catalyst design, so the influence of the anionic base and its counter cation on the outcome of the direct arylation should be taken into account.[30] Thus, CMD and nCMD (non-concerted metalation–deprotonation) mechanisms have been identified in the base-assisted, Pd-catalyzed direct arylation of oxazoles and thiole-4-carboxylates with aryl halides. Modulation of intrinsic basicity (K^+ *vs*. Cs^+) and ligand electronic effects were shown to be important for controlling the subtle CMD/nCMD competition.[31]



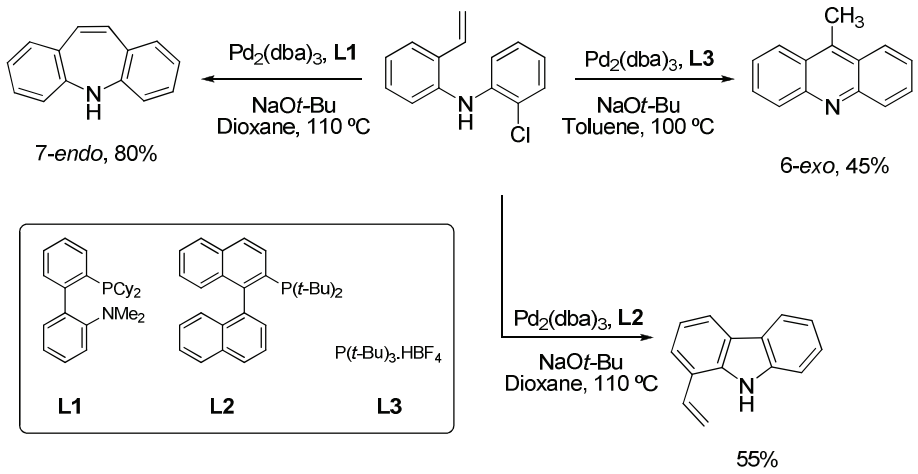
Scheme 3.6

Since Mizoroki-Heck and direct arylation share common conditions, a competition between both palladium-catalyzed reactions may occur when using suitable

[30] a) de Mendoza, P.; Echavarren, A. M. In *Modern Arylation Methods*, Ackermann, L. Ed., Wiley-VCH: Weinheim, **2009**, p. 363. b) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1119. c) Fagnou, K. *Top. Curr. Chem*. **2010**, *292*, 35. d) Verrier, C.; Lassalas, P.; Theveau, L.; Queguiner, G.; Trecourt, F.; Marsais, F.; Hoarau, C. *Beilstein J. Org. Chem.* **2011**, *7*, 1584. e) Ackermann, L. *Chem. Rev*. **2011**, *111*, 1315. f) Gorelsky, S. I. *Coord. Chem. Rev.* **2013**, *257*, 153. g) Wakioka, M.; Nakamura, Y.; Hihara, Y.; Ozawa, F.; Sakaki, S. *Organometallics* **2013**, 32, 4423.

[31] a) Theveau, L.; Verrier, C.; Lassalas, P.; Martin, T.; Dupas, G.; Querolle, O.; Van Hijfte, L.; Marsais, F.; Hoarau, C. *Chem. Eur. J.* **2011**, *17*, 14450. b) Theveau, L.; Querolle, O.; Dupas, G.; Hoarau, C. *Tetrahedron* **2013**, *69*, 4375.

substrates. Buchwald and coworkers[32] have been able to obtain carbazoles, acridines and dibenzazepines from a common precursor, such as 2-chloro-*N*-(2-vinyl)aniline. The selectivity could be controlled by phosphane ligands and the reaction could be directed either to the Heck reaction (6-*exo* or 7-*endo* cyclization) or to a direct arylation process (Scheme 3.7). Although a complete selectivity was initially reported in the study,[32a] further research provided evidence of byproducts derived from other competing reactions.[32b]

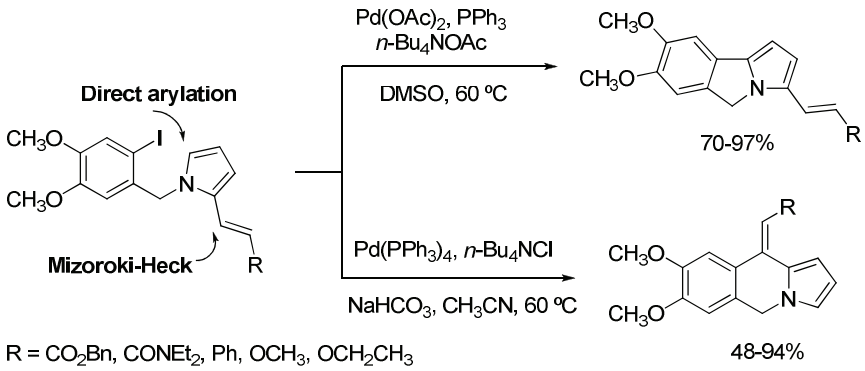


Scheme 3.7

In this context, our group has reported the selective synthesis of pyrrolo[1,2-*b*]isoquinolines and pyrrolo[2,1-*a*]isoindoles in excellent yields by adequately controlling the cyclization to the alkene moiety (Mizoroki-Heck) or pyrrole nucleus (direct arylation) respectively, changing the catalytic system.[33] In this way, when conditions that favor the formation of cationic Pd(II) intermediates or a CMD

[32] a) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14048. b) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc*. **2012**, *134*, 16917 (Erratum the previous document).
[33] Lage, S.; Martínez-Estíbalez, U.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2009**, *351*, 2460.

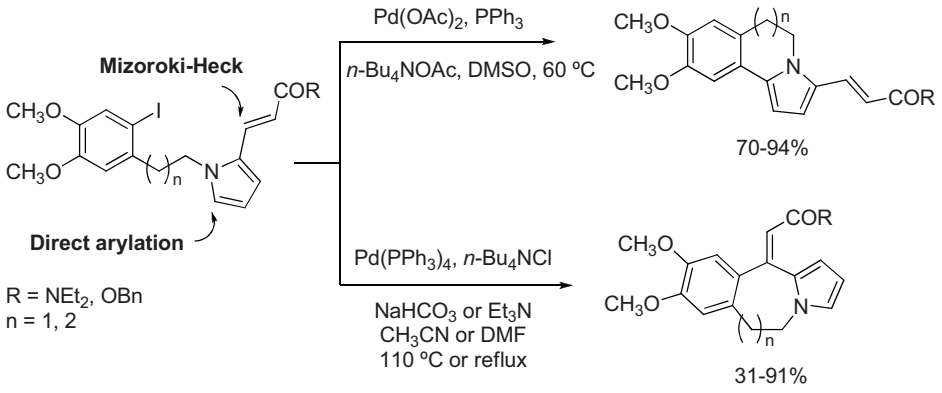
mechanism are used, such as $Pd(OAc)_2$, PPh_3, *n*-Bu_4NOAc in DMSO, C-2 direct arylation products were obtained with complete chemoselectivity. On the other hand, under conditions that favor the neutral pathway for the Heck reaction, such as $Pd(PPh_3)_4$, *n*-Bu_4NCl, $NaHCO_3$ in acetonitrile, pyrrolo[1,2-*b*]isoquinolines were obtained (Scheme 3.8). The substitution in the alkene moiety did not affect the course of the reactions.



Scheme 3.8

This protocol can be also applied for the selective synthesis of medium sized rings.[34] Thus, an access to pyrroloisoquinoline, pyrroloazepine, pyrroloazocine systems has been achieved by adequately choosing reaction conditions (Scheme 3.9).

[34] Coya, E.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal*. **2014**, *356*, 1853.



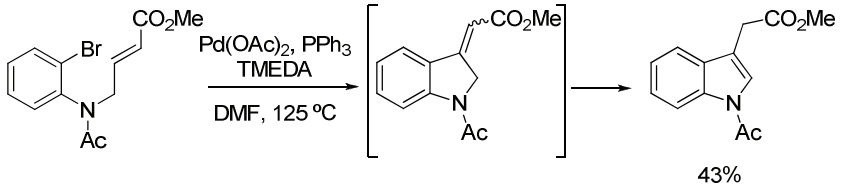
Scheme 3.9

3.1.2. Synthetic applications of the intramolecular Mizoroki-Heck reaction

As we have mentioned before, the intramolecular Mizoroki-Heck reaction has proved to be a powerful and useful tool for the synthesis of carbocycles and heterocycles.[13] Some representative examples of the application of the intramolecular Heck reaction of aryl and heteroaryl halides with alkenes for the synthesis of nitrogen heterocycles, related to this work, will be discussed below.

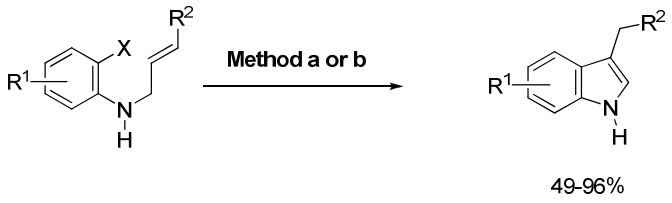
The first attempt to synthesize a nitrogen heterocycle through Mizoroki-Heck cyclization was published in 1977 by Mori and coworkers.[35] An indole nucleus was readily prepared by treatment of an aryl bromide bearing an electron-deficient olefin using $Pd(OAc)_2$ and PPh_3 in the presence of TMEDA. The cyclization took place in a 5-*exo* fashion, and after isomerization, led to the indole derivative (Scheme 3.10).

[35] Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, *18*, 1037.



Scheme 3.10

Similar results were obtained by Hegedus and coworkers,[36] who reported the synthesis of substituted indoles starting from unactivated 2-halo-*N*-allylanilines (Scheme 3.11, Method a). In this case, the presence of an electron-withdrawing group in the olefin moiety was not required to perform the intramolecular Mizoroki-Heck reaction. Kasahara *et al*.[37] broadened the scope to different substitution patterns both in the aryl ring and the alkene to generate substituted indoles in high yields (Scheme 3.11, Method b).



Method a: (Ref. 36)
$Pd(OAc)_2$, Et_3N, CH_3CN, 110 ºC, 72 h

X = I
R^1 = Me, OMe, OEt, Cy
R^2 = H

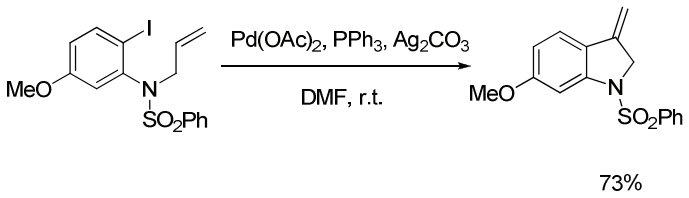
Method b: (Ref. 37)
$Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, CH_3CN, 100 ºC, 20 h

X = Br
R^1 = H, 6-OMe, 4-CO_2Me, 5-CO_2Me, 6-CO_2Me,
R^2 = COMe, CO_2Et

Scheme 3.11

[36] Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709.
[37] Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 927.

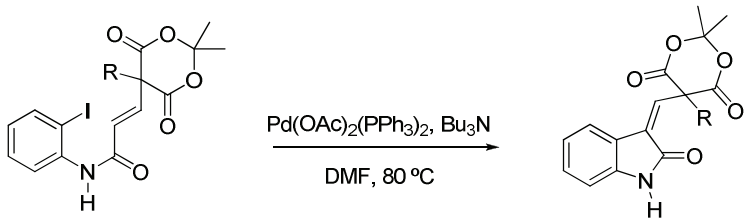
The isomerization of the initially formed *exo* double bond is known to take place by reinsertion of the hydropalladium species generated after β-elimination, which could follow a second elimination process. This fact can be prevented by employing specific reaction conditions. In this way, Yamanaka and coworkers[38] described the selective synthesis of a 3-methyleneindole derivative in the presence of silver carbonate, which neutralized the H-Pd(II)-X species (Scheme 3.12).



Scheme 3.12

This reaction has also been applied to the synthesis of highly functionalized heterocycles. For instance, Cacchi *et al.*[39] performed the synthesis of 3-alkylidene oxindoles through 5-*exo* Heck reaction of 5-alkyl-5-[2-(*o*-iodophenylcarbamoyl)vinyl] derivatives of Meldrum´s acid using palladium-based catalytic system (Scheme 3.13). In all cases a *Z* double bond is formed, even when sterically demanding groups, such as isopropyl units, were located in the adjacent quaternary carbon.

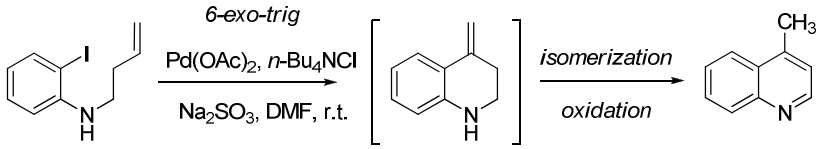
[38] Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc. Perkin Trans.* **1993**, *1*, 1941.
[39] Arcadi, A.; Cacchi, S.; Marinelli, F.; Pace, P. *Synlett* **1993**, 743.



Scheme 3.13

Intramolecular Mizoroki-Heck reaction has also been widely applied to the synthesis of six-membered rings. In this context, formation of quinoline derivatives through 6-*exo-trig* processes has been described, although, as reported for five-membered heterocycles, in some cases isomerization and oxidation reactions may happen.

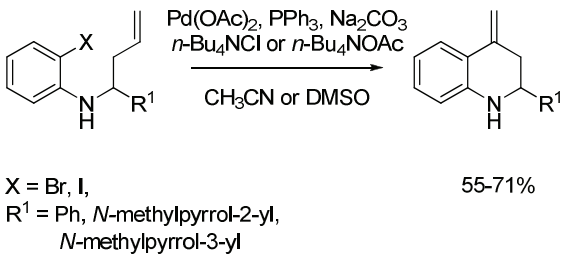
Thus, Larock and Babu[40] reported the synthesis of 4-methylquinoline *via* 6-*exo* ring-closure through formation of a methylenetetrahydroquinoline intermediate, followed by double bond migration and oxidation to the more stable quinoline (Scheme 3.14).



Scheme 3.14

[40] Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291.

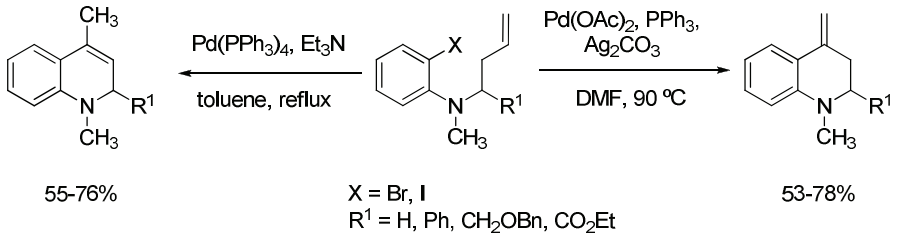
In this context, our group has developed a methodology for the regioselective synthesis of 4-alkylidenetetrahydroquinoline derivatives from *N*-alkenyl-substituted secondary 2-haloanilines, avoiding isomerization and oxidation of the tetrahydroquinoline to the quinoline derivative.[41] The treatment of *N*-butenylanilines with an aryl or heteroaryl group in α to the nitrogen atom, under Pd-catalyzed reaction conditions, resulted in the generation of the 4-methylenetetrahydroquinolines in moderate to good yields *via* 6-*exo* cyclization (Scheme 3.15).



Scheme 3.15

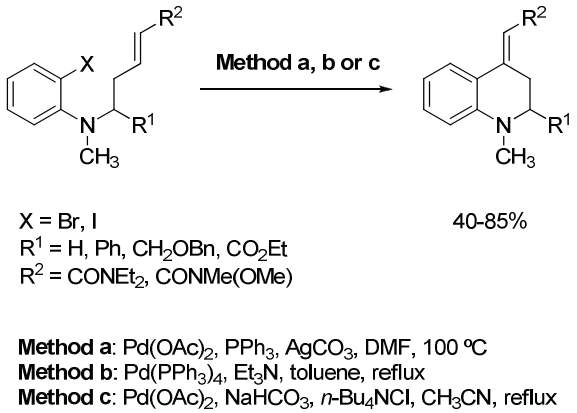
Starting from tertiary anilines with a non-activated olefin as precursors, the regioselectivity of the reaction could be controlled by the use of specific catalytic systems, which permitted or avoided isomerization after cyclization in an *exo* manner.[41] In this sense, the presence of a silver salt promoted the 6-*exo* ring closure to 2-substituted 4-methylenetetrahydroquinolines, while the use of $Pd(PPh_3)_4/Et_3N$ as catalytic system afforded 2,4-disubstituted 1,2-dihydroquinolines in good yields (Scheme 3.16).

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



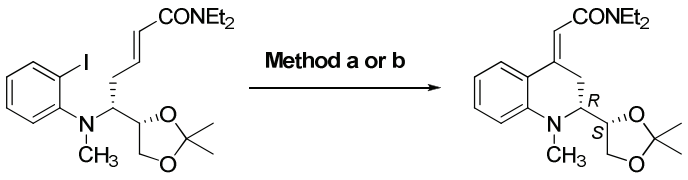
Scheme 3.16

When the alkene was substituted with an electron-withdrawing group (amide), no isomerization processes were observed under different catalytic conditions, always obtaining alkylidenetetrahydroquinolines as single (*E*)-isomers (Scheme 3.17).[41]



Scheme 3.17

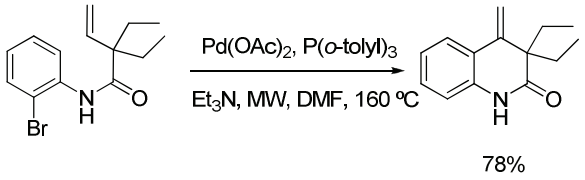
Moreover, the same reaction conditions could be applied to the synthesis of enantiopure tetrahydroquinolines, starting from chiral non-racemic anilines derived from D-glyceraldehyde. In this case, the reaction proceeded with no racemization (Scheme 3.18).[41]



Method a: $Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF, 100 ºC 68-72%
Method b: $Pd(PPh_3)_4$, Et_3N, toluene, reflux

Scheme 3.18

Smalley and Mills[42] similarly reported the 6-*exo* Heck cyclization of a bromophenyl butenamide in the presence of $Pd(OAc)_2$ under microwave irradiation, affording the 4-methylenedihydroquinolone depicted in Scheme 3.19. In this case, no isomerization pathway was possible, as there was no possibility of hydrogen removal in α carbon atom to the *exo*-double bond.



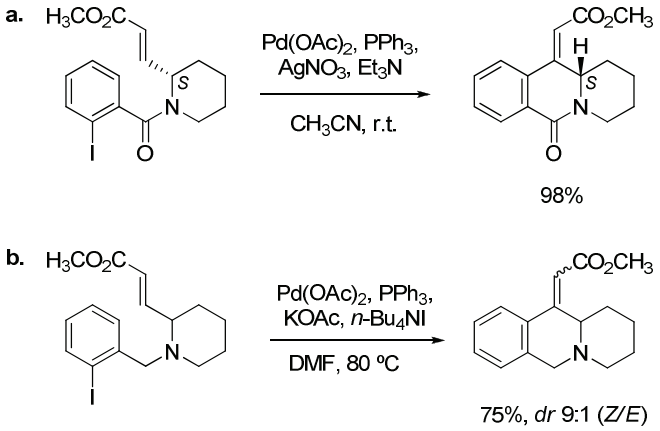
78%

Scheme 3.19

For related substrates, Herradón and coworkers[43] showed that the stereochemistry of the new exocyclic double bond formed may depend on the substrate and the reaction conditions. In this way, they reported that treatment of methyl (*E*)-3-[1-(2-iodobenzoyl)piperidin-2-yl]acrylate with $Pd(OAc)_2$ in the presence of silver salts, led to pyrido[1,2-*b*]isoquinoline as a single (*Z*)-stereoisomer *via* a 6-*exo* cyclization

[42] Smalley, T. L. Jr.; Mills, W. Y. *Heterocycl. Chem.* **2005**, *42*, 327.
[43] Sánchez-Sancho, F.; Mann, E.; Herradón, B. *Adv. Synth. Catal.* **2001**, *343*, 360.

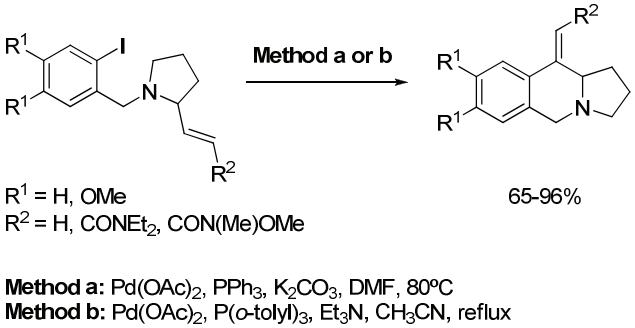
(Scheme 3.20a). On the other hand, the reaction of the *N*-benzyl analogue under Jeffery´s conditions,[15] resulted in a 9:1 mixture of *Z/E* isomers, while no reaction was observed under formerly described conditions (Scheme 3.20b). No isomerization or oxidation processes were observed in any case.



Scheme 3.20

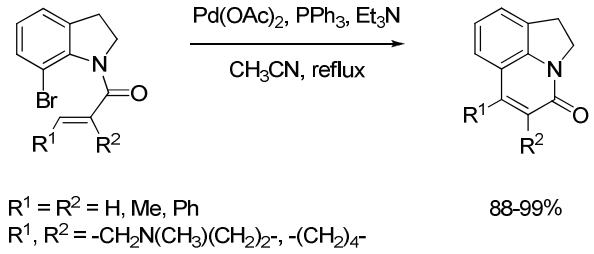
Similarly, we have reported the regioselective intramolecular 6-*exo* cyclization of *N*-(*o*-iodobenzyl)pyrrolidines for the generation of hexahydropyrrolo[1,2-*b*]-isoquinolines in good yields, always as single diastereomers. Different experimental conditions should be used when the alkene moiety was unactivated[44] (Scheme 3.21, Method a) or substituted with an electron-withdrawing carbamoyl group[45] (Scheme 3.21, Method b).

[44] García-Calvo, O.; Sotomayor, N.; Lete, E.; Coldham, I. *Arkivoc* **2011** (v), 57.
[45] García-Calvo, O. Ph.D Thesis, University of the Basque Country, **2011**.



Scheme 3.21

As has been shown, 6-*exo* cyclizations are much more common than 6-*endo* processes. However, in some cases 6-*endo* cyclizations are also viable, although 5-*exo* cyclization may also be a competitive pathway. Thus, Dankwardt *et al.*[46] reported the regioselective Heck cyclization reaction of differently substituted *N*-acryloyl-7-bromoindolines *via* a 6-*endo-trig* ring-closure (Scheme 3.22).



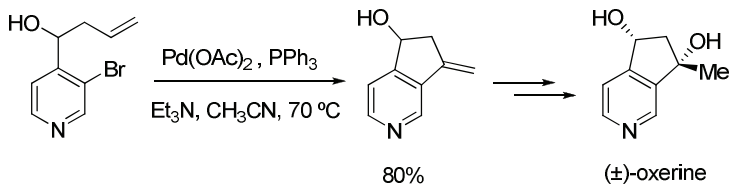
Scheme 3.22

All the examples that have been highlighted previously involve the intramolecular Heck reaction of aryl halides. Some selected examples for the generation of five

[46] Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem.* **1995**, *60*, 2312.

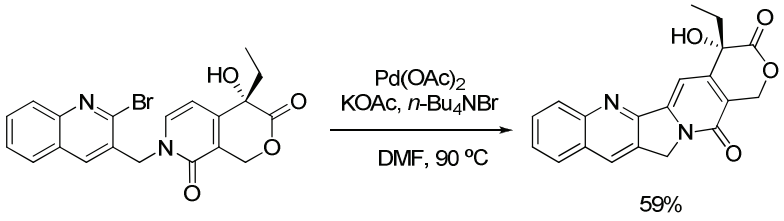
and six-membered rings, using heteroaryl halides will be discussed, although these are less common.

In this context, nitrogen containing heteroaryl halides, such as pyridinyl and quinolinyl halides, have been used. In this sense, Zhai and coworkers[47] reported the synthesis of the cyclopenta[*c*]pyridine core, by 5-*exo* Heck cyclization of 1-(3-bromopyridin-4-yl)but-3-en-1-ol, which had been used as intermediate to obtain (±)-oxerine alkaloid (Scheme 3.23).



Scheme 3.23

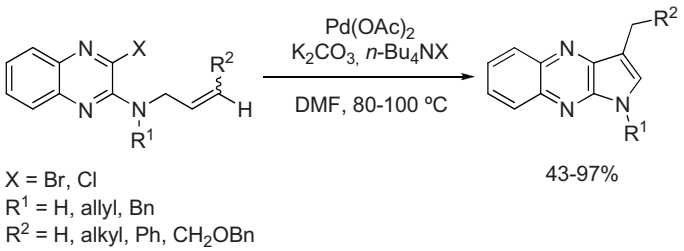
Similarly, Comins *et al*.[48] reported the synthesis of (*S*)-camptothecin alkaloid that is known to be a natural anticancer agent, by intramolecular 5-*exo* Heck reaction using a quinolinyl bromide as coupling partner (Scheme 3.24).



Scheme 3.24

[47] Zhao, J.; Yang, X.; Jia, X.; Luo, S.; Zhai, H. *Tetrahedron* **2003**, *59*. 9379.
[48] Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971.

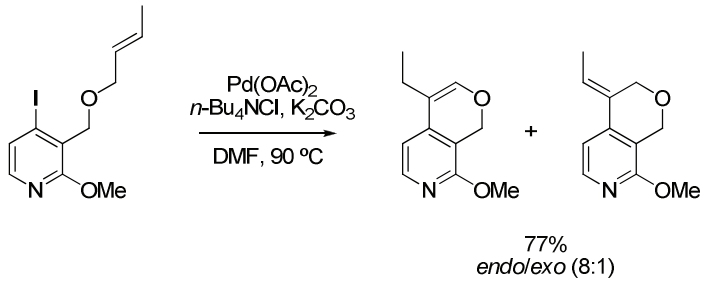
An efficient strategy to synthesize 3-substituted pyrrolo[2,3-*b*]quinoxalines from allyl (3-haloquinoxalin-2-yl)amines has been published by Li[49] under Jeffery's "ligand-free" conditions (Scheme 3.25). In this case, a 5-*exo* cyclization took place, following an isomerization process, as previously seen in the indole nucleus synthesis. However, when the method was applied to substrates containing electron-withdrawing groups on the benzene ring of the quinoxaline unit, low yields (26-32%) were obtained.



Scheme 3.25

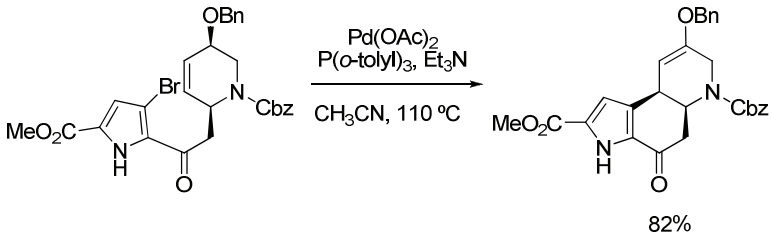
4-Iodopyridine derivatives have also been used in the synthesis of six-membered rings. In this way, Fang *et al*.[50] reported the synthesis of a bicyclic ether as a 8:1 mixture of *endo:exo(Z)* regioisomers by treatment of the corresponding crotyl ether under Jeffery´s conditions. This reaction undergoes a 6-*exo* Mizoroki-Heck cyclization to afford firstly the allylic ether (*exo*-regioisomer), which is followed by partial olefin isomerization to give enol ether (*endo*-regioisomer) as major product (Scheme 3.26).

[49] Li, J. J. *J. Org. Chem*. **1999**, *64,* 8425.
[50] Fang, F. G.; Xie, S.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142.



Scheme 3.26

On the other hand, electron-rich heteroaromatics have also been used. Natsume and coworkers[51] described ring closure of a pyrrolyl bromide with a cyclic olefin to provide a tricyclic derivative, which was used as intermediate in the 12-step total synthesis of (±)-duocarmycin SA (Scheme 3.27).

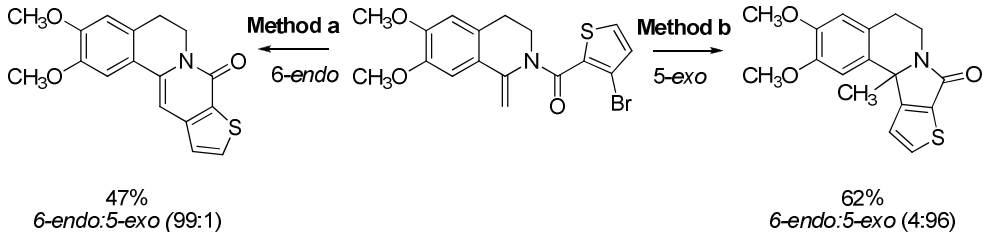


Scheme 3.27

Sageot and Bombrun[52] have studied the competition between 6-*endo* and 5-*exo* cyclization by using thiophenyl bromides. They have been able to control the regioselectivity of the Mizoroki-Heck reaction by adequately changing experimental conditions (Scheme 3.28). Thus, under classical conditions, 6-*endo*

[51] Muratake, H.; Abe, I.; Natsume, M. *Tetrahedron Lett.* **1994**, *35*, 2573.
[52] Bombrun, A.; Sageot, O. *Tetrahedron Lett.* **1997**, *38*, 1057.

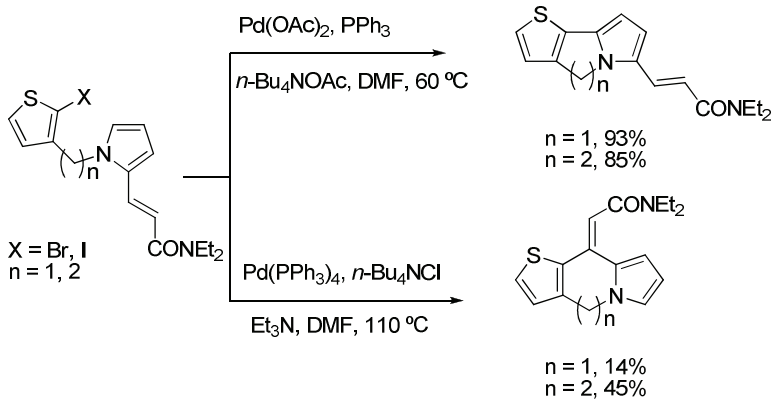
cyclization took place selectively (Method a), while in the presence of a hydride source as HCO_2Na (Method b), the 5-*exo* cyclization product could be obtained, generating a quaternary stereocenter.



Method a: $Pd(OAc)_2$, PPh_3, Na_2CO_3, CH_3CN, Et_4NCl
Method b: $Pd(OAc)_2$, PPh_3, HCO_2Na, CH_3CN, Et_4NCl

Scheme 3.28

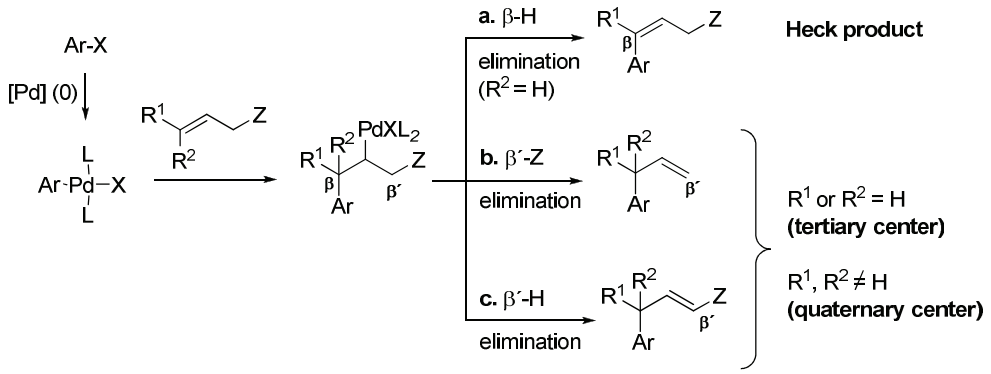
Moreover, our group has investigated the competition between Mizoroki-Heck and direct arylation reactions on electron-rich heteroaryl halides, such as thiophenyl halides, for the synthesis of (hetero)fused indolizine and pyrrolizine cores (Scheme 3.29).[34] In this case, direct arylation is the main pathway, obtaining thienopyrrolizines (n = 1) and thienoindolizines (n = 2), under conditions which favored a cationic or a CMD mechanism. However, when using conditions to favor neutral mechanism, it has not been possible to achieve intramolecular Mizoroki-Heck reaction, obtaining also direct arylation products, thus thienoindolizine (n = 1) and benzazepine (n = 2) derivatives were obtained in low yields. In general, higher catalyst loadings and longer reaction times were required to perform direct arylation reactions on thiophenyl halides compared to the reactions of aryl halides.



Scheme 3.29

3.1.3. Generation of tertiary and quaternary centers

In the Mizoroki-Heck reactions discussed in the previous section, the formation of a sp^2 hybridized carbon center is promoted by the *syn* β-elimination of a hydride in the carbon atom directly involved in the new carbon-carbon bond formation (Scheme 3.30a). Nevertheless, it is also possible to generate tertiary and quaternary centers through the Mizoroki-Heck reaction. For that purpose, it is necessary to avoid the *syn* β-hydride elimination in the *σ*-alkylpalladium intermediate formed after the insertion of the arylpalladium to the alkene, so that the elimination takes place in another β′ position and not on the carbon directly involved in bond formation. Scheme 3.30 shows three possible pathways in an intermolecular Heck reaction, with additional placement of a heteroatom (Z group) in an allylic position of the olefin.



Scheme 3.30

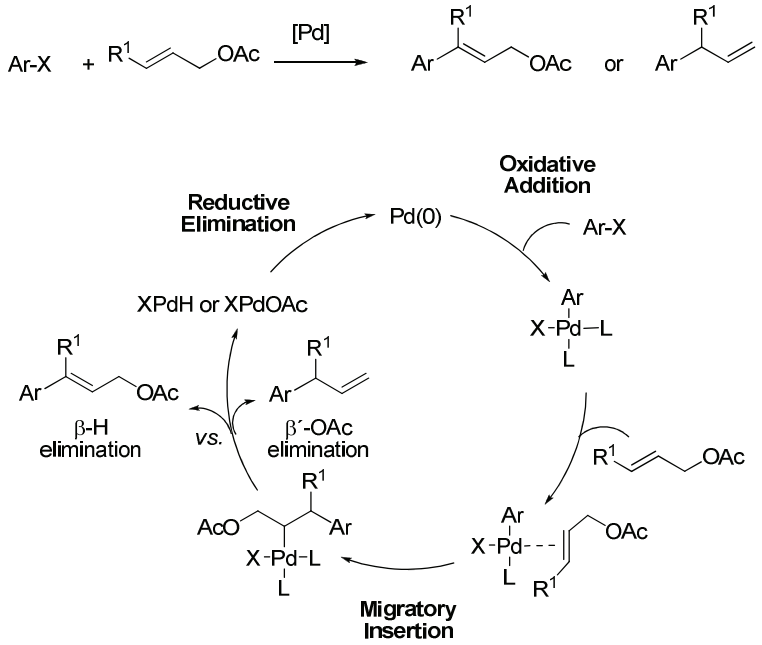
Different strategies have been used to direct elimination to β´ position. The first implies the introduction of a good leaving group (Z = acetate, silane…) in the allylic position of the olefin in order to promote the elimination of this leaving group (Scheme 3.30b). On the contrary, when protected (Z = $OSiR_3$…) or unprotected allylic alcohols (Z = OH) are used, the formation of the corresponding enol ether or enol, which would tautomerize in the former case to an aldehyde or a ketone,[53] may act as thermodynamic driving force in favor of β´-hydride elimination (Scheme 3.30c). These strategies can be applied to the formation of both tertiary centers (R^1 or R^2 = H) and quaternary centers. In the latter case, the olefin should be blocked with substituents (R^1, $R^2 \neq$ H), in order to prevent from β-hydride elimination.

Some examples of these strategies are shown below.

[53] a) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265. b) Jeffery, T. *Tetrahedron Lett.* **1990**, *31*, 6641. c) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121. d) Zhao, H.; Cai, M.-Z.; Hu, R.-H.; Song, C.-S. *Synth. Commun.* **2001**, *31*, 3665. e) Calò, V.; Nacci, A.; Monopoli, A.; Ferola, V. *J. Org. Chem.* **2007**, *72*, 2596.

3.1.3.1. Generation of tertiary centers

As we have pointed above, a common strategy for generation of tertiary centers involves the use of allylic esters as coupling partners, directing the elimination to an alternative β´ position. When palladium-catalyzed coupling of aryl halides with allylic esters is performed, the reaction could be regioselectively driven to the usual β-hydride elimination process (Heck product) or to β´-acetoxy elimination pathway[54] (Scheme 3.31).



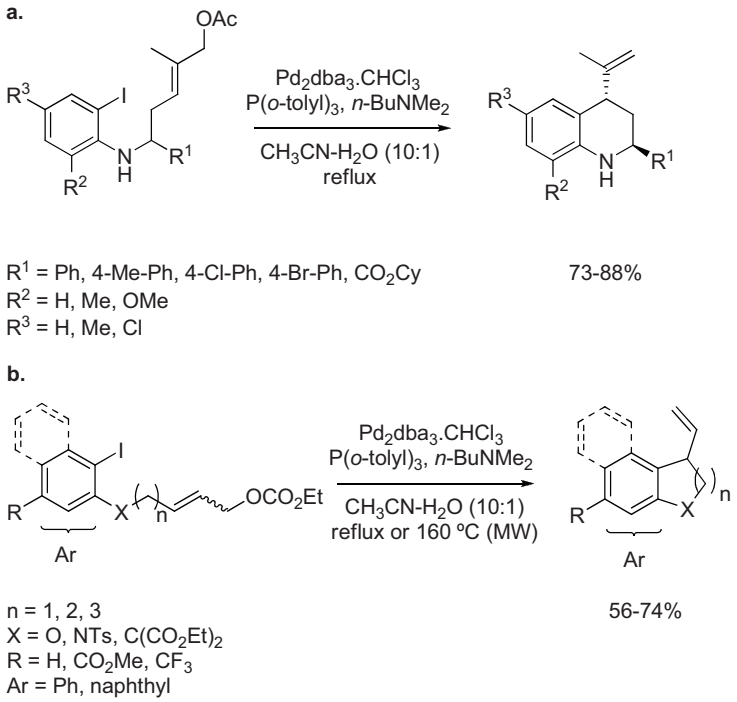
Scheme 3.31

[54] Pan, D.; Jiao, N. *Synlett* **2010**, 1577.

In the literature, there are some examples of intermolecular Mizoroki-Heck reaction that take place regioselectively by β´-elimination of different leaving groups, such as acetate or carbonate groups,[55] silane[56] or halide[57] moieties. However, there are very few examples described for the use of this strategy in an intramolecular fashion.[58] Some selected examples involving coupling of aryl halides with allylic derivatives, related to our work, will be discussed.

Lautens and coworkers[59] showed that is possible to generate tertiary stereocenters by palladium-catalyzed cyclization of *o*-iodoanilines with an allyl ester or carbonate moiety, using thermal and microwave-assisted conditions. Thus, a new synthetic approach to a variety of *trans*-2,4-disubstituted 1,2,3,4-tetrahydroquinolines, with excellent diastereoselectivity, was developed by preferential elimination of β´-acetoxy over β-hydride (Scheme 3.32a). For this purpose, the combination of $Pd_2(dba)_3.CHCl_3$ or $Pd(OAc)_2$ with bulky phosphane ligands as P(*o*-tolyl)$_3$ gave similar results as complex $PdCl_2[P(o\text{-tolyl})_3]_2$, always in the presence of *n*-$BuNMe_2$ as base. Furthermore, the presence of H_2O in the solvent was necessary to reach full conversion and avoid generation of Pd-black. The reaction was extended to the synthesis of five- to seven-membered carbo- and heterocycles with the same catalytic system [$Pd_2(dba)_3.CHCl_3$, P(*o*-tolyl)$_3$ and *n*-$BuNMe_2$ as base] by β´-carbonate elimination (Scheme 3.32b).

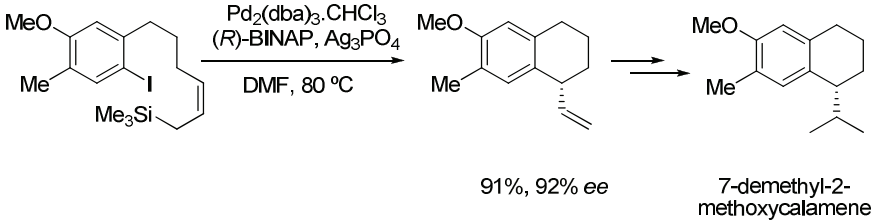
[55] a) Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745. b) Liu, Y.; Yao, B.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G.; Ling, J.-H. *Org. Lett.* **2011**, *13*, 1126.
[56] Jeffery, T.; *Tetrahedron Lett.* **2000**, *41*, 8445.
[57] Wang, J.; Cui, Z.; Zhang, Y.; Li, H.; Wu, L.-M.; Liu, Z. *Org. Biomol. Chem* **2011**, *9*, 663.
[58] Steinig, A. G.; de Meijere, A. *Eur. J. Org. Chem*. **1999**, 1333.
[59] Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc*. **2005**, *127*, 72.



Scheme 3.32

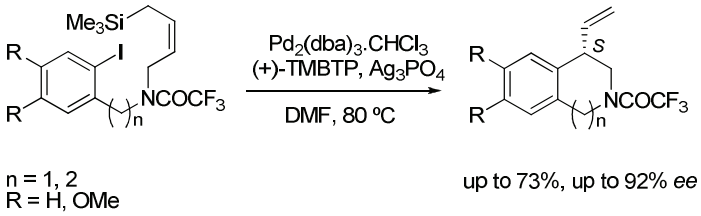
Tietze and coworkers[60] demonstrated that regioselective β´-leaving group elimination may be possible for aryl halides that contain (*Z*)-allyl silanes in the side chain. Furthermore, the reaction could be carried out in an enantioselective fashion, when a chiral bidentated ligand as (*R*)-BINAP was used. In this example, a highly regio- and enantioselective intramolecular Heck reaction takes place through elimination of the silane group allowing the generation of a tertiary stereocenter of a vinyltetralin, which could be used as a precursor in the synthesis of norsesquiterpene 7-demethyl-2-methoxycalamene[60c] (Scheme 3.33).

[60] a) Tietze, L. F.; Schimpf, R. *Angew. Chem. Int. Ed.* **1994**, *33*, 1089. b) Tietze, L. F.; Raschke, T. *Synlett* **1995**, 597. c) Tietze, L. F; Raschke, T. *Liebigs Ann. Chem*. **1996**, 1981.



Scheme 3.33

The same group[61] described an extension of this methodology to other (*Z*)-allyl silane derivatives with different substitution patterns in the phenyl ring, to synthesize tetrahydroisoquinolines and benzazepines in high enantioselectivities, in the presence of (+)-TMBTP as chiral ligand (Scheme 3.34).

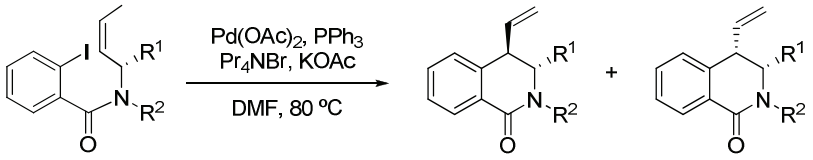


Scheme 3.34

Additionally, a tertiary center can also be formed through regioselective β′-hydride elimination, even if a hydride in β-position is available. Tietze *et al*. have reported an efficient approach to achieve the highly diastereoselective synthesis of 4-vinyl-substituted 3,4-dihydroisoquinolin-1(2*H*)-ones, in favor of the *trans*-diastereomer, through Heck cyclization of *N*-allyl-2-iodobenzamides *via* regioselective β′-hydride elimination (Scheme 3.35).[62] In addition, the diastereoselectivity of the

[61] Tietze, L. F.; Thede, K.; Schimpf, R.; Sannicolò, F. *Chem. Commun*. **2000**, 583.
[62] Tietze, L. F.; Burkhardt, O. *Liebigs Ann.* **1995**, 1153.

reaction improved, with the size of the substituents located at the stereogenic centre.



R^1 = Me, Et, *i*-Pr, Bn; R^2 = Boc
R^1, R^2 = -$(CH_2)_3$-

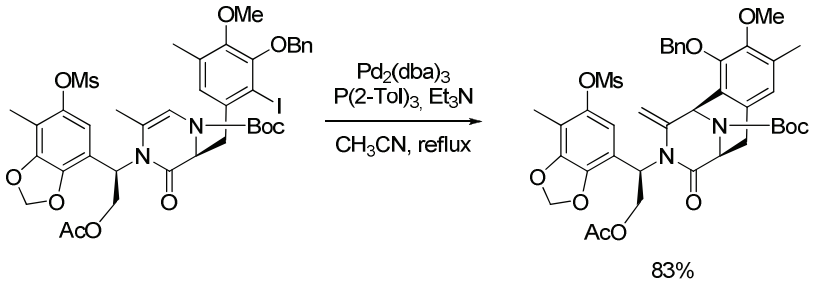
up to 82%, up to *dr* 30:1

Scheme 3.35

In this case, the reason to explain the hydride elimination in the β′-position may be that the σ-alkylpalladium intermediate, formed after the insertion into the alkene, would not require the rotation needed for *syn* β-elimination, so it would be kinetically favored.

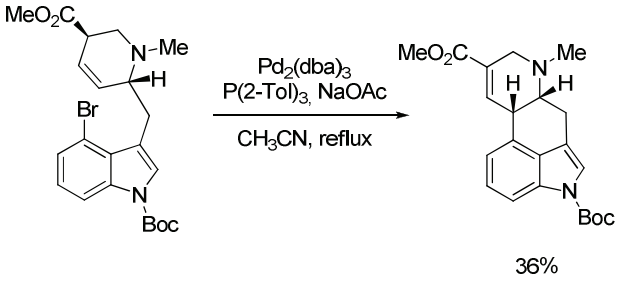
A different approach implies the use of cyclic alkenes so that, after migratory insertion, the β-hydrogen is always *anti* to palladium with any possibility of rotation restricted, so the β′-elimination is always favored. Thus, Fukuyama and coworkers[63] reported the synthesis of the tricyclic core of ecteinascidin 743 through intramolecular Mizoroki-Heck reaction (Scheme 3.36).

[63] Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552.



Scheme 3.36

The same group[64] has recently developed the synthesis of lysergic acid, involving as a key step the Heck cyclization of a 3-substituted 4-bromoindole that resulted in the formation of the tetracyclic ergoline nucleus. The formation of a six-membered carbocycle is achieved by β´-hydride elimination generating a tertiary stereocenter (Scheme 3.37).



Scheme 3.37

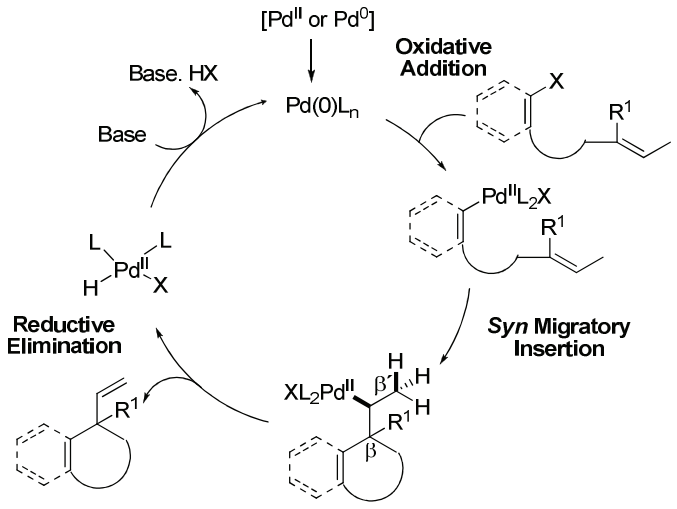
[64] Inoue, T.; Yokoshima, S.; Fukuyama, T. *Heterocycles* **2009**, *79*, 373.

3.1.3.2. Generation of quaternary centers

As stated previously, the introduction of substituents in the carbon atom of the olefin that suffers directly the coupling drives the elimination to a contiguous β´-position to form a quaternary center. However, the generation of quaternary centers is less common than tertiary centers, because it requires the use of tri- or tetrasubstituted olefins where steric hindrances could affect their reactivity.

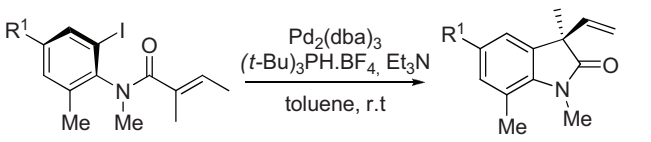
The following Scheme 3.38 shows the mechanism of the intramolecular Mizoroki-Heck reaction for aryl or alkenyl halides with blocked olefins ($R^1 \neq H$), known to proceed *via* classical neutral manifold.[65] The cycle starts with the formation of the catalytic Pd(0) species, which suffers oxidative addition of the aryl or alkenyl halide to generate a Pd(II) intermediate. Coordination and *syn* migratory insertion into the alkene moiety to form a C-C bond provides the *σ*-alkylpalladium intermediate, which contains another position available for competitive *syn* β´-hydride elimination. Favoring this alternative pathway, a new center would be created in the coupled product, in association with the release of hydropalladium complex that may be neutralized with base to generate the Pd(0) active species, ready to start a new cycle.

[65] a) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. b) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.



Scheme 3.38

Some examples for the generation of quaternary stereocenters have been selected, as they are relevant to our work. Curran and coworkers[66] described the synthesis of 3-methyl-3-vinyloxindoles through Heck cyclization of α-substituted *N*-(2-iodoaryl)acrylamides with generation of a quaternary center (Scheme 3.39). In this case, when *o*-iodoacrylamides with axial chirality were submitted to Heck reaction at room temperature, the chirality was efficiently transferred, obtaining the indolinones with high *ee*.



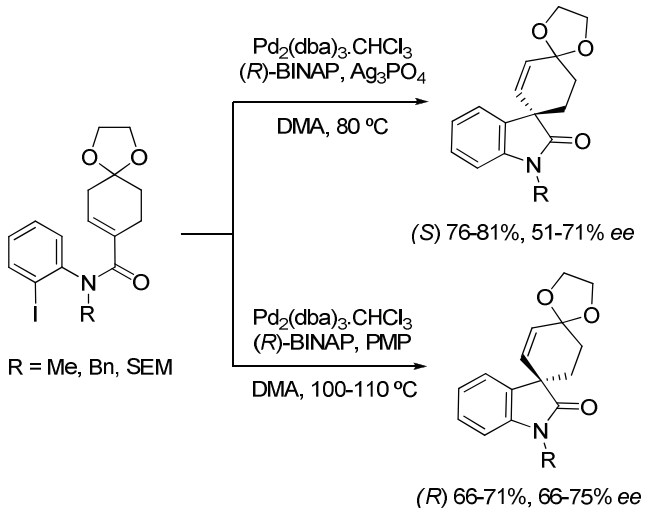
R1 = Me, Br

up to 95%, up to 89% *ee*

Scheme 3.39

[66] Lapierre, A. J. B.; Geib, S. J.; Curran, D. P. *J. Am Chem. Soc.* **2007**, *129*, 494.

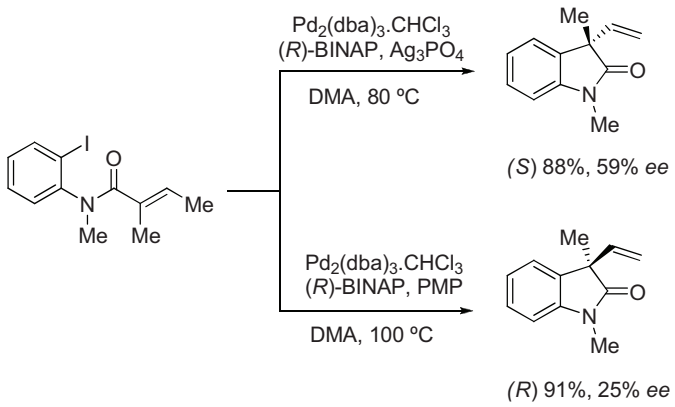
Overman and coworkers[67] reported the synthesis of spirooxindoles in good yields and moderate enantioselectivities through an asymmetric Heck cyclization, which allowed the formation of a quaternary stereogenic spirocenter. As illustrated below in Scheme 3.40, ring closure of the same *o*-iodoaniline over a (*E*)-configuration cyclic alkene, provided opposite enantiomers depending on the use of a halide scavenger or a tertiary amine as base. In this sense, the use of a silver salt as Ag_3PO_4 afforded the (*S*)-enantiomer in good yields and enantioselectivities, while the use of PMP provided the (*R*)-enantiomer in similar yields and *ee.*



Scheme 3.40

[67] a) Ashimori, A.; Bachand, B.; Calter, M. A.; Overman, L.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **2000**, *122*, 192 (Erratum the previous document).

Similarly, for analogous substrates as (*E*)-α,β-unsaturated 2-iodoanilines, under the same conditions, depending on the use of Ag_3PO_4 or PMP as the base, either of the enantiomers of the oxindole could be obtained through cyclization over the alkene, as represented Scheme 3.41.[67]

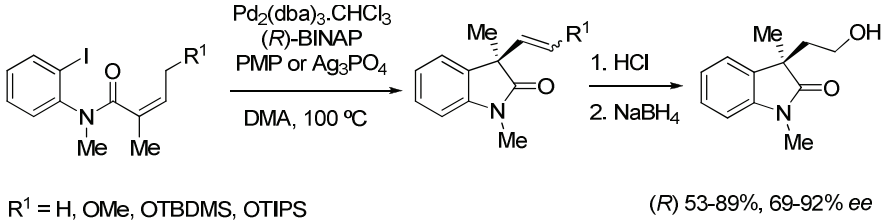


Scheme 3.41

In addition, the same group[68] reported the generation of quaternary stereocenters through highly enantioselective intramolecular Mizoroki-Heck reaction, starting from (*Z*)-α,β-unsaturated 2-iodoanilines by treatment with $Pd_2(dba)_3.CHCl_3$ as catalyst and (*R*)-BINAP ligand. In this case, the use of a silver salt such as Ag_3PO_4 (cationic pathway) or an amine as PMP (neutral pathway), provided both high regio- and enantioselective substituted oxindoles of the same (*R*)-configuration (Scheme 3.42). It is worth to mention that silyloxy group is retained in the coupling step and cleavage of silyl group took place by acidic hydrolysis. Bidentated ligand partial dissociation has been postulated to be the cause of low stereoinduction in

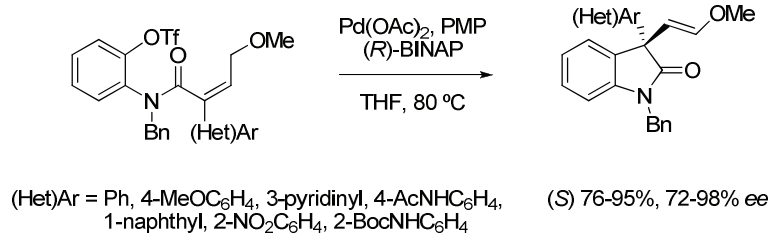
[68] Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.

Heck cyclizations *via* neutral mechanism, while the cationic mechanism provides a reasonable higher enantioselectivity due to total chelation of the bidentated ligand, in the presence of silver and thallium salts. However, the authors concluded that the phosphane remained chelated, even when neutral manifold conditions were used, which led to high enantioselectivities. The change in stereoinduction observed in the oxindoles, starting from (*E*)- and (*Z*)-iodoanilides, when Ag_3PO_4 is used as HI acceptor, while the sense of stereoinduction is independent of alkene geometry when using PMP, is explained by theoretical calculations.[68]



Scheme 3.42

Some time later, the group of Overman[69] reported the synthesis of analogous 3-(hetero)aryl-3-alkyloxindoles with high enantioselectivities, using aryl triflates as precursors (Scheme 3.43).

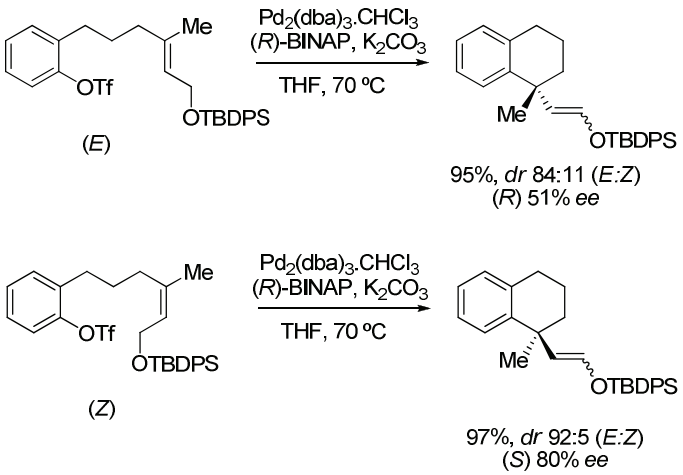


Scheme 3.43

[69] Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261.

The application of former methodologies in the synthesis of enantioselective 3,3-disubstituted oxindoles has allowed the access to different natural products, such as the Calabar alkaloids (–)-physostigmine and (–)-physovenine, which contain an hexahydropyrrolo[2,3-*b*]indole core in its structure.[70]

Shibasaki and coworkers[71] described an additional example of quaternary stereocenter construction, this time *via* 6-*exo* cyclization, to afford structurally simple alkaloid (–)-eptazocine. The alkene configuration influenced the asymmetric outcome of the process. Therefore, subjecting (*E*)-alkenyl aryl triflate to reaction with $Pd_2(dba)_3.CHCl_3$ provided (*R*)-enantiomer in high yield and moderate enantiomeric excess, while (*Z*)-alkenyl aryl triflate afforded (*S*)-enantiomer in both high yield and enantioselectivity (Scheme 3.44).



Scheme 3.44

[70] a) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem*. **1993**, *58*, 6949. b) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500.
[71] Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc*. **1993**, *115*, 8477.

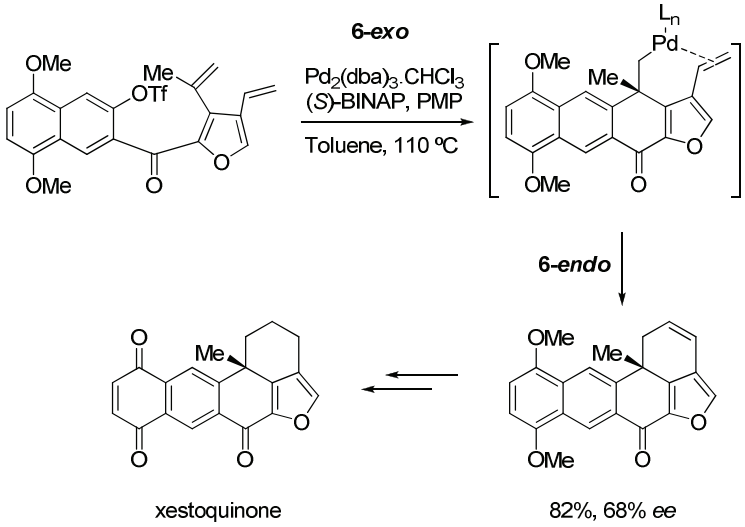
A potential utility of the asymmetric intramolecular Mizoroki-Heck reaction may be the design of substrates that allow σ-alkylpalladium intermediate to follow an alternative pathway to β´-elimination, to perform cascade reactions. In this way, the σ-alkylpalladium complex can react with an external nucleophile[72] or can undergo an insertion to another alkene inter- or intramolecularly, the last case being more frequent and leading to polyene cyclizations.[73]

As an example to illustrate asymmetric Heck cascade reactions, Keay and coworkers[74] described the total synthesis of xestoquinone, which represents the first asymmetric palladium catalyzed polyene cyclization for the synthesis of a natural product. In this paper, a naphthoyl triflate is treated with $Pd_2(dba)_3$ in the presence of (*S*)-BINAP. In this case, the σ-alkylpalladium intermediate formed through a 6-*exo* process, undergoes a second insertion into the alkene *via* 6-*endo* pathway to finally result in a pentacyclic derivative in high yield and moderate enantioselectivity (Scheme 3.45).

[72] For some representative examples, see: a) Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc*. **1996**, *118*, 7108. b) Itano, W.; Ohshima, T.; Shibasaki, M. *Synlett* **2006**, 3053. c) Jaegli, S.; Vors, J. P.; Neuville, L.; Zhu, J. *Tetrahedron* **2010**, *66*, 8911.

[73] For selected reviews on palladium-catalyzed polyene cyclizations, see: a) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem*. **1992**, *64*, 1813. b) Tietze, L. F.; Levy, L. M. In *The Mizoroki–Heck Reaction*, Oestreich, M. Ed., Wiley: Chichester, **2009**, p. 281. For reviews on the asymmetric variant, see: c) Link, J. T.; Wada, C. K. In *The Mizoroki-Heck Reaction*, Oestreich, M. Ed., Wiley: Chichester, **2009**, p. 433. d) Clavier, H.; Pellissier, H. *Adv. Synth. Catal*. **2012**, *354*, 3347.

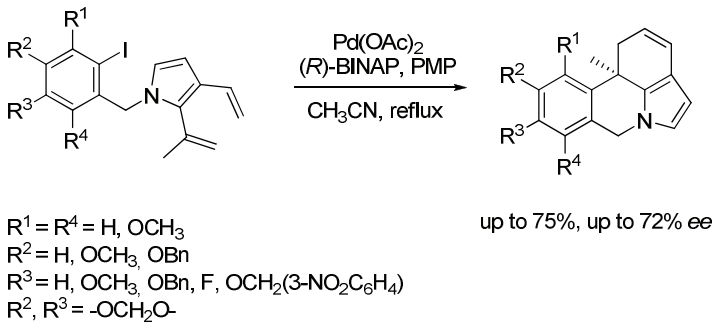
[74] a) Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766. b) Lau, S. Y. W.; Keay, B. A. *Synlett* **1999**, 605. c) Rankic, D. A.; Lucciola, D.; Keay, B. A. *Tetrahedron Lett*. **2010**, *51*, 5724.



Scheme 3.45

In connection with the polyene cyclization, our group has also been able to perform a 6-*exo*/6-*endo* cascade reaction of *N*-benzyl 2,3-dialkenylpyrroles to access the Lycorane tetracyclic core present in the *Amaryllidaceae* alkaloids.[75] This methodology allows the synthesis of enantiomerically enriched (11*bR*)-substituted pyrrolophenanthridines with different substitution patterns on the aromatic ring, and also heteroaromatic rings (Scheme 3.46).

[75] Coya, E.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2015**, *357*, 3206.



Scheme 3.46

In conclusion, as has been shown through these selected examples, tertiary and quaternary centers may be generated by Heck reaction of aryl halides or triflates. Enantiomerically enriched products have been obtained starting from chiral non-racemic substrates or inducing chirality by the use of chiral ligands. Thus, the asymmetric Heck cyclization can be considered an interesting method for natural product total synthesis, allowing the access to several types of compounds, such as terpenoids or alkaloids.

3.2. Results and discussion

Our group has described the synthesis of pyrrolo[1,2-*b*]isoquinolines and pyrrolo[2,1-*a*]isoindoles from 2-alkenyl-substituted *o*-iodobenzylpyrroles by controlling the chemoselectivity associated with the competition between Mizoroki-Heck (M-H) and direct arylation (C-H activation) reactions.[33] Thus, the ring closure can be switched from the alkene to the pyrrole nucleus by choosing an adequate catalytic system. This methodology has been further applied to substrates that contain electron-rich heteroaryl halides such as thiophenyl halides in the selective formation of thieno[3,2-*g*]indolizine and thieno[2,3-*a*]pyrrolizine, but difficulties in the Mizoroki-Heck reaction outcome have arised.[34]

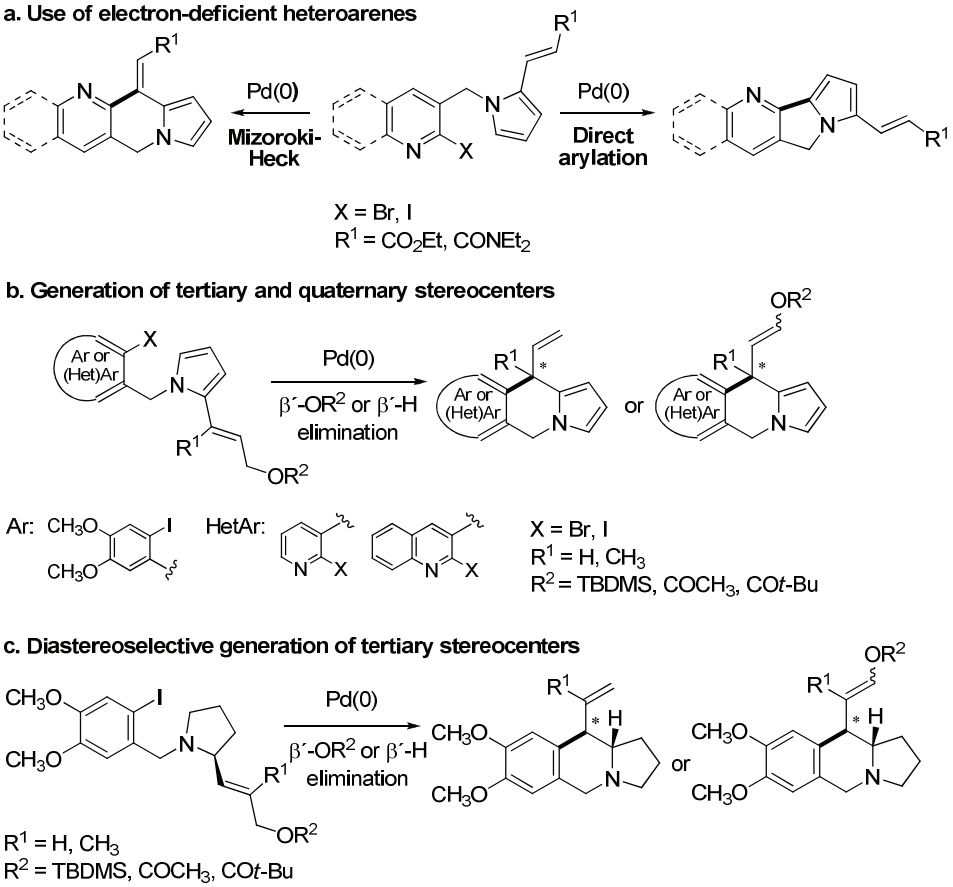
In this context, our goal was to extend this process to electron-deficient heteroaryl halides, such as pyridinyl and quinolinyl halides, in order to be able to obtain a good control in the chemoselectivity for the synthesis of naphthyridine and pyrrolizine systems (Scheme 3.47a).

Our group has also recently studied the synthesis of enantioenriched pyrroloisoquinolines through intramolecular Mizoroki-Heck reaction of a properly substituted 2-alkenyl *N*-(*o*-iodobenzyl)pyrrole *via* β′-hydride elimination with the generation of quaternary stereocenter.[76] In this context, we decided to investigate the generation of tertiary and quaternary stereocenters through Heck cyclization *via* β′-hydride or β′-leaving group elimination in different *o*-halo(hetero)arylmethylpyrroles (Scheme 3.47b). For this purpose, we selected pyrroles incorporating a protected allylic alcohol moiety. Different leaving groups (OR^2) have been selected. The reactions would be carried out first in a racemic

[76] Coya, E. Ph.D Thesis, University of the Basque Country, **2013**.

fashion and then in the presence of chiral phosphanes to study the enantioselective version.

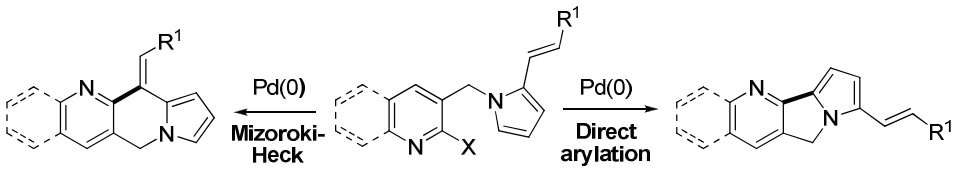
Using the same strategy, our last objective involved the study of the diastereoselectivity when enantiopure *o*-iodobenzylpyrrolidines are subjected to palladium-catalyzed conditions to obtain pyrroloisoquinolines with the generation of a tertiary stereogenic centre (Scheme 3.47c).



Scheme 3.47

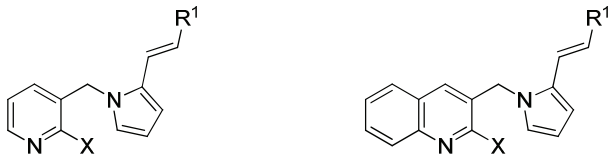
3.2.1. Intramolecular Mizoroki-Heck and direct arylation of *N*-(*o*-haloheteroarylmethyl)pyrrolylacrylates and acrylamides

We firstly focused on the first objective, which involves the study of the competition of intramolecular Mizoroki-Heck and direct arylation reactions on (*o*-haloheteroarylmethyl)pyrroles (Scheme 3.48).



Scheme 3.48

In our previous work on intramolecular carbolithiation (see Chapter 2), we have synthesized a series of *o*-haloheteroarylmethylpyrroles, bearing alkenes that are activated with electron-deficient groups, which are also suitable for intramolecular Mizoroki-Heck and direct arylation reactions (Figure 3.1).

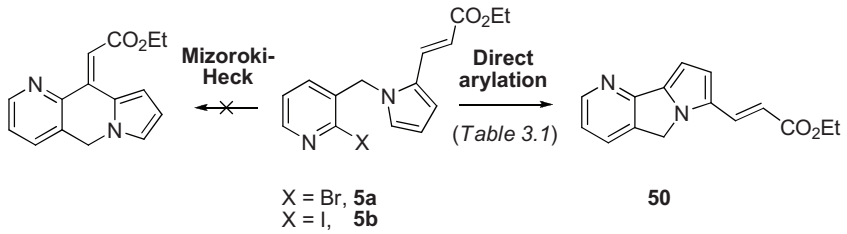


X = Br, R^1 = CO_2Et, **5a**
X = I, R^1 = CO_2Et, **5b**
X = Br, R^1 = $CONEt_2$, **5c**
X = I, R^1 = $CONEt_2$, **5d**

X = Br, R^1 = CO_2Et, **9a**
X = I, R^1 = CO_2Et, **9b**
X = Br, R^1 = $CONEt_2$, **9c**
X = I, R^1 = $CONEt_2$, **9d**

Figure 3.1

We started to study a possible control in the chemoselectivity of the process subjecting pyrrolylacrylates **5a** and **5b** to different catalytic systems in order to obtain pyrrolo[1,2-*g*][1,6]naphthyridines or pyrido[2,3-*a*]pyrrolizines through Mizoroki-Heck or direct arylation reactions respectively, as illustrated in Scheme 3.49.



Scheme 3.49

With the aim of performing a Mizoroki-Heck reaction over the alkene moiety, conditions previously reported for 6-*exo* cyclization [$Pd(PPh_3)_4$, Et_3N, toluene, reflux] in the synthesis of tetrahydroquinolines[41] were applied to pyrroles **5a**, **5b**. However, instead of the desired cyclization, the starting material was recovered (Table 3.1, Entries 1-2). A change in the solvent to acetonitrile did not afford the expected cyclized product (Entry 3). A change in base to $NaHCO_3$ for the reaction of pyrrole **5a** gave the arylation product **50**, although in low yield and conversion (Entry 4). Under these conditions, the corresponding iodide **5b** was much more reactive, affording **50** in a higher yield (68%) (Entry 5). The use of DMF as solvent provided pyrrolizine **50** in low to moderate yields (37-58%) (Entries 6-7). When **5a** was treated with $Pd(OAc)_2$ in the presence of PPh_3 and a silver salt,[41] **50** was obtained again in low yield (Entry 8).

*Table 3.1. Mizoroki-Heck reaction vs. direct arylation reaction of o-halopyridines **5a**, **5b**.*

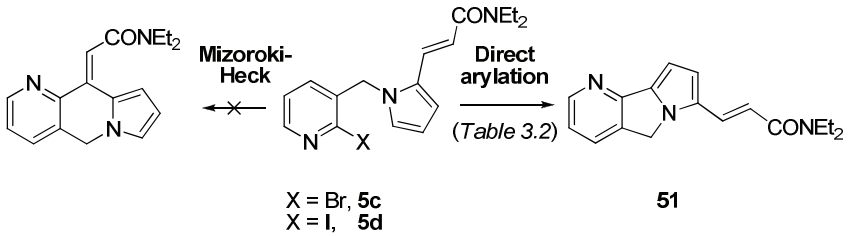
Entry	Subs.	[Pd] (10 mol%)	Base	Ligand	Solvent	Time (h)	Yield 50 (%)[a]
1	**5a**	$Pd(PPh_3)_4$	Et_3N[b]	-	Toluene[k]	48	-[p]
2	**5b**	$Pd(PPh_3)_4$	Et_3N[b]	-	Toluene[k]	48	-[p]
3	**5a**	$Pd(PPh_3)_4$	Et_3N[b]	-	CH_3CN[k]	48	-[p]
4	**5a**	$Pd(PPh_3)_4$	$NaHCO_3$[b]	-[d]	CH_3CN[k]	48	12[q]
5	**5b**	$Pd(PPh_3)_4$	$NaHCO_3$[b]	-[d]	CH_3CN[k]	48	68
6	**5a**	$Pd(PPh_3)_4$	Et_3N [b]	-	DMF[l]	20	37
7	**5b**	$Pd(PPh_3)_4$	Et_3N[c]	-[d]	DMF[m]	48	58
8	**5a**	$Pd(OAc)_2$	-	PPh_3[e][f]	DMF[m]	48	25[r]
9	**5b**	$Pd(OAc)_2$	-	dppp[g][h]	CH_3CN[k]	48	-[p]
10	**5a**	$Pd(OAc)_2$	-	PPh_3[i][j]	DMSO[n]	48	-[p]
11	**5a**	$Pd(OAc)_2$	-	PPh_3[i][j]	DMF[n]	48	-[p]
12	**5a**	$Pd(OAc)_2$	-	PPh_3[i][j]	DMF[o]	48	22[s]
13	**5a**	$Pd(OAc)_2$	-	PPh_3[i][j]	DMF[m]	2	71
14	**5b**	$Pd(OAc)_2$	-	PPh_3[i][j]	DMF[m]	1	85

[a] Isolated yield. [b] 2.5 eq. [c] 12.0 eq. [d] *n*-Bu_4NCl (1.5 eq.) was also added. [e] 30 mol%. [f] Ag_2CO_3 (1.5 eq.) was also added. [g] 5 mol%. [h] *n*-Bu_4NI (10 eq.) was also added. [i] 10 mol%. [j] *n*-Bu_4NOAc (1.5 eq.) was also added. [k] Heated under reflux. [l] Heated at 130 ºC. [m] Heated at 110 ºC. [n] Heated at 60 ºC. [o] Heated at 80 ºC. [p] Starting material was recovered. [q] Conversion 32%. [r] Conversion 86%. [s] Conversion 91%.

As a last attempt, **5b** was treated with a catalytic system based on $Pd(OAc)_2$, dppp and *n*-Bu_4NI, which has been reported to direct selectively the cyclization to the alkene moiety for *o*-iodobenzylpyrroles,[33] but no cyclization was observed (Entry 9).

In view of the impossibility to achieve Mizoroki-Heck reaction, conditions to favor direct arylation were studied. In this context, standard conditions to promote direct arylation on the pyrrole nucleus were applied to **5a** with $Pd(OAc)_2$ catalyst, PPh_3 and a source of acetate anions, such as *n*-Bu_4NOAc, in different polar aprotic solvents, such as DMSO and DMF at 60 ºC, which unfortunately did not afford the arylation compound (Entries 10-11). An increase in temperature resulted in the formation of the expected pyrrolizine **50** in low yield (22%) (Entry 12). Further increase of the temperature afforded **50** in good to high yields (71-85%), for both bromo and iodo derivatives **5a**, **5b**, in just 1-2 h (Entries 13-14).

We next moved to the study of the competition between Mizoroki-Heck and direct arylation reactions on pyrrolylacrylamides **5c**, **5d** (Scheme 3.50).



Scheme 3.50

*Table 3.2. Mizoroki-Heck reaction vs. direct arylation reaction of o-halopyridines **5c**, **5d**.*

Entry	Subs.	[Pd] (mol%)	Base (2.5 eq.)	Ligand	Solvent	Time (h)	Yield 51 (%)[a]
1	**5c**	$Pd(PPh_3)_4$[b]	Et_3N	-	Toluene[f]	48	39[i]
2	**5d**	$Pd(PPh_3)_4$[b]	Et_3N	-	Toluene[f]	48	67
3	**5c**	$Pd(PPh_3)_4$[b]	$NaHCO_3$	-[d]	CH_3CN[f]	48	46[j]
4	**5d**	$Pd(PPh_3)_4$[b]	$NaHCO_3$	-[d]	CH_3CN[f]	48	15[k]
5	**5c**	$Pd(PPh_3)_4$[b]	Et_3N	-[d]	DMF[g]	48	38[l]
6	**5d**	$Pd(PPh_3)_4$[b]	Et_3N	-[d]	DMF[g]	48	49
7	**5c**	$Pd(dba)_2$[c]	Et_3N	P(*o*-tolyl)$_3$[b]	DMF[h]	48	57[l]
8	**5d**	$Pd(dba)_2$[c]	Et_3N	P(*o*-tolyl)$_3$[b]	DMF[h]	48	78
9	**5c**	$Pd(dba)_2$[c]	Et_3N	$P(Cy)_3$[b]	DMF[h]	48	70
10	**5d**	$Pd(dba)_2$[c]	Et_3N	$P(Cy)_3$[b]	DMF[h]	48	46
11	**5c**	$Pd(dba)_2$[c]	Et_3N	P(*t*-Bu)$_3$[b]	DMF[h]	24	78
12	**5d**	$Pd(dba)_2$[c]	Et_3N	P(*t*-Bu)$_3$[b]	DMF[h]	48	44
13	**5c**	$Pd(OAc)_2$[b]	-	PPh_3[b][e]	DMF[g]	2	73
14	**5d**	$Pd(OAc)_2$[b]	-	PPh_3[b][e]	DMF[g]	2	66

[a] Isolated yield. [b] 10 mol%. [c] 5 mol%. [d] *n*-Bu_4NCl (1.5 eq.) was also added. [e] *n*-Bu_4NOAc (1.5 eq.) was also added. [f] Heated under reflux. [g] Heated at 110 ºC. [h] Heated at 130 ºC. [i] Conversion 60%. [j] Conversion 78%. [k] Conversion 24%. [l] Conversion 70%.

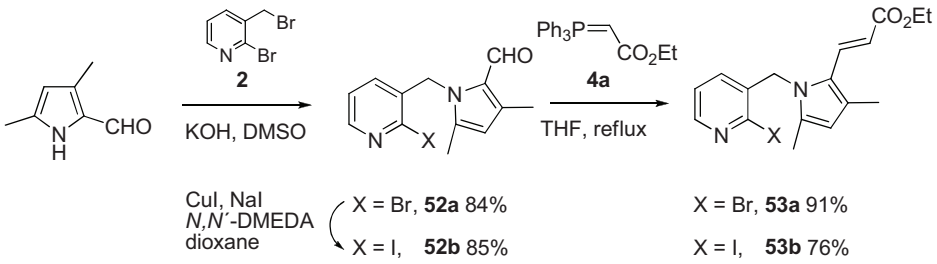
As a starting point, we tried conditions reported as efficient in the synthesis of tetrahydroquinolines through Mizoroki-Heck reaction,[41] based in $Pd(PPh_3)_4$ and Et_3N as base in toluene under reflux, which had shown unreactive for former pyrrolylacrylates **5a**, **5b**. In this case, both of the amides **5c**, **5d** reacted under these

conditions to provide the arylation product **51** in 39% and 67% yields, respectively, as only reaction product, with no evidence of Mizoroki-Heck cyclization (Table 3.2, Entries 1-2). As in the previous case, standard Mizoroki-Heck conditions,[33] which involve the use of $Pd(PPh_3)_4$, $NaHCO_3$, *n*-Bu_4NCl in acetonitrile over **5c**, **5d** yielded again pyrrolizine **51** as only product in low yields and conversions (Entries 3-4). However this time, bromide **5c** provided better results than iodo derivative **5d.**

The change in base to Et_3N and in solvent to DMF afforded the same chemoselectivity outcome in the reaction to give pyrrolizine **51** in moderate yields (38-49%) (Entries 5-6). So far, even under reaction conditions that would favor a neutral pathway for a Heck reaction, arylation reaction is predominant. So, different phosphanes were tried, as it has been demonstrated that the nature of the ligands affected directly the reactivity of Mizoroki-Heck reactions. In this context, bulky trialkylphosphanes are known to stabilize highly reactive palladium species.[77] Nevertheless, when the reaction was carried out using P(*o*-tolyl)$_3$, P(Cy)$_3$ or P(*t*-Bu)$_3$, for both bromo- and iodopyrrolylacrylamides **5c**, **5d**, pyrrolizine **51** was obtained as only reaction product (Entries 7-12). The formation of the Heck product was not detected. Finally, treatment of both amides **5c**, **5d** under standard arylation conditions, which are known to favor a cationic electrophilic Pd(II) species or CMD pathway, afforded the expected arylation product **51** in good yields in a short reaction time, as it happened to former pyrrolylacrylates **5a**, **5b** (Entries 13-14).

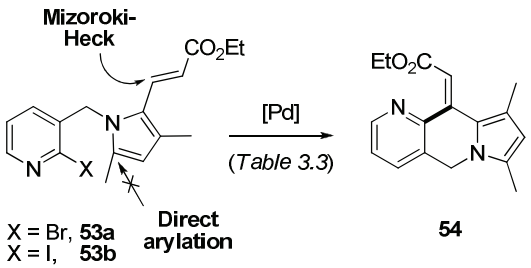
[77] Fu, G. C. *Acc. Chem. Res*. **2008**, *41*, 1555.

It is noteworthy that under all conditions tested, the arylation reaction is favored over the Heck reaction. Thus, we decided to block the position susceptible for direct arylation on the pyrrole, introducing a methyl substituent. For this purpose, we prepared pyrroles **53a**, **53b**, by the same synthetic route already reported for pyrroles **5a**, **5b** in Chapter 2 (Schemes 2.31, 2.33). The synthesis started from commercially available 3,5-dimethylpyrrole-2-carboxaldehyde following typical *N*-alkylation, iodination and Wittig olefination reactions (Scheme 3.51).



Scheme 3.51

Once pyrroles **53a**, **53b** were prepared, we started the study using standard Mizoroki-Heck conditions (Scheme 3.52), but no reaction was observed, recovering starting material (Table 3.3, Entries 1-4).



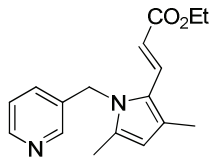
Scheme 3.52

*Table 3.3. Mizoroki-Heck reaction of o-halopyridines **53a**, **53b**.*

Entry	Subs.	[Pd] (10 mol%)	Base	Ligand	Solvent	Time (h)	Yield 54 (%)[a]
1	**53a**	$Pd(PPh_3)_4$	$NaHCO_3$[b]	-[d]	CH_3CN[h]	48	-[j]
2	**53b**	$Pd(PPh_3)_4$	$NaHCO_3$[b]	-[d]	CH_3CN[h]	48	-[j]
3	**53a**	$Pd(PPh_3)_4$	Et_3N[c]	-[e]	DMF[i]	48	-[j]
4	**53b**	$Pd(PPh_3)_4$	Et_3N[c]	-[e]	DMF[i]	48	-[j]
5	**53a**	$Pd(OAc)_2$	-	PPh_3[f][g]	DMF[i]	48	6[k][l]
6	**53b**	$Pd(OAc)_2$	-	PPh_3[f][g]	DMF[i]	48	14[m][n]

[a] Isolated yield. [b] 2.5 eq. [c] 12.0 eq. [d] *n*-Bu_4NCl (1.5 eq.) was also added. [e] *n*-Bu_4NCl (2.0 eq.) was also added. [f] 10 mol%. [g] *n*-Bu_4NOAc (1.5 eq.) was also added. [h] Heated under reflux. [i] Heated at 110 ºC. [j] Starting material was recovered. [k] Dehalogenated product **55** (9%) was also obtained. [l] Conversion 73%. [m] Dehalogenated product **55** (6%) was also obtained. [n] Conversion 43%.

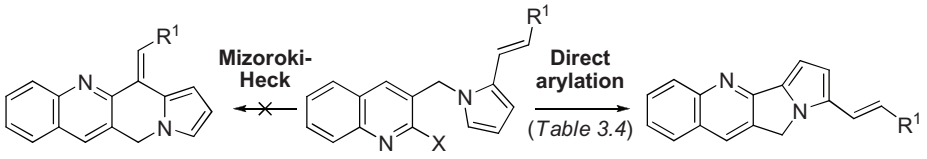
Treatment of bromopyridine **53a** with $Pd(OAc)_2/PPh_3$ provided the desired naphthyridine **54** with a (*Z*)-configuration in low yield (6%), together with dehalogenated pyridine **55** (9%) (Figure 3.2), as the reaction was sluggish and the conversion of substrate incomplete (Entry 5). Similar results were obtained with iodopyridine **53b** (Entry 6). So these 2-pyridinyl halides are unreactive with the internal alkene, even when the arylation position is blocked.



55

Figure 3.2

Subsequently, we continued with the research in intramolecular palladium-catalyzed reactions of *N*-(*o*-haloquinolinylmethyl)acrylates and acrylamides **9a**-**9d**, as illustrated in Scheme 3.53, in order to obtain benzo[*b*]pyrrolo[1,2-*g*][1,6]naphthyridines and pyrrolizino[1,2-*b*]quinolines.



X = Br, R^1 = CO_2Et, **9a**
X = I, R^1 = CO_2Et, **9b**
X = Br, R^1 = $CONEt_2$, **9c**
X = I, R^1 = $CONEt_2$, **9d**

R^1 = CO_2Et, **56**
R^1 = $CONEt_2$, **57**

Scheme 3.53

*Table 3.4. Mizoroki-Heck reaction vs. direct arylation reaction of o-haloquinolines **9a**-**9d**.*

Entry	Subs.	[Pd] (10 mol%)	Base	Ligand	Solvent	Time (h)	Prod.	Yield (%)[a]
1	**9a**	$Pd(PPh_3)_4$	$NaHCO_3$[b]	-[c]	CH_3CN[f]	48	**56**	88
2	**9b**	$Pd(PPh_3)_4$	$NaHCO_3$[b]	-[c]	CH_3CN[f]	48	**56**	85
3	**9c**	$Pd(PPh_3)_4$	$NaHCO_3$[b]	-[c]	CH_3CN[f]	48	**57**	67[h]
4	**9d**	$Pd(PPh_3)_4$	$NaHCO_3$[b]	-[c]	CH_3CN[f]	48	**57**	95
5	**9a**	$Pd(OAc)_2$	-	PPh_3[d][e]	DMF[g]	1	**56**	77
6	**9b**	$Pd(OAc)_2$	-	PPh_3[d][e]	DMF[g]	1	**56**	84
7	**9c**	$Pd(OAc)_2$	-	PPh_3[d][e]	DMF[g]	24	**57**	75
8	**9d**	$Pd(OAc)_2$	-	PPh_3[d][e]	DMF[g]	24	**57**	88

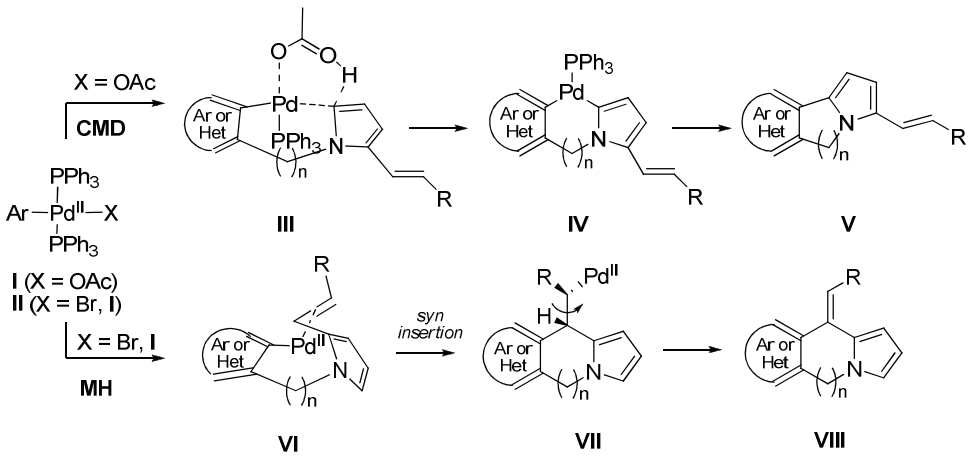
[a] Isolated yield. [b] 2.5 eq. [c] *n*-Bu_4NCl (1.5 eq.) was also added. [d] 10 mol%. [e] *n*-Bu_4NOAc (1.5 eq.) was also added. [f] Heated under reflux. [g] Heated at 110 ºC. [h] Conversion 75%.

For this purpose, we chose standard Mizoroki-Heck conditions,[33] which although are reported to favor a neutral mechanism, provided the arylation products **56** and **57** in good to excellent yields (67-95%), when quinolines **9a-9d** were used as substrates (Table 3.4, Entries 1-4). In these cases, the pyrrolizines were obtained even in higher yields than those obtained with the former pyridines **5a-5d**. As expected, the treatment of haloquinolines **9a-9d** under standard arylation conditions afforded the same pyrrolizine derivatives **56** and **57** in high yields (75-88%) (Entries 5-8).

In conclusion, when electron-deficient heteroaryl halides, such as pyridinyl **5a-5d** and quinolinyl halides **9a-9d**, are used, in all cases, the direct arylation emerges as the predominant process under all conditions tested, even under conditions that should favor a neutral mechanism.

As stated in the introduction of this chapter, our group has been able to control the chemoselectivity towards the alkene or the pyrrole nucleus for *o*-iodobenzylpyrroles by adequately changing experimental conditions, in order to obtain the corresponding pyrroloisoquinoline and pyrroloisoindole skeletons.[33] The change in the chemoselectivity of the reaction was explained through the formation of different intermediate palladium species in the catalytic cycle, as explained in detail by Jutand.[21] Therefore, the intermediate species generated after the oxidative addition to the heteroaryl halide **I** (X = OAc), formed when $Pd(OAc)_2$/n PPh_3 (n>2) is used, or **II** (X = I), formed in the presence of $Pd(PPh_3)_4$ with an iodide ligand, should be taken into account (Scheme 3.54). Thus, it has been reported that the acetate ion is easily dissociable, and an equilibrium could be established between [*trans*-(Het)ArPd$(PPh_3)_2$(OAc)] species **I** and cationic $[ArPd(PPh_3)_2]^+$ in polar

aprotic solvents. Therefore, when the reaction is carried out in the presence of a source of acetate anions, as *n*-Bu_4NOAc, electrophilic Pd(II) species would be formed that would react preferentially with the electron-rich pyrrole, and a cationic mechanism could take place. Besides, acetate ion would be able to assist the abstraction of the proton in α position to the nitrogen atom in the pyrrole nucleus (**III**) and finally result in arylation product **V**, through a CMD mechanism.[27] On the contrary, in the presence of $Pd(PPh_3)_4$ as catalyst, the neutral pathway may take place providing arylation of the alkene and giving **VIII** as main product.

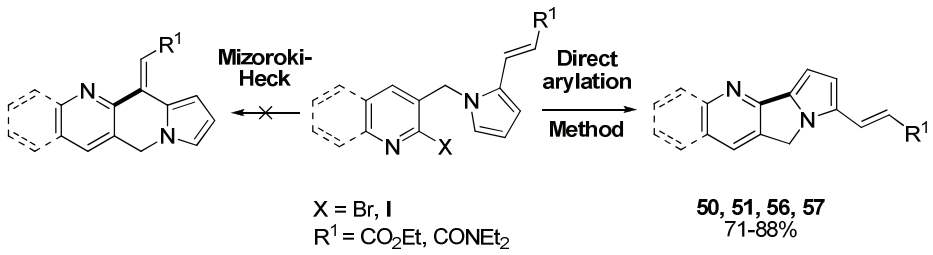


Scheme 3.54

More recently, an extension to medium-sized rings has been achieved, also controlling the competition between Mizoroki-Heck and direct arylation reactions, which has led to the synthesis of pyrroloisoquinoline, pyrrolobenzazepine and pyrrolobenzazocine cores.[34] However, when electron-rich heteroaryl halides, such as thiophenyl halides, were used as coupling partners, although direct arylation reaction was selectively controlled by appropriate experimental conditions, the

Mizoroki-Heck reaction was not so effective affording thienoindolizine and thienoazepine frameworks in low yields. [34]

In our case, the priority to undergo direct arylation onto the pyrrole nucleus could be explained by assuming that the electrophilic Pd(II) intermediate would react preferentially with the electron-rich pyrrole nucleus in all cases, even under conditions that would favor neutral pathway. In this sense, the synthesis of pyrrolizines **50**, **51**, **56** and **57** has been accomplished in good yields *via* direct arylation standard conditions (Scheme 3.55). The study of intramolecular palladium-catalyzed reaction of pyrroles **53a**, **53b**, prepared to avoid direct arylation, led the expected 6-*exo* products **54** through Mizoroki-Heck reaction in very low yields, showing that this attack on the activated double bond was not favored.

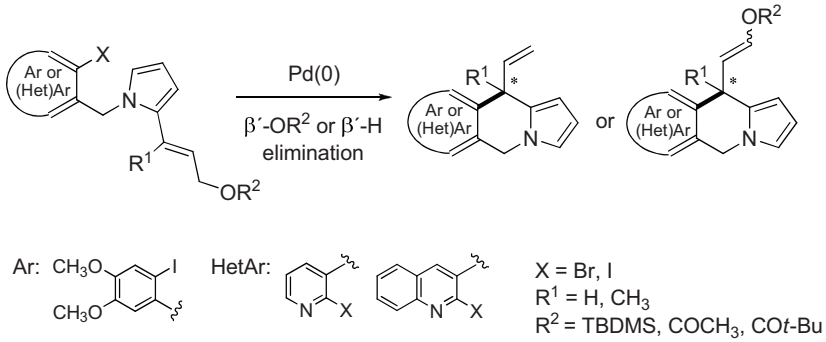


Method: $Pd(OAc)_2$, *n*-Bu_4NOAc, DMF, 110 ºC

Scheme 3.55

3.2.2. Intramolecular Mizoroki-Heck reaction of *N*-(*o*-iodobenzyl) and *N*-(*o*-haloheteroarylmethyl)pyrrolyl allylic alcohol derivatives. Generation of tertiary and quaternary stereocenters

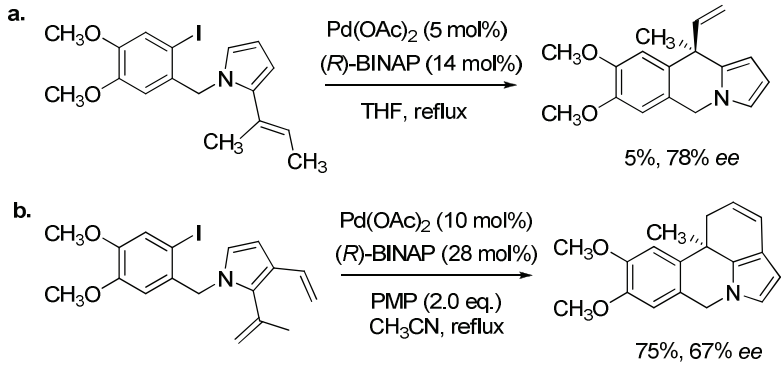
According to the next objective of this work, we decided to investigate the generation of quaternary and tertiary centers in the synthesis of pyrroloisoquinolines and naphthyridines through β´-hydride or β´-leaving group elimination (Scheme 3.56), selecting different leaving groups.



Scheme 3.56

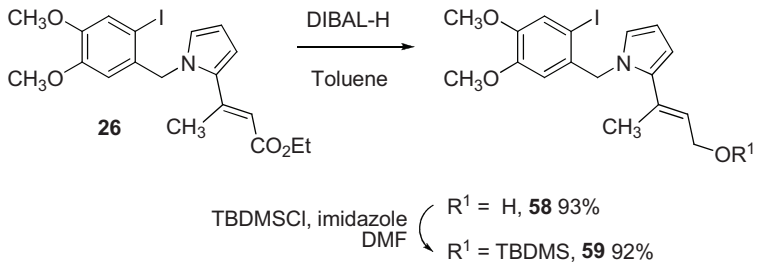
*3.2.2.1. Intramolecular enantioselective Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrrole **59**. Generation of a quaternary stereocenter.*

Our group has studied the formation of a quaternary center through intramolecular cyclization of an *o*-iodobenzylpyrrole *via* β´-hydride elimination for the synthesis of enantioenriched pyrroloisoquinolines,[76] as depicted Scheme 3.57a. Although a reasonable *ee* was achieved, the corresponding pyrroloisoquinoline was obtained in very low yield. The same procedure was much more effective when it was applied to an *o*-iodobenzylpyrrole carrying two alkene moieties, accessing enantioenriched tetracyclic Lycorane core through a cascade process[75] (Scheme 3.57b).



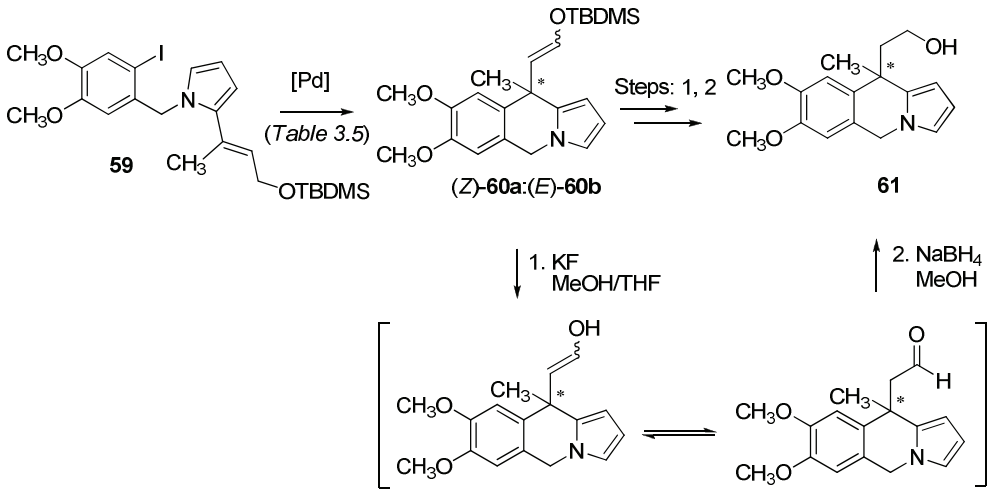
Scheme 3.57

Firstly, compound **59**, in which the possibility of β-hydride elimination is blocked with a methyl group, was selected. The TBDMS group was chosen, so β′-hydride elimination could be favored by formation of a silyl enol ether.[68,71] Alternatively, the β′-elimination of the leaving group would give access to a vinyl substituted pyrroloisoquinoline. *N-o*-iodobenzylpyrrole **59** was prepared from the previously synthesized acrylate **26** (Chapter 2, Scheme 2.46), through reduction to the allylic alcohol **58** and protection of the alcohol with TBDMSCl (Scheme 3.58).



Scheme 3.58

We started performing the reaction of **59** in a racemic fashion. Therefore, treatment of **59** under Mizoroki-Heck conditions previously reported in our group[41] provided the racemic silyl enol ether **60** as 10:90 mixture of *Z:E* diastereomers in high yield (81%), which were isolated and characterized separately (Scheme 3.59, Table 3.5, Entry 1). In this case, β′-elimination of the leaving group did not occur, and ring-closure followed an alternative β′-hydride elimination pathway with retention of the silyloxy group. This type of β′-elimination has been observed in several related examples.[68,71]



Scheme 3.59

Different methods to cleave the silyl protecting group were tried in order to derivatize compound **60**. All attempts to deprotect silyl alcohol with strong acids, such as HCl[68] and TFA,[78] or with TBAF[79] failed. Fortunately, the mixture of silyl

[78] Trost, B. M.; Surivet, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15592.
[79] Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282.

enol ether isomers **60** was derivatized by treatment with KF in MeOH/THF,[80] followed by reduction with $NaBH_4$ in MeOH affording alcohol **61** in an excellent yield (95%, over 2 steps) as depicted Scheme 3.59.

*Table 3.5. Enantioselective Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrrole **59**.*

Entry	[Pd] (10 mol%)	Base	Ligand	Solvent	Time (h)	Yield 60 (%) *dr* (*Z:E*)[a]	Yield 61 (%) (% *ee*)[b]
1	$Pd(PPh_3)_4$	Et_3N[e]	-	Toluene[k]	24	81 (10:90)	95
2	$Pd(OAc)_2$	K_2CO_3[f]	(*R*)-BINAP[i]	THF[k]	48	7 (12:88)[n]	-
3	$Pd(OAc)_2$	PMP[g]	(*R*)-BINAP[i]	CH_3CN[k]	48	61 (19:81)	79 (11)
4	$Pd(OAc)_2$	PMP[g]	(*R*)-BINAP[i]	DMF[l]	96	38 (8:92)[o]	89 (2)
5	$Pd(OAc)_2$	PMP[g]	(*R*)-BINAP[i]	THF[k]	48	Traces[p]	-
6	$Pd(OAc)_2$	Ag_3PO_4[g]	(*R*)-BINAP[i]	CH_3CN[k]	18	n.d.[q]	37 (0)[t]
7	$Pd(OAc)_2$	-	(*R*)-BINAP[i]	CH_3CN[k]	72	18 (22:78)[r]	80 (-10)
8	$Pd(OAc)_2$	PMP[g]	**L4**[i]	CH_3CN[k]	96	38 (14:86)[p]	83 (-1)
9	$Pd(OAc)_2$	PMP[g]	**L5**[i]	CH_3CN[k]	48	5 (1:99)	-
10	$Pd_2(dba)_3$[c][d]	PMP[h]	(*R*)-BINAP[j]	DMA[m]	92	20 (11:89)[s]	82 (0)
11	$Pd_2(dba)_3$[d]	PMP[g]	(*R*)-BINAP[i]	CH_3CN[k]	72	65 (11:89)	75 (6)
12	$Pd_2(dba)_3$[d]	Ag_3PO_4[g]	(*R*)-BINAP[i]	CH_3CN[k]	4	65 (34:66)	80 (18)

[a] Diastereomer ratio determined by GC-MS. [b] Isolated yield over 2 steps of derivatization. % *ee* determined by using Chiral Stationary Phase HPLC using a ADH column and hexane/*i*-PrOH 10% as eluent. tr (major): 35.5 min. tr (minor): 58.4 min. [c] 5 mol%. [d] $CHCl_3$ adduct was used. [e] 2.5 eq. [f] 3.0 eq. [g] 2.0 eq. [h] 4.0 eq. [i] 28 mol%. [j] 12 mol%. [k] Heated under reflux. [l] Heated at 80 ºC. [m] Heated at 100 ºC. [n] Conversion 23%. [o] Conversion 84%. [p] Conversion 20%. [q] Ratio of aldehyde:enol-*Z*:enol-*E* (46:9:45) was determined by GC-MS of the crude, which was derivatized without previous purification. [r] Conversion 28%. [s] Conversion 85%. [t] Yield of **61** over 3 steps.

[80] Hoppe, H.-W.; Stammrn, B.; Werner, U.; Stein, H.; Welzel, P. *Tetrahedron* **1989**, *45*, 3695.

Having established the formation of the quaternary stereocenter in racemic fashion, we decided to optimize the reaction conditions for the enantioselective version using (*R*)-BINAP as has been recognized to be a privileged ligand for this type of reaction.[81] Thus, subjecting substrate **59** to Shibasaki conditions[71] in the presence of K_2CO_3 as base in THF provided **60** in low yield (7%), so derivatization was not worth to be carried out (Entry 2). Subsequently, conditions reported by our group in the asymmetric cascade reaction[75] using PMP as base[82] were employed to achieve the synthesis of the final alcohol **61** in 79% yield, but low *ee* (11%) (Entry 3). These conditions were a starting point to explore different conditions, in order to increase the enantioselectivity.

A change in the solvent did not improve the yield or *ee* (Entries 4-5). Subsequently, we decided to change the base. The addition of a silver salt such as Ag_3PO_4, which is reported to act as a halide scavenger driving the cyclization towards a cationic mechanism[83] and favoring higher degrees of enantioselection, was tried providing the alcohol **61** in an overall 37% (3 steps) with no *ee* improvement (Entry 6). When

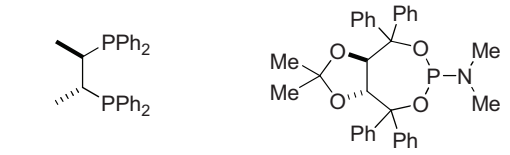
[81] For selected reviews on the asymmetric Heck reaction, see: a) Dounay, A. B.; Overman, L. E. *Chem. Rev*. **2003**, *103*, 2945. b) Guiry, P. J.; Kiely, D. *Curr. Org. Chem*. **2004**, *8*, 781. c) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533. d) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev*. **2004**, *104*, 3453. e) Tietze, L. F.; Lotz, F. In *Asymmetric Heck and other palladium-catalyzed reactions*, Christmann, M.; Bräse, S. Eds., Wiley-VCH: Weinhein, **2007**, p. 147. f) Link, D. T.; Wada, C. K. In *The Mizoroki-Heck Reaction*, Oestreich, M. Ed., Wiley-VCH: Chinchester, **2009**, p. 533. g) McCartney, D.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122. h) Broggini, G.; Borsini, E.; Piarulli, U. In *Science of Synthesis, Cross Coupling and Heck-Type Reactions 3*, Molander, G. A.; Wolfe, J. P.; Larhed, M. Eds., Thieme: Stuttgart, **2013**, p. 521.

[82] PMP base (1,2,2,6,6-pentamethylpiperidine) is reported to be a highly basic, sterically hindered and stable tertiary amine, which demonstrated to increase selectivity and reactivity *via* neutral pathway, see: Ref. 81g.

[83] a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett*. **1990**, 1953. b) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. c) Shibasaki, M.; Erasmus, M. V. In *Comprehensive Asymmetric Catalysis*, Vol. 2, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds., Springer: Berlin, **1999**, Chapter 14. d) Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, Ojima, I. Ed., Wiley-VCH: New York, **2000**, Chapter 8G. e) Donay, A. B.; Overman, L. E. *Chem. Rev*. **2003**, *103*, 2945.

performing the reaction in absence of base, the reactivity dropped, affording **60** in low yield. This issue can be explained by the fact that base plays a role in the reductive elimination step, generating active Pd(0) to enter again the catalytic cycle. However, an inversion in the *ee* was detected (-10%) (Entry 7).

The nature of chiral ligands is also a fundamental parameter, which can influence the stereochemical outcome of Mizoroki-Heck reactions.[84] Therefore, we decided next to study the use of other type of ligands, represented in Figure 3.3, which have been reported as efficient in the synthesis of enantioenriched vinyl substituted pyrroloisoquinolines.[76]



L4
(*R,R*)-CHIRAPHOS

L5
Phosphoramidite

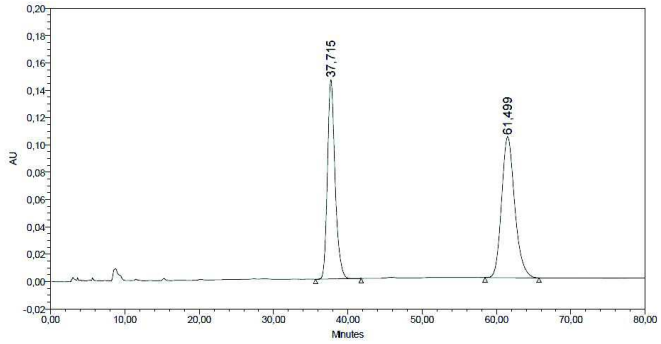
Figure 3.3

Neither the use of (*R,R*)-CHIRAPHOS **L4** or phosphoramidite **L5** ligands provided better results (Entries 8-9). We decided to keep (*R*)-BINAP as the chiral ligand and we tried a change in the precatalyst to $Pd_2(dba)_3$. The use of Overman reported conditions using DMA or acetonitrile for 5-*exo* enantioselective cyclization of 2-iodoanilines,[67,68] did not afford any improvement (Entries 10-11). However, best results were obtained with the use of Ag_3PO_4, providing **61** in good yield (52% over 3 steps), and with slight increase in *ee* (18%) (Entry 12).

[84] For a review on ligand design in the asymmetric Mizoroki-Heck reaction, see: Coyne, A. G.; Fitzpatrick, M. O.; Guiry, P. J. In *The Mizoroki-Heck reaction*, Oestrich, M. Ed., Wiley: Chinchester, **2009**, p. 406.

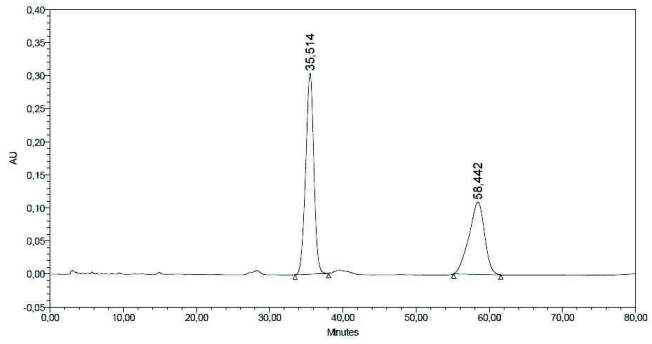
The % *ee* measurements of **61** were determined by chiral stationary phase HPLC, in comparison with the racemic mixture. Figure 3.4A shows the HPLC chromatogram for reactions in absence of base (Table 3.5, Entry 7), while Figure 3.4B shows the HPLC chromatogram for the best results obtained in enantioselection (Table 3.5, Entry 12). Due to the low *ee* obtained, the absolute configuration could not be determined.

A.



	RT	Area	% Area	Height
1	37,715	10357703	45,01	145724
2	61,499	12655618	54,99	103090

B.



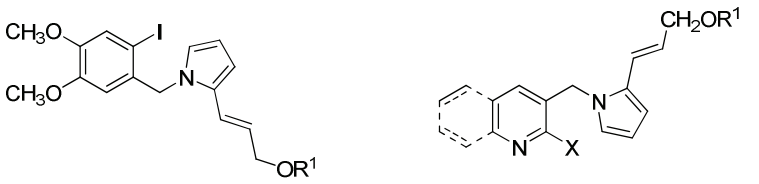
	RT	Area	% Area	Height
1	35,514	23418443	59,20	303955
2	58,442	16138701	40,80	109252

*Figure 3.4. HPLC Chromatograms of **61**, Chiralcel ADH, hexane/i-PrOH 10%, 1 mL/min: A) -10% ee. B) 18% ee.*

*3.2.2.2. Intramolecular Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrroles **44b**, **44c**, o-halopyridines **34a**, **34b** and o-haloquinolines **35a**, **35b**. Generation of a tertiary stereocenter.*

We decided to continue the intramolecular asymmetric Mizoroki-Heck reaction study by using analogous substrates in order to promote generation of a tertiary stereocenter by elimination of the leaving group or just simple β´-hydride elimination with retention of the leaving group, as has been shown in Section 3.2.2.1.

For this purpose, we selected *N*-(*o*-iodobenzyl)pyrroles **44b** and *N*-(*o*-haloheteroarylmethyl)pyrroles **34a, 34b, 35a, 35b**, whose synthesis has been previously described in Chapter 2, as they are also suitable to perform intramolecular Mizoroki-Heck reactions with the generation of a tertiary stereocenter (Figure 3.5). Furthermore, pivaloyl protected alcohol **44c** was obtained in 87% yield from previously prepared allylic alcohol **43** (Scheme 2.65), by treatment with pivaloyl chloride and pyridine in CH_2Cl_2.

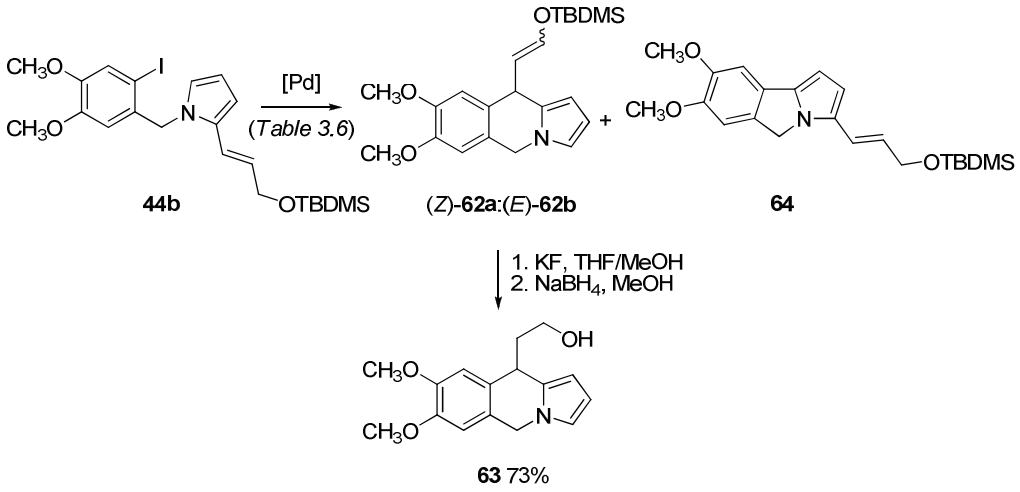


R^1 = TBDMS, **44b**
R^1 = CO*t*-Bu, **44c**

pyridine, X = Br, R^1 = TBDMS, **34a**
pyridine, X = I, R^1 = TBDMS, **34b**
quinoline, X = Br, R^1 = TBDMS, **35a**
quinoline, X = I, R^1 = TBDMS, **35b**

Figure 3.5

We started to perform 6-*exo* cyclization of substrate **44b** in a racemic fashion under the same conditions used in the former section, providing silyl enol ether **62** in good yield (80%) as a 45:55 mixture of *Z:E* diastereomers (Scheme 3.60, Table 3.6, Entry 1), which were isolated and characterized separately. Diastereomer mixture **62** was derivatized to alcohol **63** (73% yield over two steps), following the same sequence described before.



Scheme 3.60

Once the racemic version for the construction of the tertiary center had been established, we decided to optimize the asymmetric variant as in the previous case. Applying Shibasaki reported conditions[71] to compound **44b**, a complex mixture of products was obtained (Entry 2). We next moved to the catalytic system reported for cascade process,[75] which provided again a complex mixture of products, where **62** and **64** could be detected by GC/MS of the crude reaction mixture, but we were unable to isolate them separately (Entry 3). The change in solvent (Entries 4-6) and

in base (Entries 7-8) did not afford better results. A change in catalyst to $Pd_2(dba)_3$ was also unsuccessful (Entries 9-10).

*Table 3.6. Enantioselective Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrrole **44b**.*

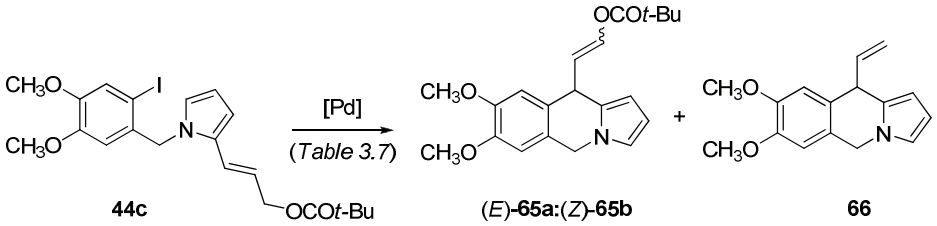
Entry	[Pd] (10 mol%)	Base	Ligand	Solvent	Time (h)	Prod.	Yield (%)[a]
1	$Pd(PPh_3)_4$	Et_3N[d]	-	Toluene[l]	16	**62**	80[p]
2	$Pd(OAc)_2$	K_2CO_3[e]	(*R*)-BINAP[h]	THF[o]	72	-	-[q][r]
3	$Pd(OAc)_2$	PMP[f]	(*R*)-BINAP[h]	CH_3CN[l]	42	-	-[q][s]
4	$Pd(OAc)_2$	PMP[g]	(*R*)-BINAP[h]	Toluene[l]	44	**64**	Traces[t]
5	$Pd(OAc)_2$	PMP[g]	(*R*)-BINAP[h]	THF[l]	44	**64**	Traces[t]
6	$Pd(OAc)_2$	PMP[g]	(*R*)-BINAP[h]	DMF[m]	48	-	-[q][u]
7	$Pd(OAc)_2$	Et_3N[g]	(*R*)-BINAP[h]	CH_3CN[l]	48	-	-[q][v]
8	$Pd(OAc)_2$	Cy_2NMe[g]	(*R*)-BINAP[h]	CH_3CN[l]	48	-	-[q][w]
9	$Pd_2(dba)_3$[b][c]	PMP[g]	(*R*)-BINAP[i]	DMA[n]	48	-	-[q]
10	$Pd(dba)_2$	PMP[g]	(*R*)-BINAP[h]	CH_3CN[l]	48	-	-[q][x]
11	$Pd(OAc)_2$[b]	-	PPh_3[j][k]	DMSO[o]	1.5	**64**	82
12	$Pd(OAc)_2$[b]	-	PPh_3[j][k]	DMF[o]	1.5	**64**	81

[a] Isolated yield. [b] 5 mol%. [c] $CHCl_3$ adduct was used. [d] 2.5 eq. [e] 3.0 eq. [f] 2.0 eq. [g] 4.0 eq. [h] 28 mol%. [i] 12 mol% [j] 10 mol%. [k] *n*-Bu_4NOAc (1.5 eq.) was also added. [l] Heated under reflux. [m] Heated at 80 ºC. [n] Heated at 100 ºC. [o] Heated at 60 ºC. [p] Diastereomers ratio (*Z:E,* 45:55) determined by GC-MS. [q] Complex mixture of products unable to isolate, in which **62** and **64** were detected by GC-MS. [r] Conversion 54%. [s] Conversion 69%. [t] Starting material was recovered. [u] Conversion 72%. [v] Conversion 76%. [w] Conversion 94%. [x] Conversion 65%.

As described, all conditions tested were inefficient to afford Mizoroki-Heck reaction products, and efforts to isolate product **62** were ineffective. For this reason, derivatization and *ee* measurements were not conducted.

Finally, to unambiguously confirm the structure of the arylation product, standard arylation conditions were tried, which selectively afforded pyrrolo[2,1-*a*]isoindole **64** in high yields (81-82%) (Entries 11-12).

We next moved to the study of intramolecular Heck cyclization of pivaloyl protected allylic alcohol **44c**. In this case, a better leaving group, as pivalate, was selected to favor β′-pivalate elimination to form the 10b-substituted vinyl derivative **66** (Scheme 3.61).



Scheme 3.61

Firstly we began with the formation of the tertiary center in racemic fashion. The use of previous standard Mizoroki-Heck conditions [$Pd(PPh_3)_4$, Et_3N in toluene] provided a mixture of (*E:Z*) diastereomers **65** in low yield, formed selectively by β′-hydride elimination (Table 3.7, Entry 1), with no detection of **66**. A change in the solvent (DMF, CH_3CN), promoted selectively again β′-hydride elimination obtaining compound **65** in lower yields (Entries 2-3). Addition of tetraalkylammonium salts, such as *n*-Bu_4NCl led to a mixture of (*E*)-**65** and **66** in a 48:52 ratio (established by GC/MS) (Entry 4). The mixture could be separated and the products characterized to afford (*E*)-**65** (8%) and **66** (9%). Treatment of **44c** under Mizoroki-Heck reaction conditions, in the presence of $NaHCO_3$ and again *n*-Bu_4NCl, provided a mixture of (*E*)-**65** and **66** (Entry 5). A change in the additive to

other tetraalkylammonium salts, afforded compound **65** as a mixture of isomers in low yields (Entries 6-8).

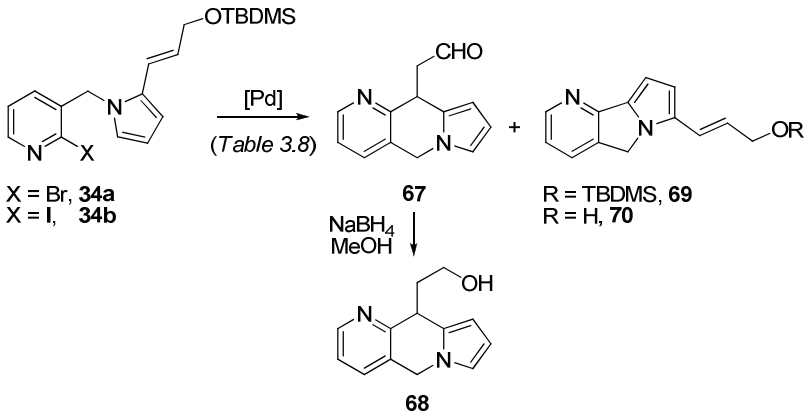
*Table 3.7. Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrrole **44c**.*

Entry	[Pd] (10 mol%)	Base	Ligand	Solvent	Time (h)	(*E*)-65: (*Z*)-65:66[a]	Yield (%)
1	$Pd(PPh_3)_4$	Et_3N[c]	-	Toluene[m]	24	72:28:0	28
2	$Pd(PPh_3)_4$	Et_3N[d]	-	DMF[n]	5	100:0:0	19
3	$Pd(PPh_3)_4$	Et_3N[c]	-	CH_3CN [m]	6	88:12:0	11
4	$Pd(PPh_3)_4$	Et_3N[d]	-[g]	DMF[n]	5	48:0:52	17
5	$Pd(PPh_3)_4$	$NaHCO_3$[c]	-[g]	CH_3CN [m]	16	56:0:44	-[q]
6	$Pd(PPh_3)_4$	$NaHCO_3$[c]	-[h]	CH_3CN [m]	16	83:17:0	13
7	$Pd(PPh_3)_4$	$NaHCO_3$[c]	-[i]	CH_3CN [m]	16	95:5:0	13
8	$Pd(PPh_3)_4$	$NaHCO_3$[c]	-[j]	CH_3CN [m]	16	87:23:0	10
9	$Pd(OAc)_2$	Ag_2CO_3[e]	PPh_3[k]	DMF[o]	24	-	-[r]
10	$Pd(OAc)_2$	Ag_2CO_3[e]	PPh_3[k]	CH_3CN [m]	24	100:0:0	2
11	$Pd(OAc)_2$	Et_3N[f]	PPh_3[k]	CH_3CN [m]	48	90:10:0	12
12	$Pd(OAc)_2$	Et_3N[c]	dppp[k]	CH_3CN [m]	48	-	-
13	$Pd(OAc)_2$	Et_3N[f]	P(*o*-tolyl)$_3$[l]	$CH_3CN:H_2O$[p]	6	-	-
14	$Pd_2(dba)_3$[b]	Et_3N[f]	P(*o*-tolyl)$_3$[l]	$CH_3CN:H_2O$[p]	24	-	-
15	$PdCl_2[(o\text{-tolyl})_3P]_2$	Et_3N[f]	-	$CH_3CN:H_2O$[p]	24	-	-

[a] Products ratio determined by GC-MS. [b] 5 mol%, $CHCl_3$ adduct was used. [c] 2.5 eq. [d] 12.5 eq. [e] 1.5 eq. [f] 2.2 eq. [g] *n*-Bu_4NCl (1.5 eq.) was also added. [h] *n*-Bu_4NBF_4 (1.5 eq.) was also added. [i] *n*-Bu_4NOAc (1.5 eq.) was also added. [j] *n*-Bu_4NI (1.5 eq.) was also added. [k] 0.3 eq. [l] 0.22 eq. [m] Heated under reflux. [n] Heated at 110 ºC. [o] Heated at 90 ºC. [p] Heated under reflux in a (10:1) mixture of solvents. [q] Yield not determined. [r] Starting material was recovered.

In view of these results, we decided to change the catalyst. For this purpose, we tried previously reported conditions by our group[41] [$Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF], but they did not afford the cyclized product (Entries 9-10). Finally, treatment under Lautens conditions, for the cyclization of aryl iodides with allylic moieties *via* elimination of acetoxy group,[59] resulted in no success even with different palladium sources (Entries 13-15).

We decided to continue our study of cyclization with electron-deficient heteroaryl halides, such as *o*-halopyridines **34a**, **34b** (Scheme 3.62). We first studied the generation of the tertiary center in a racemic fashion by treatment of brominated **34a** with reported selective conditions for Mizoroki-Heck with $Pd(PPh_3)_4$ as catalyst, although no cyclization was observed (Table 3.8, Entries 1-2). The treatment of **34a** under Lautens conditions,[59] gave a mixture of pyrrolizine **69** (27%) and aldehyde **67** (26%), formed by deprotection of the silyl group and tautomerization of the enol to the aldehyde *in situ* (Entry 3). As aldehyde **67** was unstable, we decided to repeat cyclization reaction followed by a reduction, thus obtaining **69** (25%) and alcohol **68** (35%), which was stable (Entry 4).



Scheme 3.62

*Table 3.8. Mizoroki-Heck reaction of N-(o-halopyridinylmethyl)pyrroles **34a, 34b**.*

Entry	Subs.	[Pd] (10 mol%)	Base	Ligand	Solvent	Time (h)	Prod.	Yield (%)[a]
1	**34a**	$Pd(PPh_3)_4$	Et_3N[d]	-	Toluene[j]	48	-	-[n]
2	**34a**	$Pd(PPh_3)_4$	$NaHCO_3$[d]	-[f]	DMF[k]	48	-	-[n]
3	**34a**	$Pd(OAc)_2$	Et_3N[e]	P(*o*-tolyl)$_3$[g]	-[l]	7	**67**/**69**	26/27
4	**34a**	$Pd(OAc)_2$	Et_3N[e]	P(*o*-tolyl)$_3$[g]	-[l]	7	**68**/**69**	35/25[o]
5	**34b**	$Pd(OAc)_2$	Et_3N[e]	P(*o*-tolyl)$_3$[g]	-[l]	7	**68**/**69**	20/62[o]
6	**34a**	Pd_2dba_3[b][c]	Et_3N[e]	P(*o*-tolyl)$_3$[g]	-[l]	7	**68**/**69**	30/19[o]
7	**34a**	$PdCl_2$[(*o*-tolyl)$_3$P]$_2$	Et_3N[e]	-	-[l]	7	**68**/**69**	31/16[o]
8	**34a**	$Pd(OAc)_2$	-	PPh_3[h][i]	DMF[m]	1	**69**	23
9	**34b**	$Pd(OAc)_2$	-	PPh_3[h][i]	DMF[m]	1	**69**/**70**	38/40
10	**34a**	$Pd(OAc)_2$	-	PPh_3[h][i]	DMF[k]	5	**69**/**70**	25/24

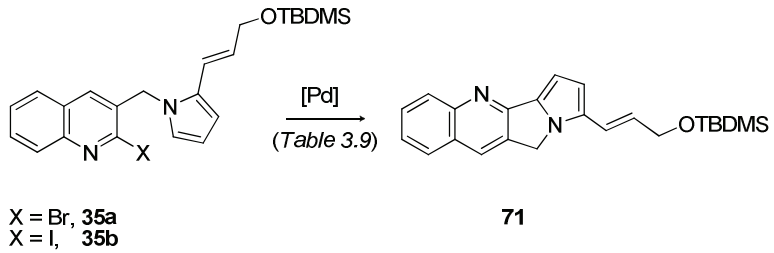
[a] Isolated yield. [b] 5 mol%. [c] $CHCl_3$ adduct was used. [d] 2.5 eq. [e] 2.0 eq. [f] *n*-Bu_4NCl (1.5 eq.) was added. [g] 0.22 eq. [h] 10 mol%. [i] *n*-Bu_4NOAc (1.5 eq.) was added. [j] Heated under reflux. [k] Heated at 80 ºC. [l] Heated under reflux in a CH_3CN:H_2O (10:1) mixture of solvents. [m] Heated at 110 ºC. [n] Starting material was recovered. [o] The yield over 2 steps.

Iodinated **34b** afforded similarly both arylation product **69** (62%) and alcohol **68** (20%) under the same conditions (Entry 5). The chemoselectivity of the reaction was tried to be controlled by changing palladium source, but similar results were obtained (Entries 6-7).

By treatment of **34a**, **34b** under standard arylation conditions, the reaction could be directed to cyclization on the pyrrole nucleus affording arylation products **69** and **70**, this latter one derived from desilylation of pyrrolizine **69** in the media (Entries

8-10). The asymmetric variant was not performed, due to the high difficulty emerged to control the selectivity of the reaction.

We then moved to *o*-haloquinolines **35a**, **35b** (Scheme 3.63), but only arylation product **71** was obtained under Lautens conditions[59] (Entries 1-2) or, as expected, under standard arylation conditions (Entries 3-4). Unfortunately enantioselective studies could not be conducted, since Mizoroki-Heck product formation was not observed.



Scheme 3.63

*Table 3.9. Mizoroki-Heck reaction of N-(o-haloquinolinylmethyl)pyrroles **35a**, **35b**.*

Entry	Subs.	[Pd] (mol%)	Base	Ligand	Solvent	Time (h)	Yield 71 (%)
1	**35a**	$Pd(OAc)_2$[a]	Et_3N[b]	P(*o*-tolyl)$_3$[a]	$CH_3CN:H_2O$[d]	22	14
2	**35b**	$Pd(OAc)_2$[a]	Et_3N[b]	P(*o*-tolyl)$_3$[a]	$CH_3CN:H_2O$[d]	5	43
3	**35a**	$Pd(OAc)_2$[a]	-	PPh_3[a][c]	DMF[e]	1	14
4	**35b**	$Pd(OAc)_2$[a]	-	PPh_3[a][c]	DMF[e]	1	50

[a] 10 mol%. [b] 2.0 eq. [c] *n*-Bu_4NOAc (1.5 eq.) was also added. [d] Heated under reflux in a (10:1) mixture of solvents. [e] Heated at 110ºC.

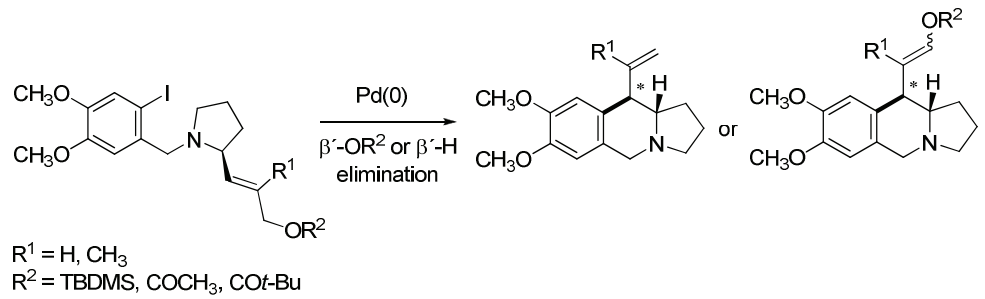
In conclusion, we have been able to efficiently synthesize pyrroloisoquinolines **60**, **62** in a racemic manner, by formation of tertiary and quaternary centers, starting from silyl protected *N*-(*o*-iodobenzyl)pyrrolyl allylic alcohols **59**, **44b** through selective β´-H elimination. However, the reaction is not efficient when it is carried out in the presence of chiral phosphanes.

When pivaloyl protected *N*-(*o*-iodobenzyl)pyrrolyl allylic alcohol **44c** is used, in order to promote β´-elimination of the leaving group in the formation of a tertiary center, the efficiency and selectivity of the reaction could not be controlled, leading in mixtures of β´-hydride elimination product **65** and β´-leaving group elimination product **66**, always in low yields.

When the same procedure is applied to the corresponding heteroaryl derivatives **34** and **35**, the direct arylation reaction is always competitive, and only in the case of 2-halopyridines **34a**, **34b**, the formation of naphthyridine **67** was observed, always in low yields and with no selectivity.

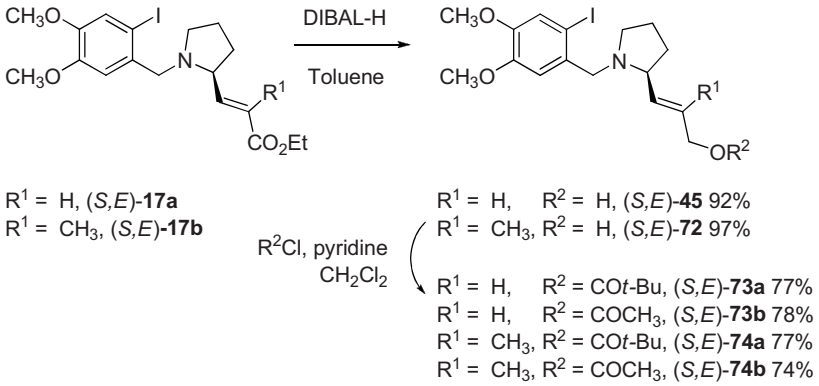
3.2.3. Diastereoselective intramolecular Mizoroki-Heck reaction of *N*-(*o*-iodobenzyl)pyrrolidinyl allylic alcohol derivatives. Generation of a tertiary stereocenter

In view of the difficulties found for the stereocontrolled generation of tertiary and quaternary centers described in the previous section, we decided to study the possibility of obtaining enantiomerically pure pyrroloisoquinolines using a diastereoselective approach. Thus, the last objective of this work involves the study of Heck cyclization of enantiopure pyrrolidines that bear a protected allylic alcohol moiety to obtain diastereoselectively the pyrroloisoquinolines *via* β´-elimination of the leaving group or β´-hydride elimination (Scheme 3.64). The same protecting groups used in the previous section (TBDMS, CO*t*-Bu and also $COCH_3$) were selected.



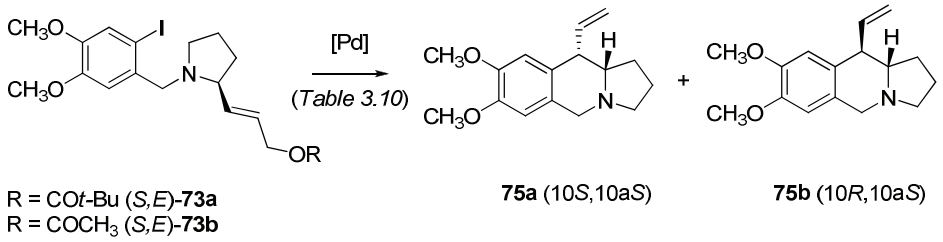
Scheme 3.64

Scheme 3.65 shows the preparation of acyl protected *N*-(*o*-iodobenzyl)pyrrolidinyl alcohols **73a**, **73b**, **74a**, **74b**, starting from enantiomerically pure acrylates (*S*,*E*)-**17a**, (*S*,*E*)-**17b**, which had been previously synthesized (Scheme 2.41). Additionally, we have chosen compound (*S*,*E*)-**46** that has been already synthesized in Chapter 2 (Scheme 2.66), as it appears suitable for Mizoroki-Heck cyclization studies.



Scheme 3.65

Firstly, we chose chiral non racemic acyl protected alcohols (*S*,*E*)-**73a**, (*S*,*E*)-**73b** with the aim of studying diastereoselective synthesis of pyrroloisoquinolines through intramolecular Heck reactions with generation of a second tertiary stereocenter (Scheme 3.66). A possible problem in regioselectivity may arise due to β′-leaving group or β′-hydride elimination (with retention of leaving group) competitive pathways, as already seen for *N*-(*o*-iodobenzyl)pyrrolyl pivaloyl derivative **44c** (Scheme 3.61).



Scheme 3.66

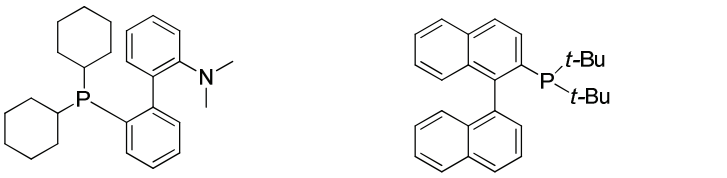
*Table 3.10. Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrrolidine **73a**.*

Entry	[Pd] (10 mol%)	Base	Ligand	Solvent	Time (h)	Yield 75 (%)[a] *dr* (75a:75b)[b]
1	$Pd(PPh_3)_4$	Et_3N[e]	-	Toluene[m]	5	-
2	$Pd(PPh_3)_4$	$NaHCO_3$[e]	-[i]	CH_3CN [m]	48	16 (66:34)
3	$Pd(OAc)_2$	Ag_2CO_3[f]	PPh_3[j]	DMF[n]	72	-
4	$Pd(OAc)_2$	Et_3N[g]	P(*o*-tolyl)$_3$[k]	CH_3CN[m]	72	51 (83:17)
5	$Pd(OAc)_2$	Et_3N[g]	P(*o*-tolyl)$_3$[k]	$CH_3CN:H_2O$[o]	5	53 (78:22)
6	$Pd(OAc)_2$	Et_3N[g]	P(*t*-Bu)$_3$[k]	$CH_3CN:H_2O$[o]	5	32 (78:22)
7	$Pd(OAc)_2$	Et_3N[g]	P(Cy)$_3$[k]	$CH_3CN:H_2O$[o]	5	45 (78:22)
8	$Pd(OAc)_2$	Et_3N[g]	DavePhos[k]	$CH_3CN:H_2O$[o]	5	51 (76:24)
9	$Pd(OAc)_2$	Et_3N[g]	PPh_3[k]	$CH_3CN:H_2O$[o]	5	32 (66:34)
10	$Pd(OAc)_2$	Et_3N[g]	Dppp[k]	$CH_3CN:H_2O$[o]	5	27 (50:50)
11	$Pd(OAc)_2$	Et_3N[g]	**L2**[k]	$CH_3CN:H_2O$[o]	22	34 (80:20)[p]
12	$Pd(OAc)_2$[c]	Et_3N[g]	P(*o*-tolyl)$_3$[k]	$CH_3CN:H_2O$[o]	22	46 (79:21)
13	$Pd(OAc)_2$	Et_3N[g]	P(*o*-tolyl)$_3$[l]	$CH_3CN:H_2O$[o]	5	39 (80:20)
14	$Pd(OAc)_2$	*n*-$BuNMe_2$[g]	P(*o*-tolyl)$_3$[k]	$CH_3CN:H_2O$[o]	5.5	35 (72:28)
15	$Pd_2(dba)_3$[c][d]	Et_3N[h]	P(*o*-tolyl)$_3$[l]	$CH_3CN:H_2O$[o]	5	53 (82:18)
16	$Pd_2(dba)_3$[c][d]	*n*-$BuNMe_2$[h]	P(*o*-tolyl)$_3$[l]	$CH_3CN:H_2O$[o]	5	52 (77:23)
17	$Pd_2(dba)_3$[d]	*n*-$BuNMe_2$[h]	P(*o*-tolyl)$_3$[l]	$CH_3CN:H_2O$[o]	5	39 (71:29)
18	$Pd_2(dba)_3$[c][d]	*n*-$BuNMe_2$[h]	P(*o*-tolyl)$_3$[k]	$CH_3CN:H_2O$[o]	6	34 (77:23)
19	$PdCl_2$[(*o*-tolyl)$_3$]	*n*-$BuNMe_2$[h]	-	$CH_3CN:H_2O$[o]	5	38 (76:24)

[a] Isolated yield of the mixture. [b] Diastereomer ratio determined by GC-MS. [c] 5 mol%. [d] $CHCl_3$ adduct was used. [e] 2.5 eq. [f] 1.5 eq. [g] 2.2 eq. [h] 2.0 eq. [i] *n*-Bu_4NCl (1.5 eq.) was also added. [j] 0.3 eq. [k] 0.1 eq. [l] 0.22 eq. [m] Heated under reflux. [n] Heated at 100 ºC. [o] Heated under reflux in a (10:1) mixture of solvents. [p] Conversion 36%.

We started studying the cyclization of (*S*,*E*)-**73a**. Under standard conditions with $Pd(PPh_3)_4$, no cyclization was observed (Table 3.10, Entry 1). However, treatment of (*S*,*E*)-**73a** with $Pd(PPh_3)_4$, $NaHCO_3$ as base, *n*-Bu_4NCl in acetonitrile under reflux provided a 66:34 mixture of diastereomers **75a**:**75b** in 16% yield (Scheme 3.61, Entry 2), which derived from β´-pivaloxy group elimination. No β´-hydride elimination product was detected. Further attempts were conducted to increase both the yield and diastereoselectivity of the process using $Pd(OAc)_2$. In the presence of a silver salt, no cyclization product was observed (Entry 3). The use of bulkier phosphanes[59] in acetonitrile as solvent, resulted in an increase of diastereoselectivity (**75a**:**75b**, 83:17) and yield (51%) after 72 h (Entry 4). The use of a mixture of acetonitrile:H_2O (10:1), provided similar results but only in 5 h (53%, **75a**:**75b** 78:22) (Entry 5).

We decided to try other bulky phosphane ligands (Figure 3.6), but no improvements in yield or diastereoselectivity were obtained (Entries 6-11).



DavePhos rac-2-(Di*tert*-butylphosphino)-1,1´-binaphtyl L2

Figure 3.6

A decrease of catalyst loading, an increase of phosphane loading or a change in base, afforded similar results (Entries 12-14). Attempts conducted with other palladium sources resulted in yields up to 53% and diastereomers ratios up to (82:18) (Entries 15-19).

Thus, in all cases β′-elimination of the pivaloxy group was observed. The yield indicated is the isolated yield of the mixture of diastereomers **75a** and **75b**, whose ratios were determined by GC-MS in each case. Additionally, both diastereomers have been isolated and characterized separately using NMR spectroscopy and X-Ray Diffraction techniques to unambiguously confirm their absolute configuration.

2D NOESY experiments showed enhancement between H-10a and an olefinic proton H_A of the substituent at C-10 for the *trans*-**75b** diastereomer (10*R*,10a*S*) (Figure 3.7B), while that enhancement was not observed for *cis*-**75a** diastereomer (10*S*,10a*S*) (Figure 3.7A). Further supporting evidences for these configurations, could be additional enhancements shown in **75a** between H-10 and H-9, and between olefinic H_A and H-1 from the pyrrolidine ring. In **75b**, enhancements between H-10a and olefinic H_A could also be observed.

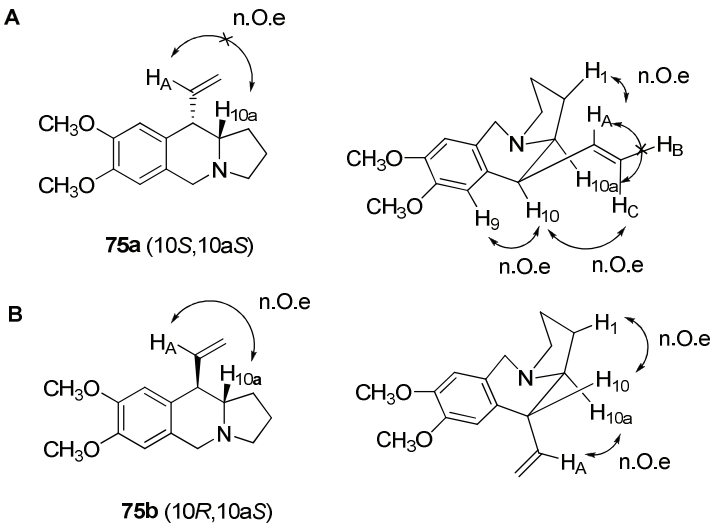
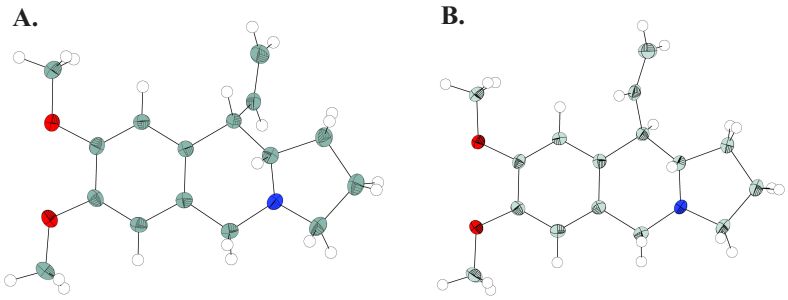


Figure 3.7

In addition, the configuration of each diastereomer was unambiguously confirmed by X-Ray diffraction techniques, assigning a *cis*-(10*S*,10a*S*)[85] configuration to the major diastereomer **75a** (Figure 3.8A), and a *trans*-(10*R*,10a*S*)[86] configuration to the minor diastereomer **75b** (Figure 3.8B).

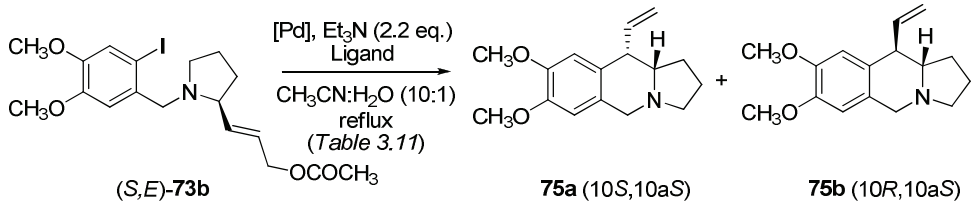


75a (10*S*,10a*S*) **75b** (10*R*,10a*S*)

*Figure 3.8. ORTEP plots of compounds **75a** and **75b***

Similar results were also obtained for acetyl protected alcohol (*S*,*E*)-**73b**, when conditions that provide a higher diastereoselectivity and efficiency in the former synthesis of 10b-vinyl pyrroloisoquinolines were applied (Scheme 3.67). In this case, similar diastereomer ratios for **75a**:**75b** were determined in the crudes, but difficulties in the purification just allowed to isolate the major isomer **75a** in 30-32% yield (Table 3.11, Entries 1-2).

[85] CCDC 1062658 contains the supplementary crystallographic data for **75a**. These data can be obtained from The Cambridge Crystallographic Data Centre (see Appendix).
[86] CCDC 1062659 contains the supplementary crystallographic data for **75b**. These data can be obtained from The Cambridge Crystallographic Data Centre (see Appendix).



(*S,E*)-**73b** **75a** (10*S*,10a*S*) **75b** (10*R*,10a*S*)

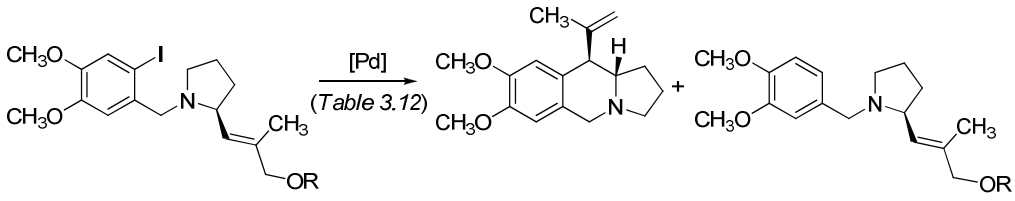
Scheme 3.67

Table 3.11. Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrrolidine ***73b****.*

Entry	[Pd] (mol%)	Ligand	*dr* (75a:75b)[a]	Yield 75a (%)[b]
1	$Pd(OAc)_2$[c]	P(*o*-tolyl)$_3$[f]	78:22	30
2	$Pd_2(dba)_3$[d[e]]	P(*o*-tolyl)$_3$[g]	82:18	32

[a] Diastereomer ratio in the crude, determined by GC-MS. [b] Isolated yield. [c] 10 mol%. [d] 5 mol%. [e] $CHCl_3$ adduct was used. [f] 0.22 eq. [g] 0.1 eq.

In the same way, we studied the Mizoroki-Heck reaction of related *N*-(*o*-iodobenzyl)pyrrolidines (*S,E*)-**74a**, (*S,E*)-**74b** shown in Scheme 3.68.



R = CO*t*-Bu, (*S,E*)-**74a**
R = $COCH_3$, (*S,E*)-**74b**

76 (10*R*,10a*S*)

R = CO*t*-Bu, (*S,E*)-**77a**
R = $COCH_3$, (*S,E*)-**77b**

Scheme 3.68

*Table 3.12. Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrrolidines **74a**, **74b**.*

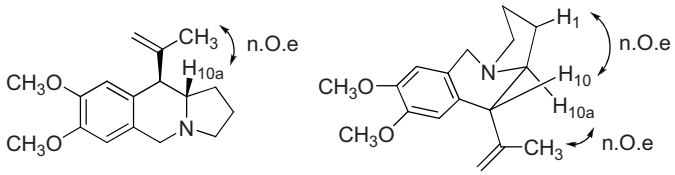
Entry	Subs.	[Pd] (10 mol%)	Base (2.2 eq.)	Ligand	Solvent	Time (h)	Yield 76 (%)[a]
1	**74a**	$Pd(OAc)_2$	Et_3N	P(*o*-tolyl)$_3$[e]	$CH_3CN:H_2O$ [g]	26	-[k]
2	**74b**	$Pd(OAc)_2$	*n*-$BuNMe_2$	P(*o*-tolyl)$_3$[e]	$CH_3CN:H_2O$[g]	48	Traces
3	**74b**	$Pd(OAc)_2$	*n*-$BuNMe_2$	P(*o*-tolyl)$_3$[e]	DMF[h]	5	-[l]
4	**74a**	$Pd_2(dba)_3$[b][c]	Et_3N	P(*o*-tolyl)$_3$[e]	$CH_3CN:H_2O$[g]	26	-[k]
5	**74b**	$Pd_2(dba)_3$[b][c]	*n*-$BuNMe_2$	P(*o*-tolyl)$_3$[e]	$CH_3CN:H_2O$[g]	48	Traces
6	**74a**	$Pd_2(dba)_3$[c]	Et_3N	P(*o*-tolyl)$_3$[e]	Toluene[i]	48	-[m]
7	**74a**	$Pd_2(dba)_3$[c]	Et_3N	P(*o*-tolyl)$_3$[f]	DMF[j]	48	-[n]
8	**74a**	$Pd_2(dba)_3$[c]	Et_3N	P(*o*-tolyl)$_3$[f]	DMF[h]	4	39
9	**74a**	$Pd_2(dba)_3$[c]	Et_3N	P(*o*-tolyl)$_3$[e]	DMF[h]	16	-[m]
10	**74a**	$Pd_2(dba)_3$[c]	Et_3N	P(Cy)$_3$[f]	DMF[h]	4	16[o]
11	**74b**	$Pd_2(dba)_3$[b][c]	*n*-$BuNMe_2$	P(*o*-tolyl)$_3$[e]	DMF[h]	5	Traces
12	**74b**	$Pd_2(dba)_3$[c]	*n*-$BuNMe_2$	P(*o*-tolyl)$_3$[e]	DMF[h]	16	11[p]
13	**74b**	$PdCl_2$[(*o*-tolyl)P_3]$_2$	*n*-$BuNMe_2$	-	$CH_3CN:H_2O$[g]	48	Traces

[a] Isolated yield. [b] 5 mol%. [c] $CHCl_3$ adduct was used. [e] 0.22 eq. [f] 0.44 eq. [g] Heated under reflux and 10:1 mixture of solvents. [h] Heated to 130 ºC. [i] Heated under reflux. [j] Heated to 80 ºC. [k] Starting material was recovered. [l] Deiodinated product **77b** (20%) was obtained. [m] Complex mixture of products. [n] Deiodinated product **77a** (23%) was obtained. [o] Deiodinated product **77a** (24%) was also obtained. [p] Deiodinated product **77b** (37%) was also obtained.

Treating (*S,E*)-**74a**, (*S,E*)-**74b** under former conditions, which proved successful in the synthesis of 10b-vinyl pyrroloisoquinolines, no cyclization was observed (Table 3.12, Entries 1-2). A change in the solvent, proved also unsuccessful (Entry 3). Treatment of (*S,E*)-**74a** with $Pd_2(dba)_3$ in DMF at 80 ºC provided small amounts of (*S,E*)-**77a** (Entry 7). An increase of temperature to 130 ºC gave

pyrroloisoquinoline **76** in 39% yield as a single diastereomer in 4 h (Entry 8). Reaction of (*S,E*)-**74a** using other bulky phosphanes as $P(Cy)_3$ provided **76** in low yield after 4 h (Entry 10). When (*S,E*)-**74b** was treated with $Pd_2(dba)_3.CHCl_3$, *n*-$BuNMe_2$, P(*o*-tolyl)$_3$ in DMF at 130 ºC, **76** (11%) and deiodinated substrate (*S,E*)-**77b** (37%) were isolated. This issue points that longer reaction times may be needed, but always with a risk of decomposition (Entry 12).

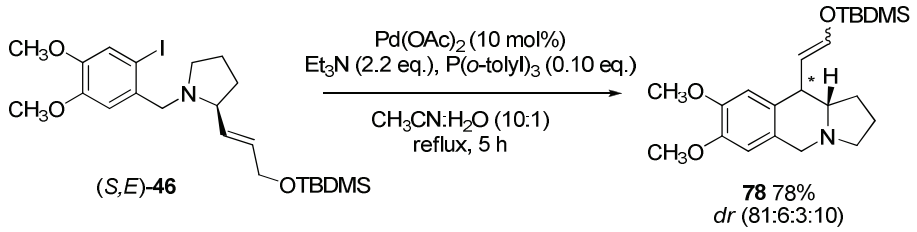
The configuration of **76** has been assigned as *trans*-(10*R*,10a*S*) by 2D NOESY experiments that show enhancements between CH_3 group at the olefin and H-10a and between H-10 and H-1 of the pyrrolidine ring, and by analogy to the former compound **75b** (Figure 3.9).



76 (10*R*,10a*S*)

Figure 3.9

Finally, the protecting group of the alcohol was changed to TBDMS. Thus, enantiopure pyrrolidine (*S,E*)-**46** was subjected to the best conditions in terms of diastereoselectivity for the reaction of (*S,E*)-**73a**. In this case, β´-hydride elimination occurred, obtaining the silyl enol ether **78** in high yield (78%) as a mixture of diastereomers that correspond to (*E*)- and (*Z*)-alkenes of both (10*S*,10a*S*) and (10*R*,10a*S*) diastereomers (Scheme 3.69).



Scheme 3.69

We were able to determine the configuration of the major diastereomer in **78** by 2D NOESY experiments of the mixture. Firstly, the configuration of the alkene was assigned as *E*, as indicated by the coupling constant value between olefinic protons (J_{trans} = 12.0 Hz) detected by ^{1}H NMR spectroscopy, orders of value similar to those obtained for analogous pyrroloisoquinolines (*E*)-**60b** and (*E*)-**62b**.[87] 2D NOESY experiments showed no enhancements between the olefinic proton H_A and H-10a, so a (10*S*,10a*S*)-configuration could be assigned, by analogy to the former pyrroloisoquinoline **75a** (Figure 3.9). Further issues to support this configuration could be the enhancements shown between olefinic H_A and H-1 of the pyrrolidine ring, at the same time than those shown between H-10 and both, H-9 and olefinic H_B.

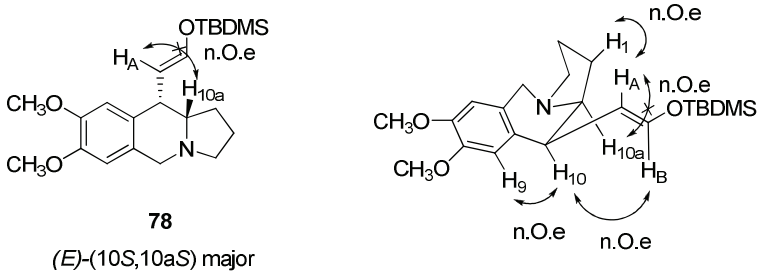
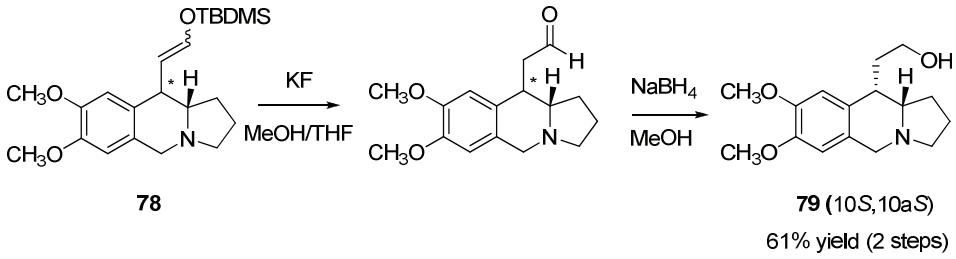


Figure 3.9

[87] See Experimental section.

To confirm the stereochemistry of C-10, the silyl enol eter mixture **78** was deprotected and the resulting aldehyde was reduced to alcohol **79**, which was obtained as a single diastereomer in a 61% yield (over 2 steps) (Scheme 3.70). In this case, we also assigned the absolute configuration of this diastereomer as (10*S*,10a*S*) by 2D NOESY experiments and by analogy to the former pyrroloisoquinoline **75a**. Thus, enhancement shown between H-1 from the pyrrolidine ring and one of the methylenic protons was observed. Additionally, enhancement between H-10 and H-9 could be detected. Similarly, no enhancement between methylenic protons bounded to C-10 and H-10a was observed (Figure 3.10).



Scheme 3.70

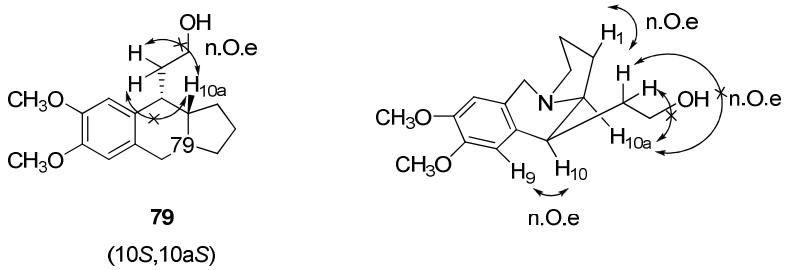
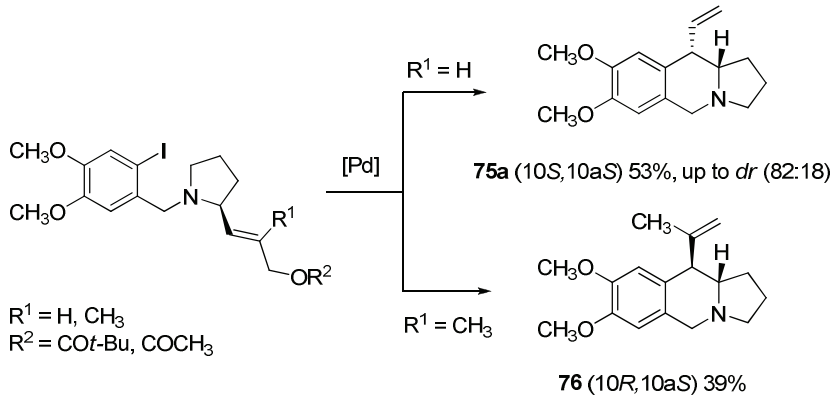


Figure 3.10

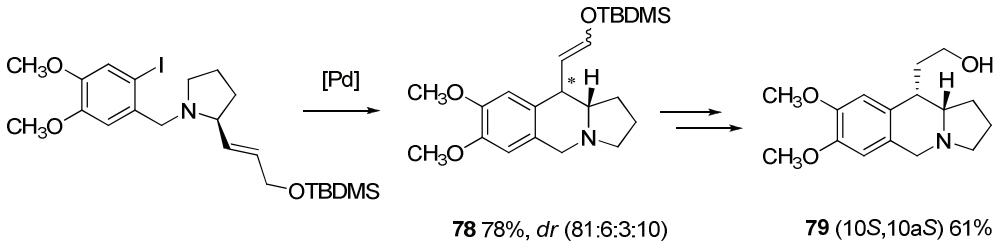
In summary, tertiary stereocenters can be efficiently generated by Mizoroki-Heck reaction of protected *N*-(*o*-iodobenzyl)pyrrolidinyl allylic alcohols. A change in the protecting group allows the selective β´-hydride elimination (when TBDMS is used) or β´-leaving group elimination (when pivalate or acetate are used), leading to the corresponding functionalized pyrroloisoquinolines.

The Mizoroki-Heck reaction proceeded with moderate diastereoselectivity for acyl protected *N*-(*o*-iodobenzyl)pyrrolidines through β´-elimination of the alkoxy group. However, when an additional substituent is placed in the alkene, there is an inversion on diastereoselectivity (Scheme 3.71).



Scheme 3.71

When the alkene moiety is substituted by a silyloxymethyl group, the application of the same methodology permits the synthesis of pyrroloisoquinolines **78** with high diastereoselectivity, this time with retention of the leaving group. In addition, derivatization of pyrroloisoquinoline **78** provides the corresponding alcohol **79** in high yield and total diastereoselectivity (Scheme 3.72).



78 78%, *dr* (81:6:3:10) **79** (10*S*,10a*S*) 61%

Scheme 3.72

The work described in Chapter IV has been carried out in the Institute of Organic Chemistry at RWTH Aachen University under the supervision of Prof. C. Bolm.

IV

Rh(III)-Catalyzed Direct Nucleophilic Addition to Polar Unsaturated Bonds *via* C-H Bond Activation

4.1. Introduction

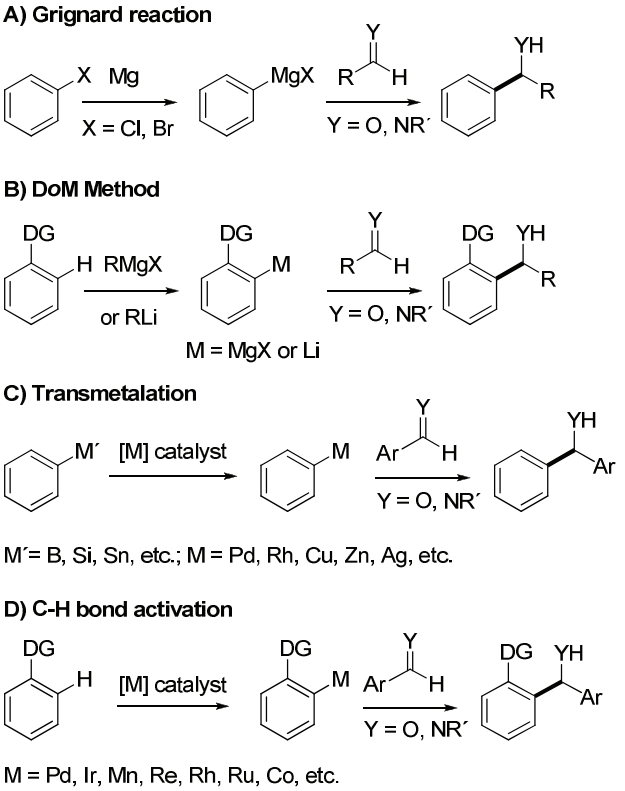
The nucleophilic addition of organometallic reagents to polar unsaturated electrophiles, such as carbonyl compounds and their derivatives, is a relevant method for the construction of carbon-carbon bonds in Organic Synthesis.[1]

Traditionally, chemists have required the use of Grignard reagents to perform this type of reactions (Scheme 4.1a), which involves the need to prepare aryl halides as starting materials associated with a raise in the costs and sometimes, a tedious preparation. In addition, directed *ortho*-metalation (D*o*M) strategies[2] of functionalized arene compounds (Scheme 4.1b) partially solves this problem as a complementary method for preparation of susbstrates, but adversely requires the use of stoichiometric amount of organometallic reagents. From a synthetic point of view, both former methods imply a number of drawbacks such as strict and complex anhydrous and anaerobic manipulation requirements for the air- and moisture-sensitive organometallic reagents, limited functional tolerance, prefunctionalization of nucleophilic coupling partners and formation of stoichiometric salt waste.

[1] a) Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagents,* Marcel Dekker: New York, **1996**. b) Richey, H. G. *Grignard Reagents: New Developments,* Wiley: Chichester, **2000**. c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. d) Katritzky, A. R.; Taylor, R. J. K. *Comprehensive Organic Functional Group Transformations II*, Elsevier: Dordrecht, **2004**, Chapter 2, p. 561.

[2] a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. b) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206. c) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1503. d) Wunderlich, S. H.; Kienle, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7256. e) Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. *Angew. Chem. Int. Ed*. **2010**, *49*, 5451.

Transition metal-catalyzed addition of more stable and air and moisture tolerant organometallic reagents (RM´, M´ = B, Si, Sn, etc.) to carbonyl and imine groups opens a new route providing a wider expansion in the reaction scope (Scheme 4.1c).[3] However, the permanent requirement of prefunctionalization of substrates resulted in a low atom- and step economy.



Scheme 4.1

[3] a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. c) Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 3364. d) Miyaura, N. *Synlett* **2009**, 2039. e) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev*. **2011**, *111*, 7774.

In the past decades, a new strategy based in transition-metal catalyzed C-H activation of substrates has emerged as a straightforward and environmentally friendly synthetic tool to overcome the main drawbacks of traditional organometallic chemistry, principally prefunctionalization issues (Scheme 4.1d).

Therefore, the elimination of prefunctionalization introduces new challenges to control the selectivity and overfunctionalization through competing reactivity of multiple bonds. Among the most promising activation strategies, we can outline the use of a chelating heteroatom (directing group) that by coordination to the metal center will facilitate reactivity at a proximal site. A wide variety of metal catalysts have appeared to promote reactivity of specific C-H bonds.

Rhodium-based catalysis has become one of the leading candidates presenting functional group tolerance and efficiency in this field. Most of the studies involving these catalysts were centered in the oxidative coupling of aryl substrates with alkene and alkyne derivatives *via* C-H activation process.[4] This pioneering work has encouraged chemists to focus on the less investigated transition-metal-catalyzed nucleophilic addition of C-H bonds to polar C-X (X = N, O) unsaturated bonds, such as aldehydes, imines, isocyanates, etc.[5] In this context, some examples

[4] For selected reviews of transition-metal catalyzed oxidative coupling with alkenes and alkynes, see: a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731. b) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212. c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, 110, 624. d) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. e) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev*. **2012**, *41*, 3651. f) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31. g) Chiba, S. *Chem. Lett.* **2012**, *41*, 1554. h) Zhu, C.; Wang, R.; Falck, J. R. *Chem. Asian J.* **2012**, *7*, 1502. i) Rao, Y.; Shan, G.; Yang, X. L. *Sci. China Chem.* **2014**, 57, 930.

[5] For selected reviews of transtition-metal catalyzed additions to unsaturated polar bonds, see: a) Yan, G.; Wu, X.; Yang, M. *Org. Biomol. Chem*. **2013**, *11*, 5558. b) Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Chem. Sci.* **2014**, 5, 2146.

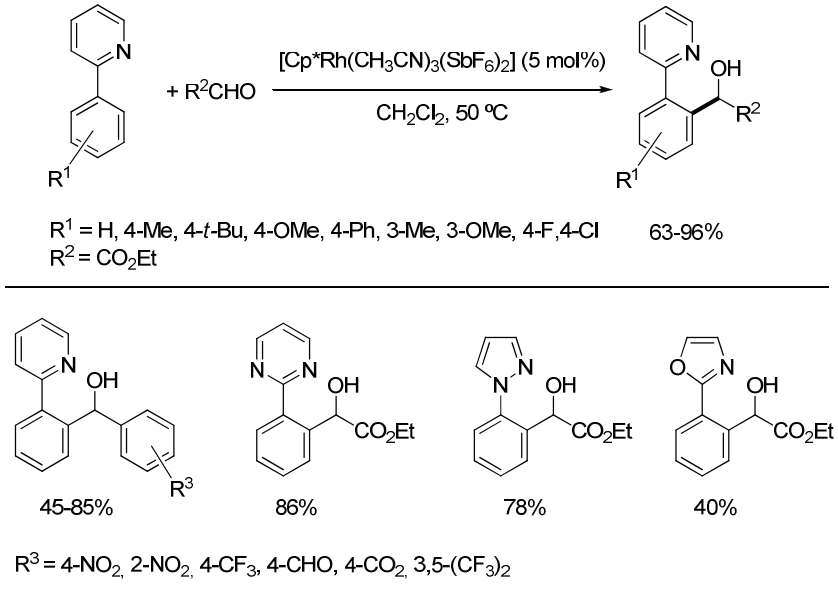
based on the nucleophilic addition of C-H bonds to different polar unsaturated electrophiles will be discussed in order to understand the background of this work.

4.2. Rh(III) catalyzed addition to polar π bonds

4.2.1. Addition of *ortho* C-H bond to aldehydes

Since Miyaura and coworkers reported the first rhodium-catalyzed addition of organoboronic acids to aldehydes, which involved a previous transmetallation process,[6] organic chemists thought about a complementary strategy based on C-H bond activation before addition to the polar electrophile. Some years later, Takai *et al*. published the chelation assisted addition of aromatic C-H bond to aldehydes by quenching the resulting alcohols with silanes, but this time, catalyzed by another transition metal such as manganese.[7] With this reaction in mind, and intrigued by a possible Rh-based C-H activation of substrates, Li and coworkers described an alternative Grignard type arylation of aldehydes to synthesize the respective benzyl alcohol derivatives (Scheme 4.2).[8] In this case, rhodium-catalyzed chelation-assisted C-H activation using a pyridine as directing group, generates an organometallic species that undergoes subsequent addition under mild conditions. Other nitrogen containing heterocycles have also been used as directing groups, such as pyrimidinyl, pyrazolyl and oxazolyl groups, providing a useful route to synthesize the corresponding alcohols. Moreover, the reaction presents a wide functional group tolerance and can proceed efficiently in the presence of air and water.

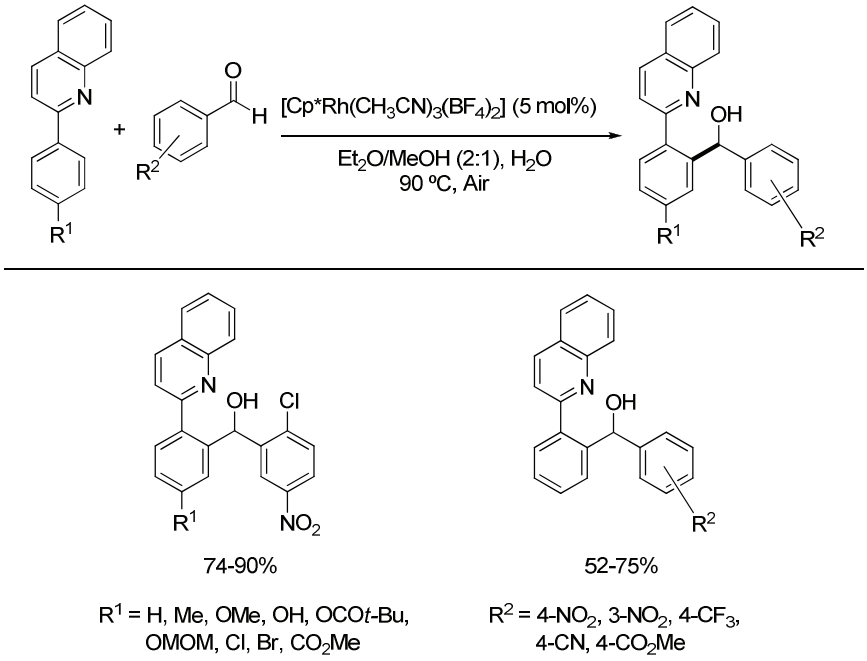
[6] Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 3279.
[7] Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. *Angew. Chem. Int. Ed*. **2007**, *46*, 6518.
[8] Yang, L.; Correia, C. A.; Li, C.-J. *Adv. Synth. Catal*. **2011**, *353*, 1269.



Scheme 4.2

Shi and coworkers similarly described the rhodium-catalyzed direct addition of aryl C-H bonds to aromatic aldehydes to synthesize biaryl methanols with a highly effective and atom-economical procedure.[9] This strategy required the presence of a *N*-containing directing group, such as a quinoline system, and showed broad group tolerance without the addition of any oxidant or reductant (Scheme 4.3).

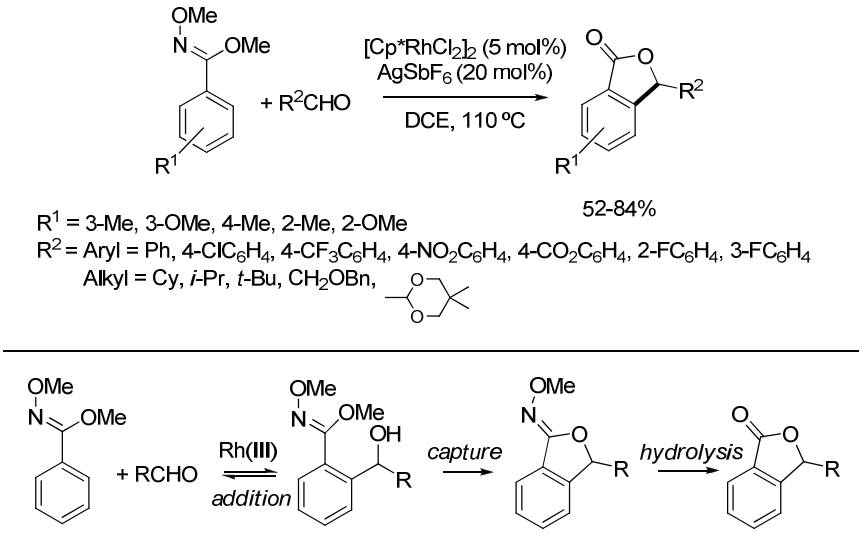
[9] Li, Y.; Zhang, X.-S.; Chen, K.; He, K.-H.; Pan, F.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 636.



Scheme 4.3

Recent developments have shown a tandem C-H bond nucleophilic addition followed by cyclization reaction where a capture of the formed alcohol intermediate occurred leading to the synthesis of heterocycles. In this context, Ellman and coworkers were able to synthesize biologically active phthalides in a single step by Rh(III) catalyzed C-H activation of benzimidates and addition to differently substituted aromatic and aliphatic aldehydes.[10] In this case, they propose a mechanism where the imidate not only acts as a directing group to direct the *ortho* C-H bond activation, but also serves to capture the alcohol intermediate formed upon addition with release of a methoxy group. A final hydrolysis would afford the final phthalide (Scheme 4.4).

[10] Lian, Y.; Bergman, R. G.; Ellman, J. A. *Chem. Sci*. **2012**, *3*, 3088.



Scheme 4.4

Following the same scheme but using a carboxylic acid as directing group, Li *et al*. reported a simple method to synthesize phthalimides by the *ortho* C-H bond addition of benzoic acids to aldehydes and subsequent cyclization.[11]

Nucleophilic addition to ketones has been less investigated, as ketone moiety represents a less reactive and more steric hindered group than aldehyde. Just a few examples involving iridium metal complexes[12] as catalysts appear in the bibliography. Thus, Shi *et al*. reported the first methodology to perform direct addition of aromatic C-H bonds to ketones catalyzed by rhodium and using a quinoline as directing group.[13]

[11] Shi, X.; Li, C.-J. *Adv. Synth. Catal*. **2012**, *354*, 2933.
[12] a) Tsuchikama, K.; Hashimoto, Y.; Endo, K.; Shibata, T. *Adv. Synth. Catal.* **2009**, *351*, 2850. b) Shibata, T.; Hashimoto, Y.; Otsuka, M.; Tsuchikama, K.; Endo, K. *Synlett* **2011**, 2075.
[13] Zhang, X.-S.; Zhu, Q.-L.; Luo, F.-X.; Chen, G.; Wang, X.; Shi, Z.-J. *Eur. J. Org. Chem*. **2013**, 6530.

4.2.2. Addition of *ortho* C-H bond to imines

Imines represent an important source of nitrogen for synthetic organic transformations. In this context, when the coupling partner is changed from an aldehyde to an imine group, the addition reaction is also effective generating amines as final products. The work described in this chapter is based in the addition of C-H bonds to this moiety, thus some examples will be described to help to understand the background of this field.

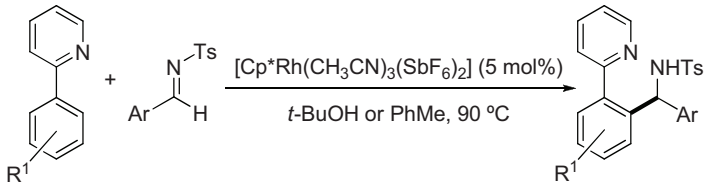
In 2011, Ellman and coworkers described the first arylation of imines based in Rh(III)-catalyzed C-H activation assisted by pyridine as chelating group to obtain branched *N*-protected Boc amines (Scheme 4.5).[14] The use of $AgSbF_6$ additive as halide abstractor was required since it favors the coordination between the cationic metal center and the nitrogen atom of imines. At that time, the activation process was thought to occur through an electrophilic deprotonation of the *ortho*-phenyl C-H bond. However, the same group reported later a detailed mechanistic study proposing a concerted metalation-deprotonation (CMD) mechanism proved by the isolation and characterization of relevant Rh(III) complex intermediates.[15]

Ar = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-$CF_3C_6H_4$, 2-MeC_6H_4 50-95%

Scheme 4.5

[14] Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc*. **2011**, *133*, 1248.
[15] Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc*. **2012**, *134*, 1482.

Shi and coworkers,[16] continuing with the work of Ellman, reported the chelation-assisted rhodium-catalyzed nucleophilic addition of aryl C-H bonds to *N*-sulfonyl arylaldimines using pyridine again as directing group. This strategy included a wider substrate scope and provided a wide range of functional group tolerance (Scheme 4.6).

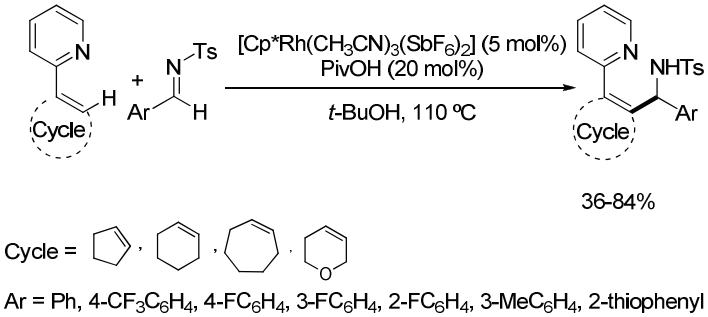


R^1 = H, 4-OMe, 4-OH,4-Cl, 4-Br, 4-$OCONMe_2$, 4-CO_2Me
Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 3-FC_6H_4, 2-thiophenyl

Scheme 4.6

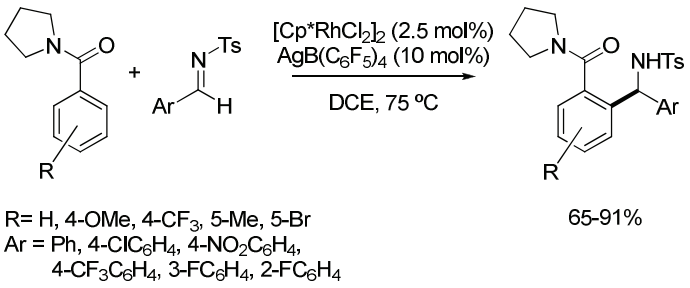
The same group developed the first strategy of direct addition of alkenyl C-H to *N*-sulfonyl aldimines and aldehydes *via* rhodium catalysis with assistance of pyridyl directing group (Scheme 4.7).[17]

[16] Li, Y.; Li, B.-J.; Wang, W.-H.: Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 2115.
[17] Li, Y.; Zhang, X.-S.; Zhu, Q.-L.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 4498.



Scheme 4.7

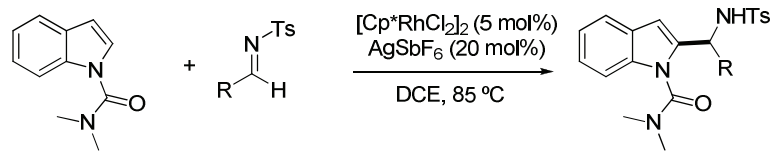
Ellman and coworkers have also shown that amides can act as directing groups in the rhodium-catalyzed C-H addition to *N*-sulfonyl aldimines.[18] In this sense, the limited utility of the pyridyl directing group was overcome by the use of a directing amide group, which was responsible of *ortho*-functionalization in the aryl group by Lewis base directed C-H cleavage. The reaction showed great functional group compatibility (Scheme 4.8).



Scheme 4.8

[18] Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Org. Lett*. **2012**, *14*, 2304.

Similarly, heteroaromatic C-H bonds may also be activated by amide chelating groups. Therefore, Zhou *et al.* reported regioselective C-2 metalation of indoles and subsequent nucleophilic addition to *N*-sulfonyl aldimines catalyzed by rhodium (Scheme 4.9).[19]



R = Ph, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$CO_2MeC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-FC_6H_4, Cy, *n*-Bu

Scheme 4.9

As has been shown through these examples, rhodium catalyzed nucleophilic addition to aldehyde and imine groups *via* C-H activation, represents an efficient approach to synthesize alcohols and amines. Finally, some examples of *ortho* C-H bond addition to isocyanate groups for the synthesis of amides will be described.

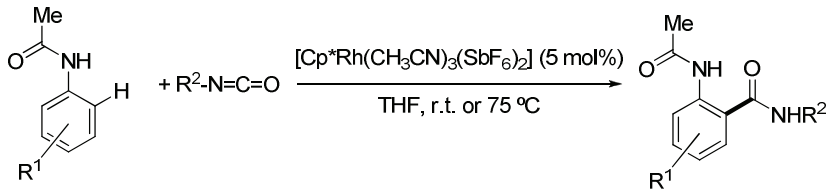
4.2.3. Addition of *ortho* C-H bond to isocyanates

In 1978, Sonogashira reported the pioneer studies of the direct addition of benzene, used as solvent, to phenyl isocyanate catalyzed by $Rh_4(CO)_{12}$ in the presence of carbon monoxide at 220 ºC to obtain benzanilide.[20] Since that, a wide number of examples involving different transition-metal catalyzed direct additions to

[19] Zhou, B.; Yang, Y.; Lin, S.; Li, Y. *Adv. Synth. Catal.* **2013**, *355*, 360.
[20] Hong, P.; Yamazaki, H.; Sonogashira, K.; Hagihara, N. *Chem. Lett*. **1978**, 535.

isocyanates group have been developed such as rhenium[21] and ruthenium[22] complexes so far.

Continuing with their studies in rhodium-based catalysis, Ellman published the efficient synthesis of *N*-acyl anthranilamides and enamine amides *via* amidation of aryl C-H bonds with isocyanates (Scheme 4.10).[23] Both aryl and alkyl isocyanates are compatible in this strategy.



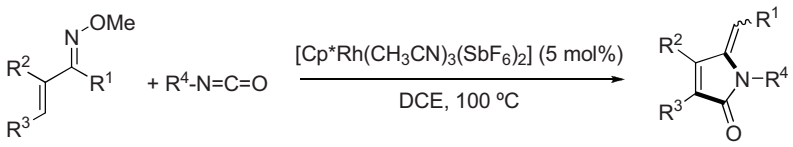
R^1 = 4-CF_3, 5-Me, 5-Cl
R^2 = Ph, Bn, *n*-Hex, Cy, 1-adamantyl

48-97%

Scheme 4.10

In 2013, Li and coworkers described synthesis of biologically active substituted 5-ylidinepyrrol-2(5*H*)-ones *via* rhodium-catalyzed nucleophilic addition of an alkenyl C-H bond to isocyanates, followed by annulation process under mild conditions (Scheme 4.11).[24] The oxime moiety directed the activation to the *ortho* C-H bond.

[21] a) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc*. **2006**, *128*, 202. b) Kuninobu, Y.; Tokunaga, Y.; Takai, K. *Chem. Lett.* **2007**, *36*, 872.
[22] Muralijaran, K.; Parthasarathy, K.; Cheng, C.-H. *Org. Lett*. **2012**, *14*, 4262.
[23] Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430.
[24] Hou, W.; Zhou, B.; Yang, Y.; Feng, H.; Li, Y. *Org. Lett*. **2013**, *15*, 1814.

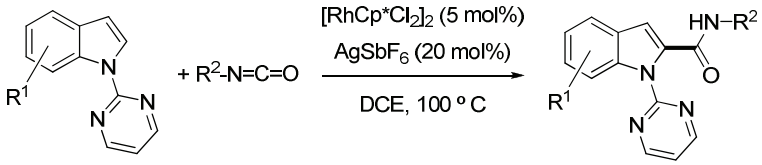


59-93%

R^1 = Me, Et
R^2 = Me; R^2 , R^3 = -$(CH_2)_4$-
R^3 = Me, Ph, 4-MeC_6H_4, 4-OMeC_6H_4, 4-FC_6H_4, naphthyl
R^4 = 4-MeC_6H_4, 4-OMeC_6H_4, 4-$NO_2C_6H_4$, $CF_3C_6H_4$, 4-CO_2EtC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, naphthyl, *n*-Hex, Cy

Scheme 4.11

Recently, Kim and coworkers have described the synthesis of C-2-amidated *N*-heterocyclic cores through rhodium-catalyzed amidation of indoles and pyrroles, which contained a pyrimidinyl group to direct *ortho* C-H activation, with different aryl and alkyl isocyanates (Scheme 4.12).[25]



38-81%

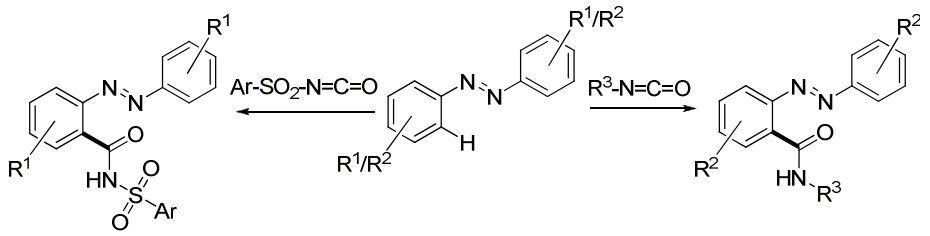
R^1 = H, 4-OMe, 4-NO_2, 4-Br, 4-Cl, 5-F
R^2 = Et, *n*-Bu, *n*-pent, *n*-Hex, -$(CH_2)_2$Ph, Bn, Ph

Scheme 4.12

The same group has reported the generation of *N*-acylsulfonamides and *ortho*-amidated azobenzenes by rhodium(III)-catalyzed nucleophilic addition of

[25] Jeong, T.; Han, S.; Mishra, N. K.; Sharma, S.; Lee,S.-Y.; Oh, J. S.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 7243.

azobenzenes to arylsulfonyl and aryl and alkyl isocyanates.[26] This effective strategy provides the ready access to a wide scope of substrates that are known to be precursors of biologically active compounds (Scheme 4.13).



Method: $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgNTf_2$ (10 mol%), NaOAc (30 mol%), DCE, 110 ºC

R^1 = H, *m*-OMe, *m*-Me, *m*-Br, *p*-OMe, *p*-Me, *p*-Br, *p*-Cl, *p*-OCF_3, *p*-CO_2Et
Ar = 4-MeC_6H_4

R^2 = H, *m*-OMe, *m*-Me, *m*-Br, *p*-OMe
R^3 = 4-$CF_3C_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 3-MeC_6H_4, 3-$CF_3C_6H_4$, naphthyl, Bn, cyclopentyl, *n*-Hex

Scheme 4.13

In conclusion, aldehydes, imines and isocyanates represent the most common groups to be used as electrophilic partners for coupling reactions based in transition-metal catalyzed nucleophilic addition, principally in rhodium catalysis. Different chelating groups such as pyridine, pyrimidine or simple amides have been used to direct activation of *ortho* C-H bonds. There is still room for improvement in this field, so the study on different electrophilic groups and other metal catalysts is on great expansion.

[26] Han, S.; Mishra, N. K.; Sharma, S.; Park, J.; Choi, M.; Lee, S.-Y.; Oh, J. S.; Jung, Y. H.; Kim, I. S. *J. Org. Chem*. **2015**, *80*, 8026.

4.3. Results and discussion

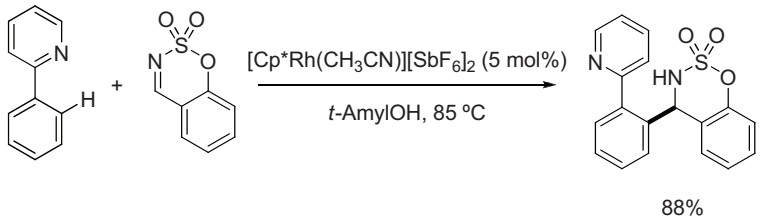
As we have stated before, metal-transition catalyzed nucleophilic addition through C-H activation and insertion in unsaturated polar bonds involves an easy and atom-economical strategy for the synthesis of more complex molecules.

Diverse metal complexes have been used to perform the addition of C-H bond of 2-arylpyridines to different polar bonds. We have already mentioned the example reported by Cheng and coworkers for ruthenium(II) catalyzed *ortho*-directed amidation of 2-arylpyridines with isocyanates *via* C-H activation.[22] In addition, cobalt(III) catalyzed C-H addition of 2-arylpyridines with imines have also been published by Matsunaga and coworkers.[27] Furthermore, transition-metal catalyzed addition of boronic acids to cyclic ketimines has also been investigated.[28] However, the *ortho*-directed addition of 2-arylpyridines with cyclic imines has never been reported. Bolm´s group had previously performed rhodium catalyzed studies in the oxidative coupling with alkenes and alkynes *via* C-H bond activation.[29]

In this context, the optimization of the catalytic conditions for the rhodium-catalyzed direct nuclephilic addition of 2-phenylpyridine to a non-substituted [1,2,3]-benzoxathiazine-2,2-dioxide *via* C-H bond activation has been carried out

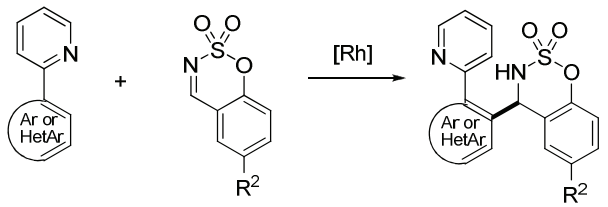
[27] a) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2207. b) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Chem. Eur. J.* **2013**, *19*, 9142.
[28] a) Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc*. **2012**, *134*, 5056. b) Yang, G.; Zhang, W. *Angew. Chem. Int. Ed*. **2013**, *52*, 7540.
[29] a) Dong, W.; Wang, L.; Parthasarathy, K.; Bolm, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11573. b) Becker, P.; Priebbenow, D. L.; Pirwerdjan, R.; Bolm, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 269. c) Parthasarathy, K.; Bolm, C. *Chem. Eur. J.* **2014**, *20*, 4896.

in the group of Bolm, by the postdoctoral student Kanniyappan Parthasarathy (Scheme 4.14).[30]



Scheme 4.14

The aim of this work was to synthesize a variety of coupling partners, such as 2-(hetero)arylpyridines and cyclic imines bearing different substitution patterns, in order to evaluate the scope of the reaction (Scheme 4.15).



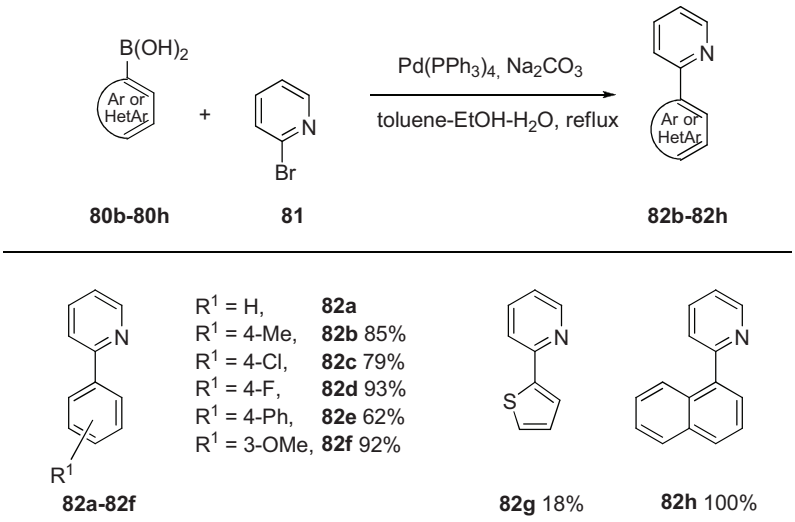
Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-PhC_6H_4, 3-$OMeC_6H_4$, 4-naphthyl
HetAr = 2-thiophenyl
R^2 = H, OMe, F, Cl, Br, -OCH_2O-

Scheme 4.15

[30] Parthasarathy, K.; Azcargorta, A. R.; Cheng, Y.; Bolm, C. *Org. Lett*. **2014**, *16*, 2538.

4.3.1. Synthesis of 2-(hetero)arylpyridines and [1,2,3]-benzoxathiazine-2,2-dioxides

Firstly, a variety of substituted 2-aryl- and 2-heteroarylpyridines were synthesized by a Suzuki cross-coupling reaction (Scheme 4.16).[31] This methodology permitted the obtention of (hetero)arylpyridines **82b-82h** by treatment of 2-pyridinyl bromide (**81**) and differently substituted aryl and heteroaryl boronic acids **80b-80h** in the presence of $Pd(PPh_3)_4$ catalyst and Na_2CO_3 as base, obtaining from low yields (18% for the 2-thiophenylpyridine) to excellent yields for the rest of products (62%-100%).[32] 2-Phenylpyridine (**82a**) was commercially available.

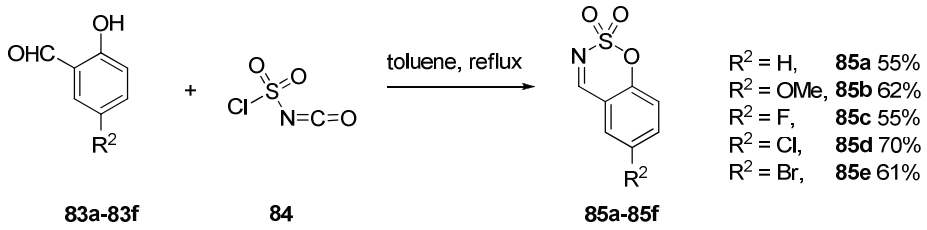


Scheme 4.16

[31] For some reviews in Suzuki coupling reaction, see: a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. b) Suzuki, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6722. c) Heravi, M. M.; Hashemi, E. *Monats. für Chem*. **2012**, *143*, 861. d) Soloducho, J.; Olech, K.; Swist, An.; Zajac, D.; Cabaj, J. *ACES*, **2013**, *3*, 19. e) Kapdi, A. R.; Prajapati, D. *RSC Adv.* **2014**, *4*, 41245. f) Zafar, M. N.; Mohsin, M. A.; Danish, M.; Nazar, M. F.; Murtaza, S. *Russ. J. Coord. Chem.* **2014**, *40*, 781. g) Maluenda, I.; Navarro, O. *Molecules* **2015**, *20*, 7528.

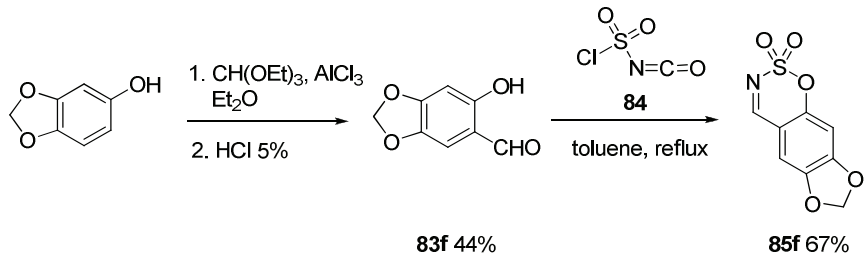
[32] Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 1251.

The preparation of the differently functionalized [1,2,3]-benzoxathiazine-2,2-dioxides **85a-85f** involved treatment of 2-hydroxybenzaldehydes **83a-83f** with commercially available chlorosulfonylisocyanate (**84**) in toluene under reflux (Scheme 4.17).[33] This procedure involves imine formation and subsequent cyclization to the expected cyclic imines **85a-85e** in moderate to good yields.



Scheme 4.17

The preparation of cyclic imine **85f** was conducted in a two step sequence starting with the formylation of sesamol by reaction with triethyl orthoformate in the presence of a Lewis acid ($AlCl_3$) as depicted Scheme 4.18. Acidic workup provided 2-hydroxy-4,5-methylenedioxybenzaldehyde (**83f**) in moderate yield, which was subjected to reaction with chlorosulfonylisocyanate (**84**) to afford ketimine **85f** (67%).



Scheme 4.18

[33] Kamal, A.; Sattur, P. B. *Synthesis* **1981**, 272.

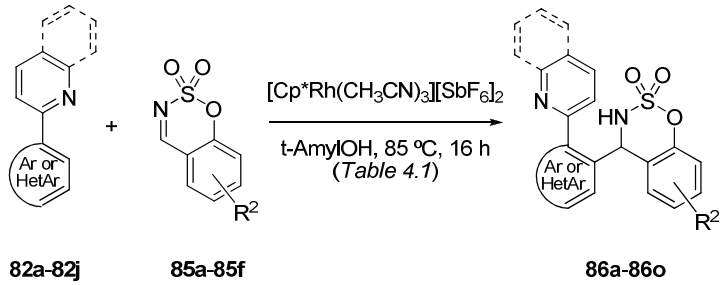
4.3.2. Scope of the reaction

We started the evaluation of the substrate scope using the best optimization conditions (Scheme 4.19).[30] All the results are depicted in Table 4.1. The treatment of various 4-substituted phenylpyridines (**82a-82e**) with cyclic imine **85a** under optimized conditions, allowed efficiently C-H activation/nucleophilic addition to obtain products **86a-86e** in high yields (72-95%) (Entries 1-5). Substrate 2-(3-methoxyphenyl)pyridine (**82f**) followed selective C-6 *ortho*-directed nucleophilic addition to ketimine **85a** catalyzed by rhodium, to afford the coupling product **86f** in high yield (81%) (Entry 6). It is noteworthy to highlight that from two possible C-H activation sites (C-2 and C-6), the less sterically hindered one C-6 at the phenyl ring was more reactive.

Different heteroarylpyridines such as 2-thienylpyridine **82g** were tried, following efficient addition to provide product **86g** (Entry 7). Treatment of (2-naphthalen-1-yl)-pyridine (**82h**) with cyclic imine **85a** under catalyzed conditions, resulted in the formation of addition product **86h** in moderate yield (57%) (Entry 8). When commercially available 2-phenyl-quinoline (**82i**) and benzo[*h*]quinolone (**82j**) were used as substrates low to moderate yields were obtained (27-56%) (Entries 9-10).

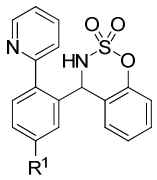
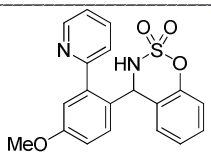
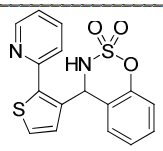
We continued with further development of the scope, this time by using 2-phenylpyridine (**82a**) as reference substrate and employing differently functionalized cyclic imines (**85b-85f**) as coupling partners. In this way, treatment of substrate **82a** with 6-methoxy- and 6-halo-[1,2,3]-benzoxathiazine-2,2-dioxide (**85b-85e**) under rhodium(III) catalyzed conditions resulted in the synthesis of products (**86k-86n**) in high yields (69-83%) (Entries 11-14). Finally, no addition

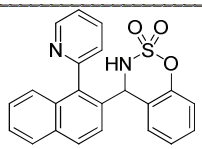
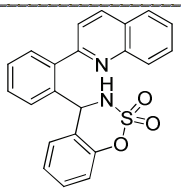
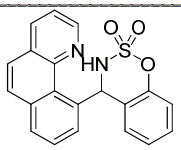
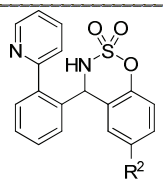
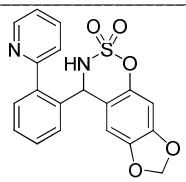
product was observed when reaction of pyridine **82a** with ketimine **85f** was performed (Entry 15).



Scheme 4.19

*Table 4.1. Nucleophilic addition of 2-arylpyridines and related substrates **82a-82j** to cyclic imines **85a-85f**.*[a]

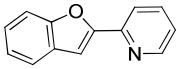
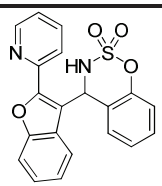
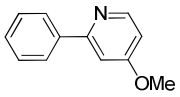
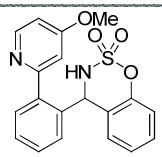
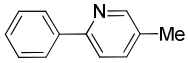
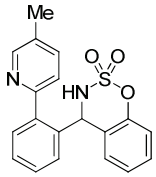
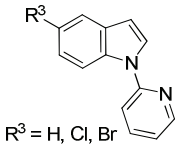
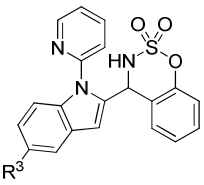
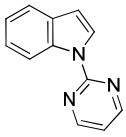
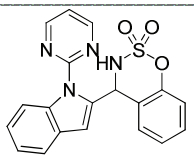
Entry	82	85	Product 86	Yield (%)
1	**82a**	**85a**	 R^1 = H, **86a**	88
2	**82b**	**85a**		R^1 = Me, **86b**	95
3	**82c**	**85a**		R^1 = Cl, **86c**	79
4	**82d**	**85a**		R^1 = F, **86d**	83
5	**82e**	**85a**		R^1 = Ph, **86e**	72
6	**82f**	**85a**		**86f**	81
7	**82g**	**85a**		**86g**	97

8	**82h**	**85a**		**86h**[b]	57
9	**82i**	**85a**		**86i**	56
10	**82j**	**85a**		**86j**	27
11	**82a**	**85b**		R^2 = OMe, **86k**	69
12	**82a**	**85c**		R^2 = F, **86l**	74
13	**82a**	**85d**		R^2 = Cl, **86m**	81
14	**82a**	**85e**		R^2 = Br, **86n**	83
15	**82a**	**85f**		**86o**[c]	Traces

[a] Reaction conditions: 2-arylpyridine **82** (1 mmol), cyclic imine **85** (1.1 mmol), $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (5 mol%) in *t*-AmylOH (3 mL) at 85 ºC for 16 h. [b] Product **86h** was not isolated pure. [c] Product **86o** was not characterized (impure).

Further extension of the scope was performed by the Ph.D. student Ying Cheng, where additional coupling partners were used.[30] The new results are included in the following Table 4.2.

Table 4.2. Extension of the scope.[a]

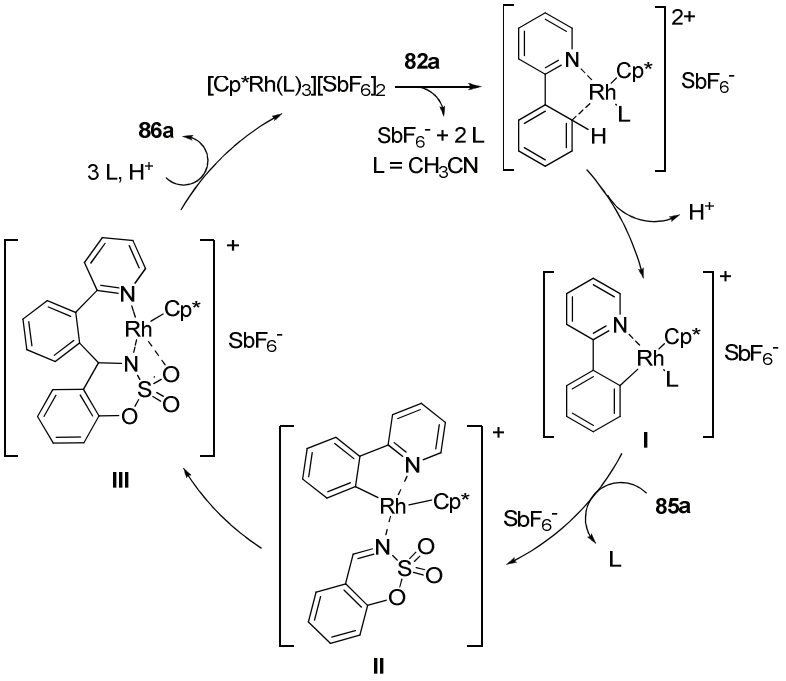
Entry	82	85	Product 86		Yield (%)
1		**85a**		**86p**	77
2		**85a**		**86q**	72
3		**85a**		**86r**	74
4		**85a**		R^3 = H, **86s**	80
5		**85a**		R^3 = Cl, **86t**	77
6		**85a**		R^2 = Br, **86u**	70
7		**85f**		**86v**	74

[a] Reaction conditions: 2-arylpyridine **82** (1 mmol), cyclic imine **85** (1.1 mmol), $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (5 mol%) in *t*-AmylOH (3 mL) at 85 ºC for 16 h.

4.3.3. Mechanism and kinetic studies

A mechanistic proposal and determination of Kinetic Isotope Effect (KIE)[30] was established by postdoctoral student Kanniyappan Parthasarathy, on the basis of previously reported studies in this field.[13,16,17,26]

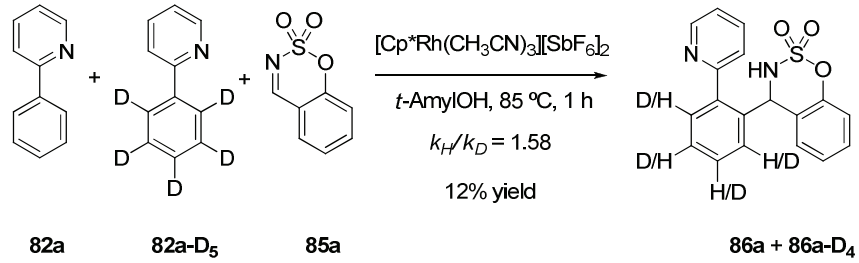
The catalytic cycle illustrated in Scheme 4.20, starts with the coordination of the nitrogen atom of the 2-phenylpyridine (**82a**) to the cationic rhodium center which is followed by insertion of the metal in the activated C-H bond in order to form the five-membered rhodacycle **I**, together with the loss of a proton. Then, coordination of the cyclic imine **85a** to the rhodium takes place to generate intermediate **II** by ligand exchange, which directly undergoes nucleophilic addition or insertion of C=N bond of the imine into Rh-C bond to afford seven-membered rhodacycle **III**. Finally, proton abstraction of intermediate **III** gives the desired addition product **86a**, accompanied by the regeneration of the active rhodium catalyst which could enter the catalytic cycle again. External additives are not required to perform this catalytic cycle.



Scheme 4.20

Intermolecular competition experiment was carried out by treatment of cyclic imine **85a** and a mixture 1:1 of 2-phenylpyridine (**82a**) and deuterated phenylpyridine **82a-D$_5$**. The ratio of the two products **86a** and **86a-D$_4$** was calculated by integration of ^{1}H NMR signals, to provide intermolecular kinetic isotope effect (KIE) of k_H/k_D = 1.58, which determined that C-H bond cleavage is rate determining (Scheme 4.21).[34]

[34] Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066.



82a **82a-D_5** **85a** **86a + 86a-D_4**

Scheme 4.21

In conclusion, an efficient and selective strategy to synthesize amine derivatives has been developed through rhodium(III) catalyzed *ortho*-directed chelation assisted C-H activation, followed by nucleophilic addition of differently functionalized arylpyridines with cyclic imines. Additionally, this C-H functionalization method provides high functional group tolerance.

V

Final Conclusions

5.1. Conclusions

5.1. Conclusions

- The application of intramolecular carbolithiation reaction *via* conjugate addition of electron-deficient heteroaryllithiums, such as pyridinyl and quinolinyllithiums, generated by halogen-lithium exchange on 2-alkenyl substituted *N*-(haloheteroarylmethyl)pyrroles, has allowed the synthesis of pyrrolo[1,2-*g*]naphthyridine and benzo[*b*]pyrrolo[1,2-*g*]naphthyridine derivatives in low to moderate yields. However, these Parham type cyclizations *via* S_N2'reaction on the corresponding allylic alcohol derivatives proved unsuccessful, due to competitive side addition reactions.

- The intramolecular carbolithiation reaction *via* conjugate addition on *N-(o*-iodobenzyl)pyrrolidinylacrylates, derived from L-proline, takes place diastereoselectively affording the corresponding enantiomerically pure (10*R*,10a*S*)-pyrroloisoquinoline. On the other hand, intramolecular carbolithiation reaction *via* S_N2'reaction is not favored when TBDMS or acetyl protected allylic alcohols are used as internal electrophiles.

- Intramolecular Palladium(0)-catalyzed reaction of 2-alkenyl substituted *N*-(haloheteroarylmethyl)pyrroles always led to the direct arylation reaction on the pyrrole nucleus, using catalytic systems that would favor either a neutral or a cationic mechanism. Thus, the synthesis of heterofused indolizine systems, such as pyrido[2,3-*a*]pyrrolizines and pyrrolizino[1,2-*b*]quinolines, can be achieved in high yields.

- Tertiary and quaternary stereocenters can be efficiently generated through intramolecular Mizoroki-Heck reaction over silyl protected *N*-(*o*-iodobenzyl)pyrrolyl allylic alcohol derivatives for the synthesis of pyrroloisoquinolines through β´-hydride elimination. However, no good enantioselection could be achieved using chiral phosphanes under all conditions tested. When the corresponding pivaloyl protected allylic alcohol derivatives were used, the reaction was not regioselective, obtaining mixtures of β´-hydride and β´-leaving group elimination products in low yields. On the *N*-(*o*-haloheteroarylmethyl)pyrrolyl allylic alcohol derivatives the direct arylation reactions is always competitive.

- The generation of tertiary stereocenters have been efficiently achieved *via* intramolecular Mizoroki-Heck reaction of *N*-(*o*-iodobenzyl)pyrrolyl allylic alcohol derivatives for the synthesis of pyrroloisoquinolines in a diastereoselective manner. It has been possible to control the β´-hydride or β´-leaving group elimination in the formation of the stereocenter, by changing the protecting group in the alcohol moiety. When acyl protecting groups (pivalate or acetate) are used, the cyclization takes place through β´-alkoxy group elimination to afford 10-vinyl substituted pyrroloisoquinolines in moderate yields and diastereoselectivities. However, when the corresponding silyl protected allylic alcohol (TBDMS) derivatives are used as substrates, the reaction takes also place in a diastereoselective way with retention of the protecting group.

- An efficient and selective Rhodium(III)-catalyzed direct nucleophilic addition of 2-(hetero)arylpyridines to cyclic imines *via* C-H bond activation has been developed. This methodology allows the synthesis of a wide variety of amine derivatives using (hetero)arylpyridines as electrophilic coupling partners, where the pyridine group would act as a directing group to assist the C-H activation.

VI

Experimental Section

6.1. General methods and materials

6.2. Intramolecular carbolithiation reaction via conjugate addition on N-(o-haloheteroarylmethyl)pyrrolylacrylates and acrylamides

6.2.1. Synthesis of *o*-halopyridines 5a-5d and *o*-haloquinolines 9a-9d

6.2.2. Intramolecular carbolithiation reaction of *o*-halopyridines 5a-5d. Synthesis of 5,10-dihydropyrrolo[1,2-*g*][1,6]naphthyridines 10a, 10b

6.2.3. Intramolecular carbolithiation reaction of *o*-haloquinolines 9a-9d. Synthesis of 5,12-dihydrobenzo[*b*]pyrrolo[1,2-*g*][1,6]naphthyridines 12a, 12b

6.3. Intramolecular carbolithiation reaction via conjugate addition on N-(o-iodobenzyl)pyrrolidinylacrylates

6.3.1. Synthesis of *N-(o*-iodobenzyl)pyrrolidinylacrylates 17a, 17b

6.1. General methods and materials

RMN

Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H NMR and ^{13}C NMR) were acquired at 25 ºC on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) and on a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C). During the stay in RWTH Aachen University, spectra were acquired at 25 ºC on a Agilent VNMR 600 spectrometer (600 MHz for ^{1}H and 151 MHz for ^{13}C), on a Agilent VNMR 400 spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C) and on a Varian Mercury 300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR; $(CD_3)_2CO$, 2.05 ppm for ^{1}H NMR, $(CD_3)_2CO$, 28.8 ppm for ^{13}C NMR; CD_3OD, 3.31 ppm for ^{1}H NMR, CD_3OD, 49.0 ppm for ^{13}C NMR) and coupling constants (*J*) are expressed in hertz (Hz). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; brs, broad singlet. Assignments of individual ^{13}C and ^{1}H resonances are supported by DEPT experiments and 2D correlations experiments (COSY, HSQCed or HMBC). Selective nOe or NOESY experiments were performed when necessary.[1]

[1] Kinss, M.; Sanders, J. K. M. *J. Mag. Res*. **1984**, *56*, 518.

IR

IR spectra were obtained using an ATR in a JASCO FT/IR 4100 in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case. During the stay in RWTH Aachen University, IR spectra were recorded as film with ATR in a PerkinElmer Spectrum 100 spectrometer with an attached UATR device Diamond KRS-5.

MS

GC-MS analyses were performed on an Agilent 7890A, using a column HP-1 (100% methylpolysiloxane, 30 m × 0.25 mm × 0.25 μm). Mass spectra were recorded using electron impact conditions (EI) at 70 eV on an Agilent MSD 5975C spectrometer. High resolution mass spectra (HRMS) were performed by the Mass Spectrometry General Service at the University of the Basque Country using a Micromass GCT, equipped with a TOF detector under chemical ionization (CI) to 230 eV (methane as the reagent gas, positive mode), using a hybrid mass spectrometer MALDI-LTQ-Orbitrap XL (Thermofisher Scientific) operating in positive mode or using a ultra performance liquid chromatograph (Acquity UPLC, Waters Cromatografía S.A.), in tandem with a QTOF mass spectrometer (SYNAPT G2 HDMS, Waters Cromatografía S.A.), with an electrospray ionization source in a positive mode. During the stay in RWTH Aachen University, high resolution mass spectra (HRMS) were acquired on a Finnigan MAT 95 spectrometer.

m.p.

Melting points were measured in a Büchi B-540 apparatus in open capillary tubes and are uncorrected.

Polarimetry

Optical rotations were measured at 20 ºC on a Jasco P-2000 polarimeter with sodium lamp at 589 nm and a path length of 1 dm. Solvent and concentration are specified in each case.

HPLC

High performance liquid chromatography on a chiral stationary phase experiments were performed on a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector. Daicel Chiralpak IC and ADH columns (0.46 cm x 25 cm) were used in isocratic elution mode (otherwise indicated): specific conditions are indicated for each case.

Reagents and Solvents

Anhydrous solvents were purified according to standard procedures, and dried with activated molecular sieves prior to their use.[2] *n*-Hexane used as solvent for flash column chromatography was distilled prior to its use.

Commercially available starting materials and reagents (Sigma-Aldrich, Fluka and Acros Organics) were used without further purification. The supplier´s specified assay or purity of the reagents were accounted when the reaction batches were calculated, including: ethyl (triphenylphosphoranylidene)acetate 95% purity, (carbethoxyethylidene)triphenylphosphorane 94% purity, TBDMSCl 97% purity, 3,5-dimethylpyrrole-2-carboxaldehyde 95% purity, *n*-Bu_4NOAc 97% purity and P(*o*-tolyl)$_3$ 97% purity. TMEDA was distilled prior to its use and stored under argon atmosphere. Palladium catalysts were purchased from Sigma-Aldrich and were used without further purification: $Pd(OAc)_2$ 98% purity, $Pd(dba)_2$ 99.9% purity, $Pd_2(dba)_3.CHCl_3$ 99.9% purity, $Pd(PPh_3)_4$ 99% purity and $PdCl_2$(*o*-tolyl)$_3$ 97% purity.

During the stay in RWTH Aachen University, rhodium(III) complex $[Cp^*Rh(MeCN)_3][SbF_6]_2$ was prepared according to a literature protocol[3] by postdoctoral student Kanniyappan Parthasarathy.

[2] 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. *J. Org. Chem.* **2010**, *75*, 8351.
[3] White, C.; Thompson, S. J.; Maitlis, P. M. *J. C. S. Dalton* **1977**, 1654.

Miscellaneous

The reactions were monitored by thin layer chromatography (TLC) in pre-coated aluminum-backed plates Merck F_{254}. Visualization was accomplished with UV light (λ = 254 nm and 360 nm) or by immersion in phosphomolybdic acid, potassium permanganate or vanillin solution.[4] For column chromatographic separations Silicagel 60 (Merck), 230-400 mesh ASTM, or aluminum oxide neutral active 90 (Merck), 70-230 mesh ASTM, were used when performed under pressure.[5]

All air and moisture sensitive reactions were performed under argon.

All the glassware was previously dried for 12 h prior to utilizing in an oven at 130 ºC and allowed to cool under a dehumidified atmosphere, and purged with argon. The addition of solutions and liquids was carried out by oven-dried syringe or cannula.[6]

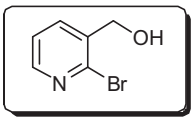
The solvents were removed at reduced pressure on Rotavapors Büchi R210, R200 and R114. Weighs were made in analytical balances Mettler AE-260 or Sartorius Practum 224-1S. Low temperature reactions were performed using baths or immersion coolers TERMO HAAKE EK90.

[4] Stahl, E. *Thin layer chromatography*. Springer-Verlag: Berlín, **1969**.
[5] Still, W. C.; Kann, H.; Miltra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.
[6] Harwood, L. M.; Moody, C. J.; Percy, J. M. *Experimental organic chemistry. Standard and microscale,* 2nd Ed., Blackwell Science: Oxford, **1999**.

6.2. Intramolecular carbolithiation reaction via conjugate addition on N-(o-haloheteroarylmethyl)pyrrolylacrylates and acrylamides

6.2.1. Synthesis of *o*-halopyridines 5a-5d and *o*-haloquinolines 9a-9d

Synthesis of (2-bromopyridin-3-yl)metanol (1)[7]



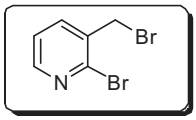
To a solution of 2-bromo-3-pyridinecarboxaldehyde (1.00 g, 5.38 mmol) in dry methanol (20 mL) cooled at 0 ºC, $NaBH_4$ (0.29 g, 7.77 mmol) was added portion wise. After the addition, the ice bath was removed and the mixture allowed to warm up to room temperature and stirred for 2 h. The reaction was followed by TLC. When the reaction was completed, the mixture was eluted with EtOAc (20 mL) and washed with a saturated NH_4Cl solution (2 x 10 mL) and brine (1 x 10 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. Product **1** was obtained pure as a white solid (0.99 g, 5.27 mmol, 98% yield) and was used for the next step without further purification.

m.p.: 74-76 ºC (Hexane/EtOAc); **IR (ATR):** 3264 cm^{-1} (brs, O-H st), 1565 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 3.27 (brs, 1H, $CH_2\underline{OH}$), 4.72 (s, 2H, $C\underline{H_2}OH$), 7.28 (dd, J = 7.6, 4.8 Hz, 1H, $H_{5pyridine}$), 7.80 – 7.91 (m, 1H, $H_{4pyridine}$), 8.22 (dd, J = 4.8, 1.8 Hz, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 63.1 (CH_2OH), 123.1 (C_5), 136.6 (C_4), 137.5 (C_3), 141.3 (C_2), 148.4 (C_6);

[7] a) Martin, N.; Pierre, C.; Davi, M.; Jazzar, R. *Chem. Eur. J.* **2012**, *18*, 4480. b) Spivey, A. C.; Shukla, L.; Hayer, J. F. *Org. Lett.* **2007**, *9*, 891.

MS (CI): (*m/z*) 188 (MH^+, 100); 172 (88); 170 (89); 110 (19); 108 (28); **HRMS (CI):** Calculated for $C_6H_7NOBr^{79}$ (MH^+): 187.9711. Found: 187.9721.

Synthesis of 2-bromo-3-(bromomethyl)pyridine (2)[8]

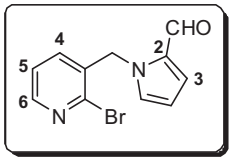


To a solution of (2-bromopyridin-3-yl)methanol (**1**) (1.00 g, 5.32 mmol) in dry CH_2Cl_2 (20 mL), PBr_3 (0.61 mL, 6.38 mmol) was added dropwise. The reaction was stirred overnight at room temperature. After that time, an aqueous $NaHCO_3$ saturated solution was added slowly until release of gas stopped. Subsequently, the organic phase was separated and further washed with the $NaHCO_3$ saturated solution (3 x 20 mL). The aqueous phase was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. Product **2** was obtained pure as a light yellow solid (1.22 g, 4.87 mmol, 91% yield) and was used for the next step without further purification.

m.p.: 52-53 ºC (CH_2Cl_2); **IR (ATR):** 1578 cm^{-1} (C=C st), 1050 cm^{-1} (C-Br st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 4.53 (s, 2H, CH_2Br), 7.26 (dd, J = 7.6, 4.7 Hz, 1H, $H_{5pyridine}$), 7.75 (dd, J = 7.6, 1.9 Hz, 1H, $H_{4pyridine}$), 8.28 (dd, J = 4.7, 1.9 Hz, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 31.4 (CH_2Br), 123.2 (C_5), 134.6 (C_3), 139.2 (C_4), 143.6 (C_2), 149.6 (C_6). **MS (CI):** (*m/z*) 254 (45); 252 (100); 250 (MH^+, 50); 170 (44). **HRMS (CI):** Calculated for $C_6H_6NBr^{79}{}_2$ (MH^+): 249.8867. Found: 249.8885.

[8] Ruiz, J.; Lete, E.; Sotomayor, N. *Tetrahedron* **2006**, *62*, 6182.

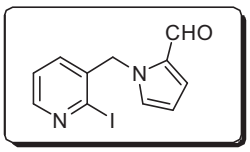
Synthesis of 1-((2-bromopyridin-3-yl)methyl)-1*H*-pyrrole-2-carbaldehyde (3a)



To a suspension of KOH (0.35 g, 6.24 mmol) in DMSO (20 mL), pyrrole 2-carboxaldehyde (0.15 g, 1.55 mmol) was added. The mixture was stirred for 2 h at room temperature. After that time, 2-bromo-3-(bromomethyl)pyridine (**2**) (0.59 g, 2.35 mmol) was added to the former solution and the reaction was stirred for 4 h more at room temperature. The reaction was quenched with H_2O (20 mL) and the crude was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was washed with H_2O (3 x 20 mL) and brine (1 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **3a** as a white solid (0.35 g, 1.32 mmol, 85% yield).

m.p.: 92-94 ºC (Hexane/EtOAc); **IR (ATR):** 3012 cm^{-1} (C-H_{arom} st), 2810 cm^{-1} (C-H_{aliph} st), 1657 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.56 (s, 2H, CH_2N), 6.30 (dd, *J* = 4.0, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.80 – 6.83 (m, 1H, $H_{4pyridine}$), 6.99 (dd, *J* = 4.0, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.00 – 7.03 (m, 1H, $H_{3pyrrole}$), 7.10 (dd, *J* = 7.6, 4.7 Hz, 1H, $H_{5pyridine}$), 8.19 (dd, *J* = 4.7, 1.9 Hz, 1H, $H_{6pyridine}$), 9.50 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 50.9 (CH_2N), 110.6 ($C_{4pyrrole}$) 123.0 ($C_{5pyridine}$), 124.9 ($C_{5pyrrole}$), 131.2 ($C_{2pyrrole}$), 131.5 ($C_{3pyrrole}$), 134.7 ($C_{3pyridine}$), 135.8 ($C_{4pyridine}$), 141.5 ($C_{2pyridine}$), 148.7 ($C_{6pyridine}$), 179.2 (CHO). **MS (CI):** (*m/z*) 267 (89); 265 (MH^+, 100); 185 (64). **HRMS (CI):** Calculated for $C_{11}H_{10}N_2OBr^{79}$ (MH^+): 264.9976. Found: 264.9979.

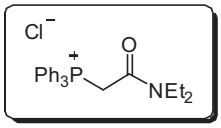
Synthesis of 1-((2-iodopyridin-3-yl)methyl)-1*H*-pyrrole-2-carbaldehyde (3b)



(Bromopyridinylmethyl)pyrrole carbaldehyde **3a** (1.08 g, 4.07 mmol) in dry dioxane (10 mL) was added *via* canula to a suspension of CuI (38.80 mg, 0.20 mmol), *N,N′*-dimethylethylenediamine (0.04 mL, 0.41 mmol) and NaI (1.22 g, 8.15 mmol) in dry dioxane (30 mL) under an inert atmosphere. The mixture was heated to reflux for 24 h. H_2O (20 mL) was added and the crude was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was washed with brine (3 x 20 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **3b** as a white solid (0.92 g, 2.94 mmol, 72% yield).

m.p.: 141-142 ºC (Hexane/EtOAc); **IR (ATR):** 3098 cm^{-1} (C-H_{arom} st), 2813 cm^{-1} (C-H_{aliph} st), 1640 cm^{-1} (C=O st), 1570 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.52 (s, 2H, CH_2N), 6.34 (dd, *J* = 4.0, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.66 – 6.72 (m, 1H, $H_{4pyridine}$), 6.98 – 7.06 (m, 2H, $H_{3pyrrole}$, $H_{5pyrrole}$), 7.12 (dd, *J* = 7.7, 4.7 Hz, 1H, $H_{5pyridine}$), 8.22 (dd, *J* = 4.7, 1.8 Hz, 1H, $H_{6pyridine}$), 9.55 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 55.1 (CH_2N), 110.8 ($C_{4pyrrole}$) 121.3 ($C_{2pyridine}$), 123.3 ($C_{5pyridine}$), 125.0 ($C_{3pyrrole}$), 131.3 ($C_{2pyrrole}$), 131.4 ($C_{5pyrrole}$), 134.5 ($C_{4pyridine}$), 138.2 ($C_{3pyridine}$), 149.5 ($C_{6pyridine}$), 179.4 (CHO). **MS (ESI$^+$):** (*m/z*) 313 (MH^+, 100); 185 (29). **HRMS (ESI$^+$):** Calculated for $C_{11}H_{10}N_2OI$ (MH^+): 312.9838. Found: 312.9836.

Synthesis of (2-(diethylamino)-2-oxoethyl)triphenylphosphonium chloride[9]

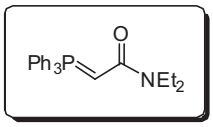


PPh_3 (5.26 g, 20.1 mmol) was added to a solution of 2-chloro-*N,N*-diethylacetamide (2.76 mL, 20.1 mmol) in dry CH_3CN (40 mL). The mixture was heated to reflux and stirred for 18 h. The solvent was evaporated under reduced pressure and the crude was subjected to flash chromatography (silica gel, EtOAc/MeOH 5/5) obtaining the product as a white solid (6.72 g, 16.31 mmol, 81% yield).

m.p.: 197-198 ºC (hexane/EtOAc); **IR (ATR):** 3006 cm^{-1} (C-H_{arom} st), 2987 cm^{-1} (C-H_{aliph} st), 1631 cm^{-1} (st, C=O); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.87 (t, *J* = 7.1 Hz, 3H, $NCH_2C\underline{H}_3$, *cis* to CO), 1.12 (t, *J* = 7.1 Hz, 3H, $NCH_2C\underline{H}_3$, *trans* to CO, 3.13 (q, *J* = 7.1 Hz, 2H, $NC\underline{H}_2CH_3$, *cis* to CO), 3.68 (q, *J* = 7.1 Hz, 2H, $NC\underline{H}_2CH_3$, *trans* to CO), 5.48 (d, $J_{H\text{-}P}$ = 13.0 Hz, 2H, CH_2), 7.40 – 7.67 (m, 9H, H_{arom}), 7.67 – 7.91 (m, 6H, H_{arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 12.8 ($NCH_2\underline{C}H_3$, *cis* to CO), 14.5 ($NCH_2\underline{C}H_3$, *trans* to CO), 34.0 (d, $^1J_{C\text{-}P}$ = 67.2 Hz, $\underline{C}H_2CO$), 40.8 ($N\underline{C}H_2CH_3$, *cis* to CO), 43.9 ($N\underline{C}H_2CH_3$, *trans* to CO), 119.9 (d, $^1J_{C\text{-}P}$ = 90.2 Hz, C_{1arom}), 129.8 (d, $^2J_{C\text{-}P}$ = 13.0 Hz, $C_{2arom,}$ C_{6arom}), 134.0 (d, $^3J_{C\text{-}P}$ = 10.4 Hz, $C_{3arom,}$ C_{5arom}), 134.2 (d, $^4J_{C\text{-}P}$ = 3.0 Hz, C_{4arom}), 163.2 (d, $^2J_{C\text{-}P}$ = 3.6 Hz, $\underline{C}ONEt_2$).

[9] Lage, S.; Martinez-Estibalez, U.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2009**, *351*, 2460.

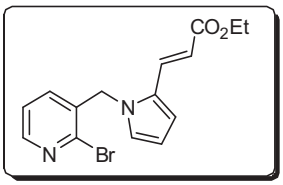
Synthesis of *N, N*-diethyl-2-(triphenyl-λ^5-phosphanyliden)acetamide (4b)[9]



Over a solution of (2-(diethylamino)-2-oxoethyl)triphenylphosphonium chloride (6.16 g, 15 mmol) in dry THF (55 mL), *t*-BuOK (1.72 g, 15 mmol) was added portion wise at -5 ºC. The mixture was stirred for 1 h at that temperature and after that time, the solvent was evaporated under reduced pressure. The crude was crystallized by addition of hot Et_2O (200 mL) and cooling down to -15 ºC for 3 h. The resulting mixture was filtered under vacuum and washed with cold pentane, affording product **4b** as a white solid (4.45 g, 11.85 mmol, 79% yield).

m.p.: 150-151 ºC (Et_2O); **IR (ATR):** 3056 cm^{-1} (C-H_{arom} st), 2987 cm^{-1} (C-H_{aliph} st), 1633 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.14 (t, *J* = 7.0 Hz, 6H, $N(CH_2C\underline{H}_3)_2$), 3.35 (q, *J* = 7.0 Hz, 4H, $N(C\underline{H}_2CH_3)_2$), 7.32 – 7.77 (m, 16H, PPh_3=C<u>H</u>-, H_{arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 13.1 ($NCH_2\underline{C}H_3$, *cis* to CO), 14.2 ($NCH_2\underline{C}H_3$, *trans* to CO), 40.0 ($N\underline{C}H_2CH_3$, *cis* to CO), 42.8 ($N\underline{C}H_2CH_3$, *trans* to CO), 77.2 (PPh_3=<u>C</u>H-), 128.5 (d, $^2J_{C\text{-}P}$ = 12.2 Hz, $C_{2arom,}$ C_{6arom}), 131.9 (d, $^4J_{C\text{-}P}$ = 2.7 Hz, C_{4arom}), 132.1 (d, $^3J_{C\text{-}P}$ = 9.8 Hz, $C_{3arom,}$ C_{5arom}), 133.1 (d, $^1J_{C\text{-}P}$ = 104.1 Hz, C_{1arom}), 169.7 ($\underline{C}ONEt_2$).

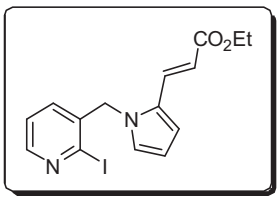
Synthesis of (*E*)-ethyl 3-(1-((2-bromopyridin-3-yl)methyl)-1*H*-pyrrol-2-yl)acrylate (5a)



To a solution of (bromopyridinylmethyl)pyrrole carbaldehyde **3a** (1.36 g, 5.14 mmol) in dry CH_2Cl_2 (50 mL), ethyl (triphenylphosphoranylidene)acetate (**4a**) (4.48 g, 12.22 mmol) was added and the mixture was heated under reflux for 16 h. After that time, the crude was concentrated to dryness and subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **5a** as a white solid (1.64 g, 4.89 mmol, 95% yield).

m.p.: 124-125 ºC (Hexane/EtOAc); **IR (ATR):** 3113 cm^{-1} (C-H_{arom} st), 2980 cm^{-1} (C-H_{aliph} st), 1697 cm^{-1} (C=O st), 1620 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.27 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.18 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.23 (s, 2H, CH_2N), 6.14 (d, *J* = 15.6 Hz, 1H, -CH=C<u>H</u>-CO_2Et), 6.28 – 6.35 (m, 1H, $H_{4pyrrole}$), 6.61 – 6.68 (m, 1H, $H_{4pyridine}$), 6.77 (dd, *J* = 3.9, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.83 (dd, *J* = 2.4, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.16 (dd, *J* = 7.7, 4.7 Hz, 1H, $H_{5pyridine}$), 7.39 (d, *J* = 15.6 Hz, 1H, -C<u>H</u>=CH-CO_2Et), 8.28 (dd, *J* = 4.7, 1.8 Hz, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.3 ($OCH_2\underline{C}H_3$), 49.8 (CH_2N), 60.3 ($O\underline{C}H_2CH_3$), 110.8 ($C_{4pyrrole}$), 112.4 ($C_{3pyrrole}$), 114.4 (-CH=<u>C</u>H-CO_2Et), 123.5 ($C_{5pyridine}$), 126.2 ($C_{5pyrrole}$), 129.1 ($C_{2pyrrole}$), 131.1 (-<u>C</u>H=CH-CO_2Et), 134.5 ($C_{3pyridine}$), 135.7 ($C_{4pyridine}$), 141.0 ($C_{2pyridine}$), 149.2 ($C_{6pyridine}$), 167.3 (-CH=CH-<u>C</u>O_2Et). **MS (CI):** (*m/z*) 337 (MH^++2, 100); 336 (50); 335 (MH^+, 100); 334 (35); 291 (94); 289 (94); 255 (55). **HRMS (CI):** Calculated for $C_{15}H_{16}N_2O_2Br^{79}$ (MH^+): 335.0395. Found: 335.0381.

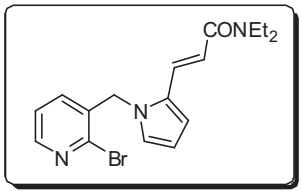
Synthesis of (*E*)-ethyl 3-(1-((2-iodopyridin-3-yl)methyl)-1*H*-pyrrol-2-yl)acrylate (5b)



To a solution of (iodopyridinylmethyl)pyrrole carbaldehyde **3b** (0.88 g, 2.82 mmol) in CH_2Cl_2 (30 mL), ethyl (triphenylphosphoranylidene)acetate (**4a**) (2.58 g, 7.04 mmol), and the mixture was heated under reflux for 16 h. After that time, the crude was concentrated to dryness and subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **5b** as a white solid (1.00 g, 2.62 mmol, 93% yield).

m.p.: 96-97 ºC (Hexane/EtOAc); **IR (ATR):** 2980 cm^{-1} (C-H_{aliph} st), 1698 cm^{-1} (C=O st), 1623 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.26 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.17 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.12 (s, 2H, CH_2N), 6.12 (d, *J* = 15.6 Hz, 1H, -CH=C<u>H</u>-CO_2Et), 6.27 – 6.33 (m, 1H, $H_{4pyrrole}$), 6.51 (dd, *J* = 7.7, 1.3 Hz, 1H, $H_{4pyridine}$), 6.75 (dd, *J* = 3.8, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.78 – 6.81 (m, 1H, $H_{5pyrrole}$), 7.13 (dd, *J* = 7.7, 4.7 Hz, 1H, $H_{5pyridine}$), 7.36 (d, *J* = 15.6 Hz, 1H, -C<u>H</u>=CH-CO_2Et), 8.23 (dd, *J* = 4.7, 1.3 Hz, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.3 ($OCH_2\underline{C}H_3$), 53.8 (CH_2N), 60.2 ($O\underline{C}H_2CH_3$), 110.7 ($C_{4pyrrole}$) 112.4 ($C_{3pyrrole}$), 114.3 (-CH=<u>C</u>H-CO_2Et), 120.3 ($C_{2pyridine}$), 123.5 ($C_{5pyridine}$), 126.1 ($C_{5pyrrole}$), 129.0 ($C_{2pyrrole}$), 131.1 (-<u>C</u>H=CH-CO_2Et), 134.4 ($C_{4pyridine}$), 137.7 ($C_{3pyridine}$), 149.8 ($C_{6pyridine}$), 167.3 (-CH=CH-<u>C</u>O_2Et). **MS (MALDI):** (*m/z*) 383 (MH^+, 58); 382 (M^+, 21); 337 (21); 258 (16); 257 (88); 256 (17); 255 (100). **HRMS (MALDI):** Calculated for $C_{15}H_{16}N_2O_2I$ (MH^+): 383.0250. Found: 383.0257.

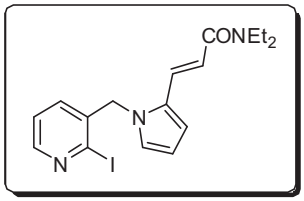
Synthesis of (*E*)-3-(1-((2-bromopyridin-3-yl)methyl)-1*H*-pyrrol-2-yl)-*N*,*N*-diethylacrylamide (5c)



To a solution of (bromopyridinylmethyl)pyrrole carbaldehyde **3a** (0.11 g, 0.41 mmol) in dry CH_2Cl_2 (20 mL), previously synthesized ylide **4b** (0.38 g, 1.01 mmol) was added and the mixture was heated under reflux for 16 h. After that time, the crude was concentrated to dryness and subjected to flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining product **5c** as a white solid (0.14 g, 0.39 mmol, 95% yield).

m.p.: 108-109 ºC (Hexane/EtOAc); **IR (ATR):** 2976 cm^{-1} (C-H_{aliph} st), 1641 cm^{-1} (C=O st), 1593 cm^{-1} (C=C st), 1562 (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.01 – 1.18 (m, 6H, $N(CH_2C\underline{H}_3)_2$), 3.25 – 3.41 (m, 4H, $N(C\underline{H}_2CH_3)_2$), 5.20 (s, 2H, CH_2N), 6.23 – 6.29 (m, 1H, $H_{4pyrrole}$), 6.41 (d, *J* = 15.1 Hz, 1H, -CH=C<u>H</u>-$CONEt_2$), 6.59 – 6.63 (m, 1H, $H_{4pyridine}$), 6.67 (dd, *J* = 3.8, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.76 (dd, *J* = 2.5, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.11 (dd, *J* = 7.6, 4.7 Hz, 1H, $H_{5pyridine}$), 7.45 (d, *J* = 15.1 Hz, 1H, -C<u>H</u>=CH-CO_2Et), 8.18 – 8.24 (m, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 13.2, 15.0 ($N(CH_2\underline{C}H_3)_2$), 41.1, 42.2 ($N(\underline{C}H_2CH_3)_2$), 50.0 ($CH_2N$), 110.3 ($C_{4pyrrole}$) 111.9 ($C_{3pyrrole}$), 113.8 (-CH=<u>C</u>H-$CONEt_2$), 123.5 ($C_{5pyridine}$), 125.6 ($C_{5pyrrole}$), 129.5 (-<u>C</u>H=CH-$CONEt_2$), 129.9 ($C_{2pyrrole}$), 134.7 ($C_{3pyridine}$), 135.8 ($C_{4pyridine}$), 141.0 ($C_{2pyridine}$), 149.0 ($C_{6pyridine}$), 165.7 (-CH=CH-<u>C</u>$ONEt_2$). **MS (ESI^+):** (*m/z*) 362 (MH^+, 100); 364 (MH^+ + 2, 100); 384 ($[M + Na]^+$,13); 386 ($[M + Na]^+$ + 2, 13). **HRMS (ESI^+):** Calculated for $C_{17}H_{21}N_3OBr^{79}$ (MH^+): 362.0868. Found: 362.0863.

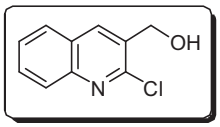
Synthesis of *(E)*-*N*,*N*-diethyl-3-(1-((2-iodopyridin-3-yl)methyl)-1*H*-pyrrol-2-yl)acrylamide (5d)



To a solution of (iodopyridinylmethyl)pyrrole carbaldehyde **3b** (0.64 g, 2.05 mmol) in dry CH_2Cl_2 (20 mL), previously synthesized ylide **4b** (1.57 g, 4.18 mmol) was added and the mixture was heated under reflux for 24 h. After that time, the crude was concentrated to dryness and subjected to flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining product **5d** as a white solid (0.82 g, 2.00 mmol, 98% yield).

m.p.: 121-122 ºC (Hexane/EtOAc); **IR (ATR):** 2976 cm^{-1} (C-H_{aliph} st), 1642 cm^{-1} (C=O st), 1591 cm^{-1} (C=C st), 1555 (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.11 – 1.17 (m, 6H, N($CH_2C\underline{H}_3)_2$), 3.28 – 3.47 (m, 4H, N($C\underline{H}_2CH_3)_2$), 5.14 (s, 2H, CH_2N), 6.28 – 6.32 (m, 1H, $H_{4pyrrole}$), 6.43 (d, *J* = 15.1 Hz, 1H, -CH=C<u>H</u>-CONEt$_2$), 6.50 – 6.54 (m, 1H, $H_{4pyridine}$), 6.70 (dd, *J* = 3.8, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.77 (dd, *J* = 2.5, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.13 (dd, *J* = 7.7, 4.7 Hz, 1H, $H_{5pyridine}$), 7.49 (d, *J* = 15.1 Hz, 1H, -C<u>H</u>=CH-CONEt$_2$), 8.21 – 8.25 (m, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 13.1, 14.9 (N($CH_2\underline{C}H_3)_2$), 40.9, 42.0 (N(<u>C</u>$H_2CH_3)_2$), 54.0 (CH_2N), 110.2 ($C_{4pyrrole}$) 111.8 ($C_{3pyrrole}$), 113.6 (-CH=<u>C</u>H-CONEt$_2$), 120.2 ($C_{2pyridine}$), 123.4 ($C_{5pyridine}$), 125.4 ($C_{5pyrrole}$), 129.4 (-<u>C</u>H=CH-CONEt$_2$), 129.7 ($C_{2pyrrole}$), 134.3 ($C_{3pyridine}$), 137.7 ($C_{4pyridine}$), 149.5 ($C_{6pyridine}$), 165.5 (-CH=CH-<u>C</u>ONEt$_2$). **MS (ESI$^+$):** (*m/z*) 411 (MH^+ + 1, 14); 410 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{17}H_{21}N_3OI$ (MH^+): 410.0729. Found: 410.0723.

Synthesis of (2-chloroquinolin-3-yl)methanol (6)[10]

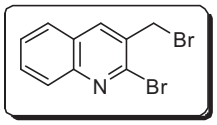


To a solution of 2-chloroquinoline-3-carbaldehyde (1.50 g, 7.83 mmol) in dry MeOH: dry THF (1:1) (40 mL) cooled at 0 ºC, $NaBH_4$ (0.59 g, 15.54 mmol) was added dropwise. After the addition, the ice bath was removed and the mixture allowed to warm up to room temperature and stirred for 2 h. The reaction was followed by TLC. When the reaction was completed, the mixture was eluted with EtOAc (60 mL) and washed with a saturated NH_4Cl solution (2 x 20 mL) and brine (1 x 20 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. Product **6** was crystallized from $CHCl_3$ and obtained pure as a light yellow solid (1.28 g, 6.61 mmol, 84% yield).

m.p.: 162-164 ºC ($CHCl_3$); **IR (ATR):** 3397 cm^{-1} (brs, O-H st), 2916 cm^{-1} (C-H_{aliph} st); **^{1}H NMR** (DMSO, 25 ºC): δ (ppm) = 3.33 (s, 1H, HDO), 4.70 (d, *J* = 5.5 Hz, 2H, CH_2OH), 5.71 (t, *J* = 5.5 Hz, 1H, CH_2OH), 7.65 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, $H_{6quinoline}$), 7.79 (ddd, *J* = 8.2, 6.9, 1.5 Hz, 1H, $H_{7quinoline}$), 7.96 (dd, *J* = 8.2, 1.2 Hz, 1H, $H_{8quinoline}$), 8.09 (dd, *J* = 8.2, 1.5 Hz, 1H, $H_{5quinoline}$), 8.47 (s, 1H, $H_{4quinoline}$); **^{13}C NMR** (DMSO, 25 ºC): δ (ppm) = 59.9 (CH_2OH), 127.2 ($C_{4a,quinoline}$), 127.3 ($C_{6quinoline}$), 127.5 ($C_{8quinoline}$), 127.9 ($C_{5quinoline}$), 130.2 ($C_{7quinoline}$), 133.9 ($C_{3quinoline}$), 135.9 ($C_{4quinoline}$), 146.0 ($C_{8a,quinoline}$), 148.4 ($C_{2quinoline}$). **MS (CI):** (*m/z*) 194 (MH^+, 100); 193 (21); 178 (34); 176 (89); 164 (23); 158 (76). **HRMS (CI):** Calculated for $C_{10}H_9NOCl$ (MH^+): 194.0373. Found: 194.0372.

[10] Vanlaer, S.; Voet, A.; Gielens, C.; De Maeyer, M.; Compernolle, F. *Eur. J. Org. Chem*. **2009**, 643.

Synthesis of 2-bromo-3-(bromomethyl)quinoline (7)[11]

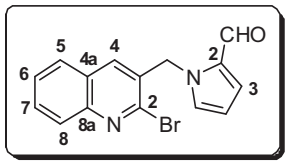


(2-chloroquinolin-3-yl)methanol (**6**) (1.00 g, 5.22 mmol) was dissolved in PBr_3 (30 mL, 312.81 mmol) and heated to 150 ºC for 16 h. After that time, the reaction was slowly quenched adding a saturated aqueous solution of $NaHCO_3$ at 0 ºC, until release of gas stopped. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were washed with the same saturated $NaHCO_3$ solution (3 x 50 mL). Subsequently, the organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. Product **7** was obtained pure as a light pink solid (1.20 g, 3.99 mmol, 76% yield) and was used for the next step without further purification.

m.p.: 140-141 ºC (CH_2Cl_2); **IR (ATR):** 2923 cm^{-1} (C-H_{arom} st), 1567 cm^{-1} (C=C st), 750 cm^{-1} (C-Br st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 4.73 (s, 2H, CH_2Br), 7.59 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H, $H_{6quinoline}$), 7.74 (ddd, *J* = 8.5, 7.0, 1.4 Hz, 1H, $H_{7quinoline}$), 7.81 (brd, *J* = 8.2 Hz, 1H, $H_{5quinoline}$), 8.04 (brd, *J* = 8.5 Hz, 1H, $H_{8quinoline}$), 8.21 (s, 1H, $H_{4quinoline}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 32.1 (CH_2Br), 127.2 ($C_{4a,quinoline}$), 127.6, 127.7 ($C_{5quinoline}$, $C_{6quinoline}$), 128.5 ($C_{8quinoline}$), 131.1 ($C_{7quinoline}$), 131.5 ($C_{3quinoline}$), 138.6 ($C_{4quinoline}$), 143.1 ($C_{2quinoline}$), 147.9 ($C_{8a,quinoline}$). **MS (CI):** (*m/z*) 304 ($[MH+4]^+$, 26); 302 ($[MH+2]^+$, 53); 300 ($[MH]^+$, 27); 222 (100); 220 (89). **HRMS (CI):** Calculated for $C_{10}H_8NBr^{79}{}_2$ (MH^+): 299.9023. Found: 299.9026.

[11] Ruiz, J. Ph.D Thesis, University of the Basque Country, **2004**.

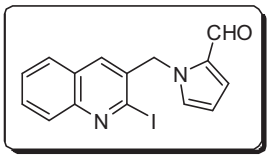
Synthesis of 1-((2-bromoquinolin-3-yl)methyl)-1*H*-pyrrole-2-carbaldehyde (8a)



To a suspension of KOH (0.69 g, 12.30 mmol) in DMSO (30 mL), pyrrole 2-carboxaldehyde (0.29 g, 3.09 mmol) was added. The mixture was stirred for 2 h at room temperature. After that time, 2-bromo-3-(bromomethyl)quinoline (**7**) (1.40 g, 4.64 mmol) was added to the former solution and the reaction was stirred for 4 h more at room temperature. The reaction was quenched with H_2O (20 mL) and the crude was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was washed with H_2O (3 x 20 mL), brine (1 x 10 mL) and finally dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **8a** as a white solid (0.68 g, 2.16 mmol, 70% yield).

m.p.: 145-146 ºC (Hexane/EtOAc); **IR (ATR):** 1656 cm^{-1} (C=O st), 1592 cm^{-1} (C=C st), 750 cm^{-1} (C-Br st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.80 (s, 2H, CH_2N), 6.42 (dd, *J* = 3.8, 2.7 Hz, 1H, $H_{4pyrrole}$), 7.07 – 7.16 (m, 2H, $H_{3pyrrole}$, $H_{5pyrrole}$), 7.30 (s, 1H, $H_{4quinoline}$), 7.49 – 7.58 (m, 1H, $H_{6quinoline}$), 7.67 (d, *J* = 8.3 Hz, 1H, $H_{5quinoline}$), 7.69 – 7.77 (m, 1H, $H_{7quinoline}$), 8.04 (d, *J* = 8.5 Hz, 1H, $H_{8quinoline}$), 9.62 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 51.4 (CH_2N), 110.8 ($C_{4pyrrole}$) 125.1 ($C_{3pyrrole}$), 127.3 ($C_{6quinoline}$), 127.4 ($C_{4a,quinoline}$), 127.6 ($C_{5quinoline}$), 128.3 ($C_{8quinoline}$), 130.5 ($C_{7quinoline}$), 131.5 ($C_{2pyrrole}$), 131.6 ($C_{5pyrrole}$), 131.9 ($C_{3quinoline}$), 135.4 ($C_{4quinoline}$), 141.6 ($C_{2quinoline}$), 147.70 ($C_{8a,quinoline}$), 179.5 (CHO). **MS (CI):** (*m/z*) 317 ($[MH+2]^+$, 71); 315 ($[MH]^+$, 73); 236 (16); 235 (100). **HRMS (CI):** Calculated for $C_{15}H_{12}N_2OBr^{79}$ (MH^+): 315.0133. Found: 315.0137.

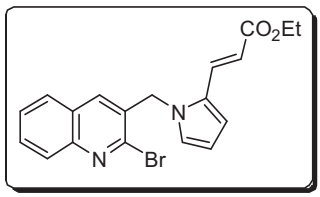
Synthesis of 1-((2-iodoquinolin-3-yl)methyl)-1*H*-pyrrole-2-carbaldehyde (8b)



(Bromoquinolinylmethyl)pyrrole carbaldehyde **8a** (0.52 g, 1.66 mmol) in dry dioxane (10 mL) was added *via* canula to a suspension of CuI (15.84 mmol, 0.08 mmol), *N,N′*-dimethylethylenediamine (0.02 mL, 0.17 mmol) and NaI (0.50, 3.33 mmol) in dry dioxane (30 mL) under an inert atmosphere. The mixture was heated under reflux for 24 h. H_2O (20 mL) was added and the crude was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was washed with brine (3 x 20 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **8b** as a white solid (0.48 g, 1.34 mmol, 80% yield).

m.p.: 150-151 ºC (Hexane/EtOAc); **IR (ATR):** 1657 cm^{-1} (C=O st), 1586 cm^{-1} ($C{=}C_{arom}$ st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.69 (s, 2H, CH_2N), 6.39 (dd, *J* = 4.0, 2.6 Hz, 1H, $H_{4pyrrole}$), 7.04 – 7.10 (m, 3H, $H_{3pyrrole}$, $H_{5pyrrole}$, $H_{4quinoline}$), 7.51 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H, $H_{6quinoline}$), 7.62 (brd, *J* = 8.1 Hz, 1H, $H_{5quinoline}$), 7.67 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H, $H_{7quinoline}$), 8.03 (brd, *J* = 8.5 Hz, 1H, $H_{8quinoline}$), 9.60 (s, 1H, CHO). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 55.4 (CH_2N), 110.8 ($C_{4pyrrole}$) 122.0 ($C_{2quinoline}$), 125.0 ($C_{5pyrrole}$), 127.3 ($C_{4a,quinoline}$), 127.4 ($C_{6quinoline}$), 127.6 ($C_{5quinoline}$), 128.5 ($C_{8quinoline}$), 130.2 ($C_{7quinoline}$), 131.4 ($C_{3pyrrole}$), 133.6 ($C_{4quinoline}$), 134.3 ($C_{3quinoline}$), 148.8 ($C_{8a,quinoline}$), 179.5 (CHO). ($C_{2pyrrole}$ peak overlapped). **MS (ESI$^+$):** (*m/z*) 364 ($[MH+1]^+$, 13); 363 ($[MH]^+$, 100); 235 (27). **HRMS (ESI$^+$):** Calculated for $C_{15}H_{12}N_2OI$ (MH^+): 362.9994. Found: 362.9989.

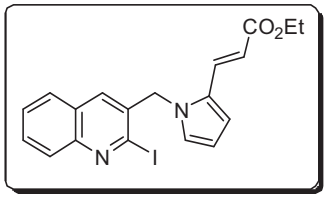
Synthesis of (*E*)-ethyl 3-(1-((2-bromoquinolin-3-yl)methyl)-1*H*-pyrrol-2-yl)acrylate (9a)



To a solution of (bromoquinolinylmethyl)pyrrole carbaldehyde **8a** (1.29 g, 4.09 mmol) in dry CH_2Cl_2 (50 mL), ethyl (triphenylphosphoranylidene)acetate (**4a**) (3.75 g, 10.23 mmol) was added. The mixture was heated under reflux for 16 h. After that time, the crude was concentrated to dryness and subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **9a** as a white solid (1.50 g, 3.89 mmol, 95% yield).

m.p.: 125-126ºC (Hexane/EtOAc); **IR (ATR):** 2980 cm^{-1} (C-H_{arom} st), 1698 cm^{-1} (C=O st), 1622 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.25 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.15 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.37 (s, 2H, CH_2N), 6.17 (d, *J* = 15.6 Hz, 1H, -CH=C<u>H</u>-CO_2Et), 6.33 – 6.40 (m, 1H, $H_{4pyrrole}$), 6.82 (dd, J = 3.9, 1.6 Hz, 1H, $H_{3pyrrole}$), 6.88 (dd, *J* = 2.4, 1.6 Hz, 1H, $H_{5pyrrole}$), 7.05 (s, 1H, $H_{4quinoline}$), 7.44 (d, *J* = 15.6 Hz, 1H, -C<u>H</u>=CH-CO_2Et), 7.49 – 7.55 (m, 1H, $H_{6quinoline}$), 7.63 (d, *J* = 8.1 Hz, 1H, $H_{5quinoline}$), 7.68 – 7.72 (m, 1H, $H_{7quinoline}$), 8.03 (d, *J* = 8.5 Hz, 1H, $H_{8quinoline}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.3 ($OCH_2\underline{C}H_3$), 50.1 (CH_2N), 60.3 ($O\underline{C}H_2CH_3$), 110.8 ($C_{4pyrrole}$), 112.4 ($C_{3pyrrole}$), 114.3 (-CH=<u>C</u>H-CO_2Et), 126.3 ($C_{5pyrrole}$), 127.4 ($C_{4a,quinoline}$), 127.5 ($C_{6quinoline}$), 127.7 ($C_{5quinoline}$), 128.3 ($C_{8quinoline}$), 129.1 ($C_{2pyrrole}$), 130.6 ($C_{7quinoline}$), 131.2 (-<u>C</u>H=CH-CO_2Et), 131.5 ($C_{3quinoline}$), 135.1 ($C_{4quinoline}$), 140.7 ($C_{2quinoline}$), 147.8 ($C_{8a,quinoline}$), 167.3 (<u>C</u>O_2Et). **MS (ESI$^+$):** (*m/z*) 387 (MH^+ + 2, 31); 385 (MH^+, 31); 306 (18); 305 (100). **HRMS (ESI$^+$):** Calculated for $C_{19}H_{18}N_2O_2Br^{79}$ (MH^+): 385.0552. Found: 385.0548.

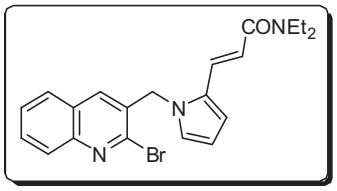
Synthesis of (*E*)-ethyl 3-(1-((2-iodoquinolin-3-yl)methyl)-1*H*-pyrrol-2-yl)acrylate (9b)



To a solution of (iodoquinolinylmethyl)pyrrole carbaldehyde **8b** (0.63 g, 1.74 mmol) in CH_2Cl_2 (20 mL), ethyl (triphenylphosphoranylidene)acetate (**4a**) (1.65 g, 4.50 mmol) was added. The mixture was heated under reflux for 16 h. After that time, the crude was concentrated to dryness and subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **9b** as an oil (0.67 g, 1.55 mmol, 89% yield).

IR (ATR): 2980 cm^{-1} (C-H_{arom} st), 1697 cm^{-1} (C=O st), 1621 cm^{-1} (C=C st), 1585 (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.20 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.10 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.20 (s, 2H, CH_2N), 6.13 (d, *J* = 15.6 Hz, 1H, -CH=C<u>H</u>-CO_2Et), 6.32 (dd, *J* = 3.9, 2.9 Hz, 1H, $H_{4pyrrole}$), 6.78 (dd, *J* = 3.9, 1.6 Hz, 1H, $H_{3pyrrole}$), 6.83 (dd, *J* = 2.9, 1.6 Hz, 1H, $H_{5pyrrole}$), 6.87 (s, 1H, $H_{4quinoline}$), 7.37 – 7.45 (m, 2H, $H_{6quinoline}$, -C<u>H</u>=CH-CO_2Et), 7.54 (brd, *J* = 8.2 Hz, 1H, $H_{5quinoline}$), 7.60 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H, $H_{7quinoline}$), 7.95 (brd, *J* = 8.5 Hz, 1H, $H_{8quinoline}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.1 ($OCH_2\underline{C}H_3$), 53.8 (CH_2N), 60.0 ($O\underline{C}H_2CH_3$), 110.6 ($C_{4pyrrole}$), 112.3 ($C_{3pyrrole}$), 114.0 (-CH=<u>C</u>H-CO_2Et), 120.9 ($C_{2quinoline}$), 126.1 ($C_{5pyrrole}$), 127.0 ($C_{3quinoline}$), 127.3 ($C_{6quinoline}$), 127.5 ($C_{5quinoline}$), 128.2 ($C_{8quinoline}$), 128.7 ($C_{2pyrrole}$), 130.2 ($C_{7quinoline}$), 131.0 (-<u>C</u>H=CH-CO_2Et), 133.3 ($C_{4quinoline}$), 133.5 ($C_{4a,quinoline}$), 148.6 ($C_{8a,quinoline}$), 167.1 (<u>C</u>O_2Et). **MS (ESI$^+$):** (*m/z*) 434 (MH^+ + 1, 17); 433 (MH^+, 100); 306 (19); 305 (93). **HRMS (ESI$^+$):** Calculated for $C_{19}H_{18}N_2O_2I$ (MH^+): 433.0413. Found: 433.0411.

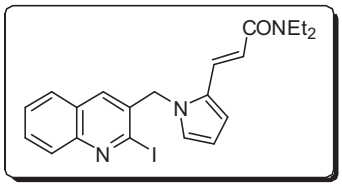
Synthesis of (*E*)-3-(1-((2-bromoquinolin-3-yl)methyl)-1*H*-pyrrol-2-yl)-*N*,*N*-diethylacrylamide (9c)



To a solution of (bromoquinolinylmethyl)pyrrole carbaldehyde **8a** (0.59 g, 1.87 mmol) in CH_2Cl_2 (20 mL), synthesized ylidene **4b** (1.56 g, 4.16 mmol) was added. The mixture was heated under reflux for 16 h. After that time, the crude was concentrated to dryness and subjected to flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining product **9c** as a white solid (0.74 g, 1.79 mmol, 96% yield).

m.p.: 153-154 ºC (Hexane/EtOAc); **IR (ATR):** 2975 cm^{-1} (C-H_{arom} st), 1639 cm^{-1} (C=O st), 1592 cm^{-1} (C=C st), 1563 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.07 (t, *J* = 7.1 Hz, 6H, $N(CH_2C\underline{H}_3)_2$), 3.22 -3.43 (m, 4H, $N(C\underline{H}_2CH_3)_2$), 5.36 (s, 2H, CH_2N), 6.31 – 6.36 (m, 1H, $H_{4pyrrole}$), 6.46 (d, *J* = 15.1 Hz, 1H, -CH=C<u>H</u>-$CONEt_2$), 6.74 (dd, *J* = 3.8, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.81 – 6.86 (m, 1H, $H_{5pyrrole}$), 7.04 (s, 1H, $H_{4quinoline}$), 7.44 – 7.55 (m, 2H, $H_{6quinoline}$, -C<u>H</u>=CH-CO_2Et), 7.59 (d, *J* = 8.1 Hz, 1H, $H_{5quinoline}$), 7.63 – 7.69 (m, 1H, $H_{7quinoline}$), 7.99 (d, *J* = 8.5 Hz, 1H, $H_{8quinoline}$).**^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 13.1, 14.9 ($N(CH_2\underline{C}H_3)_2$), 41.0, 42.1 ($N(\underline{C}H_2CH_3)_2$), 50.2 ($CH_2N$), 110.2 ($C_{4pyrrole}$), 111.8 ($C_{3pyrrole}$), 113.8 (-CH=<u>C</u>H-$CONEt_2$), 125.6 ($C_{5pyrrole}$), 127.2 ($C_{6quinoline}$), 127.3 ($C_{4a,quinoline}$), 127.6 ($C_{5quinoline}$), 128.2 ($C_{8quinoline}$), 129.5 (-<u>C</u>H=CH-$CONEt_2$), 129.9 ($C_{2pyrrole}$), 130.4 ($C_{7quinoline}$), 131.6 ($C_{3quinoline}$), 135.1 ($C_{4quinoline}$), 140.6 ($C_{2quinoline}$), 147.6 ($C_{8a,quinoline}$), 165.6 (<u>C</u>$ONEt_2$). **MS (MALDI):** (*m/z*) 415 (21); 414 (MH^+ + 2, 98); 413 (MH^+ + 1, 22); 412 (MH^+, 100); 334 (33); 332 (84). **HRMS (MALDI):** Calculated for $C_{21}H_{23}N_3OBr^{79}$ (MH^+): 412.1024. Found: 412.1019.

Synthesis of (*E*)-*N*,*N*-diethyl-3-(1-((2-iodoquinolin-3-yl)methyl)-1*H*-pyrrol-2-yl)acrylamide (9d)

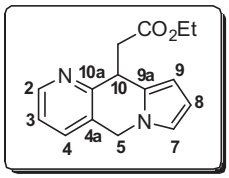


To a solution of (iodoquinolinylmethyl)pyrrole carbaldehyde **8b** (0.47 g, 1.28 mmol) in CH_2Cl_2 (20 mL), synthesized ylidene **4b** (1.06 g, 2.82 mmol) was added. The mixture was heated under reflux for 16 h. After that time, the crude was concentrated to dryness and subjected to flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining product **9d** as a white solid (0.54 g, 1.18 mmol, 92% yield).

m.p.: 158-159 ºC (Hexane/EtOAc); **IR (ATR):** 2973 cm^{-1} (C-H_{arom} st), 1639 cm^{-1} (C=O st), 1588 cm^{-1} (C=C st), 1557 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.95 – 1.15 (m, 6H, $N(CH_2C\underline{H}_3)_2$), 3.21 -3.43 (m, 4H, $N(C\underline{H}_2CH_3)_2$), 5.27 (s, 2H, CH_2N), 6.34 (dd, *J* = 3.8, 2.7 Hz, 1H, $H_{4pyrrole}$), 6.45 (d, *J* = 15.1 Hz, 1H, -CH=C<u>H</u>-$CONEt_2$), 6.74 (dd, *J* = 3.8, 1.9 Hz, 1H, $H_{3pyrrole}$), 6.82 (dd, *J* = 2.7, 1.9 Hz, 1H, $H_{5pyrrole}$), 6.90 (s, 1H, $H_{4quinoline}$), 7.43 – 7.54 (m, 2H, $H_{6quinoline}$, -C<u>H</u>=CH-$CONEt_2$), 7.54 – 7.59 (m, 1H, $H_{5quinoline}$), 7.65 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H, $H_{7quinoline}$), 8.01 (brd, *J* = 8.5 Hz, 1H, $H_{8quinoline}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 13.2, 15.0 ($N(CH_2\underline{C}H_3)_2$), 41.0, 42.1 ($N(\underline{C}H_2CH_3)_2$), 54.4 ($CH_2N$), 110.3 ($C_{4pyrrole}$), 112.0 ($C_{3pyrrole}$), 113.8 (-CH=<u>C</u>H-$CONEt_2$), 120.9 ($C_{2quinoline}$), 125.6 ($C_{5pyrrole}$), 127.3 ($C_{3quinoline}$), 127.5 ($C_{5quinoline}$), 127.7 ($C_{6quinoline}$), 128.4 ($C_{8quinoline}$), 129.6 (-<u>C</u>H=CH-$CONEt_2$), 129.9 ($C_{2pyrrole}$), 130.3 ($C_{7quinoline}$), 133.6 ($C_{4quinoline}$), 133.8 ($C_{4a,quinoline}$), 148.8 ($C_{8a,quinoline}$), 165.7 (<u>C</u>$ONEt_2$). **MS ($ESI^+$):** (*m/z*) 461 ($MH^+$ + 1, 19); 460 (MH^+, 100). **HRMS (ESI^+):** Calculated for $C_{21}H_{23}N_3OI$ (MH^+): 460.0886. Found: 460.0889.

6.2.2. Intramolecular carbolithiation reaction of *o*-halopyridines 5a-5d. Synthesis of 5,10-dihydropyrrolo[1,2-*g*][1,6]naphthyridines 10a, 10b

Synthesis of ethyl 2-(5,10-dihydropyrrolo[1,2-*g*][1,6]naphthyridin-10-yl)acetate (10a) (Table 2.1, Entry 7)

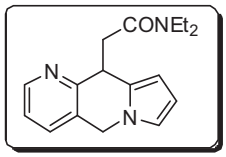


t-BuLi (0.68 mL of a solution 1.53 M in hexane, 1.04 mmol) was added dropwise to a solution of 2-bromomesitylene (0.08 mL, 0.51 mmol) in dry THF (5 mL) at -78 ºC and under an inert atmosphere. The reaction was stirred for 1 h at -20 ºC and after that time, a solution of (iodopyridinylmethyl)pyrrolylacrylate **5b** (100.00 mg, 0.26 mmol) in dry THF (5 mL) was added *via* canula at -105 ºC. The mixture was stirred for 5 min at -105 ºC and quenched at low temperature with a saturated solution of NH_4Cl (5 mL). Et_2O (20 mL) and H_2O (10 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (neutral alumina, hexane/EtOAc 8/2) obtaining product **10a** as a yellow oil (33.00 mg, 0.13 mmol, 49% yield).

IR (ATR): 2979 cm^{-1} (C-H_{arom} st), 2924 cm^{-1} (C-H_{aliph} st), 1730 cm^{-1} (C=O st), 1580 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.23 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.98 (dd, *J* = 15.8, 6.3 Hz, 1H, -$C\underline{H}_AH_BCO_2Et$), 3.15 (dd, *J* = 15.8, 6.3 Hz, 1H, -$CH_A\underline{H}_BCO_2Et$), 4.13 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.67 (t, *J* = 6.3 Hz, 1H, H_{10}), 5.12 (d, *J* = 15.8 Hz, 1H, H_{5A}), 5.20 (d, *J* = 15.8 Hz, 1H, H_{5B}), 6.03 – 6.11 (m, 1H, H_9), 6.20 – 6.25 (m, 1H, H_8), 6.73 (brs, 1H, H_7), 7.18 (dd, *J* = 7.7, 4.6 Hz, 1H, H_3), 7.53 (d, *J* = 7.7 Hz, 1H, H_4), 8.52 (d, *J* = 4.6 Hz, 1H, H_2); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.1 ($OCH_2\underline{C}H_3$), 37.6 (C_{10}), 39.6 (-$\underline{C}H_AH_BCO_2Et$), 47.0

(C_5), 60.4 (O<u>C</u>$H_2$$CH_3$), 104.3 ($C_9$) 109.0 ($C_8$), 118.5 ($C_7$), 121.5 ($C_3$), 127.1 ($C_{4a}$), 130.0 ($C_{9a}$), 133.8 ($C_4$), 148.3 ($C_2$), 155.4 ($C_{10a}$), 171.9 (<u>C</u>$O_2$Et). **MS (ESI$^+$):** (*m/z*) 258 ($MH^+$ + 1, 15), 257 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{15}H_{17}N_2O_2$ (MH^+): 257.1290. Found: 257.1296.

Synthesis of 2-(5,10-dihydropyrrolo[1,2-*g*][1,6]naphthyridin-10-yl)-*N*,*N*-diethylacetamide (10b) (Table 2.1, Entry 5)

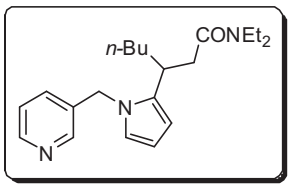


t-BuLi (0.71 mL of a solution 1.38 M in hexane, 0.98 mmol) was added dropwise to a solution of 2-bromomesitylene (0.08 mL, 0.50 mmol) in dry THF (5 mL) at -78 ºC and under an inert atmosphere. The reaction was stirred for 1 h at -20 ºC and after that time, a solution of (iodopyridinylmethyl)pyrrolylacrylamide **5d** (100.00 mg, 0.24 mmol) in dry THF (5 mL) was added *via* canula at -105 ºC. The mixture was stirred for 10 min at -105 ºC and quenched at low temperature with a saturated solution of NH_4Cl (5 mL). Et_2O (20 mL) and H_2O (10 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **10b** as a yellow oil (38.90 mg, 0.14 mmol, 56% yield).

IR (ATR): 2976 cm^{-1} (C-H_{arom} st), 2926 cm^{-1} (C-H_{aliph} st), 1627 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.05 – 1.15 (m, 6H, N(CH_2C<u>H_3</u>)<u>$_2$</u>), 2.93 (dd, *J* = 15.1, 6.3 Hz, 1H, -C<u>H_A</u>$H_B$$CONEt_2$), 3.13 – 3.43 (m, 5H, N(C<u>H_2</u>CH_3)<u>$_2$</u>), -CH_A<u>H_B</u>$CONEt_2$), 4.79 (t, *J* = 6.3 Hz, 1H, H_{10}), 5.10 (d, *J* = 15.7 Hz, 1H, H_{5A}), 5.20 (d, *J* = 15.7 Hz, 1H, H_{5B}), 6.01 – 6.06 (m, 1H, H_9), 6.17 – 6.22 (m, 1H, H_8), 6.68 – 6.73 (m, 1H, H_7), 7.15 (dd, *J* = 7.7, 4.8 Hz, 1H, H_3), 7.51 (d, *J* = 7.7 Hz, 1H, H_4),

8.45 – 8.52 (m, 1H, H_2); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 12.9, 14.2 ($N(CH_2\underline{C}H_3)_2$), 37.7 (-$\underline{C}H_AH_BCONEt_2$), 37.9 ($C_{10}$), 40.3, 42.0 ($N(\underline{C}H_2CH_3)_2$), 47.1 ($C_5$), 104.2 ($C_9$) 108.8 ($C_8$), 118.2 ($C_7$), 121.2 ($C_3$), 127.3 ($C_{4a}$), 130.8 ($C_{9a}$), 133.6 ($C_4$), 148.1 ($C_2$), 156.4 ($C_{10a}$), 170.2 ($\underline{C}ONEt_2$). **MS (ESI$^+$):** (*m/z*) 285 ($MH^+$ + 1, 16), 284 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{17}H_{22}N_3O$ (MH^+): 284.1763. Found: 284.1761.

Synthesis of *N,N*-diethyl-3-(1-(pyridin-3-ylmethyl)-1*H*-pyrrol-2-yl)heptanamide (11) (Table 2.1, Entry 1)



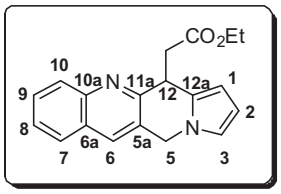
n-BuLi (0.61 mL of a solution 0.97 M in hexane, 0.59 mmol) was added dropwise to a solution of (bromopyridinylmethyl)pyrrolylacrylamide **5c** (97.50 mg, 0.27 mmol) in dry THF (5 mL) at -90 ºC and under an inert atmosphere. The reaction was stirred for 5 min and quenched at low temperature with a saturated solution of NH_4Cl (5 mL). Et_2O (20 mL) and H_2O (10 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 8/2) obtaining product **11** as a colorless oil (41.60 mg, 0.12 mmol, 45% yield), and naphthyridine **10b** (7.10 mg, 25.06 mmol, 9% yield) as a minor fraction.

IR (ATR): 2953 cm^{-1} (C-H_{arom} st), 2928 cm^{-1} (C-H_{aliph} st), 1631 cm^{-1} (C=O st), 1577 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.72 (t, *J* = 7.2 Hz, 3H, $3H_4'$), 0.82 – 0.96 (m, 1H, H_{2A}'), 0.96 – 1.13 (m, 9H, H_{2B}', $2H_3'$, $N(CH_2C\underline{H}_3)_2$), 1.44 – 1.57 (m, 2H, $2H_1'$), 2.44 (d, *J* = 6.9 Hz, 2H, -CH-$C\underline{H}_2$-$CONEt_2$), 3.06 – 3.40 (m, 5H, $N(C\underline{H}_2CH_3)_2$, -$C\underline{H}$-$CH_2$-$CONEt_2$), 5.04 (d, *J* = 16.3 Hz, 1H, $C\underline{H}_AH_BN$),

5.34 (d, *J* = 16.3 Hz, 1H, $CH_A\underline{H_B}N$), 5.95 (dd, *J* = 3.3, 1.6 Hz, 1H, $H_{3pyrrole}$), 6.12-6.16 (m, 1H, $H_{4pyrrole}$), 6.53 – 6.57 (m, 1H, $H_{5pyrrole}$), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H, $H_{5pyridine}$), 7.31 (brd, *J* = 7.8 Hz, 1H, $H_{4pyridine}$), 8.40 (d, *J* = 1.6 Hz, 1H, $H_{2pyridine}$), 8.48 (dd, *J* = 4.8, 0.9 Hz, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 13.0, 13.9 ($N(CH_2\underline{C}H_3)_2$), 14.3 ($C_4'$), 22.5 ($C_3'$), 29.7 ($C_2'$), 32.9 (-$\underline{C}$H-$CH_2$-$CONEt_2$), 35.9 ($C_1'$), 40.3 ($N(\underline{C}H_2CH_3)_2$), 40.7 (-CH-$\underline{C}H_2$-$CONEt_2$), 41.9 ($N(\underline{C}H_2CH_3)_2$), 47.8 ($\underline{C}H_AH_BN$), 104.7 ($C_{3pyrrole}$) 107.7 ($C_{4pyrrole}$), 120.3 ($C_{5pyrrole}$), 123.4 ($C_{5pyridine}$), 134.5 ($C_{4pyridine}$), 134.6 ($C_{3pyridine}$), 137.1 ($C_{2pyrrole}$), 148.4 ($C_{2pyridine}$), 148.7 ($C_{6pyridine}$), 170.8 (-CH-$CH_2$-$\underline{C}ONEt_2$). **MS (ESI$^+$):** (*m/z*) 343 ($MH^+$ + 1, 23), 342 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{21}H_{32}N_3O$ (MH^+): 342.2545. Found: 342.2549.

6.2.3. Intramolecular carbolithiation reaction of *o*-haloquinolines 9a-9d. Synthesis of 5,12-dihydrobenzo[*b*]pyrrolo[1,2-*g*][1,6]naphthyridines 12a, 12b

Synthesis of ethyl 2-(5,12-dihydrobenzo[*b*]pyrrolo[1,2-*g*][1,6]naphthyridin-12-yl)acetate (12a) (Table 2.2, Entry 2)

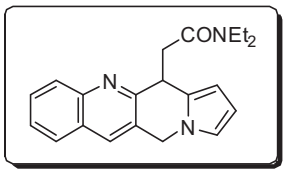


t-BuLi (0.86 mL of a solution 1.08 M in hexane, 0.93 mmol) was added dropwise to a solution of 2-bromomesitylene (0.07 mL, 0.46 mmol) in dry THF (5 mL) at -78 ºC and under an inert atmosphere. The reaction was stirred for 1 h at -20 ºC and after that time, a solution of (iodoquinolinylmethyl)pyrrolylacrylate **9b** (100.00 mg, 0.23 mmol) in dry THF (5 mL) was added *via* canula at -105 ºC. The mixture was stirred for 10 min at -105 ºC and quenched at low temperature with a saturated solution of NH_4Cl (5 mL). Et_2O (20 mL) and H_2O (10 mL) was added and the organic layer was separated.

The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (neutral alumina, hexane/EtOAc 8/2) obtaining product **12a** as yellow oil (21.0 mg, 0.07 mmol, 30% yield).

IR (ATR): 2980 cm^{-1} (C-H_{arom} st), 1730 cm^{-1} (C=O st), 1622 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.29 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 3.08 (dd, *J* = 15.8, 6.7 Hz, 1H, $C\underline{H_A}H_B$-CO_2Et), 3.33 (dd, *J* = 15.8, 6.7 Hz, 1H, $CH_A\underline{H_B}$-CO_2Et), 4.14 – 4.27 (m, 2H, $OC\underline{H_2}CH_3$), 4.82 (t, *J* = 6.7 Hz, 1H, H_{12}), 5.27 (d, *J* = 15.4 Hz, 1H, H_{5A}), 5.33 (d, *J* = 15.4 Hz, 1H, H_{5B}), 6.07 – 6.12 (m, 1H, H_1), 6.20 – 6.24 (m, 1H, H_2), 6.74 – 6.81 (m, 1H, H_3), 7.50 – 7.54 (m, 1H, H_8), 7.69 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H, H_9), 7.78 (brd, *J* = 7.7 Hz, 1H, H_7), 7.99 (s, 1H, H_6), 8.02 (brd, *J* = 8.5 Hz, 1H, H_{10}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.3 ($OCH_2\underline{C}H_3$), 38.2 ($\underline{C}H_AH_B$-CO_2Et), 38.7 (C_{12}), 47.6 (C_5), 60.5 ($O\underline{C}H_2CH_3$), 104.2 (C_1) 108.6 (C_2), 118.8 (C_3), 125.7 (C_{5a}), 126.5 (C_8), 126.6 (C_{6a}), 127.2 (C_7), 129.1 (C_{10}), 129.4 (C_9), 130.3 (C_{12a}), 132.6 (C_6), 147.1 (C_{10a}), 156.8 (C_{11a}), 172.3 ($\underline{C}O_2Et$). **MS (ESI$^+$):** (*m/z*) 308 (MH^+ + 1, 18), 307 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{19}H_{19}N_2O_2$ (MH^+): 307.1447. Found: 307.1453.

Synthesis of 2-(5,12-dihydrobenzo[*b*]pyrrolo[1,2-*g*][1,6]naphthyridin-12-yl)-*N*,*N*-diethylacetamide (12b) (Table 2.2, Entry 5)



t-BuLi (0.81 mL of a solution 1.08 M in hexane, 0.87 mmol) was added dropwise to a solution of 2-bromomesitylene (0.07 mL, 0.45 mmol) in dry THF (5 mL) at -78 ºC and under an inert atmosphere. The reaction was stirred for 1 h at -20 ºC and after that time, a solution of (iodoquinolinylmethyl)pyrrolylacrylamide **9d** (100.00 mg, 0.22 mmol) in dry THF

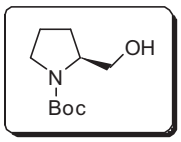
(5 mL) was added *via* canula at -105 ºC. The mixture was stirred for 30 min at -105 ºC and quenched at low temperature with a saturated solution of NH_4Cl (5 mL). Et_2O (20 mL) and H_2O (10 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (silica, hexane/EtOAc 6/4) obtaining product **12b** as yellow oil (20.40 mg, 0.06 mmol, 28% yield).

IR (ATR): 2963 cm^{-1} (C-H_{arom} st), 2925 cm^{-1} (C-H_{aliph} st), 1631 cm^{-1} (C=O st), 1490 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.16 (t, *J* = 7.1 Hz, 3H, $N(CH_2C\underline{H}_3)_2$), 1.25 (t, *J* = 7.1 Hz, 3H, $N(CH_2C\underline{H}_3)_2$), 3.03 (dd, *J* = 15.1, 6.1 Hz, 1H, $C\underline{H}_AH_B$-$CONEt_2$), 3.34 – 3.46 (m, 5H, $CH_A\underline{H}_B$-$CONEt_2$, $N(C\underline{H}_2CH_3)_2$), 4.98 (t, *J* = 6.1 Hz, 1H, H_{12}), 5.27 (d, *J* = 15.3 Hz, 1H, H_{5A}), 5.32 (d, *J* = 15.3 Hz, 1H, H_{5B}), 6.04 – 6.09 (m, 1H, H_1), 6.19 (dd, *J* = 3.4, 2.8 Hz, 1H, H_2), 6.76 – 6.78 (m, 1H, H_3), 7.47 – 7.52 (m, 1H, H_8), 7.66 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H, H_9), 7.77 (brd, *J* = 8.1 Hz, 1H, H_7), 7.94 – 8.00 (m, 2H, H_6, H_{10}); **^{13}C NMR** (300 MHz, $CDCl_3$, 25 ºC): δ (ppm) = 13.1, 14.4 ($N(CH_2\underline{C}H_3)_2$), 35.8 ($\underline{C}H_AH_B$-$CONEt_2$), 39.1 ($C_{12}$), 40.6, 42.3 ($N(\underline{C}H_2CH_3)_2$), 47.8 ($C_5$), 103.7 ($C_1$) 108.4 ($C_2$), 118.5 ($C_3$), 126.2 ($C_{5a}$), 126.3 ($C_8$), 126.6 ($C_{6a}$), 127.2 ($C_7$), 129.0 ($C_{10}$), 129.2 ($C_9$), 131.3 ($C_{12a}$), 132.3 ($C_6$), 147.1 ($C_{10a}$), 157.9 ($C_{11a}$), 170.7 ($\underline{C}ONEt_2$). **MS (ESI$^+$):** (*m/z*) 335 ($MH^+$ + 1, 22), 334 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{21}H_{24}N_3O$ (MH^+): 334.1919. Found: 334.1926.

6.3. Intramolecular carbolithiation reaction of N-(o-iodobenzyl)pyrrolidinylacrylates

6.3.1. Synthesis of *N*-(*o*-iodobenzyl)pyrrolidines 17a, 17b

Synthesis of (*S*)-*tert*-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (13)[12]



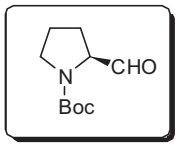
To a solution of Boc-L-proline (3.00 g, 13.94 mmol) in dry THF (75 mL), $BH_3.SMe_2$ (7.70 mL of a 2.00 M THF solution, 15.33 mmol) was added dropwise and under inert atmosphere. The mixture was heated under reflux for 1 h, cooled to room temperature and concentrated to dryness. The resulting crude was eluted with CH_2Cl_2 (100 mL), and washed subsequently with water (2 x 50 mL), saturated $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. Product **13** was obtained as a white solid (2.61 g, 13.00 mmol, 93% yield) and was used without further purification.

m.p. = 60-61 ºC (CH_2Cl_2); **IR (ATR):** 3416 cm^{-1} (brs, O-H st), 2972 cm^{-1} (C-H_{aliph} st), 1668 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.44 (s, 9H, C($\underline{CH_3}$)$_3$), 1.48 – 1.68 (m, 1H, H_{3A}), 1.70 – 1.90 (m, 2H, 2 x H_4), 1.92 – 2.06 (m, 1H, H_{3B}), 3.28 (dt, *J* = 10.9, 6.8 Hz, 1H, H_{5A}), 3.42 (dt, *J* = 10.9, 6.8 Hz, 1H, H_{5B}), 3.49 – 3.65 (m, 2H, $C\underline{H_2}OH$), 3.83 – 4.0 (m, 1H, H_2). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 24.0 (C_{4p}), 28.4 ($C(\underline{C}H_3)_3$), 28.6 (C_{3p}), 47.5 (C_{5p}), 60.1 (C_{2p}), 67.5 (CH_2OH), 80.1 ($\underline{C}(CH_3)_3$), 157.0 (CO_2*t*-Bu). **MS (CI):** (*m/z*) 170 ([M – CH_2OH]$^+$, 53); 146 (100); 128 (52); 114 (43); 102 (42). **HRMS (CI):** Calculated for $C_9H_{16}NO_2$ [M –

[12] Reed, P. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 2624.

$CH_2OH]^+$: 170.1181. Found: 170.1192. $[\alpha]_D^{20}$: -49.5 (c = 1.0 g/L, $CHCl_3$). [Lit.[13] $[\alpha]_D^{20}$: -47.5 (c = 1.0 g/L, $CHCl_3$)].

Synthesis of (*S*)-*tert*-butyl 2-formylpyrrolidine-1-carboxylate (14)[12]



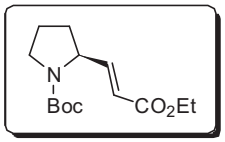
To a water cooled solution of Boc-L-prolinol (**13**) (4.33 g, 21.51 mmol) in dry CH_2Cl_2 (30 mL), PCC (7.10 g, 32.28 mmol), 1 g of 4 Å molecular sieves powder and acetic acid (2.0 mL, 34.94 mmol) were added subsequently. The mixture was stirred for 2 h at room temperature. After that time, celite (1.00 g) and Et_2O (250 mL) were added and the precipitate was filtered through celite. The filtrate was washed with toluene (200 mL), Et_2O (250 mL) and concentrated to dryness. The crude was eluted in Et_2O and further filtered through a small plug of SiO_2. Product **14** was obtained as colorless oil (3.21 g, 16.11 mmol, 75% yield) and was used without further purification.

IR (ATR): 2977 cm^{-1} (C-H_{aliph} st), 1735 cm^{-1} (C=O st, aldehyde), 1689 cm^{-1} (C=O st, carbamate); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = (rotamer relation 1.5:1) = 1.32 (s, 5.4H, $C(CH_3)_3$, major rotamer), 1.37 (s, 3.6H, $C(CH_3)_3$, minor rotamer), 1.67 – 2.12 (m, 4H, 2 x H_3, 2 x H_4), 3.28 – 3.51 (m, 2H, 2 x H_5), 3.89 – 4.01 (m, 0.6H, H_2, major rotamer), 4.02 – 4.15 (m, 0.4H, H_2, minor rotamer), 9.36 (s, 0.6H, CHO, major rotamer), 9.44 (s, 0.4H, CHO, minor rotamer); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 23.7 (C_{4p}, major rotamer), 24.4 (C_{4p}, minor rotamer), 26.5 (C_{3p}, minor rotamer), 27.7 (C_{3p}, major rotamer), 28.0 ($C(\underline{C}H_3)_3$, major rotamer), 28.1 ($C(\underline{C}H_3)_3$, minor rotamer), 46.5 (C_{5p}, major rotamer), 46.6 (C_{5p}, minor rotamer), 64.6 (C_{2p}, minor rotamer), 64.8 (C_{2p}, major rotamer), 79.9 ($\underline{C}(CH_3)_3$, minor rotamer), 80.2 ($\underline{C}(CH_3)_3$, major rotamer), 153.7 (CO_2t-Bu, major rotamer), 154.6 (CO_2t-Bu,

[13] Souček, M.; Urban, J.; Šaman, D. *Collect. Czech. Chem. Commun.* **1990**, *55*, 761.

minor rotamer), 200.0 (CHO, major rotamer), 200.3 (CHO, minor rotamer). **MS (CI):** (*m/z*) 170 ((M – CHO)$^+$, 55); 144 (100); 126 (58); 114 (66); 100 (46). **HRMS (CI):** Calculated for $C_9H_{16}NO_2$ [M – CHO]$^+$: 170.1181. Found: 170.1181. **$[\alpha]_D^{20}$**: -93.5 (c = 1.1 g/L, CH_2Cl_2). [Lit.[14] **$[\alpha]_D^{20}$**: -90.1 (c = 1.0 g/L, $CHCl_3$)].

Synthesis of (*S,E*)-*tert*-butyl 2-(3-ethoxy-3-oxoprop-1-enyl)pyrrolidine-1-carboxylate (15a)[15]



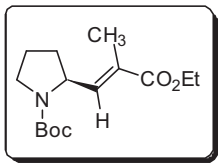
To a solution of Boc-L-prolinal (**14**) (1.34 g, 6.73 mmol) in CH_2Cl_2 (40 mL), ylide **4a** (4.93 g, 13.44 mmol) was added. The reaction was stirred for 16 h at room temperature. After that time, the crude was washed with H_2O (3 x 20 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 6/4) obtaining product **15a** as a yellow oil (1.43 g, 5.31 mmol, 79% yield).

IR (ATR): 2976 cm^{-1} (C-H_{aliph} st), 1720 cm^{-1} (C=O st, ester), 1691 cm^{-1} (C=O st, carbamate), 1657 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = (rotamer relation 1.5:1) = 1.21 (t, *J* = 6.8 Hz, 3H, $OCH_2C\underline{H_3}$), 1.29 – 1.37 (m, 5.4H, $C(C\underline{H_3})_3$, major rotamer), 1.37 – 1.42 (m, 3.6H, $C(C\underline{H_3})_3$, minor rotamer), 1.64 – 1.74 (m, 1H, H_{3A}), 1.74 – 1.82 (m, 2H, 2 x H_4), 1.93 – 2.10 (m, 1H, H_{3B}), 3.22 - 3.42 (m, 2H, 2 x H_5), 4.01 – 4.19 (m, 2H, $OC\underline{H_2}CH_3$), 4.21 – 4.35 (m, 0.6H, H_2, major rotamer), 4.35 – 4.49 (m, 0.4H, H_2, minor rotamer), 5.74 (d, *J* = 15.3 Hz, 1H, -CH=C$\underline{H}$-CO_2Et), 6.67 – 6.81 (m, 1H, -C$\underline{H}$=CH-CO_2Et); **^{13}C NMR** ($CDCl_3$, 25

[14] Song, X.-N.; Yao, Z.-J. *Tetrahedron* **2010**, *66*, 2589.
[15] Zoute, L.; Kociok-Köhn, G.; Frostv, C. V. *Org. Lett.* **2009**, *11*, 2491.

ºC): δ (ppm) = 14.0 ($OCH_2\underline{C}H_3$), 22.7 (C_{4p}, major rotamer), 23.4 (C_{4p}, minor rotamer), 28.2 ($C(\underline{C}H_3)_3$), 30.7 (C_{3p}, minor rotamer), 31.5 (C_{3p}, major rotamer), 46.0 (C_{5p}, major rotamer), 46.4 (C_{5p}, minor rotamer), 57.3 (C_{2p}, minor rotamer), 57.6 (C_{2p}, major rotamer), 60.1 ($O\underline{C}H_2CH_3$), 79.4 ($\underline{C}(CH_3)_3$), 120.3 (-CH=$\underline{C}$H-CO_2Et), 148.1 (-$\underline{C}$H=CH-CO_2Et, minor rotamer), 148.3 (-$\underline{C}$H=CH-CO_2Et, major rotamer), 154.1 (CO_2*t*-Bu), 166.2 (CO_2Et). **MS (CI):** (*m/z*) 196 (M – O*t*-Bu, 4); 170 (100); 168 (M – CO_2*t*-Bu, 6); 124 (50). **HRMS (CI):** Calculated for $C_9H_{16}NO_2$ (MH^+-(CH=CH-CO_2Et)): 170.1181. Found: 170.1169. **$[\alpha]_D^{20}$:** -64.4 (c = 1.2 g/L, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be >99% [Chiralcel IC, hexane:*i*-PrOH 95:05, 1 mL/min, t_r (*S*)= 24.9 min (>99 %), t_r (*R*)= 55.0 min (<1 %)].

Synthesis of (*S*,*E*)-*tert*-butyl 2-(3-ethoxy-2-methyl-3-oxoprop-1-enyl)pyrrolidine-1-carboxylate (15b)[16]



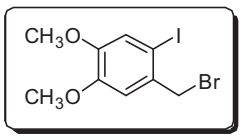
To a suspension of ylide **4c** (3.87 g, 10.04 mmol) in tert-butyl methyl ether (50 mL) under argon atmospehere, Boc-L-prolinal (**14**) (1.00 g, 5.02 mmol) dissolved in *tert*-butyl methyl ether (10 mL) was added *via* canula. The reaction was heated under reflux for 16 h under an inert atmosphere. After that time, the crude was washed with H_2O (3 x 20 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography

[16] Grison C.; Gèneve, S.; Halbin, E.; Coutrot, P. *Tetrahedron* **2001**, *57*, 4903.

(silica gel, hexane/EtOAc 8/2) to afford **15b** as a colorless oil (1.35 g, 4.76 mmol, 95% yield).[17]

IR (ATR): 2975 cm^{-1} (C_{aliph}-H st), 1693 cm^{-1} (C=O st, carbamate), 1655 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.25 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.37 (brs, 9H, $C(C\underline{H}_3)_3$), 1.56 – 1.69 (m, 1H, H_{3A}), 1.72 – 1.99 (m, 5H, -CH=C($C\underline{H}_3$)-CO_2Et, 2 x H_4), 2.01 – 2.20 (m, 1H, H_{3B}), 3.27 – 3.57 (m, 2H, 2 x H_5), 4.08 – 4.24 (m, 2H, $OC\underline{H}_2CH_3$), 4.33 – 4.65 (m, 1H, H_2), 6.55 – 6.61 (m, 1H, -C$\underline{H}$=C(CH_3)-CO_2Et); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 12.4 (-CH=C($\underline{C}H_3$)-CO_2Et), 14.2 ($OCH_2\underline{C}H_3$), 23.8 (C_{4p}, major rotamer), 24.4 (C_{4p}, minor rotamer), 28.3 ($C(\underline{C}H_3)_3$), 31.8 (C_{3p}, minor rotamer), 32.3 (C_{3p}, major rotamer), 46.4 (C_{5p}), 55.2 (C_{2p}), 60.5 ($O\underline{C}H_2CH_3$), 79.4 ($\underline{C}(CH_3)_3$), 126.3 (-CH=$\underline{C}$(CH_3)-CO_2Et, major rotamer), 127.3 (-CH=$\underline{C}$(CH_3)-CO_2Et, minor rotamer), 143.3 (-$\underline{C}$H=C(CH_3)-CO_2Et), 154.4 (CO_2t-Bu), 167.9 (CO_2Et). **MS (CI):** (*m/z*) 284 (MH^+, <1); 228 (MH^+-$(CH_3)_3$, 55); 184 (51); 183 (30); 154 (31); 138 (100). **HRMS (CI):** Calculated for $C_{15}H_{26}NO_4$ (MH^+): 284.1862. Found: 284.1880. **$[\alpha]_D^{20}$:** -9.3 (c = 0.6 g/L, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be >99% [Chiralcel IC, hexane:*i*-PrOH 95:5, 1 mL/min, t_r (*S-E*)= 19.40 min (>99 %), t_r (*R-E*)= 41.20 min (<1 %)].

Synthesis of 1-(bromomethyl)-2-iodo-4,5-dimethoxybenzene (16)[18]



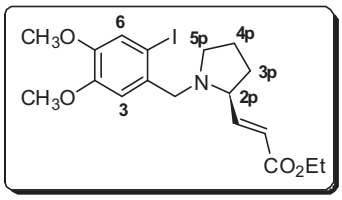
To a solution of (2-iodo-4,5-dimethoxyphenyl)methanol (2.87 g, 9.76 mmol) in dry CH_2Cl_2 (40 mL), PBr_3 (1.20 mL, 12.64 mmol) was added. The mixture was stirred for 2 h at

[17] (*Z*)-isomer was not detected by NMR spectroscopy techniques, but HPLC spectrometry showed product **15b** as a 95:5 mixture of diastereomers (*E:Z*).
[18] Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311.

room temperature. Once the reaction was completed, an aqueous solution of saturated $NaHCO_3$ was carefully added, until the release of gas totally finished. Subsequently, the organic layer was further washed with H_2O (3 x 40 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The product **16** was obtained pure as a white solid (3.09 g, 8.66 mmol, 89% yield).

m.p.: 80-81 ºC (CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.58 (s, 2H, Ar-CH_2-Br), 6.96 (s, 1H, H_{6arom}), 7.22 (s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 39.6 (CH_2Br), 56.2, 56.4 (2 x OCH_3), 88.7 (C_{2arom}), 112.9 (C_{6arom}), 122.0 (C_{3arom}), 132.6 (C_{1arom}), 149.7 (C_{4arom}), 149.8 (C_{5arom}). **MS (CI):** (*m/z*) 359 (8); 357 (MH^+, 8); 279 (13); 278 (21); 277 (100); 152 (14). **HRMS (CI):** Calculated for $C_9H_{11}BrIO_2$ (MH^+): 356.8987. Found: 356.8970.

Synthesis of (*S,E*)-ethyl 3-(1-(2-iodo-4,5-dimethoxybenzyl)pyrrolidin-2-yl)acrylate (17a)

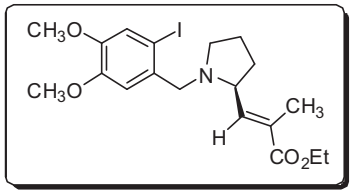


To a solution of pyrrolidinylacrylate **15a** (0.74 g, 2.75 mmol) in CH_2Cl_2 (20 mL), trifluoroacetic acid (2.13 mL, 27.56 mmol) was added. The reaction was stirred overnight at room temperature. Next day, the solvent was evaporated to dryness under reduced pressure obtaining (*S,E*)-2-(3-ethoxy-3-oxoprop-1-enyl)pyrrolidinium trifluoroacetate salt (0.78 g, 2.75 mmol, quant.) as a crude which was used in the next step without any purification. This salt was dissolved in DMSO (20 mL) and KOH (0.46 g, 8.20 mmol) was added. The reaction was stirred at room temperature for 2 h, and after that time, benzyl bromide **16** (0.49 g, 1.37 mmol) was added to the mixture. The reaction was left stirring for 16 h at room temperature. After that

time, the mixture was quenched with H_2O (10 mL) and eluted with CH_2Cl_2 (20 mL). The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 20 mL). Combined organic extracts were washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 6/4) obtaining product **17a** as a yellow oil (0.55 g, 1.24 mmol, 90% yield).

IR (ATR): 2955 cm^{-1}(C_{arom}-H st), 1716 cm^{-1} (C=O st), 1657 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.25 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.57 – 1.92 (m, 3H, H_{3A}, 2 x H_4), 1.92 – 2.09 (m, 1H, $1H_{3B}$), 2.27 (q, *J* = 8.4 Hz, 1H, H_{5A}), 2.96 – 3.08 (m, 1H, H_{5B}), 3.14 (q, *J* = 8.0 Hz, 1H, H_2), 3.35 (d, *J* = 13.8 Hz, 1H, Ar-$C\underline{H}_AH_B$-N), 3.75 (d, *J* = 13.8 Hz, 1H, Ar-$CH_A\underline{H}_B$-N), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.15 (q, *J* = 7.1 Hz, 3H, $OC\underline{H}_2CH_3$), 5.93 (d, *J* = 15.6 Hz, 1H, -CH=C<u>H</u>-CO_2Et), 6.87 (dd, *J* = 15.6, 8.0 Hz, 1H, -C<u>H</u>=CH-CO_2Et), 6.98 (s, 1H, H_{6arom}), 7.17 (s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.2 ($OCH_2\underline{C}H_3$), 22.8 (C_{4p}), 31.4 (C_{3p}), 53.7 (C_{5p}), 55.9 ($O\underline{C}H_3$), 56.0 ($O\underline{C}H_3$), 60.2 ($O\underline{C}H_2CH_3$), 62.1 (Ar-$\underline{C}H_AH_B$-N), 65.8 (C_{2p}), 87.5 (C_{2arom}), 112.9 (C_{6arom}), 121.3 (C_{3arom}), 121.6 (-CH=<u>C</u>H-CO_2Et), 133.9 (C_{1arom}), 148.4 (C_{5arom}), 149.2 (C_{4arom}), 150.5 (-<u>C</u>H=CH-CO_2Et), 166.3 (<u>C</u>O_2Et). **MS (ESI$^+$):** (*m/z*) 447 (22); 446 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{18}H_{25}INO_4$ (MH^+): 446.0828. Found: 446.0826. **$[\alpha]_D^{20}$:** -49.3 (c = 1.0 g/L, CH_2Cl_2).

Synthesis of (*S,E*)-ethyl 3-(1-(2-iodo-4,5-dimethoxybenzyl)pyrrolidin-2-yl)-2-methylacrylate (17b)



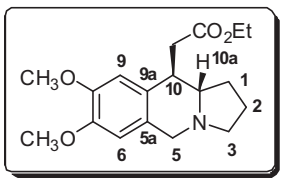
To a solution of pyrrolidinylacrylate **15b** (0.73 g, 2.58 mmol) in dry CH_2Cl_2 (20 mL), trifluoroacetic acid (2.00 mL, 25.87 mmol) was added. The reaction was stirred overnight at room temperature. Next day, the solvent was evaporated to dryness under reduced pressure obtaining (*S,E*)-2-(3-ethoxy-2-methyl-3-oxoprop-1-enyl)pyrrolidinium trifluoroacetate salt (0.77 g, 2.58 mmol, quant.) as a crude which was used in next step without any purification. This salt was dissolved in DMSO (20 mL) and KOH (0.43 g, 7.66 mmol) was added. The reaction was stirred at room temperature for 30 min, and after that time, benzyl bromide **16** (0.46 g, 1.29 mmol) was added to the mixture. The reaction was left stirring for 1.5 h at room temperature. After that time, the reaction was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (3 x 20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) to afford product **17b** as a yellow oil (0.38 g, 0.83 mmol, 64% yield).

IR (ATR): 2967 cm^{-1} (C-H_{aliph} st), 1705 cm^{-1} (C=O st), 1653 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.26 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.51 – 1.70 (m, 1H, H_{3A}), 1.87 (s, 3H, -CH=C($C\underline{H}_3$)-CO_2Et)*, 1.72 – 1.90 (m, 2H, 2 x H_4)*, 1.93 – 2.09 (m, 1H, H_{3B}), 2.18 – 2.32 (m, 1H, H_{5A}), 2.97 – 3.08 (m, 1H, H_{5B}), 3.25 – 3.39 (m, 2H, H_2, Ar-C$\underline{H}_A$$H_B$-N), 3.73 (d, *J* = 13.6 Hz, 1H, Ar-$CH_A\underline{H}_B$-N), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.15 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 6.73 (d, *J* = 8.8 Hz, 1H, -C$\underline{H}$=(CH_3)-CO_2Et), 6.97 (s, 1H, H_{3arom}), 7.18 (s, 1H, H_{6arom}); **^{13}C**

NMR (300 MHz, $CDCl_3$, 25 ºC): δ (ppm) = 12.8 (-CH=C($\underline{C}H_3$)-CO_2Et), 14.2 ($OCH_2\underline{C}H_3$), 22.7 (C_{4p}), 30.6 (C_{3p}), 53.7 (C_{5p}), 55.9, 56.0 (2 x OCH_3), 60.4 ($O\underline{C}H_2CH_3$), 62.3 (Ar-CH_AH_B-N), 62.8 (C_{2p}), 87.7 (C_{2arom}), 113.1 (C_{6arom}), 121.3 (C_{3arom}), 128.5 (-CH=$\underline{C}$(CH_3)-CO_2Et), 133.9 (C_{1arom}), 144.1 (-$\underline{C}$H=C(CH_3)-CO_2Et), 148.4, 149.2 (C_{4arom}, C_{5arom}), 167.9 (CO_2Et). **MS (CI):** (*m/z*) 460 (MH^+, 40); 458 (20); 332 (27); 278 (17); 277 (100); 196 (36); 182 (50). **HRMS (CI):** Calculated for $C_{19}H_{27}INO_4$ (MH^+): 460.0985. Found: 460.0969. **$[\alpha]_D^{20}$:** -64.2 (c = 1.5 g/L, CH_2Cl_2).* Partially overlapped signals

6.3.2. Intramolecular carbolithiation reaction of *N*-(*o*-iodobenzyl)pyrrolidines 17a, 17b. Synthesis of hexahydropyrrolo[1,2-*b*]isoquinolines 18a, 18b

Synthesis of ethyl 2-((10*R*,10a*S*)-7,8-dimethoxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetate (18a) (Table 2.3, Entry 1)

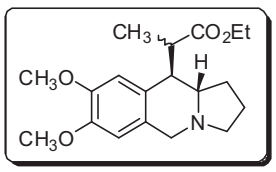


t-BuLi (1.29 mL of a solution 1.00 M in hexane, 1.29 mmol) was added dropwise to a solution of 2-bromomesitylene (0.10 mL, 0.64 mmol) in dry THF (5 mL) at -78 ºC and under an inert atmosphere. The reaction was stirred for 1 h at -20 ºC and after that time, a solution of pyrrolidinylacrylate **17a** (143.30 mg, 0.32 mmol) in dry THF (5 mL) was added *via* canula at -105 ºC. The mixture was stirred for 5 min at -105 ºC and quenched at low temperature with a saturated solution of NH_4Cl (5 mL). Et_2O (20 mL) and H_2O (10 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was

subjected to flash chromatography (silica gel, EtOAc/MeOH 9/1) to afford the product **18a** as white solid (86.80 mg, 0.27 mmol, 85% yield).

m.p.: 75-76 ºC (Hexane/EtOAc); **IR (ATR):** 2957 cm^{-1} (C-H_{aliph} st), 1729 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.23 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 1.55 – 1.67 (m, 1H, H_{1A}), 1.73 - 1.84 (m, 1H, H_{2A}), 1.84 – 1.96 (m, 1H, H_{2B}), 2.05 – 2.16 (m, 1H, H_{1B}), 2.19 – 2.32 (m, 2H, H_{3A}, H_{10a}) 2.61 (dd, *J* = 15.5, 5.8 Hz, 1H, -$C\underline{H_A}H_B$-CO_2Et), 2.70 (dd, *J* = 15.5, 5.8 Hz, 1H, -$CH_A\underline{H_B}$-CO_2Et), 3.13 – 3.27 (m, 2H, H_{3B}, H_{10}), 3.38 (d, *J* = 14.0 Hz, 1H, H_{5A}), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.96 (d, *J* = 14.0 Hz, 1H, H_{5B}), 4.13 (q, *J* = 7.1 Hz, 3H, $OC\underline{H_2}CH_3$), 6.52 (s, 1H, H_6), 6.73 (s, 1H, H_9); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.1 ($OCH_2\underline{C}H_3$), 21.4 (C_2), 30.0 (C_1), 38.6 (-$\underline{C}H_AH_B$-CO_2Et), 41.5 (C_{10}), 54.8 (C_3), 55.5 (C_5), 55.7 (OCH_3), 55.8 (OCH_3), 60.5 ($O\underline{C}H_2CH_3$), 66.1 (C_{10a}), 109.3 (C_6), 109.8 (C_9), 127.2 (C_{5a}), 129.3 (C_{9a}), 147.2 (C_7), 147.6 (C_8), 172.7 (CO_2Et). **MS (ESI$^+$):** (*m/z*) 321 (MH^+ + 1, 18), 320 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{18}H_{26}NO_4$ (MH^+): 320.1862. Found: 320.1873. **$[\alpha]_D^{20}$:** +49.7 (c = 1 g/L, CH_2Cl_2).

Synthesis of (*R/S*)-ethyl 2-((10*R*,10*aS*)-7,8-dimethoxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-10-yl)propanoate (18b) (Table 2.3, Entry 2)



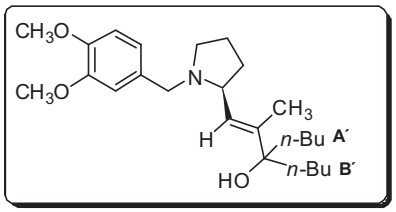
t-BuLi (1.30 mL of a solution 1.00 M in hexane, 1.30 mmol) was added dropwise to a solution of 2-bromomesitylene (0.11 mL, 0.68 mmol) in dry THF (5 mL) at -78 ºC and under an inert atmosphere. The reaction was stirred for 1 h at -20 ºC and after that time, a solution of pyrrolidinylacrylate **17b** (155.00 mg, 0.34 mmol) in dry THF (5 mL) was added *via* canula at -105 ºC. The mixture was stirred for 5 min at -105 ºC and quenched at

low temperature with a saturated solution of NH_4Cl (5 mL). Et_2O (20 mL) and H_2O (10 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (silica gel, EtOAc/MeOH 9/1) to afford product **18b** (86.40 mg, 0.26 mmol, 77% yield) as an oil, in a ratio of 50:50 mixture of diastereomers (diast.1:diast.2).

IR (ATR): 2934 cm^{-1} (C-H_{aliph} st), 1724 cm^{-1} (C=O st), 1516 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.94 (d, *J* = 7.1 Hz, 3H, -CH(C$\underline{H_3}$)-CO_2Et, diast.1) , 0. 99 (d, *J* = 7.1 Hz, 3H, -CH(C$\underline{H_3}$)-CO_2Et, diast.2), 1.18 – 1.29 (m, 6H, 2 x $OCH_2C\underline{H_3}$, diast.1, diast.2), 1.40 – 2.05 (m, 8H, 2 x $2H_1$, 2 x $2H_2$, diast.1, diast.2), 2.10 – 2.43 (m, 4H, 2 x H_{3A}, 2 x H_{10a}, diast.1, diast.2), 2.74 - 2.81 (m, 1H, C$\underline{H}$(CH_3)(CO_2Et), diast.2), 3.04 – 3.24 (m, 3H, -C$\underline{H}$(CH_3)-CO_2Et, diast.1, 2 x H_{3B}, diast.1, diast.2), 3.28 – 3.42 (m, 4H, 2 x H_{10}, 2 x C$\underline{H_{5A}}H_{5B}$, diast.1, diast.2), 3.73 – 3.96 (m, 14H, 2 x (2 x OCH_3), 2 x $CH_{5A}\underline{H_{5B}}$, diast.1, diast.2), 4.05 – 4.29 (m, 4H, 2 x O$\underline{H_2}CH_3$, diast.1, diast.2), 6.51 (s, 1H, H_6, diast.1/diast.2), 6.52 (s, 1H, H_6, diast.1/diast.2), 6.59 (s, 1H, H_9, diast.2), 6.73 (s, 1H, H_9, diast.1); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 11.1 (-CH(C$\underline{H_3}$)-CO_2Et, diast.1), 11.9 (-CH(C$\underline{H_3}$)-CO_2Et, diast.2), 14,1, 14.2 (2 x $OCH_2C\underline{H_3}$, diast.1, diast.2), 21.5, 21.6 (2 x C_2, diast.1, diast.2), 30.4, 30.9 (2 x C_1, diast.1, diast.2), 40.8 (-C$\underline{H}$(CH_3)-CO_2Et, diast.2), 41.9 (-C$\underline{H}$(CH_3)-CO_2Et, diast.1), 46.6, 46.7 (2 x C_{10}, diast.1, diast.2), 54.2, 54.9 (2 x C_3, diast.1, diast.2), 55.3, 55.4 (2 x C_5, diast.1, diast.2), 55.7, 55.8, 56.0 (2 x (2 x OCH_3), diast.1, diast.2)*, 60.4, 60.6 (2 x O$\underline{C}H_2CH_3$, diast.1, diast.2), 61.8, 64.3 (2 x C_{10a}, diast.1, diast.2), 109.5, 109.6 (2 x C_6, diast.1, diast.2), 109.7, 110.7 (2 x C_9, diast.1, diast.2), 127.1 (C_{9a}, diast.2), 128.0 (C_{5a}, diast.1/diast.2), 128.1 (C_{9a}, diast.1), 128.3 (C_{5a}, diast.1/diast.2), 147.0, 147.1, 147.3, 147.8 (2 x C_7, 2 x C_8,

diast.1, diast.2), 175.5 (CO_2Et, diast.1), 176.3 (CO_2Et, diast.2). **MS (CI):** (*m/z*) 335 (MH^+ + 1, 20), 334 (MH^+, 100), 333 (21), 332 (17), 264 (11), 231 (10). **HRMS (CI):** Calculated for $C_{19}H_{28}NO_4$ (MH^+): 334.2018. Found: 334.2001. *Overlapped signals, one peak missing

Synthesis of (*S,E*)-5-(1-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-yl)prop-1-en-2-yl)nonan-5-ol (19) (Table 2.3, Entry 3)



Pyrrolidinylacrylate **17b** (154.50 mg, 0.34 mmol) was dissolved in dry THF (10 mL) under inert atmosphere. Subsequently, readily distilled TMEDA (0.11 mL, 0.74 mmol) and *n*-BuLi (0.74 mL of a solution 1.00 M in hexane, 0.74 mmol) were added to the previous solution at -78 ºC. The mixture was stirred for 10 min at -78 ºC and quenched with a saturated solution of NH_4Cl (5 mL). The crude was extracted with Et_2O (3 x 10 mL) and the organic combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 2/8) obtaining product **19** as a yellow oil (27.90 mg, 0.07 mmol, 21% yield) and pyrroloisoquinoline **18b** (44.30 mg, 0.13 mmol, 40% yield) as a 69:31 mixture of diastereomers (diast.1:diast.2).

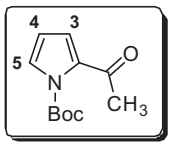
IR (ATR): 3512 cm^{-1} (brs, O-H st), 2954 cm^{-1} (C-H_{aliph} st), 1590 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.80 – 0.89 (m, 6H, 2 x $3H_4'$), 1.05 – 1.18 (m, 2H, $2H_{2A}'$), 1.21 – 1.31 (m, 6H, $2H_{2B}'$, 2 x $2H_3'$), 1.46 – 1.60 (m, 5H, 2 x $2H_1'$, H_{3A}), 1.61 (s, 3H, -CH=C(C$\underline{H_3}$)-), 1.67 – 1.87 (m, 2H, $2H_4$), 1.91 – 2.02 (m, 1H, H_{3B}), 2.11 (q, *J* = 9.0 *Hz*, 1H, H_{5A}), 2.94 (td, *J* = 9.0, 2.3 Hz, 1H, H_{5B}), 3.00 - 3.14 (m, 2H, H_2, Ar-$\underline{CH_A}H_B$-N), 3.79 – 3.96 (m, 8H, Ar-$CH_A\underline{H_B}$-N, 2 x OCH_3, OH),

5.50 (d, *J* = 8.5 Hz, 1H, -C<u>H</u>=C(CH_3)-), 6.75 – 6.91 (m, 3H, $H_{2arom,}$ $H_{3arom,}$ H_{6arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 13.68 (-CH=C(<u>C</u>H_3)-), 14.06 (2 x C_4´)*, 22.07 (C_{3A}´), 23.05 (C_{3B}´), 25.38 (C_{2A}´), 25.62 (C_{2B}´), 29.65 (C_{4p}), 31.14 (C_{3p}), 38.99 (C_{1A}´), 39.27 (C_{1B}´), 53.11 (C_{5p}), 55.82 (O<u>C</u>H_3), 55.85 (O<u>C</u>H_3), 58.20 (Ar-<u>C</u>$H_A$$H_B$-N), 62.88 ($C_{2p}$), 77.77 (-<u>C</u>(OH)(*n*-Bu)$_2$), 110.72 (C_{6arom}), 112.26 (C_{3arom}), 121.12 (C_{2arom}), 127.03 (-<u>C</u>H=C(CH_3)-), 132.01 (C_{1arom}), 140.42 (-CH=<u>C</u>(CH_3)-), 147.91, 148.71 (C_{4arom}, C_{5arom}). **MS (CI):** (*m/z*) 404 (MH^+, 14); 403 (M^+, 17); 402 (16); 387 (30); 386 (100); 385 (26); 384 (19). **HRMS (CI):** Calculated for $C_{25}H_{42}NO_3$ (MH^+): 404.3165. Found: 404.3153. **$[\alpha]_D^{20}$:** -27.79 (c = 1.4 g/L, CH_2Cl_2). *Overlapped signals

6.4. Intramolecular carbolithiation reaction via conjugate addition on N-(o-iodobenzyl)pyrrolyl)butenoate

6.4.1. Synthesis of *N*-(*o*-iodobenzyl)pyrrole 26

Synthesis of *tert*-butyl 2-acetyl-1*H*-pyrrole-1-carboxylate (20)

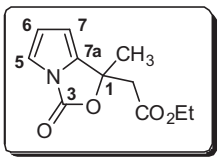


2-acetyl pyrrole (2.00 g, 18.14 mmol) was dissolved in dry THF (30 mL). Et_3N (3.83 mL, 27.48 mmol) and DMAP (44.80 mg, 0.37 mmol) were added subsequently to the previous solution. To this mixture, di-*tert*-butyl dicarbonate (6.38 mL, 27.50 mmol) was added dropwise and was stirred overnight at room temperature. After that time, the crude was washed several times with basic solutions as a saturated solution of Na_2CO_3 (3 x 20 mL) and a solution of 10% in NaOH (3 x 20 mL). The aqueous extracts were extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The product **20** was

obtained as a crude yellow oil (3.70 g, 17.68 mmol, 97% yield) which was used without further purification.

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 1.54 (s, 9H, -C($C\underline{H}_3$)$_3$), 2.41 (s, 3H, CO$C\underline{H}_3$), 6.10 – 6.15 (m, 1H, $H_{4pyrrole}$), 6.82 (dd, *J* = 3.6, 1.6 Hz, 1H, $H_{3pyrrole}$), 7.28 (dd, *J* = 3.0, 1.6 Hz, 1H, $H_{5pyrrole}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 27.42 (-C($\underline{C}H_3$)$_3$), 27.76 (CO$\underline{C}H_3$), 84.71 (-$\underline{C}$(CH_3)$_3$), 109.85 ($C_{4pyrrole}$), 121.04 ($C_{3pyrrole}$), 127.78 ($C_{5pyrrole}$), 134.06 ($C_{2pyrrole}$), 148.86 (CO_2*t*-Bu), 188.27 ($\underline{C}OCH_3$). **MS (CI):** (*m/z*) 154 (73); 136 (7, M-O*t*-Bu); 110 (100); 109 (55). **HRMS (CI):** Calculated for $C_{11}H_{15}NO_3$ (M^+): 209.1052. Found: 209.1066.

Synthesis of ethyl 2-(1-methyl-3-oxo-1,3-dihydropyrrolo[1,2-*c*]oxazol-1-yl)acetate (21)

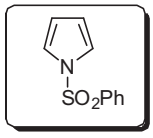


To a vacuum-flame dried round bottom flask, under an inert atmosphere provided with a magnetic stirring bar, Zn dust (0.11 g, 1.65 mmol) was added and dissolved in dry Et_2O (5 mL). Subsequently, TMSCl (0.013 mL, 0.10 mmol) was added as catalyst and the reaction was stirred at room temperature for 10 min. After that time, Boc-protected acetyl pyrrole **20** (0.17 g, 0.83 mmol) and ethyl bromoacetate (0.14 mL, 1.24 mmol) were dissolved in dry Et_2O (10 mL) and added *via* canula to the previous mixture while heating to reflux. The reaction was heated under reflux for 24 h. Then, the reaction was quenched with H_2O (10 mL) and extracted with diethyl ether (3 x 5 mL). The aqueous phase was basified with aqueous Na_2CO_3 saturated solution and further extracted with diethyl ether (3 x 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude was dissolved in dry toluene (10 mL) under an argon atmosphere and monohydrated *p*-toluensulfonic acid (14.10 mg, 0.08 mmol)

was added with a spatula of anhydrous Na_2SO_4. The mixture was heated to reflux for 24 h. After that time, the crude was filtered and subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **21** as an oil (74.60 mg, 0.33 mmol, 40% yield).

IR (ATR): 2985 cm^{-1} (C-H_{aliph} st), 1791 cm^{-1} (C=O st, carbamate), 1733 cm^{-1} (C=O st, ester); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.17 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 1.77 (s, 3H, CH_3), 2.97 (s, 2H, -$C\underline{H_2}$-CO_2Et), 4.07 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 6.04 (dd, *J* = 3.1, 0.9 Hz, 1H, H_7), 6.40 (t, *J* = 3.1 Hz, 1H, H_6), 7.01(dd, *J* = 3.1, 0.9 Hz, 1H, H_5); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 13.9 ($OCH_2\underline{C}H_3$), 26.3 (CH_3), 44.0 (-$\underline{C}H_2CO_2Et$), 60.9 ($O\underline{C}H_2CH_3$), 82.8 (C_1), 102.7 (C_7), 112.2 (C_5), 118.2 (C_6), 139.1 (C_{7a}), 149.1 (C_3), 168.1 (CO_2Et). **MS (CI):** (*m/z*) 224 (MH^+, 2); 223 (M^+, 4); 180 (100); 162 (13); 134 (75). **HRMS (CI):** Calculated for $C_{11}H_{14}NO_4$ (MH^+): 224.0923. Found: 224.0939.

Synthesis of 1-(phenylsulfonyl)-1*H*-pyrrole (22)[19]

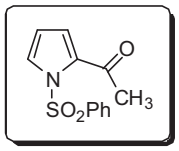


Pyrrole (0.52 mL, 7.45 mmol) was added over a suspension of NaOH (0.89 g, 22.25 mmol) in 1,2-dichloroethane (20 mL). A solution of phenylsulfonyl chloride (1.14 mL, 8.93 mmol) in 1,2-dichloroethane (20 mL) was added dropwise to the former solution at 0 ºC. After the addition, the ice bath was removed and the reaction was allowed to warm up to room temperature and stirred for 24 h. After that time, the crude was poured on water and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. Crude product **22** was characterized without further purification (1.00 g, 4.83 mmol, 65% yield).

[19] Zelikin, A.; Shastri, V. R.; Langer, R. *J. Org. Chem.* **1999**, *64,* 3379.

m.p.: 83-85 ºC (CH_2Cl_2) [Lit.[20] 87-88ºC (MeOH)]; **IR (ATR):** 1451 cm^{-1} (C=C_{arom} st), 1370 cm^{-1} (SO_2 st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 6.27 – 6.34 (m, 2H, $H_{3pyrrole}$), 7.14 – 7.20 (m, 2H, $H_{2pyrrole}$), 7.50 (tt, *J* = 8.3, 1.4 Hz, 2H, H_{3arom}), 7.55 – 7.64 (m, 1H, H_{4arom}), 7.81 – 7.91 (m, 2H, H_{2arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 113.66 ($C_{3pyrrole}$), 120.79 ($C_{2pyrrole}$), 126.73 (C_{2arom}), 129.34 (C_{3arom}), 133.79 (C_{4arom}), 139.10 (C_{1arom}). **MS (CI):** (*m/z*) 209 (13); 208 (MH^+, 100); 207 (29); **HRMS (CI):** Calculated for $C_{10}H_{10}NO_2S$ (MH^+): 208.0432. Found: 208.0439.

Synthesis of 1-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)ethanone (23)[21]



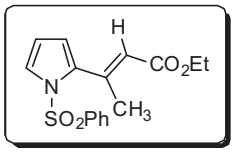
$BF_3.OEt_2$ (1.70 mL, 13.77 mmol) was added to a solution of 1-phenylsulfonyl pyrrole (**22**) (0.93 g, 4.47 mmol) in dry CH_2Cl_2 (20 mL). The reaction was stirred to room temperature for 10 min. After that time, Ac_2O (0.63 mL, 6.71 mmol) was added to the former solution and stirred overnight at room temperature. The mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness giving product **23** as a solid which was characterized without further purification (0.74 g, 2.98 mmol, 67% yield).

m.p.: 94-96 ºC (CH_2Cl_2) [Lit.[21] 96-98ºC (Hexane)]; **IR (ATR):** 1674 (C=O st), 1540 cm^{-1} (C=C_{arom} st), 1360 cm^{-1} (SO_2 st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 2.33 (s, 3H, $COCH_3$), 6.34 (dd, *J* = 3.8, 3.3 Hz, 1H, $H_{4pyrrole}$), 7.05 (dd, *J* = 3.8, 1.8 Hz, 1H, $H_{3pyrrole}$), 7.45 – 7.63 (m, 3H, H_{3arom}, H_{4arom}), 7.82 (dd, *J* = 3.3, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.92 – 8.06 (m, 2H, H_{2arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 26.8 ($CO\underline{C}H_3$), 110.4 ($C_{4pyrrole}$), 124.3 ($C_{3pyrrole}$), 128.0 (C_{2arom}), 128.6 (C_{3arom}), 130.3

[20] Fukuda, T.; Sudo, E.; Shimokawa, K.; Iwao, M. *Tetrahedron* **2008**, *64*, 328.
[21] Komoto, I.; Matsuo, J.-i.; Kobayashi, S. *Topics in Catalysis* **2002**, *19*, 43.

($C_{5pyrrole}$), 133.2 ($C_{2pyrrole}$), 133.5 (C_{4arom}), 138.8 (C_{1arom}), 185.8 ($\underline{C}OCH_3$). **MS (CI):** (*m/z*) 251 (14); 250 (MH^+, 100); 208 (71); 185 (31). **HRMS (CI):** Calculated for $C_{12}H_{12}NO_3S$ (MH^+): 250.0538. Found: 250.0533.

Synthesis of (*E*)-ethyl 3-(1-(phenylsulfonyl)-1*H*-pyrrol-2-yl)but-2-enoate (24a)



To a vacuum-flame dried round bottom flask, under an inert atmosphere provided with a magnetic stirring bar, Zn dust (0.23 g, 3.45 mmol) was added and dissolved in dry Et_2O (10 mL). Subsequently, TMSCl (0.013 mL, 0.10 mmol) and ethyl bromoacetate (0.29 mL, 2.57 mmol) were added and the reaction was stirred at room temperature for 10 min. After that time, sulphonyl protected acetyl pyrrole **23** (0.21 mg, 0.86 mmol) in dry Et_2O (10 mL) was added *via* canula to the previous mixture while heating to reflux. The reaction was heated under reflux for 16 h. The reaction is quenched with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The aqueous phase was basified with aqueous Na_2CO_3 saturated solution and further extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude was dissolved in dry toluene (10 mL) under an argon atmosphere and monohydrated *p*-toluensulfonic acid (18.00 mg, 0.09 mmol) was added with a spatula of anhydrous Na_2SO_4. The mixture was heated to reflux for 24 h. After that time, the crude was filtered and subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining isolated product **24a** as an oil (106.60 mg, 0.33 mmol, 39% yield), and isomers **24b** and **24c** (68.00 mg, 0.21 mmol, 25% yield) as a 27:73 mixture of byproducts, unable to isolate and characterize.

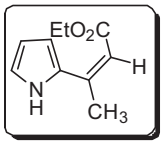
IR (ATR): 2983 cm^{-1} (C-H_{aliph} st), 1711 cm^{-1} (C=O st), 1631 cm^{-1} (C=C st), 1369 cm^{-1} (SO_2 st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.23 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.31 (d, *J* = 1.1 Hz, 3H, -$C(C\underline{H}_3)$=CH-CO_2Et), 4.13 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.62 – 5.67 (m, 1H, -$C(CH_3)$=C<u>H</u>-CO_2Et), 6.07 (dd, *J* = 3.3, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.15 (t, *J* = 3.3 Hz, 1H, $H_{4pyrrole}$), 7.23 (dd, *J* = 3.3, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.33 – 7.41 (m, 2H, H_{3arom}), 7.45 – 7.54 (m, 1H, H_{4arom}), 7.59 – 7.66 (m, 2H, H_{2arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.25 ($OCH_2\underline{C}H_3$), 21.08 (-$C(\underline{C}H_3)$=CH-CO_2Et), 59.94 ($O\underline{C}H_2CH_3$), 113.23 ($C_{4pyrrole}$), 116.28 ($C_{3pyrrole}$), 121.13 (-$C(CH_3)$=<u>C</u>H-CO_2Et), 125.65 ($C_{5pyrrole}$), 126.77 (C_{2arom}), 129.01 (C_{3arom}), 133.88 (C_{4arom}), 138.24, 138.29 (C_{1arom}, $C_{2pyrrole}$), 147.27 (-<u>C</u>(CH_3)=CH-CO_2Et), 165.99 (CO_2Et). **MS (CI):** (*m/z*) 320 (MH^+, 21); 275 (13); 274 (100); 179 (15); 134 (38); 111 (19). **HRMS (CI):** Calculated for $C_{16}H_{18}NO_4S$ (MH^+): 320.0957. Found: 320.0940.

Synthesis of (*Z*)-ethyl 3-(1H-pyrrol-2-yl)but-2-enoate (25a) and (*E*)-ethyl 3-(1H-pyrrol-2-yl)but-2-enoate (25b)[22]

Ethyl 2-butynoate (0.30 mL, 2.52 mmol) was added over a suspension of pyrrole (0.36 mL, 5.04 mmol) and $Pd(OAc)_2$ (57.79 mg, 0.25 mmol) in CH_2Cl_2 (1 mL). The reaction was left stirring during 96 h. After that time, the crude was filtered through celite and purified through flash chromatography (silica gel, hexane/EtOAc 8/2) obtaining diastereomers **25a** (113.60 mg, 0.63 mmol, 25% yield) and **25b** (59.50 mg, 0.33 mmol, 13% yield), both as yellow oils.

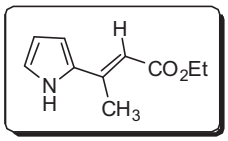
[22] Lu, W.; Jia, C.; Kitamura, T.; Fujiwara. Y. *Org. Lett.* **2000**, *2*, 2927.

Data for (*Z*)-**25a**: major diastereomer



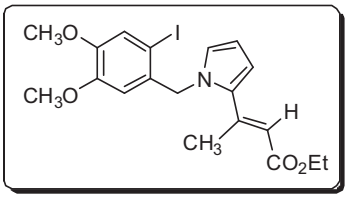
IR (ATR): 3191 cm^{-1} (N-H st), 2979 cm^{-1} (C-H_{aliph}), 1679 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.34 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 2.31 (d, *J* = 1.1 Hz, 3H, -$C(C\underline{H_3})$=CH-CO_2Et), 4.23 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 5.61 (d, *J* = 1.1 Hz, 1H, -$C(CH_3)$=C<u>H</u>-CO_2Et), 6.28 – 6.30 (m, 1H, $H_{4pyrrole}$), 6.64 – 6.68 (m, 1H, $H_{3pyrrole}$), 7.00 – 7.05 (m, 1H, $H_{5pyrrole}$), 12.97 (brs, 1H, NH); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.2 ($OCH_2\underline{C}H_3$), 24.5 (-$C(\underline{C}H_3)$=CH-CO_2Et), 60.3 ($O\underline{C}H_2CH_3$), 108.7 (-$C(CH_3)$=<u>C</u>H-CO_2Et), 109.4 ($C_{4pyrrole}$), 114.4 ($C_{3pyrrole}$), 121.9 ($C_{5pyrrole}$), 130.2 ($C_{2pyrrole}$), 144.4 (-<u>C</u>(CH_3)=CH-CO_2Et), 168.8 (CO_2Et). **MS (CI):** (*m/z*) 180 (MH^+, 28); 179 (88); 134 (100); 133 (24). **HRMS (CI):** Calculated for $C_{10}H_{14}NO_2$ (MH^+): 180.1025. Found: 180.1020.

Data for (*E*)-**25b**: minor diastereomer



IR (ATR): 3368 cm^{-1} (N-H st), 2979 cm^{-1} (C-H aliph st), 1711 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.30 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 2.54 (d, *J* = 1.1 Hz, 3H, -$C(C\underline{H_3})$=CH-CO_2Et), 4.20 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 5.95 (d, *J* = 1.1 Hz, 1H, -$C(CH_3)$=C<u>H</u>-CO_2Et), 6.25 – 6.29 (m, 1H, $H_{4pyrrole}$), 6.58 – 6.62 (m, 1H, $H_{3pyrrole}$), 6.86 – 6.91 (m, 1H, $H_{5pyrrole}$), 8.71 (brs, 1H, NH); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.3 ($OCH_2\underline{C}H_3$), 15.8 (-$C(\underline{C}H_3)$=CH-CO_2Et), 59.6 ($O\underline{C}H_2CH_3$), 108.6 (-$C(CH_3)$=<u>C</u>H-CO_2Et), 110.4 ($C_{4pyrrole}$), 111.4 ($C_{3pyrrole}$), 121.4 ($C_{5pyrrole}$), 132.6 ($C_{2pyrrole}$), 145.7 (-<u>C</u>(CH_3)=CH-CO_2Et), 167.4 (CO_2Et). **MS (CI):** (*m/z*) 180 (MH^+, 52); 179 (100); 134 (77); 133 (18). **HRMS (CI):** Calculated for $C_{10}H_{14}NO_2$ (MH^+): 180.1025. Found: 180.1023.

Synthesis of (*E*)-ethyl 3-(1-(2-iodo-4,5-dimethoxybenzyl)-1H-pyrrol-2-yl)but-2-enoate (26)

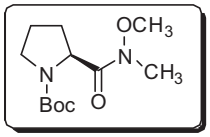


NaH (60% dispersion in mineral oil, 139.10 mg, 3.48 mmol) was added to a solution of the former (*E*) substituted pyrrole **25a** (311.70 mg, 1.74 mmol) in dry DMF (20 mL) at 0 ºC. The reaction was stirred and allowed to warm up to room temperature during 1 h. After that time, benzyl bromide **16** (750.00 mg, 2.10 mmol) was added to the mixture and stirred for 4 h at room temperature. The reaction was quenched with H_2O (10 mL) and the crude was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was washed with H_2O (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **26** as a yellow solid (300.20 mg, 0.66 mmol, 38% yield).

m.p. : 81-83 ºC (Hexane/EtOAc); **IR (ATR):** 2976 cm^{-1} (C-H_{aliph} st), 1705 cm^{-1} (C=O st), 1612 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.25 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 2.45 (d, *J* = 1.1 Hz, 3H, -$C(C\underline{H_3})$=CH-CO_2Et), 3.61 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.12 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 5.07 (s, 2H, Ar-CH_2-N), 5.69 (d, *J* = 1.1 Hz, 1H, -$C(CH_3)$=$C\underline{H}$-CO_2Et), 6.01 (s, 1H, H_{6arom}), 6.20 (dt, *J* = 3.7, 2.8 Hz, 1H, $H_{4pyrrole}$), 6.42 (dd, *J* = 3.7, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.67 – 6.72 (m, 1H, $H_{5pyrrole}$), 7.21 (s, 1H, H_{3arom}). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.21 ($OCH_2\underline{C}H_3$), 19.12 (-$C(\underline{C}H_3)$=CH-CO_2Et), 55.54 (OCH_3), 56.02 (OCH_3), 56.29 (Ar-$\underline{C}H_2$-N), 59.47 ($O\underline{C}H_2CH_3$), 84.72 (C_{2arom}), 108.89 ($C_{4pyrrole}$), 110.39 (C_{6arom}), 112.33 ($C_{3pyrrole}$), 115.36 (-$C(CH_3)$=$\underline{C}$H-CO_2Et), 121.38 (C_{3arom}), 126.25 ($C_{5pyrrole}$), 132.53 (C_{1arom}), 135.51 ($C_{2pyrrole}$), 146.36 (-$\underline{C}(CH_3)$=CH-CO_2Et), 148.72 (C_{5arom}), 149.66 (C_{4arom}), 166.61 (CO_2Et). **MS (CI):** (*m/z*) 456 (MH^+, 13); 455 (17);

328 (31); 277 (100). **HRMS (CI):** Calculated for $C_{19}H_{23}INO_4$ (MH^+): 456.0672. Found: 456.0677.

Synthesis of (*S*)-tert-butyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (27)[23,24]



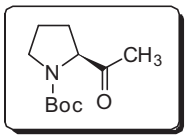
Carbonyldiimidazole (1.13 g, 6.97 mmol) was added portion wise to a solution of Boc-L-proline (1.00 g, 4.65 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred at room temperature until CO_2 liberation ceased. Then, *N*,*O*-dimethylhydroxylamine hydrochloride (0.69 g, 6.93 mmol) was added and stirred overnight at room temperature. The crude was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **27** as a colorless oil (0.96 g, 3.73 mmol, 80% yield).

IR (ATR): 2975 cm^{-1} (C-H_{aliph} st), 1695 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = (rotamer relation 1.2:1) = 1.31 (s, 5H, C(C$\underline{H}_3$)$_3$, major rotamer), 1.35 (s, 4H, C(C$\underline{H}_3$)$_3$, minor rotamer), 1.66 – 1.98 (m, 3H, H_{3A}, 2 x H_4), 1.98 – 2.18 (m, 1H, H_{3B}), 3.09 (s, 3H, CH_3), 3.24 – 3.56 (m, 2H, 2 x H_5), 3.62 (s, 1.7H, OCH_3, major rotamer), 3.68 (s, 1.3H, OCH_3, minor rotamer), 4.50 (dd, *J* = 8.3, 3.0 Hz, 0.55H, H_2, major rotamer), 4.60 (dd, *J* = 8.3, 3.0 Hz, 0.45H, H_2, minor rotamer). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 23.28 (C_{4p}, major rotamer), 23.93 (C_{4p}, minor rotamer), 28.29 (C($\underline{C}H_3$)$_3$, major rotamer), 28.38 (C($\underline{C}H_3$)$_3$, minor rotamer), 29.49 (C_{3p}, minor rotamer), 30.38 (C_{3p}, major rotamer), 32.18 (CON($\underline{C}H_3$)(OCH_3), minor rotamer),

[23] Kong, C.; Jana, N.; Driver, T.G. *Org. Lett.* **2013**, *15*, 824.
[24] Barluenga, J.; Escribano, M.; Aznar, F.; Valdés, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6856.

32.34 ($CON(\underline{C}H_3)(OCH_3)$, major rotamer), 46.47 (C_{5p}, major rotamer), 46.76 (C_{5p}, minor rotamer), 56.40 ($CON(CH_3)(O\underline{C}H_3)$, minor rotamer), 56.69 ($CON(CH_3)(O\underline{C}H_3)$, major rotamer), 61.11 (C_{2p}, major rotamer), 61.20 (C_{2p}, minor rotamer), 79.25 ($\underline{C}(CH_3)_3$, minor rotamer), 79.42 ($\underline{C}(CH_3)_3$, major rotamer), 153.77 (CO_2t-Bu, major rotamer), 154.37 (CO_2t-Bu, minor rotamer), 173.16 ($\underline{C}ON(CH_3)(OCH_3)$, minor rotamer), 173.74 ($\underline{C}ON(CH_3)(OCH_3)$, major rotamer). **MS (CI):** (*m/z*) 185 (M – O*t*-Bu, 33); 170 (M – $CON(OCH_3)(CH_3)$, 59); 159 (100); 157 (M – CO_2t-Bu, 38); 114 (50). **HRMS (CI):** Calculated for $C_{12}H_{23}N_2O_4$ (MH^+): 259.1658. Found: 259.1640. **$[\alpha]_D^{20}$:** -20.3 (c = 0.5 g/L, CH_2Cl_2). [Lit.[23] **$[\alpha]_D^{20}$**: -13.6 (c = 0.5 g/L, CH_2Cl_2)].

Synthesis of (*S*)-*tert*-butyl 2-acetylpyrrolidine-1-carboxylate (28)[23,24]



Methylmagnesium bromide (2.20 mL of a 3.00 M solution in ether, 6.60 mmol) was added to a solution of Weinreb amide (0.69 g, 2.66 mmol) in dry diethyl ether at 0 ºC. The reaction was stirred for 1.5 h at 0 ºC. After that time, the reaction was quenched with saturated NH_4Cl solution and the crude was extracted with diethyl ether (3 x 20mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining product **28** as a white solid (0.43 g, 2.03 mmol, 76% yield) whose spectroscopic details are checked with those in the bibliography.

m.p.: 46-47 ºC (Hexane/EtOAc); **IR (ATR):** 2977 cm^{-1} (C-H_{aliph} st), 1691 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = (rotamer relation 1.4:1) = 1.32 (s, 5.3H, $C(C\underline{H_3})_3$, major rotamer), 1.37 (s, 3.7H, $C(C\underline{H_3})_3$, minor rotamer), 1.62 – 1.88 (m, 3H, H_{3A}, 2 x H_4), 1.92 – 2.20 (m, 4H, H_{3B}, CH_3CO), 3.29 – 3.53 (m, 2H, 2 x

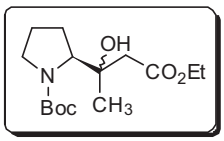
H_5), 4.06 - 4.18 (m, 0.6, H_2, major rotamer), 4.18 – 4.29 (m, 0.4H, H_2, minor rotamer); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 23.56 (C_{4p}, major rotamer), 24.22 (C_{4p}, minor rotamer), 25.38 ($\underline{C}H_3CO$, major rotamer), 26.19 ($\underline{C}H_3CO$, minor rotamer), 28.09 ($C(\underline{C}H_3)_3$, major rotamer), 28.23 ($C(\underline{C}H_3)_3$, minor rotamer), 28.54 (C_{3p}, minor rotamer), 29.61 (C_{3p}, major rotamer), 46.47 (C_{5p}, major rotamer), 46.65 (C_{5p}, minor rotamer), 65.02 (C_{2p}, minor rotamer), 65.54 (C_{2p}, major rotamer), 79.59 ($\underline{C}(CH_3)_3$, minor rotamer), 79.91 ($\underline{C}(CH_3)_3$, major rotamer), 153.68 (CO_2*t*-Bu, major rotamer), 154.43 (CO_2*t*-Bu, minor rotamer), 207.96 ($\underline{C}OCH_3$, minor rotamer), 208.07 ($\underline{C}OCH_3$, major rotamer). **MS (CI):** (*m/z*) 158 (26); 140 (M – O*t*-Bu, 21); 114 (100). **HRMS (CI):** Calculated for $C_9H_{16}NO_2$ $[M - CH_3CO]^+$: 170.1181. Found: 170.1207. **$[\alpha]_D^{20}$:** -48.37 (c = 1.0 g/L, CH_2Cl_2). [Lit.[24] **$[\alpha]_D^{20}$**: -47.69 (c = 0.1 g/L, CH_2Cl_2)].

Synthesis of (*S*)-*tert*-butyl 2-((*R/S*)-4-ethoxy-2-hydroxy-4-oxobutan-2-yl)pyrrolidine-1-carboxylate (29a) and (*S*)-*tert*-butyl 2-((*R/S*)-4-ethoxy-2-hydroxy-4-oxobutan-2-yl)pyrrolidine-1-carboxylate (29b)

To a vacuum-flame dried round bottom flask, under an inert atmosphere provided with a magnetic stirring bar, Zn dust (1.00 g, 15.00 mmol) was added. Zn was dissolved in dry Et_2O (30 mL), TMSCl (0.06 mL, 0.45 mmol) as catalyst and ethyl bromoacetate (1.27 mL, 11.25 mmol) were added and the reaction was stirred at room temperature for 10 min. After that time, Boc-protected 2-acetyl pyrrolidine **28** (0.80 g, 3.75 mmol) in dry Et_2O (10 mL) was added *via* canula to the previous mixture while heating to reflux. The reaction was heated under reflux for 16 h. The reaction is quenched with H_2O (20 mL) and extracted with Et_2O (3 x 10 mL). The aqueous phase was basified with aqueous Na_2CO_3 saturated solution and further extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude was dissolved in dry

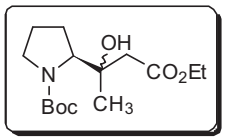
toluene (10 mL) under an argon atmosphere and monohydrated *p*-toluensulfonic acid (0.18 g, 0.94 mmol) was added with a spatula of anhydrous Na_2SO_4. The mixture was heated under reflux for 24 h. After that time, the crude was filtered and subjected to flash chromatography (silica gel, hexane/EtOAc 8/2) obtaining diastereomers **29a** (0.25 g, 0.83 mmol, 22% yield) and **29b** (0.20 g, 0.66 mmol, 18% yield), both as oils.

Data for **29a**: major diastereomer



IR (ATR): 3329 cm^{-1} (brs, O-H st), 2978 cm^{-1} (C-H_{aliph} st), 1733 cm^{-1} (C=O st, ester), 1691 cm^{-1} (C=O st, carbamate); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.15 (s, 3H, -C(C$\underline{H_3}$)(OH)-CH_2-), 1.23 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 1.42 (s, 9H, $C(C\underline{H_3})_3$), 1.64 – 2.12 (m, 4H, $2H_3$, $2H_4$), 2.37 – 2.58 (m, 2H, -$C(CH_3)$(OH)-C$\underline{H_2}$-), 3.06 – 3.25 (m, 1H, H_{5A}), 3.55 – 3.68 (m, 1H, H_{5B}), 4.00 – 4.20 (m, 3H, H_2, $OC\underline{H_2}CH_3$), 5.58 (brs, 1H, OH); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.1 ($OCH_2\underline{C}H_3$), 23.1 (-C($\underline{C}H_3$)(OH)-CH_2-), 24.4 (C_{4p}), 28.0 (C_{3p}), 28.3 ($C(\underline{C}H_3)_3$), 44.5 (-$C(CH_3)$(OH)-$\underline{C}H_2$-), 47.9 (C_{5p}), 60.4 ($O\underline{C}H_2CH_3$), 65.2 (C_{2p}), 74.7 (-$\underline{C}(CH_3)$(OH)-CH_2-), 80.2 ($\underline{C}(CH_3)_3$), 157.4 (CO*t*-Bu), 171.9 (CO_2Et). **MS (CI):** (*m/z*) 302 (MH^+, 1); 228 (M – O*t*-Bu, 11); 202 (100); 184 (25); 156 (14); 138 (11); 114 (17). **HRMS (CI):** Calculated for $C_{15}H_{28}NO_5$ (MH^+): 302.1967. Found: 302.1968. Calculated for $C_{11}H_{18}NO_4$ [M – O*t*-Bu]$^+$: 228.1236. Found: 228.1241. **$[\alpha]_D^{20}$:** -52.09 (c = 1.1 g/L, CH_2Cl_2).

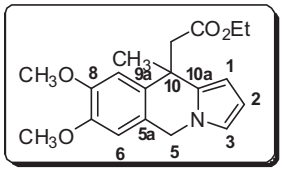
Data for **29b**: minor diastereomer



IR (ATR): 3343 cm^{-1} (brs, O-H st), 2977 cm^{-1} (C-H_{aliph} st), 1729 cm^{-1} (C=O st, ester), 1690 cm^{-1} (C=O st, carbamate); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.14 – 1.23 (m, 6H, -C(C$\underline{H_3}$)(OH)-CH_AH_B-), $OCH_2C\underline{H_3}$), 1.39 (s, 9H, C(C$\underline{H_3}$)$_3$), 1.55 – 2.00 (m, 4H, $2H_3$, $2H_4$), 2.27 (d, *J* = 14.0 Hz, 1H, -C(CH_3)(OH)-C$\underline{H_A}H_B$-), 2.43 (d, *J* = 14.0 Hz, 1H, -C(CH_3)(OH)-$CH_A\underline{H_B}$-), 3.11 (dt, *J* = 11.1, 7.4 Hz, 1H, H_{5A}), 3.51 – 3.68 (m, 1H, H_{5B}), 3.85 – 3.90 (m, 1H, H_2), 4.08 (q, *J* = 7.2 Hz, 2H, O$\underline{CH_2}CH_3$), 5.60 (brs, 1H, OH); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.0 ($OCH_2\underline{C}H_3$), 24.1 (C_{4p}), 24.5 (-C($\underline{C}H_3$)(OH)-CH_AH_B-), 27.9 (C_{3p}), 28.2 (C($\underline{C}H_3$)$_3$), 41.8 (-C(CH_3)(OH)-$\underline{C}H_AH_B$-), 48.1 (C_{5p}), 60.1 (O$\underline{C}H_2CH_3$), 66.3 (C_{2p}), 74.3 (-$\underline{C}$(CH_3)(OH)-CH_AH_B-), 80.2 ($\underline{C}$(CH_3)$_3$), 157.2 (CO*t*-Bu), 171.9 (CO_2Et). **MS (CI):** (*m/z*) 302 (MH^+, 1); 246 (13); 228 (M – O*t*-Bu, 13); 202 (100). **HRMS (CI):** Calculated for $C_{15}H_{28}NO_5$ (MH^+): 302.1967. Found: 302.1969. Calculated for $C_{11}H_{18}NO_4$ [M – O*t*-Bu]$^+$: 228.1236. Found: 228.1230. **$[\alpha]_D^{20}$:** -49.79 (c = 1.1 g/L, CH_2Cl_2).

6.4.2. Intramolecular carbolithiation of *N*-(*o*-iodobenzyl)pyrrole 26. Synthesis of 5,10-dihydropyrrolo[1,2-*b*]isoquinoline 30

Synthesis of ethyl 2-(7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetate (30) (Table 2.4, Entry 1)

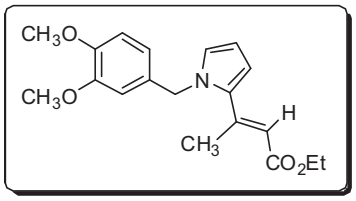


t-BuLi (0.81 mL of a solution 0.90 M in hexane, 0.73 mmol) was added dropwise to a solution of 2-bromomesitylene (0.06 mL, 0.36 mmol) in dry THF (5 mL) at -78 ºC and under an inert atmosphere. The reaction was stirred for 1 h at -20 ºC and after that time, a solution of pyrrolylacrylate **26** (82.90 mg, 0.18 mmol) in dry THF (5 mL) was added *via* canula at -105 ºC. The mixture was stirred for 5 min at -105 ºC and quenched at low temperature with a saturated solution of NH_4Cl (5 mL). Et_2O (20 mL) and H_2O (10 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 8/2) obtaining product **30** as a yellow oil (13.20 mg, 0.04 mmol, 22% yield) and deiodinated compound **31** (31.00 mg, 0.09 mmol, 52% yield) as byproduct in a 25:75 mixture of diastereomers (*Z:E*).

IR (ATR): 2932 cm^{-1} (C-H_{aliph} st), 1728 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.02 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 1.82 (s, 3H, -$C(C\underline{H_3})$-CH_AH_B-CO_2Et), 2.74 (d, *J* = 14.3 Hz, 1H, -$C(CH_3)$-$C\underline{H_A}H_B$-CO_2Et), 2.78 (d, *J* = 14.3 Hz, 1H, -$C(CH_3)$-$CH_A\underline{H_B}$-CO_2Et), 3.88 (s, 3H, OCH_3)*, 3.90 (s, 3H, OCH_3)*, 3.77 – 3.95 (m, 2H, $OC\underline{H_2}CH_3$)*, 5.04 (d, *J* = 15.5 Hz, 1H, H_{5A}), 5.13 (d, *J* = 15.5 Hz, 1H, H_{5B}), 5.99 – 6.07 (m, 1H, H_1), 6.19 – 6.28 (m, 1H, H_2), 6.69 (s, 2H, H_3, H_6), 6.94

(s, 1H, H_9); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.0 ($OCH_2\underline{C}H_3$), 27.7 (-C($\underline{C}H_3$)-CH_AH_B-CO_2Et), 37.6 (C_{10}), 47.2 (C_5), 48.8 (-C(CH_3)-$\underline{C}H_AH_B$-CO_2Et), 56.0, 56.1 (2 x OCH_3), 60.0 ($O\underline{C}H_2CH_3$), 102.6 (C_1), 108.3 (C_2), 108.5 (C_9), 108.8, 118.2 (C_3, C_6), 124.0 (C_{5a}), 132.0 (C_{9a}), 134.7 (C_{10a}), 147.6 (C_8), 148.2 (C_7), 170.5 (CO_2Et). **MS (ESI$^+$):** (*m/z*) 331 (MH^+ + 1, 18), 330 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{19}H_{24}NO_4$ (MH^+): 330.1705. Found: 330.1699. * Partially overlapped signals

Synthesis of (*E*)-ethyl 3-(1-(3,4-dimethoxybenzyl)-1*H*-pyrrol-2-yl)but-2-enoate (31) (Table 2.4, Entry 4)



t-BuLi (1.10 mL of a 1.20 M solution in hexane, 1.32 mmol) was added dropwise to a solution of 2-bromomesitylene (0.10 mL, 0.66 mmol) in dry THF (5 mL) at -78 ºC and under an inert atmosphere. The reaction was stirred for 1 h at -20 ºC and after that time, a solution of pyrrolylacrylate **26** (150.0 mg, 0.33 mmol) in dry THF (5 mL) was added *via* canula at -78 ºC. The mixture was stirred at -78 ºC for 3 h and after that time, the cooling bath was removed and the mixture was allowed to warm up to room temperature under stirring for 16 h. Then, the reaction was quenched with a saturated NH_4Cl solution (5 mL). Et_2O (20 mL) and H_2O (10 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (neutral alumina, hexane/EtOAc 8/2) obtaining product **31** as yellow oil (40.60 mg, 0.12 mmol, 37% yield).[25]

[25] Conversion 61%.

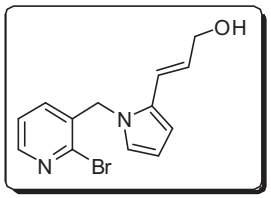
IR (ATR): 2935 cm^{-1} (C-H_{aliph} st), 1704 cm^{-1} (C=O st), 1608 cm^{-1} (C=C st), 1515 cm^{-1} (C=C_{arom} st); **RMN-^{1}H:** ($CDCl_3$, δ, ppm) = 1.26 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$), 2.47 (d, *J* = 0.9 Hz, 3H, -$C(C\underline{H_3})$=CH-CO_2Et), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.15 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 5.13 (s, 2H, Ar-CH_2-N), 5.78 (d, *J* = 0.9 Hz, 1H, -$C(CH_3)$=C<u>H</u>-CO_2Et), 6.19 – 6.22 (m, 1H, $H_{4pyrrole}$), 6.41 (dd, *J* = 3.7, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.53 – 6.56 (m, 1H, H_{6arom}), 6.58 (d, *J* = 8.2 Hz, 1H, H_{2arom}), 6.73 – 6.76 (m, 1H, $H_{5pyrrole}$), 6.79 (d, *J* = 8.2 *Hz*, 1H, H_{3arom}); **RMN-^{13}C:** ($CDCl_3$, δ, ppm) = 14.36 ($OCH_2\underline{C}H_3$), 19.44 (-$C(\underline{C}H_3)$=CH-CO_2Et), 51.46 (Ar-$\underline{C}H_2$-N), 55.81 (OCH_3), 55.90 (OCH_3), 59.64 ($O\underline{C}H_2CH_3$), 108.68 ($C_{4pyrrole}$), 109.82 (C_{6arom}), 111.28 (C_{3arom}), 112.36 ($C_{3pyrrole}$), 115.37 (-$C(CH_3)$=<u>C</u>H-CO_2Et), 118.94 (C_{2arom}), 126.51 ($C_{5pyrrole}$), 130.52 (C_{1arom}), 135.52 ($C_{2pyrrole}$), 146.88 (-<u>C</u>(CH_3)=CH-CO_2Et), 148.42 (C_{4arom}), 149.23 (C_{5arom}), 166.92 (CO_2Et). **MS (CI):** (*m/z*) 330 (MH^+, 14); 329 (M^+ ,16); 242 (12); 151 (100). **HRMS (CI):** Calculated for $C_{19}H_{24}NO_4$ (MH^+): 330.1705. Found: 330.1693.

6.5. Intramolecular carbolithiation reactions via S_N2' reaction

6.5.1. Intramolecular carbolithiation reaction of *N*-(*o*-haloheteroarylmethyl)pyrrolyl allylic alcohol derivatives

*6.5.1.1. Synthesis of o-halopyridines **34a**, **34b** and o-haloquinolines **35a**, **35b**.*

Synthesis of *(E)*-3-(1-((2-bromopyridin-3-yl)methyl)-1*H*-pyrrol-2-yl)prop-2-en-1-ol (32a)

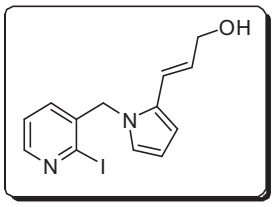


To a solution of pyrrolylacrylate **5a** (0.20 g, 0.60 mmol) in dry THF (10 mL), DIBAL-H (3.28 mL of a solution 1.00 M in toluene, 3.28 mmol) was added at -78 ºC and under an inert atmosphere. The reaction was stirred for 30 min at -78 ºC, and after that time the reaction was quenched with a H_2O:AcOH (1:1) solution (1 mL) and allowed to warm up at room temperature. The crude was eluted with EtOAc (40 mL), washed with water (3 x 20 mL), brine (2 x 20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 6/4) obtaining product **32a** as a yellow solid (0.16 g, 0.55 mmol, 92% yield).

m.p.: 114–115 ºC (Hexane/EtOAc); **IR (ATR):** 3355 cm^{-1} (brs, O-H st), 2919 (C-H_{aliph} st), 1652 cm^{-1} (C=C st), 1561 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 2.00 (brs, 1H, OH), 4.17 (d, *J* = 5.5 Hz, 2H, -CH=CH-C$\underline{H_2}$OH), 5.11 (s, 2H, CH_2N), 6.11 (dt, *J* = 15.6, 5.5 Hz, 1H, -CH=C$\underline{H}$-CH_2OH), 6.20 – 6.29 (m, 2H, $H_{4pyrrole}$, -C$\underline{H}$=CH-CH_2OH), 6.42 – 6.47 (m, 1H, $H_{3pyrrole}$), 6.62 (d, *J* = 7.5 Hz, 1H, $H_{4pyridine}$), 6.65 (s, 1H, $H_{5pyrrole}$), 7.13 (dd, *J* = 7.5, 4.8 Hz, 1H, $H_{5pyridine}$), 8.14 – 8.24 (m, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 49.5 (CH_2N), 63.4 (-

CH=CH-CH_2OH), 107.6 ($C_{3pyrrole}$) 109.4 ($C_{4pyrrole}$), 118.8 (-CH=CH-CH_2OH), 122.6 ($C_{5pyrrole}$), 123.5 ($C_{4pyridine}$), 127.4 (-CH=CH-CH_2OH), 130.7 ($C_{2pyrrole}$), 135.2 ($C_{3pyridine}$), 135.9 ($C_{5pyridine}$), 140.7 ($C_{2pyridine}$), 148.8 ($C_{6pyridine}$). **MS (ESI$^+$):** (*m/z*) 295 (M^+ + 2, 11); 293 (M^+, 12); 278 (11); 277 (98); 276 (100); 245 (14); 213 (32). **HRMS (ESI$^+$):** Calculated for $C_{13}H_{14}N_2OBr^{79}$ (MH^+): 293.0289. Found: 293.0298.

Synthesis of (*E*)-3-(1-((2-iodopyridin-3-yl)methyl)-1*H*-pyrrol-2-yl)prop-2-en-1-ol (32b)

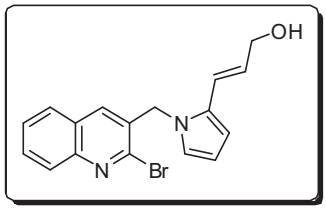


To a solution of pyrrolylacrylate **5b** (0.63 g, 1.65 mmol) in dry THF (20 mL), DIBAL-H (9.07 mL of a solution 1.00 M in toluene, 9.07 mmol) was added at -78 ºC and under an inert atmosphere. The reaction was stirred for 4 h at -78 ºC, and after that time the reaction was quenched with a H_2O:AcOH (1:1) solution (1 mL) and allowed to warm up at room temperature. The crude was eluted with EtOAc (40 mL), washed with water (3 x 20 mL), brine (2 x 20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining product **32b** as a white solid (0.38 g, 1.12 mmol, 68% yield).

m.p.: 136-137 ºC (Hexane/EtOAc); **IR (ATR):** 3343 cm^{-1} (brs, O-H st), 2923 (C-H_{aliph} st), 1652 cm^{-1} (C=C st), 1557 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($(CD_3)_2CO$, 25 ºC): δ (ppm) = 2.83 (s, 1H, HDO), 3.72 (t, *J* = 5.6 Hz, 1H, OH), 4.10 (t, *J* = 5.5 Hz, 2H, -CH=CH-CH_2OH), 5.14 (s, 2H, CH_2N), 6.10 (dt, *J* = 15.6, 5.5 Hz, 1H, -CH=CH-CH_2OH), 6.14 – 6.17 (m, 1H, $H_{4pyrrole}$), 6.35 – 6.43 (m, 2H, $H_{3pyrrole}$, -CH=CH-CH_2OH), 6.50 – 6.55 (m, 1H, $H_{4pyridine}$), 6.84 (dd, *J* = 2.6, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.30

(dd, J = 7.7, 4.7 Hz, 1H, $H_{5pyridine}$), 8.21 – 8.25 (m, 1H, $H_{6pyridine}$); **^{13}C NMR** ($(CD_3)_2CO$, 25 ºC): δ (ppm) = 54.20 (CH_2N), 63.2 (-CH=CH-$\underline{C}H_2OH$), 107.7 ($C_{3pyrrole}$) 109.8 ($C_{4pyrrole}$), 118.6 (-$\underline{C}$H=CH-CH_2OH), 121.0 ($C_{2pyridine}$), 123.4 ($C_{5pyrrole}$), 124.6 ($C_{5pyridine}$), 129.3 (-CH=$\underline{C}$H-CH_2OH), 131.9 ($C_{2pyrrole}$), 135.4 ($C_{4pyridine}$), 139.9 ($C_{3pyridine}$), 150.3 ($C_{6pyridine}$). **MS (ESI$^+$):** (*m/z*) 341 (MH^+, 2); 324 (11); 323 (100). **HRMS (ESI$^+$):** Calculated for $C_{13}H_{14}N_2OI$ (MH^+): 341.0151. Found: 341.0141.

Synthesis of (*E*)-3-(1-((2-bromoquinolin-3-yl)methyl)-1*H*-pyrrol-2-yl)prop-2-en-1-ol (33a)

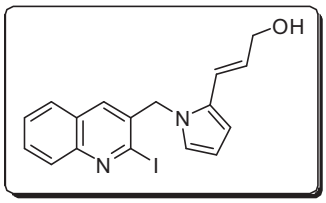


To a solution of pyrrolylacrylate **9a** (1.35 g, 3.50 mmol) in dry THF (10 mL), DIBAL-H (19.27 mL of a solution 1.00 M in toluene, 19.27 mmol) was added at -78 ºC and under an inert atmosphere. The reaction was stirred for 30 min at -78 ºC, and after that time the reaction was quenched with a H_2O:AcOH (1:1) solution (1 mL) and allowed to warm up at room temperature. The crude was eluted with EtOAc (40 mL), washed with water (3 x 20 mL), brine (2 x 20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining product **33a** as a yellow solid (1.08 g, 3.15 mmol, 90% yield).

m.p.: 138-139 ºC (Hexane/EtOAc); **IR (ATR):** 3386 cm^{-1} (brs, O-H st), 1591 cm^{-1} (C=C st), 1564 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.50 (t, J = 5.7 Hz, 1H, OH), 4.17 (m, 2H, -CH=CH-C$\underline{H_2}$OH), 5.27 (s, 2H, CH_2N), 6.15 (dt, J = 15.7, 5.7 Hz, 1H, -CH=C$\underline{H}$-CH_2OH), 6.24 - 6.43 (m, 2H, -C$\underline{H}$=CH-CH_2OH,

$H_{4pyrrole}$), 6.48 – 6.58 (m, 1H, $H_{3pyrrole}$), 6.69 – 6.77 (m, 1H, $H_{5pyrrole}$), 7.03 (s, 1H, $H_{4quinoline}$), 7.51 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H, $H_{6quinoline}$), 7.64 (brd, *J* = 8.1 Hz, 1H, $H_{5quinoline}$)*, 7.69 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H, $H_{7quinoline}$)*, 8.02 (brd, *J* = 8.4 Hz, 1H, $H_{8quinoline}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 49.9 (CH_2N), 63.6 (-CH=CH-$\underline{C}H_2OH$), 107.7 ($C_{3pyrrole}$), 109.5 ($C_{4pyrrole}$), 119.1 (-$\underline{C}H$=CH-CH_2OH), 122.7 ($C_{5pyrrole}$), 127.3, 127.4 ($C_{6quinoline}$, -CH=$\underline{C}H$-CH_2OH), 127.5 ($C_{4a,quinoline}$), 127.8 ($C_{5quinoline}$), 128.2 ($C_{8quinoline}$), 130.4 ($C_{7quinoline}$), 130.7 ($C_{2pyrrole}$), 132.1 ($C_{3quinoline}$), 135.2 ($C_{4quinoline}$), 140.7 ($C_{2quinoline}$), 147.7 ($C_{8a,quinoline}$). **MS (MALDI):** (*m/z*) 345 (10); 344 (MH^+ + 1, 40); 343 (MH^+, 11); 342 ([M^+, 41); 327 (97); 325 (100); 273 (27); 264 (17); 263 (92); 245 (19); 199 (19). **HRMS (MALDI):** Calculated for $C_{17}H_{16}N_2OBr^{79}$ (MH^+): 343.0449. Found: 343.0446.*Partially overlapped signals

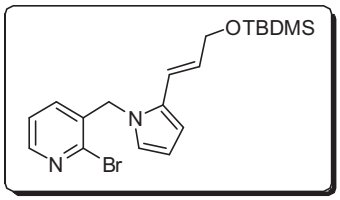
Synthesis of (*E*)-3-(1-((2-iodoquinolin-3-yl)methyl)-1*H*-pyrrol-2-yl)prop-2-en-1-ol (33b)



To a solution of pyrrolylacrylate **9b** (0.34 g, 0.79 mmol) in dry THF (10 mL), DIBAL-H (4.37 mL of a solution 1.00 M in toluene, 4.37 mmol) was added at -78 ºC and under an inert atmosphere. The reaction was stirred for 30 min at -78 ºC, and after that time the reaction was quenched with a H_2O:AcOH (1:1) solution (1 mL) and allowed to warm up at room temperature. The crude was eluted with EtOAc (40 mL), washed with water (3 x 20 mL), brine (2 x 20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining product **33b** as a yellow solid (0.19 g, 0.49 mmol, 62% yield).

m.p.: 140-141 ºC (Hexane/EtOAc); **IR (ATR):** 3357 cm^{-1} (brs, O-H st), 1586 cm^{-1} (C=C st), 1557 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($(CD_3)_2CO$, 25 ºC): δ (ppm) = 2.82 (s, HDO), 3.67 (t, *J* = 5.7 Hz, 1H, OH), 4.05 – 4.11 (m, 2H, -CH=CH-C$\underline{H}_2$OH), 5.30 (s, 2H, CH_2N), 6.13 (dt, *J* = 15.7, 5.4 Hz, 1H, -CH=C$\underline{H}$-CH_2OH), 6.19 – 6.23 (m, 1H, $H_{4pyrrole}$), 6.42 - 6.49 (m, 2H, -C$\underline{H}$=CH-CH_2OH, $H_{3pyrrole}$), 6.88 – 6.91 (m, 1H, $H_{5pyrrole}$), 7.01 (s, 1H, $H_{4quinoline}$), 7.56 – 7.64 (m, 1H, $H_{6quinoline}$), 7.73 – 7.79 (m, 2H, $H_{5quinoline}$, $H_{7quinoline}$), 7.97 (brd, *J* = 8.4 Hz, 1H, $H_{8quinoline}$). **^{13}C NMR** ($(CD_3)_2CO$, 25 ºC): δ (ppm) = 54.4 (CH_2N), 63.2 (-CH=CH-$\underline{C}H_2OH$), 107.7 ($C_{3pyrrole}$), 109.8 ($C_{4pyrrole}$), 118.7 (-$\underline{C}$H=CH-CH_2OH), 122.2 ($C_{2quinoline}$), 123.4 ($C_{5pyrrole}$), 128.4 ($C_{4a,quinoline}$), 128.5 ($C_{6quinoline}$), 128.8 ($C_{5quinoline}$, $C_{7quinoline}$), 129.0 ($C_{8quinoline}$), 129.3 (-CH=$\underline{C}$H-CH_2OH), 131.1 ($C_{5quinoline}$, $C_{7quinoline}$), 132.0 ($C_{2pyrrole}$), 134.3 ($C_{4quinoline}$), 136.3 ($C_{3quinoline}$), 149.5 ($C_{8a,quinoline}$). **MS (ESI$^+$):** (*m/z*) 391 (MH^+, 5); 374 (7); 373 (45); 264 (17); 263 (100). **HRMS (ESI$^+$):** Calculated for $C_{17}H_{16}N_2OI$ (MH^+): 391.0307. Found: 391.0302.

Synthesis of (*E*)-2-bromo-3-((2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-pyrrol-1-yl)methyl)pyridine (34a)

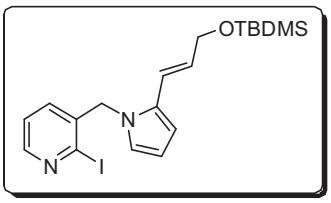


The allylic alcohol **32a** (0.12 g, 0.42 mmol) was dissolved in dry DMF (5 mL) under an inert atmosphere. Imidazole (72.00 mg, 1.06 mmol) and TBDMSCl (0.13 g, 0.85 mmol) were added to the previous solution and the mixture was stirred for 4 h at room temperature. The crude was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with water (3 x 5 mL), brine (3 x 5 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica

gel, hexane/EtOAc 9/1) obtaining product **34a** as a white solid (0.16 g, 0.39 mmol, 93% yield).

m.p.: 75-76 ºC (Hexane/EtOAc); **IR (ATR):** 2953 cm^{-1} (C-H_{aliph} st), 1650 cm^{-1} (C=C st), 1561 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -0.02 (s, 6H, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.82 (s, 9H, $Si(CH_3)_2C(C\underline{H_3})_3$), 4.22 (d, *J* = 4.7 Hz, 2H, -CH=CH-C$\underline{H_2}$OSi), 5.12 (s, 2H, CH_2N), 6.05 (dt, *J* = 15.5, 4.7 Hz, 1H, -CH=C$\underline{H}$-CH_2OSi), 6.20 – 6.27 (m, 2H, $H_{4pyrrole}$, -C$\underline{H}$=CH-CH_2OSi), 6.42 (dd, *J* = 3.6, 1.4 Hz, 1H, $H_{3pyrrole}$), 6.59 -6.64 (m, 1H, $H_{4pyridine}$), 6.66 (dd, *J* = 2.5, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.14 (dd, *J* = 7.6, 4.7 Hz, 1H, $H_{5pyridine}$), 8.25 (dd, *J* = 4.7, 1.8 Hz, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 25.8 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 49.7 ($CH_2N$), 63.4 (-CH=CH-$\underline{C}H_2OSi$), 107.0 ($C_{3pyrrole}$) 109.3 ($C_{4pyrrole}$), 117.0 (-$\underline{C}$H=CH-$CH_2OSi$), 122.2 ($C_{5pyrrole}$), 123.4 ($C_{5pyridine}$), 128.0 (-CH=$\underline{C}$H-$CH_2OSi$), 131.1 ($C_{2pyrrole}$), 135.2 ($C_{3pyridine}$), 135.9 ($C_{4pyridine}$), 140.7 ($C_{2pyridine}$), 148.8 ($C_{6pyridine}$). **MS (ESI$^+$):** (*m/z*) 409 ($MH^+$ + 2, 19); 407 (MH^+, 14); 359 (23); 328 (22); 327 (100); 277 (64); 275 (65); 195 (43). **HRMS (ESI$^+$):** Calculated for $C_{19}H_{28}N_2OBr^{79}Si$ (MH^+): 407.1154. Found: 407.1155.

Synthesis of (*E*)-3-((2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-pyrrol-1-yl)methyl)-2-iodopyridine (34b)

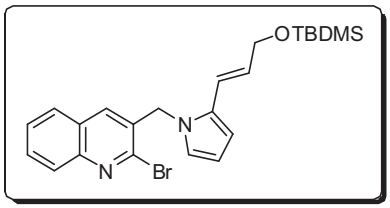


The allylic alcohol **32b** (0.36 g, 1.06 mmol) was dissolved in dry DMF (10 mL) under an inert atmosphere. Imidazole (0.18 g, 2.65 mmol) and TBDMSCl (0.33 g, 2.12 mmol) were added to the previous solution and the mixture was stirred for 4 h at room temperature. The crude was quenched with water (10 mL) and extracted

with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (3 x 10 mL), brine (3 x 10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **34b** as a white solid (0.45 g, 1.00 mmol, 94% yield).

m.p.: 79-80 ºC (Hexane/EtOAc); **IR (ATR):** 2952 cm^{-1} (C-H_{aliph} st), 1663 cm^{-1} (C=C st), 1571 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -0.02 (s, 6H, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.82 (s, 9H, $Si(CH_3)_2C(C\underline{H_3})_3$), 4.22 (d, *J* = 4.7 Hz, 2H, -CH=CH-$C\underline{H_2}$OSi), 5.02 (s, 2H, CH_2N), 6.04 (dt, *J* = 15.6, 4.7 Hz, 1H, -CH=C<u>H</u>-CH_2OSi), 6.19 – 6.26 (m, 2H, $H_{4pyrrole}$, -C<u>H</u>=CH-CH_2OSi), 6.42 (dd, *J* = 3.6, 1.8 Hz, 1H, $H_{3pyrrole}$), 6.47 - 6.51 (m, 1H, $H_{4pyridine}$), 6.65 (dd, *J* = 2.4, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.13 (dd, *J* = 7.7, 4.7 Hz, 1H, $H_{5pyridine}$), 8.21 – 8.24 (m, 1H, $H_{6pyridine}$). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 53.9 ($CH_2N$), 63.4 (-CH=CH-$\underline{C}H_2$OSi), 107.3 ($C_{3pyrrole}$) 109.3 ($C_{4pyrrole}$), 117.0 (-<u>C</u>H=CH-$CH_2$OSi), 120.1 ($C_{2pyridine}$), 122.2 ($C_{5pyrrole}$), 123.5 ($C_{5pyridine}$), 128.1 (-CH=<u>C</u>H-$CH_2$OSi), 131.1 ($C_{2pyrrole}$), 134.6 ($C_{4pyridine}$), 138.4 ($C_{3pyridine}$), 149.5 ($C_{6pyridine}$). **MS (ESI$^+$):** (*m/z*) 456 ($MH^+$ + 1, 3); 455 (MH^+, 21); 328 (10); 327 (50); 324 (11); 323 (100). **HRMS (ESI$^+$):** Calculated for $C_{19}H_{28}N_2OISi$ (MH^+): 455.1016. Found: 455.1013.

Synthesis of (*E*)-2-bromo-3-((2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-pyrrol-1-yl)methyl)quinoline (35a)

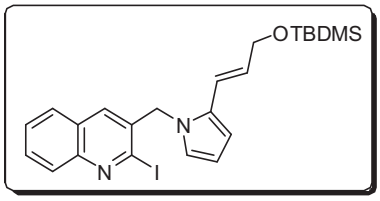


The allylic alcohol **33a** (0.60 g, 1.75 mmol) was dissolved in dry DMF (10 mL) under an inert atmosphere. Imidazole (0.30 g, 4.37 mmol) and TBDMSCl (0.54 mg, 3.50 mmol) were added to the previous solution and the mixture was stirred for 16 h at room temperature. The crude was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with water (3 x 5 mL), brine (3 x 5 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **35a** as a yellow oil (0.74 g, 1.62 mmol, 93% yield).

IR (ATR): 2954 (C-H_{aliph} st), 1663 cm^{-1} (C=C st), 1563 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.04 (s, 6H, Si($C\underline{H_3}$)$_2$C(CH_3)$_3$), 0.88 (s, 9H, Si(CH_3)$_2$C($C\underline{H_3}$)$_3$), 4.33 (d, *J* = 4.8 Hz, 2H, -CH=CH-$C\underline{H_2}$OSi), 5.39 (s, 2H, CH_2N), 6.21 (dt, *J* = 15.6, 4.8 Hz, 1H, -CH=$C\underline{H}$-CH_2OSi), 6.39 – 6.47 (m, 2H, $H_{4pyrrole}$, -$C\underline{H}$=CH-CH_2OSi), 6.60 – 6.66 (m, 1H, $H_{3pyrrole}$), 6.83 - 6.90 (m, 1H, $H_{5pyrrole}$), 7.17 (s, 1H, $H_{4quinoline}$), 7.60 – 7.65 (m, 1H, $H_{6quinoline}$), 7.75 (d, *J* = 7.7 Hz, 1H, $H_{5quinoline}$), 7.75 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H, $H_{7quinoline}$), 8.15 (d, *J* = 8.4 Hz, 1H, $H_{8quinoline}$). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.5 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), 18.1 (Si(CH_3)$_2\underline{C}$(CH_3)$_3$), 25.6 (Si(CH_3)$_2$C($\underline{C}H_3$)$_3$), 49.9 (CH_2N), 63.3 (-CH=CH-$\underline{C}H_2$OSi), 107.0 ($C_{3pyrrole}$) 109.2 ($C_{4pyrrole}$), 117.1 (-$\underline{C}$H=CH-CH_2OSi), 122.2 ($C_{5pyrrole}$), 127.1 ($C_{6quinoline}$), 127.4 ($C_{4a,quinoline}$), 127.7 ($C_{5quinoline}$), 127.9, 128.1 (-CH=$\underline{C}$H-CH_2OSi, $C_{8quinoline}$), 130.2 ($C_{7quinoline}$), 131.0 ($C_{3quinoline}$), 132.1 ($C_{2pyrrole}$), 135.1 ($C_{4quinoline}$), 140.6 ($C_{2quinoline}$), 147.6 ($C_{8a,quinoline}$). **MS (ESI$^+$):** (*m/z*) 475 (58);

474 (MH^+, 17); 473 (100); 431 (14); 429 (31); 393 (61). **HRMS (ESI^+):** Calculated for $C_{23}H_{30}N_2OBr^{79}Si$ (MH^+): 547.1311. Found: 547.1310.

Synthesis of (*E*)-3-((2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-pyrrol-1-yl)methyl)-2-iodoquinoline (35b)



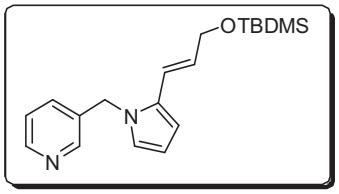
The allylic alcohol **33b** (0.19 g, 0.49 mmol) was dissolved in dry DMF (10 mL) under an inert atmosphere. Imidazole (83.70 mg, 1.23 mmol) and TBDMSCl (0.15 mg, 0.98 mmol) were added to the previous solution and the mixture was stirred for 16 h at room temperature. The crude was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with water (3 x 5 mL), brine (3 x 5 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **35b** as a yellow oil (0.22 g, 0.44 mmol, 89% yield).

IR (ATR): 2949 cm^{-1} (C-H_{aliph} st), 1664 cm^{-1} (C=C st), 1587 cm^{-1} (C=C_{arom} st). **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -0.09 (s, 6H, $Si(C\underline{H}_3)_2C(CH_3)_3$), 0.74 (s, 9H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 4.19 (d, *J* = 4.7 Hz, 2H, -CH=CH-$C\underline{H}_2$OSi), 5.17 (s, 2H, CH_2N), 6.07 (dt, *J* = 15.6, 4.7 Hz, 1H, -CH=C$\underline{H}$-CH_2OSi), 6.24 – 6.33 (m, 2H, $H_{4pyrrole}$, -C$\underline{H}$=CH-CH_2OSi), 6.45 – 6.50 (m, 1H, $H_{3pyrrole}$), 6.69 - 6.73 (m, 1H, $H_{5pyrrole}$), 6.90 (s, 1H, $H_{4quinoline}$), 7.47 – 7.51 (m, 1H, $H_{6quinoline}$), 7.62 (d, *J* = 8.0 Hz, 1H, $H_{5quinoline}$), 7.64 – 7.70 (m, 1H, $H_{7quinoline}$), 8.03 (d, *J* = 8.5 Hz, 1H, $H_{8quinoline}$). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.4 ($Si(\underline{C}H_3)_2C(CH_3)_3$), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 25.6 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 54.1 ($CH_2N$), 63.4 (-CH=CH-$\underline{C}H_2$OSi), 107.1 ($C_{3pyrrole}$) 109.3 ($C_{4pyrrole}$), 117.2 (-$\underline{C}$H=CH-$CH_2$OSi), 121.0

($C_{2quinoline}$), 122.2 ($C_{5pyrrole}$), 127.3 ($C_{6quinoline}$), 127.4 ($C_{4a,quinoline}$), 127.8 ($C_{5quinoline}$), 127.9 (-CH=CH-CH_2OSi), 128.4 ($C_{8quinoline}$), 130.1 ($C_{7quinoline}$), 131.1 ($C_{2pyrrole}$), 133.6 ($C_{4quinoline}$), 134.3 ($C_{3quinoline}$), 148.8 ($C_{8a,quinoline}$). **MS (ESI$^+$):** (*m/z*) 505 (MH^+, 3); 377 (27); 374 (17); 373 (100). **HRMS (ESI$^+$):** Calculated for $C_{23}H_{30}N_2OISi$ (MH^+): 505.1172. Found: 505.1161.

*6.5.1.2. Attempts of intramolecular carbolithiation of o-halopyridines **34a**, **34b** and o-haloquinolines **35a**, **35b** via S_N2'reation.*

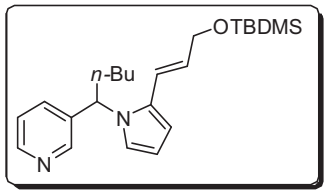
Synthesis of (*E*)-3-((2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-pyrrol-1-yl)methyl)pyridine (36) (Table 2.5, Entry 1)



The silyloxy allyl derivative **34a** (100.00 mg, 0.25 mmol) was dissolved in dry THF (5 mL) under an inert atmosphere. TMEDA (0.07 mL, 0.49 mmol) was added to the previous solution at -90 ºC, and subsequently *n*-BuLi (0.49 mL of a solution 1.10 M in hexane, 0.54 mmol) was added. The final mixture was stirred 50 min at -90 ºC and was quenched with a saturated solution of NH_4Cl (5 mL) at low temperature. H_2O (5 mL) and Et_2O (20 mL) were added to the crude, followed by the separation of the organic phase. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 8/2) obtaining product **36** as a colourless oil (50.50 mg, 0.15 mmol, 63% yield) and byproduct **37** (10.30 mg, 0.03 mmol, 11% yield).

IR (ATR): 2928 cm^{-1} (C-H_{aliph} st), 1665 cm^{-1} (C=C st), 1577 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.01 (s, 6H, Si($C\underline{H}_3$)$_2$C(CH_3)$_3$), 0.86 (s, 9H, Si(CH_3)$_2$C($C\underline{H}_3$)$_3$), 4.23 (d, *J* = 4.8 Hz, 2H, -CH=CH-$C\underline{H}_2$OSi), 5.13 (s, 2H, CH_2N), 6.05 (dt, *J* = 15.6, 4.8 Hz, 1H, -CH=C<u>H</u>-CH_2OSi), 6.18 (dd, *J* = 4.9, 1.9 Hz, 1H, $H_{4pyrrole}$), 6.32 – 6.42 (m, 2H, -C<u>H</u>=CH-CH_2OSi, $H_{3pyrrole}$), 6.65 (dd, *J* = 2.6, 1.9 Hz, 1H, $H_{5pyrrole}$), 7.17 – 7.23 (m, 2H, $H_{5pyridine,}$ $H_{4pyridine}$), 8.40 (s, 1H, $H_{2pyridine}$), 8.50 (t, *J* = 3.2 Hz, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.3 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), 18.3 (Si(CH_3)$_2\underline{C}$(CH_3)$_3$), 25.8 (Si(CH_3)$_2$C($\underline{C}H_3$)$_3$), 48.0 (CH_2N), 63.5 (-CH=CH-$\underline{C}H_2$OSi), 106.8 ($C_{3pyrrole}$) 108.9 ($C_{4pyrrole}$), 117.4 (-$\underline{C}$H=CH-CH_2OSi), 122.1 ($C_{5pyrrole}$), 123.6 ($C_{4pyridine}$), 127.8 (-CH=$\underline{C}$H-CH_2OSi), 131.2 ($C_{2pyrrole}$), 133.7 ($C_{3pyridine}$), 133.9 ($C_{5pyridine}$), 147.8 ($C_{2pyridine}$), 148.9 ($C_{6pyridine}$). **MS (ESI$^+$):** (*m/z*) 329 (MH^+, 1); 198 (12); 197 (100). **HRMS (ESI$^+$):** Calculated for $C_{19}H_{29}N_2OSi$ (MH^+): 329.2049. Found: 329.2046.

Synthesis of (*E*)-3-(1-(2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-pyrrol-1-yl)pentyl)pyridine (37) (Table 2.5, Entry 2)

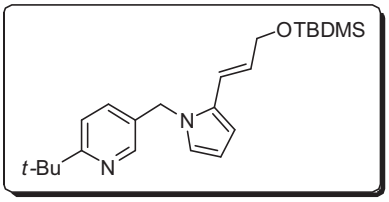


The silyloxy allyl derivative **34b** (89.50 mg, 0.20 mmol) was dissolved in dry THF (5 mL) under an inert atmosphere. TMEDA (0.06 mL, 0.39 mmol) was added to the previous solution at -90 ºC, and subsequently *n*-BuLi (0.39 mL of a solution 1.10 M in hexane, 0.43 mmol) was added. The final mixture was stirred 50 min at -90 ºC and was quenched with a saturated aqueous solution of NH_4Cl (5 mL) at low temperature. H_2O (5 mL) and Et_2O (20 mL) were added to the crude, followed by the separation of the organic phase. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel,

hexane/EtOAc 8/2) obtaining byproduct **37** as a colourless oil (16.80 mg, 0.04 mmol, 22% yield) and deiodinated byproduct **36** (34.10 mg, 0.10 mmol, 53% yield).

IR (ATR): 2928 cm^{-1} (C-H_{aliph} st), 1664 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.05 (s, 6H, Si($C\underline{H}_3)_2C(CH_3)_3$), 0.84 – 0.97 (m, 12H, $Si(CH_3)_2C(C\underline{H}_3)_3$, $3H_4'$), 1.27 – 1.45 (m, 4H, $2H_2'$+ $2H_3'$), 2.06 – 2.27 (m, 2H, $2H_1'$), 4.23 – 4.26 (m, 2H, -CH=CH-$C\underline{H}_2$OSi), 5.23 (m, 1H, -C<u>H</u>(*n*-Bu)-N), 6.03 (dt, *J* = 15.5, 4.8 Hz, 1H, -CH=C<u>H</u>-CH_2OSi), 6.20 (m, 1H, $H_{4pyrrole}$), 6.33 (dd, *J* = 3.6, 1.9 Hz, 1H, $H_{3pyrrole}$), 6.41 (d, *J* = 15.5 Hz, 1H, -C<u>H</u>=CH-CH_2OSi), 6.80 (dd, *J* = 2.6, 1.9 Hz, 1H, $H_{5pyrrole}$), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H, $H_{5pyridine}$), 7.27 – 7.30 (m, 1H, $H_{4pyridine}$), 8.42 – 8.52 (m, 2H, $H_{2pyridine}$, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.2 ($Si(\underline{C}H_3)_2C(CH_3)_3$), 13.8 ($C_4'$), 18.4 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 22.3 ($C_2'/C_3'$), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 28.6 ($C_2'/C_3'$), 35.5 ($C_1'$), 57.4 (-C<u>H</u>(*n*-Bu)-N), 63.6 (-CH=CH-$\underline{C}H_2$OSi), 106.4 ($C_{3pyrrole}$) 108.8 ($C_{4pyrrole}$), 117.7 (-<u>C</u>H=CH-CH_2OSi), 118.3 ($C_{5pyrrole}$), 123.6 ($C_{5pyridine}$), 128.1 (-CH=<u>C</u>H-CH_2OSi), 131.7 ($C_{2pyrrole}$), 133.7 ($C_{4pyridine}$), 137.9 ($C_{3pyridine}$), 147.9 ($C_{2pyridine}$), 148.7 ($C_{6pyridine}$). **MS (ESI^+):** (*m/z*) 386 (2); 385 (MH^+, 8); 254 (16); 253 (100). **HRMS (ESI^+):** Calculated for $C_{23}H_{37}N_2OSi$ (MH^+): 385.2675. Found: 385.2669.

Synthesis of (*E*)-2-*tert*-butyl-5-((2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-pyrrol-1-yl)methyl)pyridine (38) (Table 2.5, Entry 4)

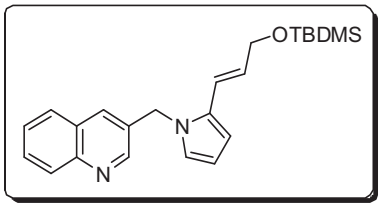


The silyloxy allyl derivative **34b** (90.80 mg, 0.20 mmol) was dissolved in dry THF (5 mL) under an inert atmosphere. TMEDA (0.06 mL, 0.40 mmol) was added to the previous solution at -78 ºC, and subsequently *t*-BuLi (0.44 mL of a solution 1.00 M in hexane, 0.44 mmol) was added. The final mixture was stirred for 3 h at -78 ºC and was allowed to warm up to room temperature for 2 h. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) at low temperature. H_2O (5 mL) and Et_2O (20 mL) were added to the crude, followed by the separation of the organic phase. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **38** as a colourless oil (12.50 mg, 0.03 mmol, 16% yield) and deiodinated byproduct **36** (27.60 mg, 0.08 mmol, 42% yield).

IR (ATR): 2935 cm^{-1} (C-H_{aliph} st), 1660 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.00 (s, 6H, $Si(C\underline{H}_3)_2C(CH_3)_3$), 0.86 (s, 9H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 1.33 (s, 9H, $C(C\underline{H}_3)_3$-$C_{6pyridine}$), 4.24 (d, *J* = 4.9 Hz, 2H, -CH=CH-$C\underline{H}_2$OSi), 5.10 (s, 2H, CH_2N), 6.05 (dt, *J* = 15.6, 4.9 Hz, 1H, -CH=C$\underline{H}$-CH_2OSi), 6.14 – 6.20 (m, 1H, $H_{4pyrrole}$), 6.35 – 6.43 (m, 2H, -C$\underline{H}$=CH-CH_2OSi, $H_{3pyrrole}$), 6.62 – 6.67 (m, 1H, $H_{5pyrrole}$), 7.15 (dd, *J* = 8.2, 2.1 Hz, 1H, $H_{4pyridine}$), 7.24 – 7.27 (m, 1H, $H_{5pyridine}$), 8.34 (d, *J* = 2.1 Hz, 1H, $H_{2pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.2 ($Si(\underline{C}H_3)_2C(CH_3)_3$), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 30.2 ($C(\underline{C}H_3)_3$-$C_{6pyridine}$), 37.2 ($\underline{C}(CH_3)_3$-$C_{6pyridine}$), 47.9 ($CH_2N$), 63.7 (-CH=CH-

$\underline{C}H_2OSi$), 106.7 ($C_{3pyrrole}$) 108.8 ($C_{4pyrrole}$), 117.7 (-$\underline{C}$H=CH-CH_2OSi), 119.2 ($C_{5pyridine}$), 122.1 ($C_{5pyrrole}$), 127.6 (-CH=$\underline{C}$H-CH_2OSi), 130.4 ($C_{3pyridine}$), 131.2 ($C_{2pyrrole}$), 134.3 ($C_{4pyridine}$), 146.7 ($C_{2pyridine}$), 168.7 ($C_{6pyridine}$). **MS (ESI$^+$):** (*m/z*) 386 (26); 385 (MH^+, 100); 254 (7); 254 (46). **HRMS (ESI$^+$):** Calculated for $C_{23}H_{37}N_2OSi$ (MH^+): 385.2675. Found: 385.2669.

Synthesis of (*E*)-3-((2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-pyrrol-1-yl)methyl)quinoline (39) (Table 2.5, Entry 8)

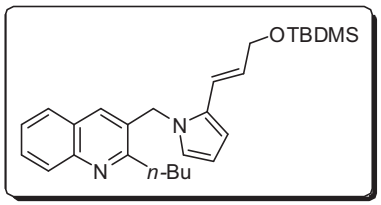


The silyloxy allyl derivative **35b** (76.30 mg, 0.15 mmol) was dissolved in dry THF (5 mL) under an inert atmosphere. TMEDA (0.05 mL, 0.30 mmol) was added to the previous solution at -78 ºC, and subsequently *t*-BuLi (0.33 mL of a solution 1.00 M in hexane, 0.33 mmol) was added. The final mixture was stirred for 3 h at -78 ºC and was allowed to warm up to room temperature for 2 h. The reaction was quenched with a saturated solution of NH_4Cl (5 mL). H_2O (5 mL) and Et_2O (20 mL) were added to the crude, followed by the separation of the organic phase. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **39** as a colourless oil (20.90 mg, 0.06 mmol, 37% yield).[26]

[26] Subproduct corresponding to the insertion of *t*-Bu group into the quinoline ring was detected but not characterized.

IR (ATR): 2928 cm^{-1} (C-H_{aliph} st), 1660 cm^{-1} (C=C st),1496 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -0.05 (s, 6H, Si($C\underline{H}_3$)$_2$C(CH_3)$_3$), 0.80 (s, 9H, Si(CH_3)$_2$C($C\underline{H}_3$)$_3$), 4.21 (d, *J* = 4.9 Hz, 2H, -CH=CH-$C\underline{H}_2$OSi), 5.32 (s, 2H, CH_2N), 6.07 (dt, *J* = 15.5, 4.9 Hz, 1H, -CH=C<u>H</u>-CH_2OSi), 6.22 – 6.25 (m, 1H, $H_{4pyrrole}$), 6.36 – 6.46 (m, 2H, -C<u>H</u>=CH-CH_2OSi, $H_{3pyrrole}$), 6.72 (dd, *J* = 2.5, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.52 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H, $H_{6quinoline}$), 7.59 (s, 1H, $H_{4quinoline}$), 7.67 - 7.74 (m, 2H, $H_{5quinoline,}$ $H_{7quinoline}$), 8.09 (d, *J* = 8.4 Hz, 1H, $H_{8quinoline}$), 8.74 (m, 1H, $H_{2quinoline}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.3 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), 18.3 (Si(CH_3)$_2$<u>C</u>(CH_3)$_3$), 25.8 (Si(CH_3)$_2$C($\underline{C}H_3$)$_3$), 48.3 (CH_2N), 63.6 (-CH=CH-<u>C</u>H_2OSi), 106.9 ($C_{3pyrrole}$) 109.0 ($C_{4pyrrole}$), 117.5 (-<u>C</u>H=CH-CH_2OSi), 122.3 ($C_{5pyrrole}$), 126.9 ($C_{6quinoline}$), 127.8 ($C_{5quinoline}$/$C_{7quinoline}$), 127.9 (-CH=<u>C</u>H-CH_2OSi), 129.2 ($C_{8quinoline}$), 129.4 ($C_{5quinoline}$/$C_{7quinoline}$), 131.1 ($C_{2pyrrole}$), 131.3 ($C_{3quinoline}$), 133.1 ($C_{4quinoline}$), 147.6 ($C_{8a,\ quinoline}$), 149.1 ($C_{2quinoline}$). $C_{4a,quinoline}$ peak is overlapped. **MS (ESI$^+$):** (*m/z*) 379 (MH^+, 10); 248 (16); 247 (100). **HRMS (ESI$^+$):** Calculated for $C_{23}H_{31}N_2OSi$ (MH^+): 379.2206. Found: 379.2196.

Synthesis of (*E*)-2-butyl-3-((2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-pyrrol-1-yl)methyl)quinoline (40) (Table 2.5, Entry 6)



The silyloxy allyl derivative **35b** (65.90 mg, 0.13 mmol) was dissolved in dry THF (5 mL) under an inert atmosphere. TMEDA (0.04 mL, 0.26 mmol) was added to the previous solution at -90 ºC, and subsequently *n*-BuLi (0.26 mL of a solution 1.10 M in hexane, 0.29 mmol) was added. The final mixture was stirred 50 min at -90 ºC and was quenched with a saturated aqueous solution of NH_4Cl (5 mL) at low temperature. H_2O (5 mL) and Et_2O (20 mL) were added to the crude, followed by the separation of the organic phase. The aqueous phase was extracted

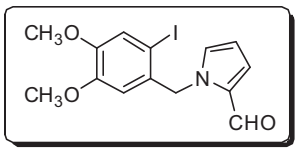
with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **40** as a colourless oil (22.80 mg, 0.05 mmol, 40% yield) and deiodinated byproduct **39** (5.30 mg, 0.01 mmol, 11% yield).

IR (ATR): 2927 cm^{-1} (C-H_{aliph} st), 1666 cm^{-1} (C=C st), 1563 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -0.08 (s, 6H, Si($C\underline{H_3}$)$_2$C(CH_3)$_3$), 0.75 (s, 9H, Si(CH_3)$_2$C($C\underline{H_3}$)$_3$), 1.00 (t, *J* = 7.4 Hz, 3H, 3H_4´), 1.47 – 1.57 (m, 2H, 2H_3´), 1.76 – 1.87 (m, 2H, 2H_2´), 2.94 – 2.99 (m, 2H, 2H_1´), 4.19 (d, *J* = 4.9 Hz, 2H, -CH=CH-$C\underline{H_2}$OSi), 5.29 (s, 2H, CH_2N), 6.06 (dt, *J* = 15.6, 4.9 Hz, 1H, -CH=C$\underline{H}$-CH_2OSi), 6.23 – 6.28 (m, 1H, $H_{4pyrrole}$), 6.31 (d, *J* = 15.6 Hz, 1H, -C$\underline{H}$=CH-CH_2OSi), 6.46 (dd, *J* = 3.6, 1.5 Hz, $H_{3pyrrole}$), 6.62 – 6.67 (m, 1H, $H_{5pyrrole}$), 7.16 (s, $H_{4quinoline}$), 7.37 – 7.46 (m, 1H, $H_{6quinoline}$), 7.59 - 7.66 (m, 2H, $H_{5quinoline,}$ $H_{7quinoline}$), 8.02 (d, *J* = 8.4 Hz, 1H, $H_{8quinoline}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.3 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), 14.0 (C_4´), 18.2 (Si(CH_3)$_2\underline{C}$(CH_3)$_3$), 23.0 (C_3´), 25.8 (Si(CH_3)$_2$C($\underline{C}H_3$)$_3$), 31.1 (C_2´), 35.7 (C_1´), 47.8 (CH_2N), 63.6 (-CH=CH-$\underline{C}H_2$OSi), 106.9 ($C_{3pyrrole}$) 109.0 ($C_{4pyrrole}$), 117.6 (-$\underline{C}$H=CH-CH_2OSi), 122.3 ($C_{5pyrrole}$), 125.9 ($C_{6quinoline}$), 127.0 ($C_{4a,quinoline}$), 127.6 ($C_{5quinoline}$/$C_{7quinoline}$), 127.8 (-CH=$\underline{C}$H-CH_2OSi), 128.5 ($C_{8quinoline}$), 129.2 ($C_{5quinoline}$/$C_{7quinoline}$), 130.0 ($C_{3quinoline}$), 131.3 ($C_{2pyrrole}$), 133.4 ($C_{4quinoline}$), 147.1 ($C_{8a,quinoline}$), 159.6 ($C_{2quinoline}$). **MS (ESI$^+$):** (*m/z*) 436 (38); 435 (MH^+, 100); 303 (27). **HRMS (ESI$^+$):** Calculated for $C_{27}H_{39}N_2OSi$ (MH^+): 435.2832. Found: 435.2821.

6.5.2. Intramolecular carbolithiation reaction of *N-(o*-iodobenzyl)pyrrolyl and pyrrolidinyl allylic alcohol derivatives

*6.5.2.1. Synthesis of N-(o-iodobenzyl)pyrroles **44a**, **44b** and pyrrolidine **46**.*

Synthesis of 1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrole-2-carbaldehyde (41)[27]



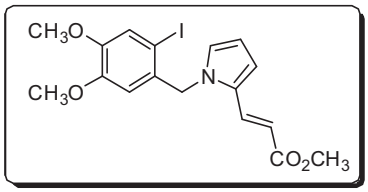
To a suspension of KOH (0.47 g, 8.43 mmol) in DMSO (20 mL), pyrrole 2-carboxaldehyde (0.21 mg, 2.21 mmol) was added. The mixture was left stirring for 1 h at room temperature. After that time, benzylbromide **16** (1.50 g, 4.21 mmol) was added to the former solution and the reaction was stirred for 4 h more at room temperature. The reaction was quenched with H_2O (20 mL) and the crude was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was washed with H_2O (3 x 20 mL) and brine (1 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **41** as a white solid (0.76 g, 2.05 mmol, 93% yield).

m.p.: 111-113 ºC (Hexane/EtOAc); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 3.69 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.55 (s, 2H, Ar-CH_2-N), 6.27 (t, *J* = 3.2 Hz, 1H, $H_{4pyrrole}$), 6.46 (s, 1H, H_{6arom}), 6,99 - 7,01 (m, 1H, $H_{3pyrrole,}$ $H_{5pyrrole}$), 7.24 (s, 1H, H_{3arom}), 9.60 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 55.8 (OCH_3), 56.1 (Ar-CH_2-N), 56.2 (OCH_3), 86.6 (C_{2arom}), 110.3 ($C_{4pyrrole}$), 111.7 (C_{6arom}), 121.6 ($C_{3pyrrole}$), 125.0 (C_{3arom}), 131.2 ($C_{5pyrrole}$), 131.6 ($C_{2pyrrole}$), 132.3 (C_{1arom}), 149.1 (C_{4arom}), 149.8 (C_{5arom}), 179.6 (CHO). **MS (CI):** (*m/z*) 372 (MH^+, 28); 276 (73); 246

[27] Lage, S.; Villaluenga, I.; Sotomayor, N.; Lete, E. *Synlett* **2008**, 3188.

(15); 245 (100); 244 (26). **HRMS (CI):** Calculated for $C_{14}H_{14}INO_3$ (MH^+): 372.0089. Found: 372.0097.

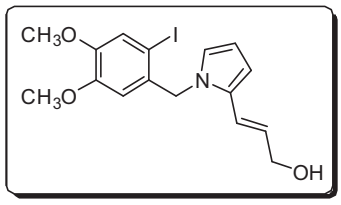
Synthesis of (*E*)-methyl 3-(1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl)acrylate (42)



To a solution of *N*-benzylpyrrole carbaldehyde **41** (3.54 g, 9.55 mmol) in CH_2Cl_2 (50 mL), methyl triphenylphosphoranylidene acetate (**4c**) (13.03 g, 38.19 mmol, 2.0 eq per day), and the mixture was stirred under reflux for 48 h. The reaction was followed by NMR and when the reaction was completed, the mixture was concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **42** as a white solid (3.50 g, 8.19 mmol, 86% yield).

m.p.: 97-99 ºC (CH_2Cl_2); **IR (ATR):** 2998 cm^{-1} (C-H_{aliph} st), 1699 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 3.62 (s, 3H, OCH_3), 3.73 (s, 3H, $CO_2C\underline{H}_3$), 3.85 (s, 3H, OCH_3), 5.10 (s, 2H, Ar-CH_2-N), 6.03 (s, 1H, H_{6arom}), 6.13 (d, *J* = 15.6 Hz, 1H, -CH=C<u>H</u>-CO_2CH_3), 6.23 – 6.29 (m, 1H, $H_{4pyrrole}$), 6.72 – 6.77 (m, 1H, $H_{3pyrrole}$), 6.77 – 6.80 (m, 1H, $H_{5pyrrole}$), 7.25 (s, 1H, H_{3arom}), 7.50 (d, *J* = 15.6 Hz, 1H, -C<u>H</u>=CH-CO_2CH_3); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 51.4 ($CO_2\underline{C}H_3$), 55.3 (Ar-CH_2-N), 55.7, 56.2 (2 x OCH_3), 84.9 (C_{2arom}), 110.2 ($C_{3pyrrole}$), 110.6 (C_{6arom}), 112.3 ($C_{2pyrrole}$), 113.1 (-CH=<u>C</u>H-CO_2CH_3), 121.6 (C_{3arom}), 126.4 ($C_{4pyrrole}$), 129.1 ($C_{1pyrrole}$), 131.7 (C_{1arom}), 132.1 (-<u>C</u>H=CH-CO_2CH_3), 149.1 (C_{4arom}), 149.9 (C_{5arom}), 167.9 ($\underline{C}O_2CH_3$). **MS (CI):** (*m/z*) 456 (20); 428 (26); 427 (MH^+, 21); 396 (10); 277 (100). **HRMS (CI):** Calculated for $C_{17}H_{19}INO_4$ (MH^+): 428.0359. Found: 428.0346.

Synthesis of (*E*)-3-(1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl)prop-2-en-1-ol (43)[28]



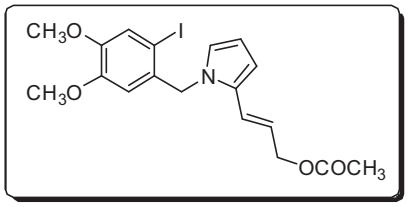
To a solution of *N*-benzylpyrrolylacrylate **42** (3.21 g, 7.51 mmol) in dry toluene (40 mL), DIBAL-H (41.32 mL of a solution 1.00 M in toluene, 41.32 mmol) was added at -78 ºC and under an inert atmosphere. The reaction was stirred for 30 min at -78 ºC, and after that time the mixture was quenched at low temperature with a H_2O:AcOH (1:1) solution (2 mL) and allowed to warm up to room temperature. The crude was eluted with EtOAc (40 mL), washed with water (3 x 20 mL), brine (2 x 20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 6/4) obtaining product **43** as a white solid (2.64 g, 6.60 mmol, 88% yield).

m.p.: 82–84 ºC (Hexane/EtOAc); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.66 (brs, 1H, OH), 3.59 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.17 (d, *J* = 5.9 Hz, 2H, -CH=CH-C$\underline{H_2}$OH), 4.98 (s, 2H, Ar-C$\underline{H_2}$-N), 5.97 (s, 1H, H_{6arom}), 6.08 (dt, *J* = 15.6, 5.9 Hz, 1H, -CH=C$\underline{H}$-CH_2OH), 6.18 (t, *J* = 3.1 Hz, 1H, $H_{4pyrrole}$), 6.31 (d, *J* = 15.6 Hz, 1H, -C$\underline{H}$=CH-CH_2OH), 6.38 – 6.45 (m, 1H, $H_{3pyrrole}$), 6.61 – 6.66 (m, 1H, $H_{5pyrrole}$), 7.22 (s, 1H, H_{3arom}). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 55.2 (Ar-$\underline{C}H_2$-N), 55.7, 56.2 (2 x OCH_3), 63.9 (-CH=CH-$\underline{C}H_2OH$), 84.3 (C_{2arom}), 107.4 ($C_{3pyrrole}$), 108.9 ($C_{4pyrrole}$), 110.5 (C_{6arom}), 119.9 (-$\underline{C}$H=CH-CH_2OH), 121.4 (C_{3arom}), 122.8 ($C_{5pyrrole}$), 126.6 (-CH=$\underline{C}$H-CH_2OH), 130.8 ($C_{2pyrrole}$), 132.6 (C_{1arom}), 148.9 (C_{4arom}),

[28] Lage, S. PhD. Thesis, University of the Basque Country, **2008**.

149.9 (C_{5arom}). **MS (CI):** (*m/z*) 384 (30); 383 (25); 382 (M-OH, 42); 277 (100); 257 (15). **HRMS (CI):** Calculated for $C_{16}H_{19}INO_3$ (MH^+): 400.0409. Found: 400.0403.

Synthesis of (*E*)-3-(1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl)allyl acetate (44a)



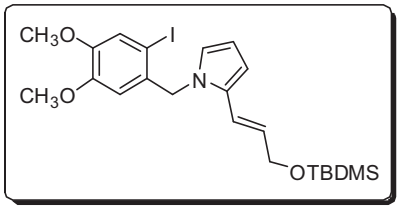
The allylic alcohol **43** (92.60 mg, 0.23 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under an inert atmosphere. Pyridine (0.04 mL, 0.45 mmol) and acetyl chloride (0.02 mL, 0.25 mmol) were added to the previous solution and the mixture was stirred for 2 h at room temperature. The reaction was followed by TLC and when it was completed, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and the organic phase was separated. The aqueous phase was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were evaporated and filtrated through a plug of basic Al_2O_3 by elution with CH_2Cl_2. Product **44a** was obtained as a yellow oil (93.90 mg, 0.21 mmol, 92% yield) and used without further purification.[29]

IR (ATR): 3001 cm^{-1} (C-H_{arom} st), 1739 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 2.05 (s, 3H, $COCH_3$), 3.61 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.60 (d, *J* = 6.7 Hz, 2H, -CH=CH-CH_2O), 5.00 (s, 2H, Ar-CH_2-N), 5.94 – 6.07 (m, 2H, H_{6arom}, -CH=CH-CH_2O), 6.18 - 6.22 (m, 1H, $H_{4pyrrole}$), 6,36 (d, *J* = 15.8 Hz, 1H, -CH=CH-CH_2O), 6.46 (d, *J* = 2.3 Hz, 1H, $H_{3pyrrole}$), 6.64 – 6.68 (m, 1H, $H_{5pyrrole}$), 7.24 (s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 21.0 ($COCH_3$), 55.2 (Ar-

[29] Product **44a** was unstable to column cromatography both in silica gel or neutral alumina.

$\underline{C}H_2$-N), 55.7, 56.2 (2 x OCH_3), 65.4 (-CH=CH-$\underline{C}H_2O$), 84.3 (C_{2arom}), 107.9 ($C_{3pyrrole}$), 109.0 ($C_{4pyrrole}$), 110.5 (C_{6arom}), 120.8 (-CH=$\underline{C}$H-CH_2O), 121.4 (C_{3arom}), 123.0 (-$\underline{C}$H=CH-CH_2O), 123.2 ($C_{5pyrrole}$), 130.3 ($C_{2pyrrole}$), 132.5 (C_{1arom}), 148.9 (C_{4arom}), 149.9 (C_{5arom}), 170.8 ($\underline{C}OCH_3$). **MS (CI):** (*m/z*) 442 (MH^+, 24); 399 (32); 382 (100); 278 (11); 277 (38). **HRMS (CI):** Calculated for $C_{18}H_{21}INO_4$ (MH^+): 442.0515. Found: 442.0529.

Synthesis of (*E*)-2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrole (44b)

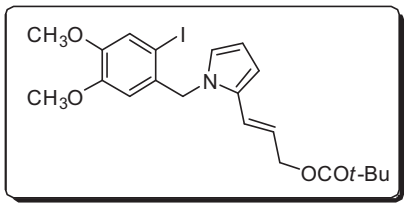


The allylic alcohol **43** (1.99 g, 4.98 mmol) was dissolved in dry DMF (30 mL) under an inert atmosphere. Imidazole (0.85 g, 12.45 mmol) and TBDMSCl (1.55 g, 9.96 mmol) were added to the previous solution and the mixture was stirred for 4 h at room temperature. The crude was quenched with water (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with water (3 x 20 mL), brine (3 x 20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **44b** as a colourless oil (2.24 g, 4.36 mmol, 88% yield).

IR (ATR): 2952 cm^{-1} (C-H_{aliph} st), 1665 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.00 (s, 6H, Si($C\underline{H}_3$)$_2$(CH_3)$_3$), 0.85 (s, 9H, Si(CH_3)$_2$($C\underline{H}_3$)$_3$), 3.59 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.24 (d, *J* = 4.9 Hz, 2H, -CH=CH-$C\underline{H}_2$OSi), 4.98 (s, 2H, Ar-$C\underline{H}_2$-N), 5.94 (s, 1H, H_{6arom}), 6.03 (dt, *J* = 15.6, 4.9 *Hz*, 1H, -CH=C$\underline{H}$-CH_2OSi), 6.18 – 6.20 (m, 1H, $H_{4pyrrole}$), 6.30 (d, *J* = 15.6 *Hz*, 1H, -C$\underline{H}$=CH-CH_2OSi), 6.40 (dd, *J* = 3.6, 1.5 *Hz*, 1H, $H_{3pyrrole}$), 6.61 – 6.65 (m, 1H, $H_{5pyrrole}$), 7.23

(s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.3 ($Si(\underline{C}H_3)_2C(CH_3)_3$), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 55.2 (Ar-$\underline{C}H_2$-N), 55.6, 56.2 (2 x OCH_3), 63.7 (-CH=CH-$\underline{C}H_2OSi$), 84.0 (C_{2arom}), 106.7 ($C_{3pyrrole}$), 108.7 ($C_{4pyrrole}$), 110.4 (C_{6arom}), 117.9 (-$\underline{C}H$=CH-CH_2OSi), 121.3 (C_{3arom}), 122.3 ($C_{5pyrrole}$), 127.3 (CH=$\underline{C}H$-CH_2OSi), 131.2 ($C_{2pyrrole}$), 132.8 (C_{1arom}), 148.7 (C_{4arom}), 149.9 (C_{5arom}). **MS (CI):** (*m/z*) 514 (MH^+, 27); 513 (21); 384 (31); 383 (33); 382 (79); 381 (29); 277 (100); 256 (26); 255 (24); 133 (23); 117 (33). **HRMS (CI):** Calculated for $C_{22}H_{33}INO_3Si$ (MH^+): 514.1274. Found: 514.1255.

Synthesis of (*E*)-3-(1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl)allyl pivalate (44c)

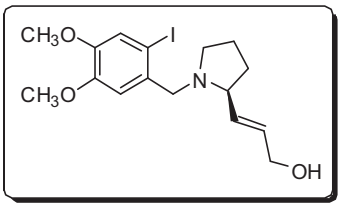


The allylic alcohol **43** (1.16 g, 2.91 mmol) was dissolved in dry CH_2Cl_2 (40 mL) under an inert atmosphere. Pyridine (0.47 mL, 5.83 mmol) and pivaloyl chloride (0.80 mL, 6.43 mmol) were added to the previous solution and the mixture was stirred overnight at room temperature. The reaction was followed by TLC and when it was completed, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL) and the organic phase was separated. The aqueous phase was further extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was filtered through a basic Al_2O_3 column (φ = 4 cm, h = 15 cm) by elution with CH_2Cl_2 and evaporation of the filtrate afforded

product **44c** as a yellow oil (1.22 g, 2.53 mmol, 87% yield), which was used without further purification.[30]

IR (ATR): 2962 cm^{-1} (C-H_{aliph} st), 1724 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.12 (s, 9H, COC($C\underline{H}_3$)$_3$), 3.55 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.56 (d, *J* = 6.2 Hz, 2H, -CH=CH-$C\underline{H}_2$O), 4.93 (s, 2H, Ar-$C\underline{H}_2$-N), 5.89 – 6.04 (m, 2H, H_{6arom}, -CH=C$\underline{H}$-CH_2O), 6.12 - 6.17 (m, 1H, $H_{4pyrrole}$), 6,31 (d, *J* = 15.8 Hz, 1H, -C$\underline{H}$=CH-CH_2O), 6.41 (dd, *J* = 3.5, 1.3 Hz, 1H, $H_{3pyrrole}$), 6.59 – 6.64 (m, 1H, $H_{5pyrrole}$), 7.19 (s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 26.9 (COC($\underline{C}H_3$)$_3$), 38.4 (CO$\underline{C}$(CH_3)$_3$), 54.9 (Ar-$\underline{C}H_2$-N), 55.3, 55.9 (2 x OCH_3), 64.6 (-CH=CH-$\underline{C}H_2$O), 84.0 (C_{2arom}), 107.5 ($C_{3pyrrole}$), 108.7 ($C_{4pyrrole}$), 110.2 (C_{6arom}), 120.9 (-CH=$\underline{C}$H-CH_2O), 121.1 (C_{3arom}), 121.7 (-$\underline{C}$H=CH-CH_2O), 122.8 ($C_{5pyrrole}$), 130.0 ($C_{2pyrrole}$), 132.2 (C_{1arom}), 148.6 (C_{4arom}), 149.6 (C_{5arom}), 177.6 ($\underline{C}$OC(CH_3)$_3$). **MS (CI):** (*m/z*) 484 (MH^+, 18); 384 (22); 383 (28); 382 (100); 381 (25); 277 (47); 103 (35). **HRMS (CI):** Calculated for $C_{21}H_{27}INO_4$ (MH^+): 484.0985. Found: 484.0972.

Synthesis of (*S,E*)-3-(1-(2-iodo-4,5-dimethoxybenzyl)pyrrolidin-2-yl)prop-2-en-1-ol (45)



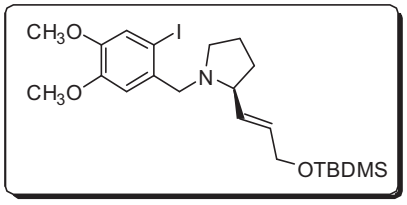
To a solution of *N*-benzylpyrrolidinylacrylate **17a** (0.62 g, 1.40 mmol) in dry toluene (20 mL), DIBAL-H (7.70 mL of a solution 1.00 M in toluene, 7.70 mmol) was added at -78 ºC and under inert atmosphere. The reaction was stirred for 30 min, and after that time the reaction was quenched with a H_2O:AcOH (1:1) solution

[30] Product **44c** was unstable to column cromatography both in silica gel or neutral alumina.

(2 mL). The crude was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The aqueous phase was basified with a 10% NaOH solution until pH = 9 and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 3/7) obtaining product **45** as a yellow oil (0.52 g, 1.29 mmol, 92% yield).

IR (ATR): 3364 cm^{-1}, (brs, O-H st), 2957 (C-H_{aliph} st), 1595 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.50 – 1.85 (m, 3H, H_{3A}, 2 x H_4), 1.86 – 2.03 (m, 1H, $1H_{3B}$), 2.10 – 2.29 (m, 2H, H_{5A}, OH), 2.85 - 3.01 (m, 2H, H_2, H_{5B}), 3.21 (d, *J* = 13.9 Hz, 1H, Ar-$\underline{CH_A}H_B$-N), 3.81 (s, 3H, OCH_3)*, 3.84 (s, 3H, OCH_3)*, 3.76 – 3.87 (m, 1H, Ar-$CH_A\underline{H_B}$-N)*, 4.07 (d, *J* = 5.4 Hz, 2H, -CH=CH-C$\underline{H_2}$OH), 5.61 (dd, *J* = 15.5, 8.1 Hz, 1H, -C$\underline{H}$=CH-CH_2OH), 5.76 (dt, *J* = 15.5, 5.4 Hz, 1H, -CH=C$\underline{H}$-CH_2OH), 6.98 (s, 1H, H_{6arom}), 7.17 (s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 22.1 (C_{4p}), 31.6 (C_{3p}), 53.4 (C_{5p}), 55.9 (OCH_3), 56.0 (OCH_3), 61.7 (Ar-$\underline{C}H_2$-N), 62.9 (-CH=CH-$\underline{C}H_2$OH), 67.1(C_{2p}), 87.7 (C_{2arom}), 113.0 (C_{6arom}), 121.2 (C_{3arom}), 131.2 (-CH=$\underline{C}$H-CH_2OH), 134.0 (-$\underline{C}$H=CH-CH_2OH), 134.2 (C_{1arom}), 148.2 (C_{5arom}), 149.1 (C_{4arom}). **MS (CI):** (*m/z*) 404 (MH^+, 23); 403 (58); 402 (29); 386 (65); 277 (100). **HRMS (CI):** Calculated for $C_{16}H_{23}INO_3$ (MH^+): 404.0723. Found: 404.0703. **$[\alpha]_D^{20}$:** -44.5 (c = 1.0 g/L, CH_2Cl_2). *Partially overlapped signals

Synthesis of *(S,E)*-2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1-(2-iodo-4,5-dimethoxybenzyl)pyrrolidine (46)



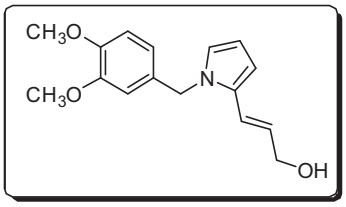
The allylic alcohol **45** (0.56 g, 1.40 mmol) was dissolved in dry DMF (20 mL) under an inert atmosphere. Imidazole (0.24 g, 3.49 mmol) and TBDMSCl (0.43 g, 2.80 mmol) were added to the previous solution and the mixture was stirred for 16 h at room temperature. The crude was quenched with water (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with water (3 x 20 mL), brine (3 x 20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 8/2) obtaining product **46** as a yellow oil (0.60 g, 1.16 mmol, 83 % yield).

IR (ATR): 2952 cm^{-1} (C-H_{aliph} st), 1597 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.05 (s, 6H, Si(C$\underline{H}_3$)$_2$C(CH$_3$)$_3$), 0.89 (s, 9H, Si(CH$_3$)$_2$C(C$\underline{H}_3$)$_3$), 1.56 – 1.82 (m, 3H, H_{3A}, 2 x H_4), 1.91 – 2.01 (m, 1H, H_{3B}), 2.18 (c, *J* = 8.7 Hz, 1H, H_{5A}), 2.88 – 3.00 (m, 2H, H_{5B}, H_2), 3.21 (d, *J* = 13.9 Hz, 1H, Ar-C$\underline{H}_A$H$_B$-N), 3.83 (s, 3H, OCH$_3$)*, 3.85 (s, 3H, OCH$_3$)*, 3.79 – 3.90 (m, 1H, Ar-CH$_A$$\underline{H}_B$-N)*, 4.16 (d, *J* = 4.8 Hz, 2H, -CH=CH-C$\underline{H}_2$OSi), 5.62 (dd, *J* = 15.4, 8.2 Hz, 1H, -C$\underline{H}$=CH-CH$_2$OSi), 5.72 (dt, *J* = 15.4, 4.8 Hz, 1H, -CH=C$\underline{H}$-CH$_2$OSi), 7.00 (s, 1H, H_{6arom}), 7.19 (s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.2 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$), 18.3 (Si(CH$_3$)$_2$$\underline{C}$(CH$_3$)$_3$), 22.2 ($C_{4p}$), 25.9 (Si(CH$_3$)$_2$C($\underline{C}H_3$)$_3$), 31.6 ($C_{3p}$), 53.4 ($C_{5p}$), 55.9 (OCH$_3$), 56.0 (OCH$_3$), 61.6 (Ar-$\underline{C}H_2$-N), 63.4 (-CH=CH-$\underline{C}H_2$OSi), 67.1 ($C_{2p}$), 87.5 ($C_{2arom}$), 113.0 ($C_{6arom}$), 121.2 ($C_{3arom}$), 131.5 (-CH=$\underline{C}$H-CH$_2$OSi), 132.7 (-$\underline{C}$H=CH-CH$_2$OSi), 134.6 ($C_{1arom}$), 148.2 ($C_{5arom}$), 149.2 ($C_{4arom}$). **MS (CI):** (*m/z*) 518 (MH^+, 88); 517 (78); 516 (66); 502 (57); 460 (47); 392 (16); 387 (19); 386

(100); 278 (22); 277 (47); 260 (38); 259 (25). **HRMS (CI):** Calculated for $C_{22}H_{37}INO_3Si$ (MH^+): 518.1587. Found: 518.1572. **$[\alpha]_D^{20}$:** -49.3 (c = 1.0 g/L, CH_2Cl_2). *Partially overlapped signals

*6.5.2.2. Attempts of intramolecular carbolithiation of N-o-iodobenzylpyrroles **44a**, **44b** and pyrrolidine **46** via S_N2' reaction.*

Synthesis of (*E*)-3-(1-(3,4-dimethoxybenzyl)-1*H*-pyrrol-2-yl)prop-2-en-1-ol (47) (Table 2.6, Entry 2)

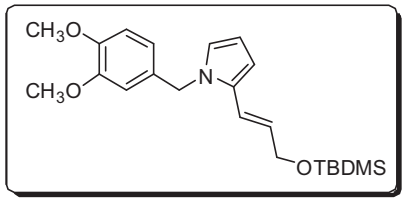


The acetylated allylic alcohol **44a** (88.00 mg, 0.20 mmol) was dissolved in dry THF (5 mL) under an inert atmosphere. *t*-BuLi (0.48 mL of a solution 0.83 M in hexane, 0.40 mmol) was added to the former solution at -78 ºC, and after being stirred for 5 min, TMEDA (0.06 mL, 0.40 mmol) was added to the mixture. The final mixture was stirred for 10 min at -78 ºC and then, the reaction was allowed to reach room temperature for 3 h. The reaction was quenched with a saturated solution of NH_4Cl (2 mL). H_2O (5 mL) and Et_2O (10 mL) were added to the crude, followed by the separation of the organic phase. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 4/6) obtaining product **47** as a yellow oil (26.30 mg, 0.10 mmol, 48% yield).

IR (ATR): 3379 cm^{-1} (brs, O-H st), 2922 cm^{-1} (C-H_{aliph} st), 1649 cm^{-1} (C=C st), 1595 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.26 (brs, 1H, OH), 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.19 (d, *J* = 6.0 Hz, 2H, -CH=CH-

C$\underline{H}_2$OH), 5.05 (s, 2H, Ar-C$\underline{H}_2$-N), 6.11 (dt, *J* =15.6, 6.0 Hz, 1H, -CH=C$\underline{H}$-CH$_2$OH), 6.16 (t, *J* = 3.1 Hz, 1H, $H_{4pyrrole}$), 6.38 – 6.46 (m, 2H, -C$\underline{H}$=CH-CH$_2$OH, $H_{3pyrrole}$), 6.53 – 6.60 (m, 2H, H_{2arom}, H_{6arom}), 6.63 – 6.69 (m, 1H, $H_{5pyrrole}$), 6.79 (d, *J* = 8.5 Hz, 1H, H_{3arom}). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 50.2 (Ar-$\underline{C}$H$_2$-N), 55.8, 55.9 (2 x OCH_3), 63.8 (-CH=CH-$\underline{C}$H$_2$OH), 107.0 ($C_{3pyrrole}$), 108.4 ($C_{4pyrrole}$), 109.6 (C_{6arom}), 111.2 (C_{2arom}), 118.6 (C_{3arom}), 120.1 (-$\underline{C}$H=CH-CH$_2$OH), 122.7 ($C_{5pyrrole}$), 126.2 (-CH=$\underline{C}$H-CH$_2$OH), 130.5 (C_{1arom}), 130.7 ($C_{2pyrrole}$), 148.3 (C_{4arom}), 149.2 (C_{5arom}). **MS (CI):** (*m/z*) 274 (MH^+, 14); 273 (14); 258 (20); 257 (19); 256 (65); 151 (100). **HRMS (CI):** Calculated for $C_{16}H_{20}NO_3$ (MH^+): 274.1443. Found: 274.1452.

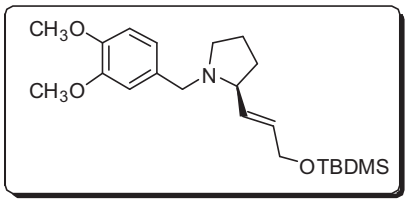
Synthesis of (*E*)-2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1-(3,4-dimethoxybenzyl)-1*H*-pyrrole (48) (Table 2.7, Entry 1)



The silyloxy allyl derivative **44b** (91.50 mg, 0.18 mmol) was dissolved in dry THF (5 mL) under inert atmosphere. *n*-BuLi (0.34 mL of a solution 1.17 M in hexane, 0.39 mmol) was added to the former solution at -90 ºC, and after being stirred for 5 min, TMEDA (0.05 mL, 0.36 mmol) was added to the mixture. The final mixture was stirred for 50 min at -90 ºC and was quenched with a saturated solution of NH_4Cl (5 mL) at low temperature. H_2O (5 mL) and Et_2O (20 mL) were added to the crude, followed by the separation of the organic phase. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **48** as an oil (47.80 mg, 0.12 mmol, 69 % yield).

IR (ATR): 2955 cm^{-1} (C-H_{aliph} st), 1515 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.03 (s, 6H, Si($C\underline{H}_3$)$_2$C(CH_3)$_3$), 0.88 (s, 9H, Si(CH_3)$_2$C($C\underline{H}_3$)$_3$), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.25 (d, *J* = 5.0 Hz, 2H, -CH=CH-$C\underline{H}_2$OSi), 5.05 (s, 2H, Ar-$C\underline{H}_2$-N), 6.05 (dt, *J* = 15.6, 5.0 *Hz*, 1H, -CH=C$\underline{H}$-CH_2OSi), 6.14 – 6.18 (m, 1H, $H_{4pyrrole}$), 6.38 (dd, *J* = 3.6, 1.5 *Hz*, 1H, $H_{3pyrrole}$), 6.42 (d, *J* = 15.6 *Hz*, 1H, -C$\underline{H}$=CH-CH_2OSi), 6.54 – 6.60 (m, 2H, H_{2arom}, H_{6arom}), 6.63 – 6.66 (m, 1H, $H_{5pyrrole}$), 6.79 (d, *J* = 8.8 Hz, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.3 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), 18.3 (Si(CH_3)$_2\underline{C}$(CH_3)$_3$), 25.9 (Si(CH_3)$_2$C($\underline{C}H_3$)$_3$), 50.2 (Ar-$\underline{C}H_2$-N), 55.7, 55.9 (2 x OCH_3), 63.7 (-CH=CH-$\underline{C}H_2$OSi), 106.4 ($C_{3pyrrole}$), 108.2 ($C_{4pyrrole}$), 109.5 (C_{6arom}), 111.3 (C_{3arom}), 118.2 (-$\underline{C}$H=CH-CH_2OSi), 118.6 (C_{2arom}), 122.2 ($C_{5pyrrole}$), 127.0 (-CH=$\underline{C}$H-CH_2OSi), 130.6 (C_{1arom}), 131.2 ($C_{2pyrrole}$), 148.3 (C_{5arom}), 149.2 (C_{4arom}). **MS (ESI$^+$):** (*m/z*) 389 (MH^+ +1, 20); 388 (MH^+, 83); 257 (14); 256 (100); 151 (21). **HRMS (ESI$^+$):** Calculated for $C_{22}H_{34}NO_3Si$ (MH^+): 388.2308. Found: 388.2317.

Synthesis of (*S,E*)-2-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1-(3,4-dimethoxybenzyl)pyrrolidine (49) (Table 2.7, Entry 2)



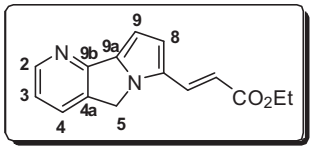
The silyloxy allyl derivative **46** (87.00 mg, 0.17 mmol) was dissolved in dry THF (5 mL) under an inert atmosphere. TMEDA (0.05 mL, 0.34 mmol) was added to the previous solution at -90 ºC, and subsequently *n*-BuLi (0.34 mL of a solution 1.10 M in hexane, 0.37 mmol) was added. The final mixture was stirred 50 min at -90 ºC and was quenched with a saturated solution of NH_4Cl (5 mL) at low temperature. H_2O (5 mL) and Et_2O (20 mL) were added to the crude, followed by the separation of the organic phase. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over

anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, EtOAc) obtaining product **49** as an oil (65.80 mg, 0.17 mmol, 100% yield).

IR (ATR): 2954 cm^{-1} (C-H_{aliph} st), 1512 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.08 (s, 6H, Si($C\underline{H_3}$)$_2$C(CH_3)$_3$), 0.91 (s, 9H, Si(CH_3)$_2$C($C\underline{H_3}$)$_3$), 1.57 – 1.82 (m, 3H, 2 x H_4, H_{3A}), 1.88 – 2.01 (m, 1H, H_{3B}), 2.09 (q, *J* = 8.8 Hz, 1H, H_{5A}), 2.79 (q, *J* = 8.2 Hz, 1H, H_2), 2.87 – 2.96 (m, 1H, H_{5B}), 3.00 (d, *J* = 12.8 Hz, 1H, Ar-$C\underline{H_A}H_B$-N), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.96 (d, *J* = 12.8 Hz, 1H, Ar-$CH_A\underline{H_B}$-N), 4.19 (d, *J* = 4.9 Hz, 2H, -CH=CH-$C\underline{H_2}$OSi), 5.63 (dd, *J* = 15.4, 8.2 Hz, 1H, -$C\underline{H}$=CH-CH_2OSi), 5.73 (dt, *J* = 15.4, 4.9 Hz, 1H, -CH=$C\underline{H}$-CH_2OSi), 6.72 – 6.87 (m, 3H, H_{2arom}, H_{3arom}, H_{6arom}). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.1 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), 18.4 (Si(CH_3)$_2\underline{C}$(CH_3)$_3$), 21.9 (C_{4p}), 25.9 (Si(CH_3)$_2$C($\underline{C}H_3$)$_3$), 31.6 (C_{3p}), 53.2 (C_{5p}), 55.8, 55.9 (2 x OCH_3), 57.9 (Ar-$\underline{C}H_AH_B$-N), 63.5 (-CH=CH-$\underline{C}H_2$OSi), 67.1 (C_{2p}), 110.7 (C_{3arom}), 112.2, 121.0 (C_{2arom}, C_{6arom}), 131.8 (-CH=$\underline{C}$H-CH_2OSi), 132.0 (C_{1arom}), 132.7 (-$\underline{C}$H=CH-CH_2OSi), 147.8, 148.7 (C_{4arom}, C_{5arom}). **MS (ESI$^+$):** (*m/z*) 393 (MH^+ +1, 26); 392 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{22}H_{38}NO_3Si$ (MH^+): 392.2621. Found: 392.2628. **$[\alpha]_D^{20}$:** -42.4 (c = 1.0 g/L, CH_2Cl_2).

6.6. Intramolecular Mizoroki-Heck and direct arylation of N-(o-haloheteroarylmethyl)pyrrolylacrylates and acrylamides

Synthesis of (*E*)-ethyl 3-(5H-pyrido[2,3-a]pyrrolizin-7-yl)acrylate (50) (Table 3.1, Entry 14)

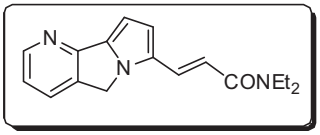


(Iodopyridinylmethyl)pyrrolylacrylate **5b** (100.00 mg, 0.26 mmol) was dissolved in dry DMF (5 mL) under an inert atmosphere. *n*-Bu_4NOAc (122.00 mg, 0.39 mmol), PPh_3 (6.90 mg, 0.03 mmol) and $Pd(OAc)_2$ catalyst (6.00 mg, 0.03 mmol) were added to the previous solution and the mixture was heated at 110 ºC for 1 h. After that time, the crude was eluted with EtOAc (50 mL) and washed with a saturated solution of NH_4Cl (2 x 20 mL) and H_2O (1 x 10 mL). The aqueous phase was further extracted with EtOAc (3 x 10mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was purified through flash chromatography (neutral alumina, CH_2Cl_2/EtOAc 9/1) obtaining product **50** as a solid (56.40 mg, 0.22 mmol, 85% yield).

m.p.: 148-150 ºC (CH_2Cl_2/EtOAc); **IR (ATR):** 2980 cm^{-1} (C-H_{aliph} st), 1696 cm^{-1} (C=O st), 1618 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25ºC): δ (ppm) = 1.30 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.21 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.89 (s, 2H, $2H_5$), 5.96 (d, *J* = 16.1 Hz, 1H, -CH=C<u>H</u>-CO_2Et), 6.60 – 6.65 (m, 1H, H_9), 6.65 – 6.69 (m, 1H, H_8), 7.02 (dt, *J* = 7.7, 4.6 Hz, 1H, H_3), 7.53 (d, *J* = 16.1 Hz, 1H, -C<u>H</u>=CH-CO_2Et), 7.58 – 7.64 (m, 1H, H_4), 8.44 (d, *J* = 4.6 Hz, 1H, H_2). **^{13}C NMR** ($CDCl_3$, 25ºC): δ (ppm) = 14.3 ($OCH_2\underline{C}H_3$), 49.2 (C_5), 60.2 ($O\underline{C}H_2CH_3$), 102.8 (C_9) 112.3 (-CH=<u>C</u>H-CO_2Et), 119.8 (C_3, C_8)*, 127.4 (C_7), 130.4 (C_4), 132.3 (-<u>C</u>H=CH-CO_2Et), 134.3 (C_{4a}), 141.0 (C_{9a}), 149.4 (C_2), 151.6 (C_{9b}), 167.3 (CO_2Et). **MS (ESI$^+$):** (*m/z*)

256 (MH^+ + 1, 15); 255 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{15}H_{15}N_2O_2$ (MH^+): 255.1134. Found: 255.1142. *Overlapped signals

Synthesis of (*E*)-*N*,*N*-diethyl-3-(5*H*-pyrido[2,3-*a*]pyrrolizin-7-yl)acrylamide (51) (Table 3.2, Entry 8)

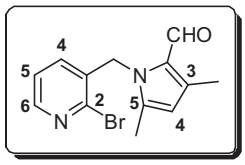


(Iodopyridinylmethyl)pyrrolylacrylamide **5d** (81.60 mg, 0.20 mmol) was dissolved in dry DMF (5 mL) under an inert atmosphere. P(*o*-tolyl)$_3$ (6.30 mg, 0.02 mmol), Et_3N (0.07 mL, 0.50 mmol) and $Pd(dba)_2$ catalyst (5.80 mg, 0.01 mmol) were added to the previous solution and the mixture was heated at 130 ºC for 48 h. After that time, the crude was eluted with EtOAc (50 mL) and washed with a saturated solution of NH_4Cl (2 x 20 mL) and H_2O (1 x 10 mL). The aqueous phase was further extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was purified through flash chromatography (neutral alumina, hexane/EtOAc 1/9) obtaining product **51** as a yellow oil (43.90 mg, 0.16 mmol, 78% yield).

IR (ATR): 2970 cm^{-1} (C-H_{aliph} st), 1641 cm^{-1} (C=O st), 1587 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25ºC): δ (ppm) = 1.12 – 1.37 (m, 6H, $N(CH_2C\underline{H}_3)_2$), 3.42 – 3.56 (m, 4H, $N(C\underline{H}_2CH_3)_2$), 5.00 (s, 2H, $2H_5$), 6.56 (d, *J* = 15.3 Hz, 1H, -CH=C<u>H</u>-CONEt$_2$), 6.69 (d, *J* = 3.9 Hz, 1H, H_9), 6.76 (d, *J* = 3.9 Hz, 1H, H_8), 7.08 (dd, *J* = 7.6, 4.6 Hz, 1H, H_3), 7.63 – 7.73 (m, 2H, H_4, -C<u>H</u>=CH-CONEt$_2$), 8.50 (d, *J* = 4.6 Hz, 1H, H_2); **^{13}C NMR** ($CDCl_3$, 25ºC): δ (ppm) = 13.3, 15.1 ($N(CH_2\underline{C}H_3)_2$), 29.7 (grease), 41.2, 42.3 ($N(\underline{C}H_2CH_3)_2$), 48.4 ($C_5$), 102.8 ($C_9$) 113.0 (-CH=<u>C</u>H-CONEt$_2$), 116.5 (C_8), 119.6 (C_3), 128.6 (C_7), 130.2, 130.5 (C_4, -<u>C</u>H=CH-CONEt$_2$), 134.1 (C_{4a}), 139.6 (C_{9a}), 149.4 (C_2), 152.4 (C_{9b}), 165.9 (CONEt$_2$). **MS (ESI$^+$):** (*m/z*)

283 (MH^+ + 1, 13); 282 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{17}H_{20}N_3O$ (MH^+): 282.1606. Found: 282.1599.

Synthesis of 1-((2-bromopyridin-3-yl)methyl)-3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (52a)

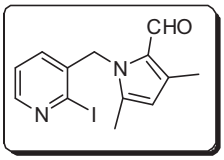


To a suspension of KOH (0.52 g, 9.26 mmol) in DMSO (20 mL), substituted pyrrole 2-carboxaldehyde (0.30 g, 2.31 mmol) was added. The mixture was stirred for 2 h at room temperature. After that time, 2-bromo-3-(bromomethyl)pyridine (**2**) (0.75 g, 3.01 mmol) was added to the former solution and the reaction was stirred for 4 h more at room temperature. The reaction was quenched with H_2O (20 mL) and the crude was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was washed with H_2O (3 x 20 mL) and brine (1 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **52a** as a white solid (0.57 g, 1.95 mmol, 84% yield).

m.p.: 170-171 ºC (Hexane/EtOAc); **IR (ATR):** 2916 cm^{-1} (C-H_{aliph} st), 1642 cm^{-1} (C=O st), 1560 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 2.09 (s, 3H, $C\underline{H_3}$-$C_{5pyrrole}$), 2.36 (s, 3H, $C\underline{H_3}$-$C_{3pyrrole}$), 5.57 (s, 2H, CH_2N), 5.95 (s, 1H, $H_{4pyrrole}$), 6.59 (dd, *J* = 7.6, 0.7 Hz, 1H, $H_{4pyridine}$), 7.12 (dd, *J* = 7.6, 4.7 Hz, 1H, $H_{5pyridine}$), 8.17 – 8.27 (m, 1H, $H_{6pyridine}$), 9.61 (s, 1H, CHO); **^{13}C NMR** (300 MHz, $CDCl_3$, 25 ºC): δ (ppm) = 10.9 ($\underline{C}H_3$-$C_{3pyrrole}$), 11.7 ($\underline{C}H_3$-$C_{5pyrrole}$), 47.6 (CH_2N), 112.4 ($C_{4pyrrole}$) 123.2 ($C_{5pyridine}$), 127.5 ($C_{2pyrrole}$), 134.9 ($C_{3pyridine}$), 135.0 ($C_{4pyridine}$), 135.7 ($C_{3pyrrole}$), 139.2 ($C_{5pyrrole}$), 141.2 ($C_{2pyridine}$), 148.5 ($C_{6pyridine}$), 176.8 (CHO). **MS**

(ESI$^+$): (*m/z*) 293 (MH^+, 5); 214 (12); 213 (100). **HRMS (ESI$^+$):** Calculated for $C_{13}H_{14}N_2OBr^{79}$ (MH^+): 293.0290. Found: 293.0285.

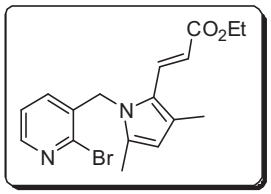
Synthesis of 1-((2-iodopyridin-3-yl)methyl)-3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (52b)



Pyrrole carbaldehyde derivative **52a** (0.55 g, 1.89 mmol) in dry dioxane (10 mL) was added *via* canula to a suspension of NaI (0.57 g, 3.77 mmol), CuI (18.00 mg, 0.09 mmol) and *N,N′*-dimethylethylenediamine (0.02 mL, 0.18 mmol) in dry dioxane (20 mL) under an inert atmosphere. The mixture was heated under reflux for 24 h. H_2O (20 mL) was added and the crude was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was washed with brine (3 x 20 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **52b** as a white solid (0.55 g, 1.61 mmol, 85% yield).

m.p.: 164-165 ºC (Hexane/EtOAc); **IR (ATR):** 2916 cm^{-1} ($C\text{-}H_{aliph}$ st), 1640 cm^{-1} (C=O st), 1554 cm^{-1} ($C{=}C_{arom}$ st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 2.09 (s, 3H, $C\underline{H_3}\text{-}C_{5pyrrole}$), 2.36 (s, 3H, $C\underline{H_3}\text{-}C_{3pyrrole}$), 5.48 (s, 2H, CH_2N), 5.95 (s, 1H, $H_{4pyrrole}$), 6.43 – 6.49 (m, 1H, $H_{4pyridine}$), 7.10 (dd, *J* = 7.7, 4.7 Hz, 1H, $H_{5pyridine}$), 8.11 – 8.23 (m, 1H, $H_{6pyridine}$), 9.61 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 10.9 ($\underline{C}H_3\text{-}C_{3pyrrole}$), 11.7 ($\underline{C}H_3\text{-}C_{5pyrrole}$), 51.8 ($CH_2N$), 112.4 ($C_{4pyrrole}$) 120.5 ($C_{2pyridine}$), 123.4 ($C_{5pyridine}$), 127.5 ($C_{2pyrrole}$), 133.6 ($C_{4pyridine}$), 135.7 ($C_{3pyrrole}$), 138.0 ($C_{3pyridine}$), 139.2 ($C_{5pyrrole}$), 149.2 ($C_{6pyridine}$), 176.8 (CHO). **MS (ESI$^+$):** (*m/z*) 341 (MH^+, 16); 214 (12); 213 (100). **HRMS (ESI$^+$):** Calculated for $C_{13}H_{14}N_2OI$ (MH^+): 341.0151. Found: 341.0151.

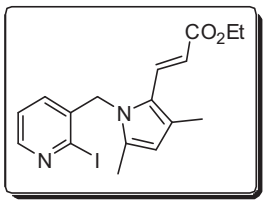
Synthesis of (*E*)-ethyl 3-(1-((2-bromopyridin-3-yl)methyl)-3,5-dimethyl-1*H*-pyrrol-2-yl)acrylate (53a)



To a solution of pyrrole carbaldehyde derivative **52a** (0.40 g, 1.36 mmol) in dry THF (30 mL), ethyl (triphenylphosphoranylidene)acetate **(4a)** (4.00 g, 10.92 mmol, 2.0 eq per day) were added and the mixture was heated under reflux for 96 h. After that time, the crude was concentrated to dryness and subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **53a** as a white solid (0.45 g, 1.24 mmol, 91 % yield).

m.p.: 141-142 ºC (Hexane/EtOAc); **IR (ATR):** 2980 cm^{-1} (C-H_{aliph} st), 1700 cm^{-1} (C=O st), 1611 cm^{-1} (C=C st), 1560 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.25 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.10 (s, 3H, $C\underline{H}_3$-$C_{5pyrrole}$), 2.26 (s, 3H, $C\underline{H}_3$-$C_{3pyrrole}$), 4.15 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.11 (s, 2H, CH_2N), 5.82 (d, *J* = 15.8 Hz, 1H, -CH=C<u>H</u>-CO_2Et), 5.96 (s, 1H, $H_{4pyrrole}$), 6.53 (dd, *J* = 7.6, 1.6 Hz, 1H, $H_{4pyridine}$), 7.14 (dd, *J* = 7.6, 4.7 Hz, 1H, $H_{5pyridine}$), 7.46 (d, *J* = 15.8 Hz, 1H, -C<u>H</u>=CH-CO_2Et), 8.25 (dd, *J* = 4.7, 1.6 Hz, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 12.2 ($\underline{C}H_3$-$C_{5pyrrole}$), 14.0 ($\underline{C}H_3$-$C_{3pyrrole}$), 14.3 ($OCH_2\underline{C}H_3$), 46.5 (CH_2N), 60.0 ($O\underline{C}H_2CH_3$), 111.1 (-CH=<u>C</u>H-CO_2Et), 112.5 ($C_{4pyrrole}$), 123.4 ($C_{5pyridine}$), 124.8 ($C_{2pyrrole}$), 126.0 ($C_{3pyrrole}$), 131.4 (-<u>C</u>H=CH-CO_2Et), 133.4 ($C_{5pyrrole}$), 134.2 ($C_{3pyridine}$), 135.4 ($C_{4pyridine}$), 140.9 ($C_{2pyridine}$), 148.9 ($C_{6pyridine}$), 168.1 (CO_2Et). **MS (ESI$^+$):** (*m/z*) 387 (11); 385 (11); 365 ($[MH+2]^+$, 47); 363 (MH^+, 48); 284 (15); 283 (100). **HRMS (ESI$^+$):** Calculated for $C_{17}H_{20}N_2O_2Br^{79}$ (MH^+): 363.0708. Found: 363.0715.

Synthesis of (*E*)-ethyl 3-(1-((2-iodopyridin-3-yl)methyl)-3,5-dimethyl-1*H*-pyrrol-2-yl)acrylate (53b)



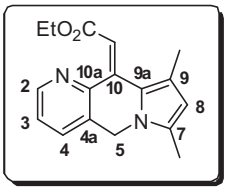
To a solution of pyrrole carbaldehyde derivative **52b** (0.55 g, 1.61 mmol) in dry THF (30 mL), ethyl (triphenylphosphoranylidene)acetate (**4a**) (4.72 g, 12.87 mmol, 2.0 eq per day) were added and the mixture was heated under reflux for 96 h. After that time, the crude was concentrated to dryness and subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **53b** as a white solid (0.50 g, 1.23 mmol, 76% yield).

m.p.: 132-133 ºC (Hexane/EtOAc); **IR (ATR):** 2978 cm^{-1} (C-H_{aliph} st), 1698 cm^{-1} (C=O st), 1609 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.26 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.10 (s, 3H, $C\underline{H}_3$-$C_{5pyrrole}$), 2.27 (s, 3H, $C\underline{H}_3$-$C_{3pyrrole}$), 4.16 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.01 (s, 2H, CH_2N), 5.82 (d, *J* = 15.8 Hz, 1H, -CH=C<u>H</u>-CO_2Et), 5.96 (s, 1H, $H_{4pyrrole}$), 6.37 – 6.43 (m, 1H, $H_{4pyridine}$), 7.12 (dd, *J* = 7.7, 4.7 Hz, 1H, $H_{5pyridine}$), 7.45 (d, *J* = 15.8 Hz, 1H, -C<u>H</u>=CH-CO_2Et), 8.24 (dd, *J* = 4.7, 1.8 Hz, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 12.2 ($\underline{C}H_3$-$C_{5pyrrole}$), 14.0 ($\underline{C}H_3$-$C_{3pyrrole}$), 14.3 ($OCH_2\underline{C}H_3$), 50.8 (CH_2N), 60.1 ($O\underline{C}H_2CH_3$), 111.1 (-CH=<u>C</u>H-CO_2Et), 112.5 ($C_{4pyrrole}$), 120.2 ($C_{2pyridine}$), 123.6 ($C_{5pyridine}$), 124.8 ($C_{2pyrrole}$), 126.1 ($C_{3pyrrole}$), 131.5 (-<u>C</u>H=CH-CO_2Et), 133.4 ($C_{5pyrrole}$), 134.2 ($C_{4pyridine}$), 137.4 ($C_{3pyridine}$), 149.6 ($C_{6pyridine}$), 168.1 (CO_2Et). **MS (ESI$^+$):** (*m/z*) 412 (MH^+ + 1, 11); 411 (MH^+, 70); 284 (15); 283 (100). **HRMS (ESI$^+$):** Calculated for $C_{17}H_{20}N_2O_2I$ (MH^+): 411.0569. Found: 411.0563.

Synthesis of (*Z*)-ethyl 2-(7,9-dimethylpyrrolo[1,2-*g*][1,6]naphthyridin-10(5*H*)-ylidene)acetate (54) and (*E*)-ethyl 3-(3,5-dimethyl-1-(pyridin-3-ylmethyl)-1*H*-pyrrol-2-yl)acrylate (55) (Table 3.3, Entry 6)

(Iodopyridinylmethyl)pyrrolylacrylate **51b** (90.00 mg, 0.22 mmol) was dissolved in dry DMF (5 mL) under an inert atmosphere. *n*-Bu_4NOAc (102.60 mg, 0.33 mmol), PPh_3 (5.80 mg, 0.02 mmol) and $Pd(OAc)_2$ catalyst (5.00 mg, 0.02 mmol) were added to the previous solution and the mixture was heated at 110 ºC for 48 h. After that time, the crude was eluted with EtOAc (50 mL) and washed with a saturated solution of NH_4Cl (2 x 20 mL) and H_2O (1 x 10 mL). The aqueous phase was further extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was purified through flash chromatography (silica gel, hexane/EtOAc 6/4) obtaining cyclized product **54** as a yellow solid (8.80 mg, 0.03 mmol, 14% yield) and deiodinated product **55** as a yellow oil (3.90 mg, 0.01 mmol, 6% yield). The conversion was 43%.

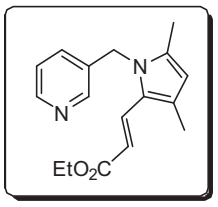
Data for **54**:



m.p.: 130-131 ºC (Hexane/EtOAc); **IR (ATR):** 2926 cm^{-1} (C-H_{aliph} st), 1706 cm^{-1} (C=O st), 1601 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.38 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.16 (s, 3H, $C\underline{H}_3$-C_9), 2.34 (s, 3H, $C\underline{H}_3$-C_7), 4.40 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.75 (s, 2H, $2H_5$), 5.92 (s, 1H, H_8), 7.16 (dd, *J* = 7.6, 4.8 Hz, 1H, H_3), 7.59 (dd, *J* = 7.6, 1.5 Hz, 1H, H_4), 7.85 (s, 1H, -C_{10}=C$\underline{H}$-CO_2Et), 8.62 (dd, *J* = 4.8, 1.5 Hz, 1H, H_2); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 11.3 ($\underline{C}H_3$-C_9), 12.3 ($\underline{C}H_3$-C_7), 14.3 ($OCH_2\underline{C}H_3$), 47.3 (C_5), 60.9 ($O\underline{C}H_2CH_3$), 111.5 (C_8), 121.8 (C_3), 123.1 (C_{10}), 124.7 (C_9), 127.0 (C_{9a}), 129.1 (-C_{10}=$\underline{C}$H-CO_2Et), 130.0 (C_{4a}), 132.9 (C_7), 135.5 (C_4), 148.7 (C_2), 155.1 (C_{10a}), 168.5 (CO_2Et). **MS (ESI$^+$):** (*m/z*)

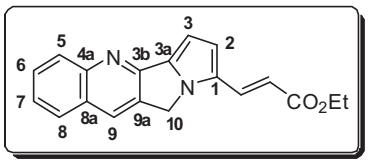
284 (MH^+ + 1, 17); 283 (MH^+, 100). **HRMS (ESI^+):** Calculated for $C_{17}H_{19}N_2O_2$ (MH^+): 283.1447. Found: 283.1444.

Data for **55:**



IR (ATR): 2928 cm^{-1} (C-H_{aliph} st), 1697 cm^{-1} (C=O st), 1609 (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.27 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.17 (s, 3H, $C\underline{H}_3$-$C_{5pyrrole}$), 2.27 (s, 3H, $C\underline{H}_3$-$C_{3pyrrole}$), 4.17 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.19 (s, 2H, CH_2N), 5.87 (d, *J* = 15.8 Hz, 1H, -CH=C<u>H</u>-CO_2Et), 5.94 (s, 1H, $H_{4pyrrole}$), 7.15 (d, *J* = 7.9 Hz, 1H, $H_{4pyridine}$), 7.23 (dd, *J* = 7.9, 4.8 Hz, 1H, $H_{5pyridine}$), 7.57 (d, *J* = 15.8 Hz, 1H, -C<u>H</u>=CH-CO_2Et), 8.32 (s, 1H, $H_{2pyridine}$), 8.51 (d, *J* = 4.8, 1H, $H_{6pyridine}$); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 12.5 ($\underline{C}H_3$-$C_{5pyrrole}$), 14.1 ($\underline{C}H_3$-$C_{3pyrrole}$), 14.4 ($OCH_2\underline{C}H_3$), 44.8 (CH_2N), 60.0 ($O\underline{C}H_2CH_3$), 110.9 (-CH=<u>C</u>H-CO_2Et), 112.4 ($C_{4pyrrole}$), 123.8 ($C_{5pyridine}$), 125.0 ($C_{2pyrrole}$), 126.0 ($C_{3pyrrole}$), 132.0 (-<u>C</u>H=CH-CO_2Et), 133.1 ($C_{3yridine}$), 133.5 ($C_{5pyrrole}$), 133.6 ($C_{4pyridine}$), 147.6 ($C_{2pyridine}$), 148.9 ($C_{6pyridine}$), 168.3 (CO_2Et). **MS (ESI^+):** (*m/z*) 286 (MH^+ + 1, 16); 285 (MH^+, 100); 239 (29). **HRMS (ESI^+):** Calculated for $C_{17}H_{21}N_2O_2$ (MH^+): 285.1603. Found: 285.15896.

Synthesis of (*E*)-ethyl 3-(10*H*-pyrrolizino[1,2-*b*]quinolin-1-yl)acrylate (56) (Table 3.4, Entry 1)

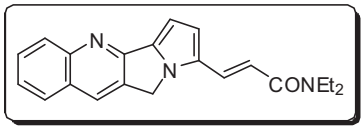


(Bromoquinolinylmethyl)pyrrolylacrylate **9a** (100.00 mg, 0.26 mmol) was dissolved in dry CH_3CN (5 mL) under an inert atmosphere. *n*-Bu_4NCl (108.20 mg, 0.39 mmol), $NaHCO_3$ (54.50 mg, 0.65 mmol) and $Pd(PPh_3)_4$ catalyst (30.30 mg, 0.03 mmol) were added to the previous solution and the mixture was heated under reflux for 48 h. After

that time, the crude was eluted with EtOAc (50 mL) and washed with a saturated solution of NH_4Cl (1 x 20 mL). The organic layer was separated and the aqueous phase further extracted with EtOAc (2 x 10mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was purified through flash chromatography (neutral alumina, CH_2Cl_2/EtOAc 9/1) obtaining the product **56** as a yellow solid (69.40 mg, 0.23 mmol, 88% yield).

m.p.: 170-171 ºC (CH_2Cl_2/EtOAc); **IR (ATR):** 2978 cm^{-1} (C-H_{aliph} st), 1698 cm^{-1} (C=O st), 1617 cm^{-1} (C=C st), 1573 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.36 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.27 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.03 (s, 2H, $2H_{10}$), 6.10 (d, *J* = 16.1 Hz, 1H, -CH=C<u>H</u>-CO_2Et), 6.77 (d, *J* = 4.0 Hz, 1H, H_2), 6.88 (d, *J* = 4.0 Hz, 1H, H_3), 7.40 – 7.48 (m, 1H, H_7), 7.58 (d, *J* = 16.1 Hz, 1H, -C<u>H</u>=CH-CO_2Et), 7.61 – 7.63 (m, 2H, H_6, H_8), 7.94 (s, 1H, H_9), 8.05 (d, *J* = 8.4 Hz, 1H, H_5); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.3 ($OCH_2\underline{C}H_3$), 48.5 (C_{10}), 60.4 ($O\underline{C}H_2CH_3$), 104.5 (C_3), 113.3 (-CH=<u>C</u>H-CO_2Et), 119.8 (C_2), 125.7 (C_{8a}), 125.8 (C_7), 127.7 (C_6), 128.1 (C_1), 128.6 (C_5), 129.3 (C_9), 129.6 (C_8), 132.1 (C_{9a}), 132.3 (-<u>C</u>H=CH-CO_2Et), 140.0 (C_{3a}), 148.2 (C_{4a}), 151.7 (C_{3b}), 167.3 (CO_2Et). **MS (MALDI):** (*m/z*) 306 (MH^+ + 1, 17); 305 (MH^+, 100); 274 (23); 200 (19). **HRMS (MALDI):** Calculated for $C_{19}H_{17}N_2O_2$ (MH^+): 305.1290. Found: 305.1282.

Synthesis of (*E*)-*N,N*-diethyl-3-(10*H*-pyrrolizino[1,2-*b*]quinolin-1-yl)acrylamide (57) (Table 3.4, Entry 4)



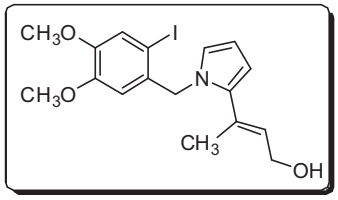
(Iodoquinolinylmethyl)pyrrolyl acrylamide derivative **9d** (80.00 mg, 0.17 mmol) was dissolved in dry CH_3CN (5 mL) under an inert atmosphere. *n*-Bu_4NCl (72.60 mg, 0.26 mmol), $NaHCO_3$ (36.60 mg, 0.44 mmol) and $Pd(PPh_3)_4$ catalyst (20.30 mg, 0.02 mmol) were added to the previous solution and the mixture was heated under reflux for 48 h. After that time, the crude was eluted with EtOAc (50 mL) and washed with a saturated solution of NH_4Cl (1 x 20 mL). The organic layer was separated and the aqueous phase further extracted with EtOAc (2 x 10mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was purified through flash chromatography (silica, hexane/EtOAc 9/1) obtaining the product **57** as a yellow solid (54.50 mg, 0.16 mmol, 95% yield).

m.p.: 190-191 ºC (CH_2Cl_2/EtOAc); **IR (ATR):** 2974 cm^{-1} (C-H_{aliph} st), 1633 cm^{-1} (C=O st), 1591 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25ºC): δ (ppm) = 1.12 – 1.43 (m, 6H, $N(CH_2C\underline{H}_3)_2$), 3.40 – 3.61 (m, 4H, $N(C\underline{H}_2CH_3)_2$), 5.12 (s, 2H, $2H_{10}$), 6.63 (d, *J* = 15.2 Hz, 1H, -CH=C<u>H</u>-$CONEt_2$), 6.83 (d, *J* = 4.0 Hz, 1H, H_2), 6.90 (d, *J* = 4.0 Hz, 1H, H_3), 7.45 – 7.50 (m, 1H, H_7), 7.66 – 7.72 (m, 2H, -C<u>H</u>=CH-$CONEt_2$, H_6), 7.74 (d, *J* = 7.6 Hz, 1H, H_8), 8.04 (s, 1H, H_9), 8.08 (d, *J* = 8.4 Hz, 1H, H_5). **^{13}C NMR** ($CDCl_3$, 25ºC): δ (ppm) = 13.3, 15.1 ($N(CH_2\underline{C}H_3)_2$), 41.2, 42.3 ($N(\underline{C}H_2CH_3)_2$), 47.8 ($C_{10}$), 104.7 ($C_3$), 114.0 (-CH=<u>C</u>H-$CONEt_2$), 116.5 ($C_2$), 125.8 ($C_7$), 125.9 ($C_{8a}$), 127.9 ($C_8$), 128.7 ($C_5$), 129.4 ($C_{3a}$), 129.6 ($C_9$), 129.7, 129.9 ($C_{6,}$ -<u>C</u>H=CH-$CONEt_2$), 132.4 (C_{9a}), 138.7 (C_1), 148.4 (C_{4a}), 152.4 (C_{3b}), 165.8 ($CONEt_2$). **MS (ESI$^+$):** (*m/z*) 333 (MH^+ + 1, 23); 332 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{21}H_{21}N_3O$ (MH^+): 332.1763. Found: 332.1771.

6.7. Intramolecular Mizoroki-Heck reaction of N-(o-iodobenzyl) and N-(o-haloheteroarylmethyl)pyrrolyl allylic alcohol derivatives. Generation of tertiary and quaternary stereocenters

6.7.1. Intramolecular Mizoroki-Heck reaction of *N*-(*o*-iodobenzyl)pyrrole 59. Generation of a quaternary stereocenter

Synthesis of (*E*)-3-(1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl)but-2-en-1-ol (58)

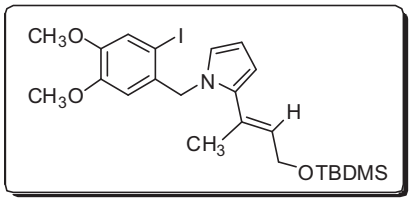


Over a solution of the former *N*-benzylpyrrole **26** (0.50 g, 1.10 mmol) in dry toluene (20 mL), DIBAL-H (6.04 mL of a solution 1.0 M in toluene, 6.04 mmol) was added at -78 ºC and under an inert atmosphere. The reaction was stirred for 30 min at -78 ºC, and after that time the reaction was quenched at low temperature with a H_2O:AcOH (1:1) solution (2 mL). The crude was washed with water (3 x 10 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/EtOAc 6/4) obtaining product **58** as a yellow oil (0.42 g, 1.02 mmol, 93% yield).

IR (ATR): 3510 cm^{-1} (brs, O-H st), 2936 cm^{-1} (C-H_{aliph} st), 1682 cm^{-1} (C=O st), 1596 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.39 (brs, 1H, OH), 1.92 (s, 3H, -C($C\underline{H}_3$)=CH-CH_2OH), 3.62 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.23 (d, *J* = 6.7 Hz, 2H, -C(CH_3)=CH-C$\underline{H}_2$OH), 5.02 (s, 2H, Ar-C$\underline{H}_2$-N), 5.51 (t, *J* = 6.7 Hz, 1H, -C(CH_3)=C$\underline{H}$-CH_2OH), 5.99 (s, 1H, H_{6arom}), 6.14 – 6.23 (m, $H_{3pyrrole}$, $H_{4pyrrole}$), 6.60 - 6.65 (m, 1H, $H_{5pyrrole}$), 7.21 (s, 1H, H_{3arom}). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ

(ppm) =17.8 (-C($\underline{C}H_3$)=CH-CH_2OH), 55.6 (OCH_3), 55.8 (Ar-$\underline{C}H_2$-N), 56.1 (OCH_3), 59.4 (-C(CH_3)=CH-$\underline{C}H_2OH$), 84.2 (C_{2arom}), 108.2, 108.7 ($C_{3pyrrole}$, $C_{4pyrrole}$), 110.4 (C_{6arom}), 121.2 (C_{3arom}), 123.2 ($C_{5pyrrole}$), 127.5 (-C(CH_3)=$\underline{C}$H-CH_2OH), 129.8, 133.4, 136.2 ($C_{2pyrrole}$, $C_{1arom,}$ -$\underline{C}$(CH_3)=CH-CH_2OH), 148.6, 149.7 ($C_{4arom,}$ C_{5arom}). **MS (CI):** (*m/z*) 396 (35); 395 (13); 277 (100); 269 (47); 268 (79). **HRMS (CI):** Calculated for $C_{17}H_{21}INO_3$ (MH^+): 414.0566. Found: 414.0555.

Synthesis of (*E*)-2-(4-(*tert*-butyldimethylsilyloxy)but-2-en-2-yl)-1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrole (59)



The former allylic alcohol **58** (0.10 g, 0.25 mmol) was dissolved in dry DMF (15 mL) under an inert atmosphere. Imidazole (42.10 mg, 0.62 mmol) and TBDMSCl (76.80 mg, 0.49 mmol) were added to the previous solution and the mixture was stirred for 4 h at room temperature. The crude was quenched with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL), brine (3 x 20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **59** as a colorless oil (0.12 g, 0.23 mmol, 92% yield).

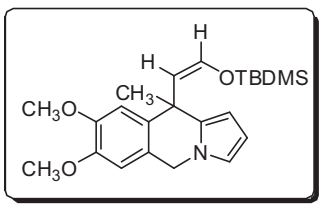
IR (ATR): 2952 cm^{-1} (C-H_{aliph} st), 1665 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.01 (s, 6H, Si($C\underline{H}_3$)$_2$C(CH_3)$_3$), 0.85 (s, 9H, Si(CH_3)$_2$C($C\underline{H}_3$)$_3$), 1.91 (s, 3H, -C($C\underline{H}_3$)=CH-CH_2OSi), 3.62 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.29 (d, *J* = 6.1 Hz, 2H, -C(CH_3)=CH-$C\underline{H}_2OSi$), 5.01 (s, 2H, Ar-$C\underline{H}_2$-N), 5.41 – 5.46 (m, 1H, -C(CH_3)=$C\underline{H}$-CH_2OSi), 5.99 (s, 1H, H_{6arom}), 6.16 (dd, *J* = 3.6, 1.8 Hz, 1H, $H_{3pyrrole}$), 6.18 – 6.20 (m, 1H, $H_{4pyrrole}$), 6.60 (dd, *J* = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.22 (s, 1H,

H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.2 ($Si(\underline{C}H_3)_2C(CH_3)_3$), 17.9 (-$C(\underline{C}H_3)$=CH-$CH_2OSi$), 18.2 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 25.9 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 55.6 ($OCH_3$), 55.7 (Ar-$\underline{C}H_2$-N), 56.1 ($OCH_3$), 60.4 (-$C(CH_3)$=CH-$\underline{C}H_2OSi$), 84.2 ($C_{2arom}$), 108.2, 108.3 ($C_{3pyrrole}$/$C_{4pyrrole}$), 110.5 ($C_{6arom}$), 121.4 ($C_{3arom}$), 122.9 ($C_{5pyrrole}$), 127.4 (-$\underline{C}(CH_3)$=CH-$CH_2OSi$), 129.1 (-$C(CH_3)$=$\underline{C}$H-$CH_2OSi$), 133.6 ($C_{1arom}$), 136.6 ($C_{2pyrrole}$), 148.6 (C_{5arom}), 149.8 (C_{4arom}). **MS (ESI$^+$):** (*m/z*) 529 (21); 528 (MH^+, 100); 397 (12); 396 (88); 270 (10); 269 (58); 241 (26). **HRMS (ESI$^+$):** Calculated for $C_{23}H_{35}INO_3Si$ (MH^+): 528.1431. Found: 528.1442.

Synthesis of (*Z*)-10-(2-(*tert*-butyldimethylsilyloxy)vinyl)-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (60a) and (*E*)-10-(2-(*tert*-butyldimethylsilyloxy)vinyl)-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (60b) (Table 3.5, Entry 1)

Silyloxy allyl derivative **59** (116.10 mg, 0.22 mmol) was dissolved in dry toluene (5 mL) under an inert atmosphere and Et_3N (0.08 mL, 0.55 mmol) and $Pd(PPh_3)_4$ catalyst (25.70 mg, 0.02 mmol) were added to the previous solution and the mixture was heated under reflux for 16 h. After that time, the solvent was evaporated under reduced pressure. The crude was purified through flash chromatography (silica gel, hexane/CH_2Cl_2 4/6) obtaining diastereomers (*Z*)-**60a** (7.10 mg, 0.02 mmol, 8% yield) and (*E*)-**60b** (63.80 mg, 0.16 mmol, 73% yield) as as colorless oils.

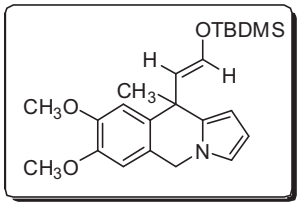
Data for (*Z*)-**60a**:



IR (ATR): 2928 cm^{-1} (C-H_{aliph} st), 1652 cm^{-1} (C=C st), 1612 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.05 (s, 6H, $Si(CH_3)_2(CH_3)_3$), 0.79 (s, 9H, $Si(CH_3)_2(C\underline{H}_3)_3$), 1.74 (s, 3H, $C\underline{H}_3$-C_{10}), 3.87 (s, 3H,

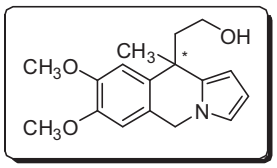
OCH_3), 3.89 (s, 3H, OCH_3), 4.64 (d, *J* = 6.4 Hz, 1H, -C<u>H</u>=CH-OSi), 5.02 (s, 2H, $2H_5$), 6.02 (dd, *J* = 3.4, 1.7 Hz, 1H, H_1), 6.15 – 6.19 (m, 1H, H_2), 6.22 (d, *J* = 6.4 Hz, 1H, -CH=C<u>H</u>-OSi), 6.61 – 6.65 (m, 1H, H_3), 6.66 (s, 1H, H_6), 7.08 (s, 1H, H_9); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.5 (Si(<u>C</u>H_3)$_2$C(CH_3)$_3$), 18.0 (Si(CH_3)$_2$<u>C</u>(CH_3)$_3$), 25.4 (Si(CH_3)$_2$C(<u>C</u>H_3)$_3$), 29.7 (grease), 30.6 (<u>C</u>H_3-C_{10}), 40.1 (C_{10}), 47.2 (C_5), 56.0, 56.1 (2 x OCH_3), 102.7 (C_1), 108.0 (C_2), 108.7 (C_6), 109.9 (C_9), 115.3 (-<u>C</u>H=CH-OSi), 117.3 (C_3), 123.0 (C_{5a}), 135.4 (C_{9a}), 137.4 (C_{10a}), 139.0 (-CH=<u>C</u>H-OSi), 147.1 (C_8), 148.2 (C_7). **MS (ESI$^+$):** (*m/z*) 401 (MH^+ + 1, 27); 400 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{23}H_{34}NO_3Si$ (MH^+): 400.2308. Found: 400.2307.

Data for (*E*)-**60b**:



IR (ATR): 2930 cm^{-1} (C-H_{aliph} st), 1652 cm^{-1} (C=C st), 1611 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.12 (s, 6H, Si(CH_3)$_2$(CH_3)$_3$), 0.92 (s, 9H, Si(CH_3)$_2$(C<u>H</u>$_3$)$_3$), 1.63 (s, 3H, C<u>H</u>$_3$-C_{10}), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.97 (d, *J* = 15.1 Hz, 1H, H_{5A}), 5.02 (d, *J* = 15.1 Hz, 1H, H_{5B}), 5.21 (d, *J* = 12.1 Hz, 1H, -C<u>H</u>=CH-OSi), 6.02 (dd, *J* = 3.5, 1.7 Hz, 1H, H_1), 6.09 (d, *J* = 12.1 Hz, 1H, -CH=C<u>H</u>-OSi), 6.18 (dd, *J* = 3.5, 2.8 Hz, 1H, H_2), 6.68 – 6.71 (m, 2H, H_3, H_6), 6.99 (s, 1H, H_9); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.1 (Si(<u>C</u>H_3)$_2$C(CH_3)$_3$), 18.4 (Si(CH_3)$_2$<u>C</u>(CH_3)$_3$), 25.8 (Si(CH_3)$_2$C(<u>C</u>H_3)$_3$), 27.5 (<u>C</u>H_3-C_{10}), 39.4 (C_{10}), 47.2 (C_5), 56.0, 56.1 (2 x OCH_3), 103.2 (C_1), 107.9 (C_2), 109.1, 109.2 (C_6, C_9), 118.2 (C_3), 119.5 (-<u>C</u>H=CH-OSi), 124.2 (C_{5a}), 134.1 (C_{9a}), 135.6 (C_{10a}), 140.5 (-CH=<u>C</u>H-OSi), 147.4 (C_8), 148.3 (C_7). **MS (ESI$^+$):** (*m/z*) 401 (MH^+ + 1, 28); 400 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{23}H_{34}NO_3Si$ (MH^+): 400.2308. Found: 400.2301.

Synthesis of 2-(7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)etanol (61) (Table 3.5, Entry 12)



Silyloxy allyl derivative **59** (83.80 mg, 0.16 mmol) was dissolved in dry CH_3CN (5 mL) under an inert atmosphere. (*R*)-BINAP (27.70 mg 0.04 mmol), Ag_3PO_4 (135.70 mg, 0.32 mmol) and $Pd_2(dba)_3.CHCl_3$ catalyst (16.40 mg, 0.02 mmol) were subsequently added to the previous solution and the mixture was heated under reflux for 4 h. After that time, the mixture was diluted with EtOAc (20 mL), filtered through celite and washed with a saturated solution of NH_4Cl (1 x 10 mL), H_2O (2 x 10 mL). The aqueous phase was extracted with EtOAc (2 x 10mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/CH_2Cl_2 4/6) obtaining the cyclized silyl enol ethers **60** (41.20 mg, 0.10 mmol, 65% yield) as a 34:66 mixture of diastereomers (**60a**:**60b**). To a solution of this mixture in dry THF (5 mL), a solution 1.00 M of KF (18.00 mg, 0.31 mmol) in dry MeOH (0.30 mL) was added *via* canula under an inert atmosphere. The reaction was stirred for 4 h at room temperature. The curse of the reaction was followed by TLC and when the conversion was completed, extractive workup was performed. The mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 20 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, extracted and evaporated to dryness. The crude was used without further purification in the following reduction reaction due to the lack of stability of the aldehyde intermediate. The so-obtained aldehyde (29.40 mg, 0.10 mmol) was dissolved in dry MeOH (5 mL) and $NaBH_4$ (7.80 mg, 0.21 mmol) was added portionwise at 0 ºC. The ice bath was removed and the mixture was allowed to reach room temperature for 30 min. The crude was quenched with H_2O (10 mL)

and extracted with EtOAc (3 x 10 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, extracted and evaporated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 6/4) obtaining product **61** as a white solid (23.70 mg, 0.08 mmol, 80% yield over two steps).

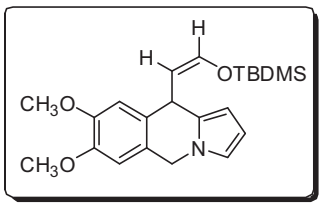
m.p.: 125-126 ºC (Hexane/EtOAc); **IR (ATR):** 3386 cm^{-1} (brs, O-H st), 2934 cm^{-1} (C-H_{aliph} st), 1514 (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.69 (s, 3H, C$\underline{H_3}$-C_{10}), 2.05 – 2.18 (m, 2H, -C$\underline{H_2}$-CH_AH_B-OH), 3.35 (dt, *J* = 11.1, 6.5 Hz, 1H, -CH_2-C$\underline{H_A}H_B$-OH), 3.42 (dt, *J* = 11.1, 6.5 Hz, 1H, -CH_2-$CH_A\underline{H_B}$-OH), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.04 (d, *J* = 15.6 Hz , 1H, H_{5A}), 5.10 (d, *J* = 15.6 Hz , 1H, H_{5B}), 6.07 (dd, *J* = 3.5, 1.7 Hz, 1H, H_1), 6.22 - 6.26 (m, 1H, H_2), 6.65 – 6.72 (m, 2H, H_3, H_6), 6.94 (s, 1H, H_9). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 28.7 (C$\underline{H_3}$-C_{10}), 37.7 (C_{10}), 47.0 (C_5), 47.6 (-C$\underline{H_2}$-CH_AH_B-OH), 55.9, 56.1 (2 x OCH_3), 60.1 (-CH_2-C$\underline{H_A}H_B$-OH), 102.4 (C_1), 108.2 (C_9), 108.6 (C_2), 108.8 (C_3), 118.3 (C_6), 123.3 (C_{5a}), 132.7 (C_{9a}), 135.0 (C_{10a}), 147.6 (C_8), 148.5 (C_7). **MS (ESI$^+$):** (*m/z*) 289 (17), 288 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{17}H_{22}NO_3$ (MH^+): 288.1600. Found: 288.1610. **$[\alpha]_D^{20}$:** -3.2 (c = 0.5 g/L, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 18% [Chiralcel ADH, hexane:*i*-PrOH 90:10, 1 mL/min, t_r (*major*)= 35.5 min (59%), t_r (*minor*)= 58.4 min (41%)].

6.7.2. Intramolecular Mizoroki-Heck reaction of *N*-(*o*-iodobenzyl)pyrroles 44b, 44c, *o*-halopyridines 34a, 34b and *o*-haloquinolines 35a, 35b. Generation of a tertiary stereocenter

Synthesis of (*Z*)-10-(2-(*tert*-butyldimethylsilyloxy)vinyl)-7,8-dimethoxy-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (62a) and (*E*)-10-(2-(*tert*-butyldimethylsilyloxy)vinyl)-7,8-dimethoxy-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (62b) (Table 3.6, Entry 1)

Silyloxy allyl derivative **44b** (92.20 mg, 0.18 mmol) was dissolved in dry toluene (5 mL) under an inert atmosphere and Et_3N (0.06 mL, 0.45 mmol) and $Pd(PPh_3)_4$ catalyst (21.00 mg, 0.02 mmol) were added to the previous solution and the mixture was heated under reflux for 16 h. After that time, the solvent was evaporated under reduced pressure. The crude was subjected to flash chromatography (silica gel, hexane/CH_2Cl_2 3/7) obtaining diastereomers (*Z*)-**62a** (24.80 mg, 0.06 mmol, 36% yield) as a colorless oil and (*E*)-**62b** (30.30 mg, 0.08 mmol, 44% yield) as a yellow oil.

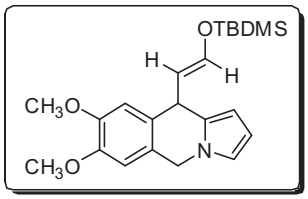
Data for (Z)-**62a**:



IR (ATR): 2953 cm^{-1} (C-H_{aliph} st), 1651 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.22 (s, 6H, $Si(CH_3)_2(CH_3)_3$), 0.98 (s, 9H, $Si(CH_3)_2(CH_3)_3$), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.67 (dd, *J* = 9.5, 5.7 Hz, 1H, -CH=CH-OSi), 5.02 - 5.10 (m, 2H, $2H_5$), 5.23 (d, *J* = 9.5 Hz, 1H, H_{10}), 5.98 - 6.04 (m, 1H, H_1), 6.22 (t, *J* = 3.0 Hz, 1H, H_2), 6.53 (d, *J* = 5.7 Hz, 1H, -CH=CH-OSi), 6.68 – 6.73 (m, 2H, H_3, H_6), 6.94 (s, 1H, H_9). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.3 ($Si(CH_3)_2C(CH_3)_3$), 18.3 ($Si(CH_3)_2C(CH_3)_3$), 25.7 ($Si(CH_3)_2C(CH_3)_3$), 32.6 (C_{10}), 47.2 (C_5), 55.8, 56.0 (2 x OCH_3), 103.8 (C_1), 108.2 (C_2), 108.7 (C_6), 110.8 (C_9), 111.8 (-CH=CH-OSi),

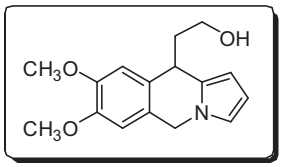
117.9 (C_3), 123.2 (C_{5a}), 129.1 (C_{9a}), 131.3 (C_{10a}), 139.7 (-CH=CH-OSi), 147.4 (C_8), 148.2 (C_7). **MS (CI):** (*m/z*) 386 (MH^+, 100), 385 (40), 370 (19). **HRMS (CI):** Calculated for $C_{22}H_{32}NO_3Si$ (MH^+): 386.2151. Found: 386.2128.

Data for (*E*)-**62b**:



IR (ATR): 2954 cm^{-1} (C-H_{aliph} st), 1656 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.21 (s, 6H, $Si(CH_3)_2(CH_3)_3$), 0.98 (s, 9H, $Si(CH_3)_2(CH_3)_3$), 3.89 (s, 6H, 2 x OCH_3), 4.38 (d, *J* = 9.3 Hz, 1H, H_{10}), 4.97 - 5.07 (m, 2H, $2H_5$), 5.11 (dd, *J* = 11.9, 9.3 Hz, 1H, -CH=CH-OSi), 5.99 - 6.04 (m, 1H, H_1), 6.22 (t, *J* = 3.0 Hz, 1H, H_2), 6.47 (d, *J* = 11.9 Hz, 1H, -CH=CH-OSi), 6.69 – 6.74 (m, 2H, H_3, H_6), 6.91 (s, 1H, H_9). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.2 ($Si(CH_3)_2C(CH_3)_3$), 18.4 ($Si(CH_3)_2C(CH_3)_3$), 25.7 ($Si(CH_3)_2C(CH_3)_3$), 29.7 (grease), 37.1 (C_{10}), 47.2 (C_5), 55.9, 56.0 (2 x OCH_3), 104.4 (C_1), 108.2 (C_2), 108.8 (C_6), 110.7 (C_9), 112.4 (-CH=CH-OSi), 118.3 (C_3), 123.6 (C_{5a}), 129.0 (C_{9a}), 131.3 (C_{10a}), 142.6 (-CH=CH-OSi), 147.6 (C_8), 148.1 (C_7). **MS (CI):** (*m/z*) 386 (MH^+, 100), 385 (38), 228 (34). **HRMS (CI):** Calculated for $C_{22}H_{32}NO_3Si$ (MH^+): 386.2151. Found: 386.2130.

Synthesis of 2-(7,8-dimethoxy-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)etanol (63)

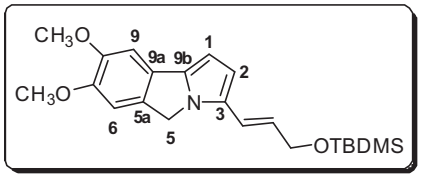


To a solution of a 45:55 mixture of silyl enol ether diastereomers **62** (56.00 mg, 0.15 mmol, **62a**:**62b**) in dry THF (5 mL), a solution 1.0 M of KF (25.30 mg, 0.44 mmol) in dry MeOH (0.44 mL) was added *via* canula under an inert atmosphere. The reaction was stirred for 5 h. The course of the reaction was followed by TLC and when the conversion was completed, extractive workup was performed. The mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 20 mL). Combined organic phases were dried over anhydrous Na_2SO_4, extracted and evaporated to dryness. The crude was used without further purification in the following reduction reaction due to the lack of stability of the aldehyde intermediate. The so-obtained aldehyde (38.80 mg, 0.14 mmol) was dissolved in dry MeOH (5 mL) and $NaBH_4$ (16.20 mg, 0.43 mmol) was added at 0 ºC. The ice bath was removed and the mixture was allowed to reach room temperature for 30 min. The crude was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, extracted and evaporated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining product **63** as a brown oil (28.60 mg, 0.10 mmol, 73% yield over two steps).

IR (ATR): 3515 cm^{-1} (O-H st), 2934 cm^{-1} (C-H st), 1515 ($C{=}C_{arom}$ st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.81 – 1.90 (m, 1H, -C$\underline{H_A}$$H_B$-$CH_2$OH), 1.95 – 2.04 (m, 1H, -$CH_A\underline{H_B}$-CH_2OH), 3.66 – 3.72 (m, 2H, -CH_AH_B-C$\underline{H_2}$OH), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.18 – 4.25 (m, 1H, H_{10}), 4.98 (d, J = 15.3 Hz, 1H, H_{5A}), 5.06 (d, J = 15.3 Hz , 1H, H_{5B}), 6.03 (dd, J = 3.3, 1.5 Hz, 1H, H_1), 6.17 - 6.22 (m, 1H, H_2), 6.70 – 6.74 (m, 2H, H_3, H_6), 6.83 (s, 1H, H_9). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ

(ppm) = 36.1 (C_{10}), 41.0 (-$\underline{C}H_AH_B$-CH_2OH), 47.3 (C_5), 56.0, 56.1 (2 x OCH_3), 60.5 (-CH_AH_B-$\underline{C}H_2OH$), 103.8 (C_1), 108.2 (C_2), 109.2 (C_6), 111.1 (C_9), 118.4 (C_3), 124.1 (C_{5a}), 130.1 (C_{9a}), 130.7 (C_{10a}), 147.5 (C_8), 148.3 (C_7). **MS (ESI$^+$):** (*m/z*) 296 (MNa^+, 33), 274 (MH^+, 100), 273 (M^+, 6), 272 (32). **HRMS (ESI$^+$):** Calculated for $C_{16}H_{20}NO_3$ (MH^+): 274.1443. Found: 274.1451.

Synthesis of (*E*)-3-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-7,8-dimethoxy-5*H*-pyrrolo[2,1-a]isoindole (64) (Entry 3.6, Entry 11)

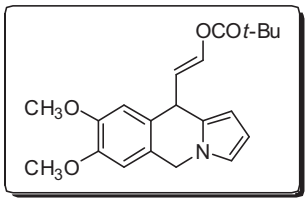


Silyloxy allyl derivative **44b** (94.30 mg, 0.18 mmol) was dissolved in dry DMSO (5 mL) under an inert atmosphere. *n*-Bu_4NOAc (85.60 mg, 0.28 mmol), PPh_3 (4.90 mg, 0.02 mmol) and $Pd(OAc)_2$ catalyst (2.10 mg, 0.009 mmol) were added to the previous solution and the mixture was stirred at 60 ºC for 1.5 h. After that time, the crude was eluted with EtOAc (50 mL) and washed with a saturated solution of NH_4Cl (2 x 20 mL) and H_2O (1 x 10 mL). The aqueous phase was further extracted with EtOAc (3 x 10mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (neutral alumina, hexane/EtOAc 8/2) obtaining the product **64** as yellow oil (58.10 mg, 0.15 mmol, 82% yield).

IR (ATR): 2953 cm^{-1} (C-H_{aliph} st), 1651 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.13 (s, 6H, $Si(CH_3)_2(CH_3)_3$), 0.96 (s, 9H, $Si(CH_3)_2(C\underline{H}_3)_3$), 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.37 (d, *J* = 5.4 Hz, 2H, -CH=CH-$C\underline{H}_2$OSi), 4.86 (s, 2H, $2H_5$), 5.93 (d, *J* = 16.1, 5.4 Hz, 1H, -CH=C$\underline{H}$-CH_2OSi), 6.21 (d, *J* = 3.6 Hz, 1H, H_1), 6.32 (d, *J* = 3.6 Hz, 1H, H_2), 6.54 (d, *J* = 16.1 Hz, 1H, -C$\underline{H}$=CH-CH_2OSi), 6.97 (s, 1H, H_6), 7.05 (s, 1H, H_9). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.1

($Si(\underline{C}H_3)_2C(CH_3)_3$), 18.4 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 26.0 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 50.5 ($C_5$), 56.1, 56.3 (2 x OCH_3), 64.4 (-CH=CH-$\underline{C}H_2$OSi), 97.8 (C_1), 102.3 (C_9), 106.9 (C_6), 112.9 (C_2), 120.3 (-$\underline{C}$H=CH-CH_2OSi), 123.8 (-CH=$\underline{C}$H-CH_2OSi), 126.2 (C_{5a}), 128.1 (C_3), 132.3 (C_{9a}), 139.6 (C_{9b}), 147.3 (C_8), 149.4 (C_7). **MS (CI):** (*m/z*) 386 (MH^+, 47), 385 (44), 256 (98), 255 (100), 253 (26), 241 (39). **HRMS (CI):** Calculated for $C_{22}H_{32}NO_3Si$ (MH^+): 386.2151. Found: 386.2128.

Synthesis of (*E*)-2-(7,8-dimethoxy-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)vinyl pivalate (65a) (Table 3.7, Entry 2)



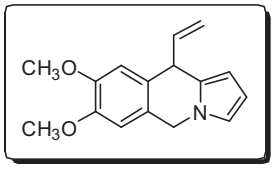
The pivaloyl allyl derivative **44c** (178.20 mg, 0.37 mmol) was dissolved in dry DMF (15 mL) under an inert atmosphere. Et_3N (0.64 mL, 4.61 mmol) and $Pd(PPh_3)_4$ catalyst (21.30 mg, 0.02 mmol) were added to the previous solution and the mixture was heated to 110 ºC for 5 h. The crude was eluted with EtOAc (20 mL) and washed with a saturated solution of NH_4Cl (3 x 10 mL) and then, with water (3 x 10 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dired over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/Et_2O 6/4) obtaining product **65a** as a yellow oil (24.90 mg, 0.07 mmol, 19% yield).[31]

IR (ATR): 2970 cm^{-1} (C_{arom}-H st), 1739 cm^{-1} (C=O st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.24 (s, 9H, $COC(C\underline{H}_3)_3$), 3.89 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.60 (d, *J* = 8.7 Hz, 1H, H_{10}), 4.98-5.13 (m, 2H, $2H_5$), 5.52 (dd, 1H, *J* = 12.3, 8.7 Hz, -C$\underline{H}$=CH-OCO*t*-Bu), 6.03-6.05 (m, 1H, H_1), 6.23 (t, *J* = 3.0 Hz, 1H, H_2), 6.70-6.75 (m, 2H, H_3, H_6), 6.84 (s, 1H, H_9), 7.18 (d, *J* = 12.3 Hz, 1H, -CH=C$\underline{H}$-OCO*t*-Bu).

[31] Product **65a** was unstable to column chromatography in both silica gel and neutral alumina.

^{13}C NMR ($CDCl_3$, 25 ºC): δ (ppm) = 26.96 ($COC(\underline{C}H_3)_3$), 37.31 (C_{10}), 38.71 ($CO\underline{C}(CH_3)_3$), 47.12 (C_5), 56.07, 56.17 (2 x OCH_3), 104.66 (C_1), 108.51 (C_2), 109.07 (C_6), 111.26 (C_9), 116.72 (-$\underline{C}$H=CH-OCO*t*-Bu), 118.59 (C_3), 123.74 (C_{10a}), 127.33 (C_{5a}), 129.48 (C_{9a}), 136.68 (-CH=$\underline{C}$H-OCO*t*-Bu); 148.04, 148.45 (C_8, C_7), 175.73 (CO*t*-Bu). **MS (CI):** (*m/z*) 357 (21), 356 (MH^+, 100), 355 (72), 270 (30), 254 (37). **HRMS (CI):** Calculated for $C_{21}H_{26}NO_4$ (MH^+): 356.1862. Found: 356.1852.

Synthesis of 7,8-dimethoxy-10-vinyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (66) (Table 3.7, Entry 4)



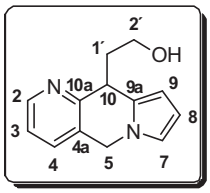
The pivaloyl allyl derivative **44c** (207.80 mg, 0.43 mmol) was dissolved in dry DMF (15 mL) under an inert atmosphere. Et_3N (0.75 mL, 5.37 mmol), *n*-Bu_4NCl (179.30 mg, 0.65 mmol) and $Pd(PPh_3)_4$ catalyst (14.90 mg, 0.01 mmol) were added to the previous solution and the mixture was heated to 110 ºC for 5 h. The reaction was diluted with EtOAc (10 mL) and washed with a saturated solution of NH_4Cl (3 x 10 mL) and water (3 x 10 mL). The organic phase was separated and further extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 8/2) obtaining cyclized **66** as a yellow oil (9.50 mg, 0.04 mmol, 9% yield) and byproduct **65a** (12.10 mg, 0.03 mmol, 8% yield).[32]

IR (ATR): 2924 cm^{-1} (C-H_{aliph} st), 1516 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 3.89 (s, 6H, 2 x OCH_3), 4.57 (d, *J* = 7.6 Hz, 1H, H_{10}), 4.98 - 5.19 (m, 4H, -CH=C$\underline{H}_2$, $2H_5$), 5.87 (ddd, *J* = 17.5, 9.8, 7.6 Hz, 1H, -C$\underline{H}$=CH_2), 6.58 – 6.02 (m,

[32] Product **66** was unstable to column chromatography in both silica gel and neutral alumina.

1H, H_1), 6.23 (t, J = 3.0 Hz, 1H, H_2), 6.73 - 6.74 (m, 1H, H_3, H_6), 6.84 (s, 1H, H_9); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 43.0 (C_{10}), 47.1 (C_5), 55.9, 56.0 (2 x OCH_3), 104.5 (C_1), 108.3 (C_2), 108.9 (C_6), 111.0 (C_9), 115.5 (-CH=$\underline{C}H_2$), 118.4 (C_3), 123.6 (C_{5a}), 127.4 (C_9a), 129.6 (C_{10a}), 139.3 (-$\underline{C}$H=CH_2), 147.7 (C_8), 148.2 (C_7). **MS (CI):** (*m/z*) 284 (17), 257 (18), 256 (MH^+, 100), 255 (67). **HRMS (CI):** Calculated for $C_{16}H_{18}NO_2$ (MH^+): 256.1338. Found: 256.1331.

Synthesis of 2-(5,10-dihydropyrrolo[2,1-*g*][1,7]naphthyridin-10-yl)etanol (68) (Table 3.8, Entry 4)



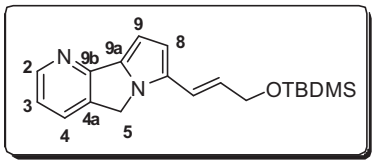
Silyloxy allyl derivative **34a** (100.00 mg, 0.25 mmol) was dissolved in a mix of CH_3CN:H_2O (10:1) (5.5 mL) under an inert atmosphere. Subsequently, Et_3N (0.07 mL, 0.49 mmol), P(*o*-tolyl)$_3$ (16.90 mg, 0.05 mmol) and $Pd(OAc)_2$ catalyst (5.60 mg, 0.02 mmol) were added to the previous solution and the mixture was heated under reflux for 7 h. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the organic phase was separated and washed with the same saturated solution (3 x 10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was used in the following reduction reaction without further purification.[33] $NaBH_4$ (9.50 mg, 0.25 mmol) was added to a solution of the crude in dry MeOH (5 mL) at 0 ºC under an inert atmosphere. After addition, the ice bath was removed to allow the reaction reach room temperature and the mixture was stirred 30 min. The mix was eluted with EtOAc (10 mL) and H_2O (10 mL), the organic phase was separated and the aqueous phase further extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed

[33] Aldehyde **67** was unstable to purification through column chromatography in both silica and neutral alumina, so derivatization to alcohol **68** was performed.

with H_2O (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, pure EtOAc) obtaining product **68** as a brown oil (18.40 mg, 0.09 mmol, 35% yield in 2 steps) and arylation product **69** (20.30 mg, 0.06 mmol, 25% in 2 steps).

IR (ATR): 3361 cm^{-1} (brs, O-H st), 2926 cm^{-1} (C-H_{aliph} st), 1582 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 2.02 – 2.10 (m, 1H, -C$\underline{H}_{1A'}$H$_{1B'}$-$CH_{2A'}H_{2B'}OH$), 2.24 – 2.32 (m, 1H, -$CH_{1A'}\underline{H}_{1B'}$-$CH_{2A'}H_{2B'}OH$), 3.70 (ddd, *J* = 11.5, 7.1, 4.5 Hz, 1H, -$CH_{1A'}H_{1B'}$-C$\underline{H}_{2A'}H_{2B'}OH$), 3.79 (ddd, *J* = 11.5, 7.1, 4.5 Hz, 1H, -$CH_{1A'}H_{1B'}$-$CH_{2A'}\underline{H}_{2B'}OH$), 4.42 (dd, *J* = 8.2, 5.9 Hz, 1H, H_{10}), 5.10 (d, *J* = 15.8 Hz, 1H, H_{5A}), 5.17 (d, *J* = 15.8 Hz, 1H, H_{5B}), 6.08 – 6.11 (m, 1H, H_9), 6.23 – 6.26 (m, 1H, H_8), 6.73 (dd, *J* = 2.5, 1.8 Hz, 1H, H_7), 7.22 (dd, *J* = 7.7, 4.9 Hz, 1H, H_3), 7.59 (d, *J* = 7.7 Hz, 1H, H_4), 8.45 - 8.52 (m, 1H, H_2); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 38.5 (-$\underline{C}H_{1A'}H_{1B'}$-$CH_{2A'}H_{2B'}OH$), 39.7 ($C_{10}$), 46.9 ($C_5$), 60.9 (-$CH_{1A'}H_{1B'}$-$\underline{C}H_{2A'}H_{2B'}OH$), 104.3 ($C_9$) 109.1 ($C_8$), 118.5 ($C_7$), 121.6 ($C_3$), 127.5 ($C_{4a}$), 131.3 ($C_{9a}$), 134.5 ($C_4$), 147.8 ($C_2$), 156.9 ($C_{10a}$). **MS (MALDI):** (*m/z*) 229 (35); 216 ([MH + 1]$^+$, 14); 215 (MH$^+$, 100); 214 (23); 213 (60), 212 (10); 200 (17); 197 (16). **HRMS (MALDI):** Calculated for $C_{13}H_{15}N_2O$ (MH$^+$): 215.1184. Found: 215.1176.

Synthesis of (*E*)-7-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-5*H*-pyrido[2,3-*a*]pyrrolizine (69) (Table 3.8, Entry 5)

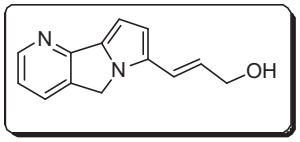


Silyloxy allyl derivative **34b** (90.00 mg, 0.20 mmol) was dissolved in a mix of CH_3CN:H_2O (10:1) (5.5 mL) under an inert atmosphere. Subsequently, Et_3N (0.06 mL, 0.40 mmol), P(*o*-tolyl)$_3$ (13.70 mg, 0.04 mmol) and $Pd(OAc)_2$ catalyst (4.50 mg, 0.02 mmol) were added to the previous solution and the mixture was heated under reflux for 5 h. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the organic phase was separated and washed with the same saturated solution (3 x 10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was used in the following reduction reaction without further purification. $NaBH_4$ (7.70 mg, 0.20 mmol) was added to a solution of the crude in dry MeOH (5 mL) at 0 ºC under an inert atmosphere. After addition, the ice bath was removed to allow the reaction warm up to room temperature and the mixture was stirred 30 min. The mix was eluted with EtOAc (10 mL) and H_2O (10 mL), the organic phase was separated and the aqueous phase further extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with H_2O (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, pure EtOAc) obtaining product **69** as a yellow solid (39.90 mg, 0.12 mmol, 62% yield in 2 steps) and byproduct **68** (8.60 mg, 0.04 mmol, 20% yield in 2 steps).

m.p.: 74-75 ºC (Hexane/EtOAc); **IR (ATR):** 2954 cm^{-1} (C-H_{aliph} st), 1601 cm^{-1} (C=C st), 1568 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.13 (s, 6H, $Si(C\underline{H_3})_2C(CH_3)_3$), 0.95 (s, 9H, $Si(CH_3)_2C(C\underline{H_3})_3$), 4.38 (d, *J* = 5.0 Hz, 2H, -

CH=CH-C$\underline{H_2}$OSi), 4.94 (s, 2H, 2H_5), 6.04 (dt, *J* = 16.1, 5.0 Hz, 1H, -CH=C$\underline{H}$-CH_2OSi), 6.44 (d, *J* = 3.8 Hz, 1H, H_9), 6.56 (d, *J* = 16.1 Hz, 1H, -C$\underline{H}$=CH-CH_2OSi), 6.65 (d, *J* = 3.8 Hz, 1H, H_8), 7.01 (dd, *J* = 7.6, 5.0 Hz, 1H, H_3), 7.64 (d, *J* = 7.6 Hz, 1H, H_4), 8.47 (d, *J* = 5.0 Hz, 1H, H_2); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.1 (Si($\underline{C}H_3$)$_2$C(CH_3)$_3$), 18.4 (Si(CH_3)$_2\underline{C}$(CH_3)$_3$), 26.0 (Si(CH_3)$_2$C($\underline{C}H_3$)$_3$), 48.6 (C_5), 64.0 (-CH=CH-$\underline{C}H_2$OSi), 101.9 (C_8), 113.5 (C_9), 118.8 (C_3), 119.2 (-$\underline{C}$H=CH-CH_2OSi), 126.2 (-CH=$\underline{C}$H-CH_2OSi), 129.7 (C_7), 130.2 (C_4), 133.8 (C_{4a}), 137.3 (C_{9a}), 149.2 (C_2), 152.7 (C_{9b}). **MS (MALDI):** (*m/z*) 328 ([MH+1]$^+$, 17); 327 (MH$^+$, 100); 326 (21); 325 (12); 287 (11). **HRMS (MALDI):** Calculated for $C_{19}H_{27}N_2OSi$ (MH$^+$): 327.1893. Found: 327.1884.

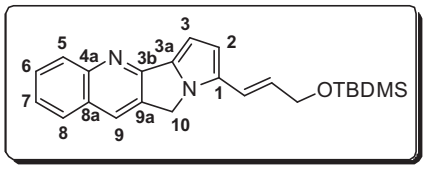
Synthesis of (*E*)-3-(5*H*-pyrido[2,3-*a*]pyrrolizin-7-yl)prop-2-en-1-ol (70) (Table 3.8, Entry 9)



Silyloxy allyl derivative **34b** (90.00 mg, 0.20 mmol) was dissolved in dry DMF (5 mL) under an inert atmosphere. *n*-Bu_4NOAc (92.30 mg, 0.30 mmol), PPh_3 (5.20 mg, 0.02 mmol) and $Pd(OAc)_2$ catalyst (4.50 mg, 0.02 mmol) were added to the previous solution and the mixture was heated at 110 ºC for 1 h. After that time, the crude was eluted with EtOAc (50 mL) and washed with a saturated solution of NH_4Cl (2 x 20 mL) and H_2O (1 x 10 mL). The aqueous phase was further extracted with EtOAc (3 x 10mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 6/4) obtaining product **70** as a yellow solid (16.90 mg, 0.08 mmol, 40% yield) and arylation product **69** (24.50 mg, 0.08 mmol, 38% yield).

m.p.: 148-149 ºC (Hexane/EtOAc); **IR (ATR):** 3238 cm^{-1} (brs, O-H st), 2919 cm^{-1} (C-H_{aliph} st), 1602 cm^{-1} (C=C st), 1572 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 2.46 (brs, 1H, OH), 4.30 (d, *J* = 5.9 Hz, 2H, -CH=CH-C$\underline{H}_2$OH, 4.83 (s, 2H, $2H_5$), 6.03 (dt, *J* = 16.1, 5.9 Hz, 1H, -CH=C$\underline{H}$-CH_2OH), 6.37 (d, *J* = 3.8 Hz, 1H, H_9), 6.43 (d, *J* = 16.1 Hz, 1H, -C$\underline{H}$=CH-CH_2OH), 6.64 (d, *J* = 3.8 Hz, 1H, H_8), 7.03 (dd, *J* = 7.5, 5.0 Hz, 1H, H_3), 7.62 (d, *J* = 7.5 Hz, 1H, H_4), 8.45 (d, *J* = 5.0 Hz, 1H, H_2). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 48.8 (C_5), 63.9 (-CH=CH-CH_2OH), 102.0 (C_8), 114.1 (C_9), 119.0 (C_3), 120.7 (-$\underline{C}$H=CH-CH_2OH), 125.6 (-CH=$\underline{C}$H-CH_2OH), 129.2 (C_7), 130.3 (C_4), 134.1 (C_{4a}), 137.6 (C_{9a}), 149.0 (C_2), 152.4 (C_{9b}). **MS (MALDI):** (*m/z*) 214 ([MH+1]$^+$, 17); 213 (MH$^+$, 100); 212 (20); 195 (12). **HRMS (MALDI):** Calculated para $C_{13}H_{13}N_2O$ (MH$^+$): 213.1028. Found: 213.1020.

Synthesis of (*E*)-1-(3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-10*H*-pyrrolizino[1,2-*b*]quinoline (71) (Table 3.9, Entry 4)

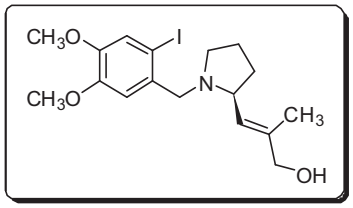


Silyloxy allyl derivative **35b** (75.00 mg, 0.15 mmol) was dissolved in dry DMF (5 mL) under an inert atmosphere. *n*-Bu_4NOAc (69.30 mg, 0.22 mmol), PPh_3 (3.40 mg, 0.01 mmol) and $Pd(OAc)_2$ catalyst (4.00 mg, 0.01 mmol) were added to the previous solution and the mixture was heated at 110 ºC for 1 h. After that time, the crude was eluted with EtOAc (50 mL) and washed with a saturated solution of NH_4Cl (2 x 20 mL) and H_2O (1 x 10 mL). The aqueous phase was further extracted with EtOAc (3 x 10mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude was subjected to flash chromatography (neutral alumina, hexane/EtOAc 7/3) obtaining product **71** as a yellow solid (28.00 mg, 0.07 mmol, 50% yield).

m.p.: 145-146 ºC (Hexane/EtOAc); **IR (ATR):** 2954 cm^{-1} (C-H_{aliph} st), 1636 cm^{-1} (C=C st), 1573 cm^{-1} (C=C_{arom} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.14 (s, 6H, $Si(C\underline{H_3})C(CH_3)_3$), 0.97 (s, 9H, $Si(CH_3)_2C(C\underline{H_3})_3$), 4.39 (d, *J* = 4.5 Hz, 2H, -CH=CH-$C\underline{H_2}$OSi), 5.07 (s, 2H, $2H_{10}$), 6.14 (dt, *J* = 16.0, 4.5 Hz, 1H, -CH=C<u>H</u>-CH_2OSi), 6.50 – 6.54 (m, 1H, H_2), 6.58 (d, *J* = 16.0 Hz, 1H, -C<u>H</u>=CH-CH_2OSi), 6.84 – 6.89 (m, 1H, H_3), 7.40 – 7.48 (m, 1H, H_7), 7.63 – 7.69 (m, 1H, H_6), 7.71 (d, *J* = 8.0 Hz, 1H, H_8), 7.97 (s, 1H, H_9), 8.07 (d, *J* = 8.4 Hz, 1H, H_5); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.1 ($Si(\underline{C}H_3)_2C(CH_3)_3$), 18.5 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 26.0 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 48.0 ($C_{10}$), 63.9 (-CH=CH-<u>C</u>$H_2$OSi), 103.9 ($C_3$), 113.9 ($C_2$), 118.7 (-<u>C</u>H=CH-$CH_2$OSi), 125.3 ($C_7$), 125.7 ($C_{8a}$), 127.3 (-CH=<u>C</u>H-$CH_2$OSi), 127.8 ($C_8$), 128.6 ($C_5$), 129.1 ($C_6$), 129.5 ($C_9$), 130.6 ($C_{3a}$, C_1), 132.6 (C_{9a}), 136.5 (C_{3a}, C_1), 148.5 (C_{4a}), 152.8 (C_{3b}). **MS (ESI$^+$):** (*m/z*) 378 (MH^+ + 1, 27); 377 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{23}H_{29}N_2OSi$ (MH^+): 377.2049. Found: 377.2052.

6.8. Diastereoselective intramolecular Mizoroki-Heck reaction of N-(o-iodobenzyl)pyrrolidinyl allylic alcohol derivatives. Generation of a tertiary stereocenter

Synthesis of (*S,E*)-3-(1-(2-iodo-4,5-dimethoxybenzyl)pyrrolidin-2-yl)-2-methylprop-2-en-1-ol (72)

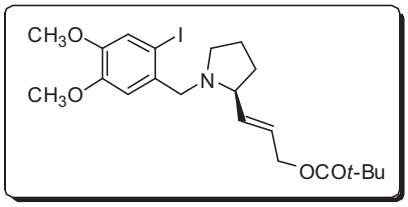


Over a solution of *N*-benzylpyrrolidine **17b** (0.36 g, 0.79 mmol) in dry toluene (20 mL), DIBAL-H (4.40 mL of a solution 1.00 M in toluene, 4.40 mmol) was added at -78 ºC under an inert atmosphere. The reaction was stirred for 30 min at -78 ºC, and after that time the reaction was quenched at low temperature with a H_2O:AcOH (1:1) solution (2 mL). The mixture was allowed to reach room temperature and the crude was washed with water (3 x 20 mL). The aqueous phase was basified with a 10% NaOH solution until pH = 9 and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 3/7) obtaining product **72** was obtained as a solid (0.32 g, 0.77 mmol, 97% yield).

m.p.: 90-92ºC (CH_2Cl_2); **IR (ATR):** 3364 cm^{-1} (brs, O-H st), 2960 cm^{-1} (C_{alk}-H st), 1597 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.48 – 1.60 (m, 1H, H_{3A}), 1.71 (s, 3H, , -CH=C(C$\underline{H_3}$)-CH_2OH)*, 1.62 – 1.87 (m, 3H, 2 x H_4, OH)*, 1.90 – 2.02 (m, 1H, 1H_{3B}), 2.19 (c, *J* = 8.8 Hz, 1H, H_{5A}), 2.99 (td, *J* = 8.8, 2.7 Hz, 1H, H_{5B}), 3.17 – 3.27 (m, 2H, H_2, Ar-$\underline{CH_A}H_B$-N), 3.79 (d, *J* = 13.8 Hz, 1H, Ar-$CH_A\underline{H_B}$-N), 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.99 (s, 1H, -CH=C(CH_3)-C$\underline{H_2}$OH), 5.43 (d, *J* = 8.2 Hz, 1H, -C$\underline{H}$=C(CH_3)-CH_2OH), 7.00 (s, 1H, H_{6arom}), 7.19

(s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.1 (-CH=C(<u>C</u>H_3)-CH_2OH), 22.3 (C_{4p}), 31.2 (C_{3p}), 53.5 (C_{5p}), 56.0 (O<u>C</u>H_3), 56.1 (O<u>C</u>H_3), 62.0 (Ar-<u>C</u>H_AH_B-N), 62.4 (C_{2p}), 68.5 (CH_2OH), 87.7 (C_{2arom}), 113.1 (C_{6arom}), 121.3 (C_{3arom}), 128.1 (-<u>C</u>H=C(CH_3)-CH_2OH), 134.4 (C_{1arom}), 137.2 (-CH=<u>C</u>(CH_3)-CH_2OH), 148.3, 149.2 (C_{4arom}, C_{5arom}). **MS (CI):** (*m/z*) 418 (MH^+, 16); 417 (41); 416 (25); 400 (75); 278 (20); 277 (100). **HRMS (CI):** Calculated for $C_{17}H_{25}INO_3$ (MH^+): 418.0879. Found: 418.0870. **$[\alpha]_D^{20}$:** -47.1 (c = 1.0 g/L, CH_2Cl_2). *Partially overlapped signals

Synthesis of (*S,E*)-3-(1-(2-iodo-4,5-dimethoxybenzyl)pyrrolidin-2-yl)allyl pivalate (73a)

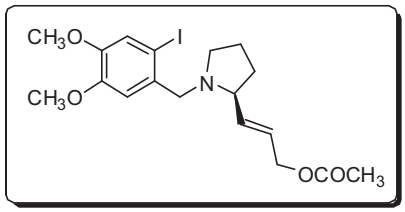


Allylic alcohol **45** (0.60 g, 1.50 mmol) was dissolved in dry CH_2Cl_2 (20 mL) under an inert atmosphere. Pyridine (0.24 mL, 2.98 mmol) and pivaloyl chloride (0.40 mL, 3.22 mmol) were added to the previous solution and the mixture was stirred overnight at room temperature. The reaction was followed by TLC and when it was completed, the reaction was quenched with a saturated solution of $NaHCO_3$ (10 mL) and the organic phase was separated and washed with H_2O (3 x 20 mL) and with a solution of 10% NaOH (3 x 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 6/4) obtaining product **73a** as a brown oil (0.56 g, 1.15 mmol, 77 % yield).

IR (ATR): 2961 cm^{-1} (C-H_{aliph} st), 1727 cm^{-1} (C=O st), 1594 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.18 (s, 9H, COC(C<u>H</u>$_3$)$_3$), 1.55 – 1.66 (m, 1H, H_{3A}), 1.66 – 1.85 (m, 2H, 2 x H_4), 1.88 – 2.03 (m, 1H, 1H_{3B}), 2.21 (c, *J* = 8.7 Hz,

1H, H_{5A}), 2.89 - 3.03 (m, 2H, H_2, H_{5B}), 3.23 (d, *J* = 13.8 Hz, 1H, Ar-$\underline{CH_A}H_B$-N), 3.83 (s, 3H, OCH_3)*, 3.85 (s, 3H, OCH_3)*, 3.77 – 3.89 (m, 1H, Ar-$CH_A\underline{H_B}$-N)*, 4.48 – 4.56 (m, 2H, -CH=CH-C$\underline{H_2}$O), 5.65 – 5.77 (m, 2H, -C$\underline{H}$=C$\underline{H}$-CH_2O), 6.98 (s, 1H, H_{6arom}), 7.19 (s, 1H, H_{3arom}). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 22.3 (C_{4p}), 27.2 (COC($\underline{C}H_3)_3$), 31.6 (C_{3p}), 38.7 (CO$\underline{C}$($CH_3)_3$), 53.5 (C_{5p}), 55.9 (O$\underline{C}H_3$), 56.1 (O$\underline{C}H_3$), 61.7 (Ar-C$\underline{H_2}$-N), 64.2 (-CH=CH-$\underline{C}H_2$O), 67.0 (C_{2p}), 87.7 (C_{2arom}), 113.0 (C_{6arom}), 121.3 (C_{3arom}), 126.1 (-CH=$\underline{C}$H-CH_2O-), 134.3 (C_{1arom}), 136.8 (-$\underline{C}$H=CH-CH_2O-), 148.3 (C_{5arom}), 149.2 (C_{4arom}), 178.1 (CO*t*-Bu). **MS (CI):** (*m/z*) 488 (MH^+, 60); 487 (51); 486 (35); 386 (100); 277 (76). **HRMS (CI):** Calculated for $C_{21}H_{31}INO_4$ (MH^+): 488.1298. Found: 488.1294. **$[\alpha]_D^{20}$**: -46.19 (c = 1.0 g/L, CH_2Cl_2).*Partially overlapped signals

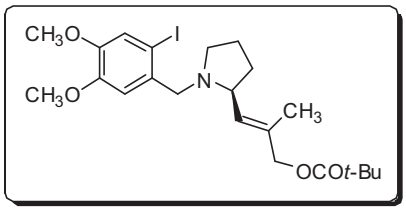
Synthesis of (*S,E*)-3-(1-(2-iodo-4,5-dimethoxybenzyl)pyrrolidin-2-yl)allyl acetate (73b)



Allylic alcohol **45** (0.35 g, 0.87 mmol) was dissolved in dry CH_2Cl_2 (20 mL) under an inert atmosphere. Pyridine (0.14 mL, 1.74 mmol) and acetyl chloride (0.14 mL, 1.92 mmol) were added to the previous solution and the mixture was stirred overnight at room temperature. The reaction was quenched with water (10 mL) and the organic phase was separated and washed with H_2O (3 x 20 mL) and with a solution of 10% NaOH (3 x 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 5/5) obtaining product **73b** as a yellow oil (0.30 g, 0.67 mmol, 78 % yield).

IR (ATR): 3002 cm^{-1} (C-H_{arom} st), 2951 cm^{-1} (C-H_{aliph} st), 1737 cm^{-1} (C=O st), 1596 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.52 – 1.86 (m, 3H, H_{3A}, 2 x H_4), 1.87 – 2.02 (m, 1H, H_{3B}), 2.04 (s, 3H, $COCH_3$), 2.19 (c, *J* = 8.7 Hz, 1H, H_{5A}), 2.87 – 3.04 (m, 2H, H_{5B}, H_2), 3.23 (d, *J* = 13.8 Hz, 1H, Ar-CH_AH_B-N), 3.81 (d, *J* = 13.8 Hz, 1H, Ar-CH_AH_B-N)*, 3.82 (s, 3H, OCH_3)*, 3.85 (s, 3H, OCH_3)*, 4.52 (d, *J* = 4.6 Hz, 2H, -CH=CH-CH_2O), 5.63 – 5.79 (m, 2H, -CH=CH-CH_2O), 6.97 (s, 1H, H_{6arom}), 7.18 (s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 20.9 ($COCH_3$), 22.3 (C_{4p}), 31.6 (C_{3p}), 53.5 (C_{5p}), 55.9 (OCH_3), 56.1 (OCH_3), 61.8 (Ar-CH_AH_B-N), 64.5 (-CH=CH-CH_2O), 66.9 (C_{2p}), 87.6 (C_{2arom}), 113.0 (C_{6arom}), 121.3 (C_{3arom}), 125.6 (-CH=CH-CH_2O), 134.3 (C_{1arom}), 137.6 (-CH=CH-CH_2O), 148.3, 149.2 (C_{4arom}, C_{5arom}), 170.7 ($COCH_3$). **MS (CI):** (*m/z*) 446 (MH^+, 31); 445 (60); 444 (29); 386 (91); 385 (22); 277 (100). **HRMS (CI):** Calculated for $C_{18}H_{25}INO_4$ (MH^+): 446.0828. Found: 446.0817. **$[\alpha]_D^{20}$:** -48.3 (c = 1.1 g/L, CH_2Cl_2). *Partially overlapped signals

Synthesis of (*S,E*)-3-(1-(2-iodo-4,5-dimethoxybenzyl)pyrrolidin-2-yl)-2-methylallyl pivalate (74a)

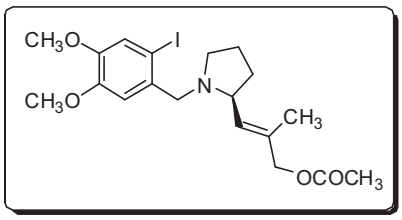


Allylic alcohol **72** (1.04 g, 2.49 mmol) was dissolved in dry CH_2Cl_2 (40 mL) under an inert atmosphere. Pyridine (0.40 mL, 4.97 mmol) and pivaloyl chloride (0.63 mL, 5.69 mmol) were added to the previous solution and the mixture was stirred overnight at room temperature. The reaction was followed by TLC and when it was completed, the reaction was quenched with water (10 mL) and the organic phase was separated and washed with H_2O (3 x 20 mL) and with a solution of 10% NaOH (3 x 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were dried

over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **74a** as a light yellow oil (0.96 g, 1.91 mmol, 77% yield).

IR (ATR): 2957 cm^{-1} (C-H_{aliph} st), 1727 cm^{-1} (C=O st), 1597 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.18 (s, 9H, COC($C\underline{H}_3)_3$), 1.44 – 1.62 (m, 1H, H_{3A}), 1.69 (s, 3H, -CH=C($C\underline{H}_3$)-CH_2O)*, 1.64 – 1.84 (m, 2H, 2 x H_4)*, 1.86 – 2.04 (m, 1H, $1H_{3B}$), 2.22 (c, *J* = 8.7 Hz, 1H, H_{5A}), 2.88 - 3.04 (m, 2H, H_2, H_{5B}), 3.13 – 3.32 (m, 2H, H_2, Ar-$\underline{C}H_AH_B$-N), 3.81 (s, 3H, OCH_3)*, 3.84 (s, 3H, OCH_3)*, 3.74 – 3.88 (m, 1H, Ar-$CH_A\underline{H}_B$-N)*, 4.44 (s, 2H, -CH=C(CH_3)-$C\underline{H}_2O$), 5.47 (d, *J* = 8.7 Hz, Hz, 1H, -$C\underline{H}$=C(CH_3)-CH_2O), 6.98 (s, 1H, H_{6arom}), 7.17 (s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.2 (-CH=C($\underline{C}H_3$)-CH_2O), 22.2 (C_{4p}), 27.1 (COC($\underline{C}H_3)_3$), 30.9 (C_{3P}), 38.9 (CO$\underline{C}$($CH_3)_3$), 53.2 (C_{5p}), 55.9 (O$\underline{C}H_3$), 56.0 (O$\underline{C}H_3$), 61.7 (Ar$C\underline{H}_2$N), 62.2 (C_{2p}), 69.1 (-CH=C(CH_3)-$\underline{C}H_2O$), 87.9 (C_{2arom}), 113.1 (C_{6arom}), 121.3 (C_{3arom}), 130.3 (-$\underline{C}$H=C(CH_3)-), 132.7 (-CH=$\underline{C}$(CH_3)-CH_2O), 134.0 (C_{1arom}), 148.3, 149.2 (C_{4arom}, C_{5arom}), 178.0 ($\underline{C}OC(CH_3)_3$). **MS (CI):** (*m/z*) 502 (MH^+, 36); 501 (57); 401 (24); 400 (100); 277 (54). **HRMS (CI):** Calculated for $C_{22}H_{33}INO_4$ (MH^+): 502.1454. Found: 502.1434. **$[\alpha]_D^{20}$:** -40.43 (c = 1.0 g/L, CH_2Cl_2). *Partially overlapped signals

Synthesis of *(S,E)*-3-(1-(2-iodo-4,5-dimethoxybenzyl)pyrrolidin-2-yl)-2-methylallyl acetate (74b)



Allylic alcohol **72** (0.75 g, 1.80 mmol) was dissolved in dry CH_2Cl_2 (20 mL) under an inert atmosphere. Pyridine (0.30 mL, 3.72 mmol) and acetyl chloride (0.28 mL, 3.85 mmol) were added to the previous solution and

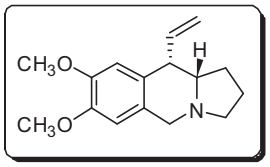
the mixture was stirred overnight at room temperature. The reaction was quenched with a water (10 mL) and the organic phase was separated and washed with H_2O (3 x 20 mL) and with a solution of 10% NaOH (3 x 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 3/7) obtaining product **74b** as a yellow oil (0.61 g, 1.33 mmol, 74% yield).

IR (ATR): 2958 cm^{-1} (C-H_{aliph} st), 1738 cm^{-1} (C=O st), 1595 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.44 – 1.62 (m, 1H, H_{3A}), 1.70 (s, 3H, -CH=C(C$\underline{H_3}$)-CH_2O)*, 1.64 – 1.87 (m, 2H, 2 x H_4)*, 1.88 – 2.03 (m, 1H, 1H_{3B}), 2.05 (s, 3H, COC$\underline{H_3}$), 2.18 (c, *J* = 8.7 Hz, 1H, H_{5A}), 2.91 – 3.03 (m, 1H, H_{5B}), 3.13 - 3.28 (m, 2H, H_2, Ar-C$\underline{H_A}H_B$-N), 3.77 (d, *J* = 13.6 Hz, 1H, Ar-$CH_A\underline{H_B}$-N), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.45 (s, 2H, -CH=C(CH_3)-C$\underline{H_2}$O), 5.47 (d, *J* = 8.6 Hz, 1H, -C$\underline{H}$=C(CH_3)-CH_2O), 6.96 (s, 1H, H_{6arom}), 7.18 (s, 1H, H_{3arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.3 (-CH=C($\underline{C}H_3$)-CH_2O), 20.9 (CO$\underline{C}H_3$), 22.3 (C_{4p}), 31.0 (C_{3p}), 53.4 (C_{5p}), 55.9 (O$\underline{C}H_3$), 56.0 (O$\underline{C}H_3$), 62.0 (Ar-$\underline{C}H_AH_B$-N), 62.2 (C_{2p}), 69.6 (-CH=C(CH_3)-$\underline{C}H_2$O), 87.7 (C_{2arom}), 113.1 (C_{6arom}), 121.3 (C_{3arom}), 131.6 (-$\underline{C}$H=C(CH_3)-CH_2O), 132.0 (-CH=$\underline{C}$(CH_3)-CH_2O), 134.4 (C_{1arom}), 148.3, 149.2 (C_{4arom}, C_{5arom}), 170.8 ($\underline{C}OCH_3$). **MS (CI):** (*m/z*) 460 (MH^+, 24); 459 (57); 401 (22); 400 (100); 277 (63). **HRMS (CI):** Calculated for $C_{19}H_{27}INO_4$ (MH^+): 460.0985. Found: 460.0967. **$[\alpha]_D^{20}$:** -51.7 (c = 1.1 g/L, CH_2Cl_2). *Partially overlapped signals.

Synthesis of (10*S*,10a*S*)-7,8-dimethoxy-10-vinyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (75a) and (10*R*,10a*S*)-7,8-dimethoxy-10-vinyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (75b) (Table 3.10, Entry 5)

Pivaloyl allyl derivative **73a** (209.80 mg, 0.43 mmol) was dissolved in a mixture of CH_3CN:H_2O (10:1) (22 mL) under inert atmosphere. Subsequently, Et_3N (0.13 mL, 0.93 mmol), P(*o*-tolyl)$_3$ (13.50 mg, 0.04 mmol) and $Pd(OAc)_2$ catalyst (9.70 mg, 0.04 mmol) were added to the previous solution and the mixture was heated under reflux for 5 h. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the organic phase was separated and washed with the same saturated solution (3 x 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, gradient of solvents: pure EtOAc → EtOAc/MeOH 9.5/0.5) obtaining product **75** as a 78:22 mixture of diasteroisomers (59.60 mg, 0.23 mmol, 53% yield, **75a**:**75b**).[34]

Data for **75a**:

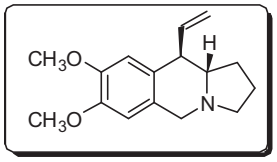


m.p.: 60-61 ºC ($CHCl_3$); **IR (ATR):** 3068 cm^{-1} (C-H_{arom} st), 2956 cm^{-1} (C-H_{aliph} st), 1631 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.71 – 1.86 (m, 4H, 2 x H_1, 2 x H_2), 2.13 – 2.25 (m, 1H, H_{3A}), 2.43 – 2.56 (m, 1H, H_{10A}), 3.19 – 3.27 (m, 1H, 1H_{3B}), 3.29 – 3.36 (m, 2H, H_{5A}, H_{10}), 3.84 (s, 6H, 2 x OCH_3), 4.07 (d, *J* = 14.3 Hz, 1H, H_{5B}), 5.05 (d, $J_{cis}B,A$ = 9.7 Hz, 1H, -CH_A=C($\underline{H_B}$)H_C), 5.10 (d, $J_{trans}C,A$ = 17.2 Hz, 1H, -CH_A=C(H_B)$\underline{H_C}$), 5.93 (dt, *J* = 17.2, 9.7 Hz, 1H, -

[34] Diastereoisomers **75a** and **75b** were separated from each other through flash chromatography (silica gel, hexane/EtOAc 7/3 with a 2% of Et_3N) and each one crystallized from $CHCl_3$.

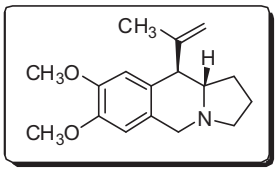
$C\underline{H}_A=C(H_B)H_C$)), 6.54 (s, 1H, H_6), 6.60 (s, 1H, H_9); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 21.8 (C_2), 26.5 (C_1), 47.5 (C_{10}), 55.1 (C_3), 55.8 (2 x OCH_3), 56.1 (C_5), 63.5 (C_{10A}), 109.0 (C_6), 112.4 (C_9), 115.3 (-$CH_A=\underline{C}(H_B)H_C$), 126.7 ($C_{9A}$), 129.3 ($C_{5A}$), 139.8 (-$\underline{C}H_A=C(H_B)H_C$), 147.4 ($C_7$), 147.5 ($C_8$). **MS (CI):** (*m/z*) 260 (MH^+, 100); 259 (51); 258 (28); 191 (29); 190 (72). **HRMS (CI):** Calculated for $C_{16}H_{22}NO_2$ (MH^+): 260.1651. Found: 260.1646. **$[\alpha]_D^{20}$:** +270.9 (c = 1.2 g/L, CH_2Cl_2).

Data for **75a**:



m.p.: 100-102 ºC ($CHCl_3$); **IR (ATR):** 3072 cm^{-1} (C-H_{arom} st), 2951 cm^{-1} (C-H_{aliph} st), 1640 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.54 – 1.66 (m, 1H, H_{1A}), 1.72 – 1.83 (m, 1H, H_{2A}), 1.84 – 1.94 (m, 1H, H_{2B}), 1.96 – 2.06 (m, 1H, $1H_{1B}$), 2.09 – 2.18 (m, 1H, H_{10A}), 2.22 – 2.32 (m, 1H, H_{3A}), 3.23 (t, *J* = 9.5 Hz, 1H, H_{10}), 3.29 (t, *J* = 8.5 Hz, 1H, H_{3B}), 3.39 (d, *J* = 14.1 Hz, 1H, H_{5A}), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.04 (d, *J* = 14.1 Hz, 1H, H_{5B}), 5.18 – 5.32 (m, 2H, -CH=C$\underline{H}_2$), 5.67 (dt, *J* = 17.2, 9.7 Hz, 1H, -C$\underline{H}$=CH_2), 6.55 (s, 1H, H_6), 6.69 (s, 1H, H_9); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 21.3 (C_2), 30.0 (C_1), 51.5 (C_{10}), 55.2 (C_3), 55.7 (C_5), 55.8 (OCH_3), 55.9 (OCH_3), 65.3 (C_{10A}), 109.3 (C_6), 111.2 (C_9), 117.6 (-CH=$\underline{C}H_2$), 126.8 (C_{9A}), 128.6 (C_{5A}), 139.3 (-$\underline{C}$H=CH_2), 147.4 (C_7), 147.5 (C_8). **MS (CI):** (*m/z*) 260 (MH^+, 100); 259 (43); 258 (27); 191 (28); 190 (73). **HRMS (CI):** Calculated for $C_{16}H_{22}NO_2$ (MH^+): 260.1651. Found: 260.1646. **$[\alpha]_D^{20}$:** -22.5 (c = 0.8 g/L, CH_2Cl_2).

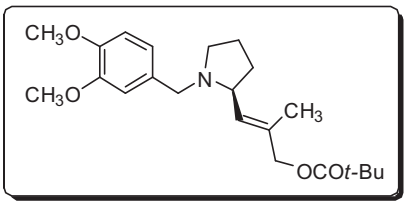
Synthesis of (10*R*,10*aS*)-7,8-dimethoxy-10-(prop-1-en-2-yl)-1,2,3,5,10,10*a*-hexahydropyrrolo[1,2-*b*]isoquinoline (76) (Table 3.2, Entry 8)



Pivaloyl allylic derivative **74a** (148.50 mg, 0.30 mmol) was dissolved in dry DMF (10 mL) under inert atmosphere. Subsequently, Et_3N (0.09 mL, 0.65 mmol), P(*o*-tolyl)$_3$ (40.90 mg, 0.13 mmol) and $Pd_2(dba)_3.CHCl_3$ catalyst (30.70 mg, 0.03 mmol) were added to the previous solution and the mixture was heated at 130 ºC for 4 h. The crude was eluted with EtOAc (20 mL) and washed with a saturated solucion of NH_4Cl (3 x 10 mL) and H_2O (3 x 10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/EtOAc 7/3 + 2% Et_3N) obtaining the product as a yellow oil (31.40 mg, 0.11 mmol, 39% yield) and deiodinated **77a** (9.40 mg, 0.03 mmol, 8% yield) as byproduct.

IR (ATR): 2958 cm^{-1} (C-H_{aliph} st), 1645 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.53 (s, 3H, -C(C$\underline{H_3}$)=CH_2)*, 1.47 – 1.68 (m, 1H, H_{1A})*, 1.70 – 1.83 (m, 1H, H_{2A}), 1.84 – 2.01 (m, 2H, $H_{1B,}$ H_{2B}), 2.24 – 2.30 (m, 2H, H_{3A}, H_{10A}), 3.26 – 3.32 (m, 1H, H_{3B}), 3.32 – 3.42 (m, 2H, H_{10}, H_{5A}), 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.03 (d, *J* = 14.0 Hz, 1H, H_{5B}), 5.00 (d, *J* = 16.1 Hz, 2H, -C(CH_3)=C$\underline{H_2}$), 6.54 (s, 1H, H_6), 6.64 (s, 1H, H_9); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 18.5 (-C($\underline{C}H_3$)=CH_2), 21.3 (C_2), 29.7 (C_1), 54.9 (C_{10}), 55.2 (C_3), 55.8 (2 x OCH_3)*, 55.9 (C_5), 63.6 (C_{10A}), 109.1 (C_6), 110.4 (C_9), 115.3 (-C(CH_3)=$\underline{C}H_2$), 127.3 (C_{9A}), 128.1 (C_{5A}), 145.0 (-$\underline{C}$(CH_3)=CH_2), 147.3 (C_7), 147.7 (C_8). **MS (CI):** (*m/z*) 275 (18); 274 (MH^+, 100); 273 (34); 272 (23); 205 (27); 204 (20). **HRMS (CI):** Calculated for $C_{17}H_{24}NO_2$ (MH^+): 274.1807. Found: 274.1795. **$[\alpha]_D^{20}$:** -8.6 (c = 0.9 g/L, CH_2Cl_2). *Partially overlapped signals.

Synthesis of (*S*,*E*)-3-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-yl)-2-methylallyl pivalate (77a) (Table 3.2, Entry 10)

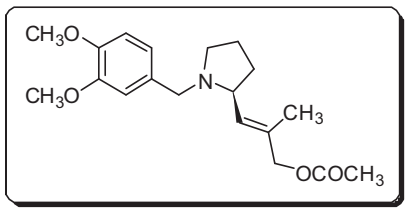


Pivaloyl allylic derivative **74a** (151.70 mg, 0.30 mmol) was dissolved in dry DMF (10 mL) under inert atmosphere. Subsequently, Et_3N (0.09 mL, 0.67 mmol), $P(Cy)_3$ (42.00 mg, 0.15 mmol) and $Pd_2(dba)_3.CHCl_3$ catalyst (31.30 mg, 0.03 mmol) were added to the previous solution and the mixture was heated to 130 ºC for 4 h. The crude was eluted with EtOAc (20 mL) and washed with a saturated solucion of NH_4Cl (3 x 10 mL) and H_2O (3 x 10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, EtOAc) obtaining product **77a** as a yellow oil (27.50 mg, 0.07 mmol, 24% yield) and pyrroloisoquinoline **76** (13.20 mg, 0.05 mmol, 16% yield) as byproduct.

IR (ATR): 2958 cm^{-1} (C-H_{aliph} st), 1730 cm^{-1} (C=O st), 1683 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.15 (s, 9H, $COC(C\underline{H}_3)_3$), 1.42 – 1.57 (m, 1H, H_{3A}), 1.63 (s, 3H, -CH=C($C\underline{H}_3$)-CH_2O)*, 1.57 – 1.81 (m, 2H, 2 x H_4)*, 1.81 – 1.95 (m, 1H, H_{3B}), 2.05 (c, *J* = 8.7 Hz, 1H, H_{5A}), 2.85 – 2.89 (m, 1H, H_{5B}), 2.92 - 3.06 (m, 2H, H_2, Ar-C$\underline{H}_A$$H_B$-N), 3.79 (s, 3H, OCH_3)*, 3.81 (s, 3H, OCH_3)*, 3.78 – 3.83 (m, 1H, Ar-$CH_A\underline{H}_B$-N)*, 4.34 – 4.51 (m, 2H, -CH=C(CH_3)-C$\underline{H}_2$O), 5.41 (d, *J* = 8.6 Hz, 1H, -C$\underline{H}$=C(CH_3)-CH_2O), 6.69 – 6.79 (m, 3H, $H_{2arom,}$ $H_{3arom,}$ H_{6arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.3 (-CH=C($\underline{C}H_3$)-CH_2O), 22.0 (C_{4p}), 27.2 ($COC(\underline{C}H_3)_3$), 31.0 (C_{3p}), 38.8 ($CO\underline{C}(CH_3)_3$), 53.1 (C_{5p}), 55.8 ($O\underline{C}H_3$), 55.9 ($O\underline{C}H_3$), 58.1 (Ar-$\underline{C}H_AH_B$-N), 62.1 (C_{2p}), 69.3 (-CH=C(CH_3)-$\underline{C}H_2O$), 110.8 (C_{3arom}), 112.2, 121.1 (C_{2arom}, C_{6arom}), 130.7 (-$\underline{C}$H=C(CH_3)-CH_2O), 131.9 (C_{1arom}),

132.7 (-CH=C(CH$_3$)-CH$_2$O), 147.9, 148.7 (C$_{4arom}$, C$_{5arom}$), 178.2 (CO*t*-Bu). **MS (CI):** (*m/z*) 274 (MH$^+$, 100); 151 (29). **HRMS (CI):** Calculated for $C_{22}H_{34}NO_4$ (MH$^+$): 376.2488. Found: 376.2495. **[α]$_D^{20}$:** -13.51 (c = 1.0 g/L, CH_2Cl_2). *Partially overlapped signals

Synthesis of (*S,E*)-3-(1-(3,4-dimethoxybenzyl)pyrrolidin-2-yl)-2-methylallyl acetate (77b) (Table 3.12, Entry 12)

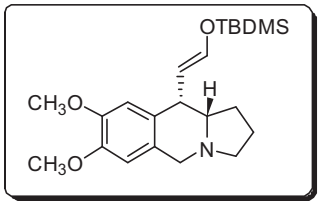


Acetyl allylic derivative **74b** (213.70 mg, 0.47 mmol) was dissolved in dry DMF (20 mL) under inert atmosphere. Subsequently, *n*-BuNMe$_2$ (1.30 mL, 9.26 mmol), P(*o*-tolyl)$_3$ (32.10 mg, 0.10 mmol) and Pd$_2$(dba)$_3$.CHCl$_3$ catalyst (48.20 mg, 0.05 mmol) were added to the previous solution and the mixture was heated to 130 ºC for 16 h. The crude was eluted with EtOAc (20 mL) and washed with a saturated solucion of NH_4Cl (3 x 10 mL) and H_2O (3 x 10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/EtOAc 7/3 + 2% Et_3N) obtaining product **77b** as a yellow oil (57.90 mg, 0.17 mmol, 37% yield) and pyrroloisoquinoline **76** (14.00 mg, 0.05 mmol, 11% yield) as byproduct.

IR (ATR): 2959 cm^{-1} (C-H$_{aliph}$ st), 1736 cm^{-1} (C=O st), 1590 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.49 – 1.61 (m, 1H, H$_{3A}$), 1.70 (s, 3H, -CH=C(C<u>H$_3$</u>)-CH$_2$O)*, 1.64 – 1.84 (m, 2H, 2 x H$_4$)*, 1.89 – 2.00 (m, 1H, 1H$_{3B}$), 2.08 (s, 3H, COC<u>H$_3$</u>)*, 2.05 – 2.17 (m, 1H, H$_{5A}$)*, 2.93 – 2.97 (m, 1H, H$_{5B}$), 2.99 - 3.15 (m, 2H, H$_2$, Ar-C<u>H$_A$</u>H$_B$-N), 3.86 (s, 3H, OCH$_3$)*, 3.88 (s, 3H, OCH$_3$)*, 3.76 – 3.93 (m, 1H, Ar-CH$_A$<u>H$_B$</u>-N)*, 4.48 (s, 2H, -CH=C(CH$_3$)-C<u>H$_2$</u>O), 5.48 (d, *J* = 8.5

Hz, 1H, -C<u>H</u>=C(CH_3)-CH_2O), 6.70 – 6.88 (m, 3H, $H_{2arom,}$ $H_{3arom,}$ H_{6arom}); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 14.4 (-CH=C(<u>C</u>H_3)-CH_2O), 21.0 (CO<u>C</u>H_3), 22.1 (C_{4p}), 31.0 (C_{3p}), 53.2 (C_{5p}), 55.8 (OCH_3), 55.9 (OCH_3), 58.2 (Ar<u>C</u>H_AH_B-N), 62.2 (C_{2p}), 69.6 (-CH=C(CH_3)-<u>C</u>H_2O), 110.8 (C_{3arom}), 112.2, 121.0 (C_{2arom}, C_{6arom}), 131.4 (-<u>C</u>H=C(CH_3)-CH_2O), 132.0 (-CH=<u>C</u>(CH_3)-CH_2O), 132.2 (C_{1arom}), 147.9, 148.7 (C_{4arom}, C_{5arom}), 170.9 (<u>C</u>OCH_3). **MS (CI):** (*m/z*) 334 (MH^+, 2); 333 (M^+, 6); 274 (86); 153 (100); 152 (28); 151 (46). **HRMS (CI):** Calculated for $C_{19}H_{28}NO_4$ (MH^+): 334.2018. Found: 334.2026. **$[\alpha]_D^{20}$:** -22.75 (c = 0.9 g/L, CH_2Cl_2). *Partially overlapped signals

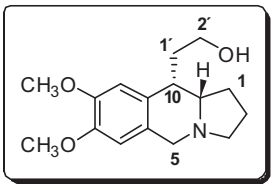
Synthesis of (10*S*,10a*S*)-10-((*E*)-2-(*tert*-butyldimethylsilyloxy)vinyl)-7,8-dimethoxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (78)



Silyloxy allyl derivative **46** (85.20 mg, 0.16 mmol) was dissolved in a mix of CH_3CN:H_2O (10:1) (5 mL) under inert atmosphere. Subsequently, Et_3N (0.05 mL, 0.36 mmol), P(*o*-tolyl)$_3$ (5.17 mg, 0.02 mmol) and $Pd(OAc)_2$ catalyst (3.80 mg, 0.02 mmol) were added to the previous solution and the mixture was heated under reflux for 5 h. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) and the organic phase was separated and washed with the same saturated solution (3 x 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, EtOAc/MeOH 9/1) obtaining the mixture of diastereomers **78** as a yellow oil (49.80 mg, 0.13 mmol, 78% yield, (**81**:6:3:10). The major diastereomer representing a **(10*S*,10a*S*)**-diastereoisomer of (*E*)-configuration was characterized.

IR (ATR): 2855 cm^{-1} (C-H_{aliph} st), 1658 cm^{-1} (C=C st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 0.12 (s, 6H, Si($C\underline{H}_3)_2C(CH_3)_3$), 0.90 (s, 9H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 1.73 – 1.81 (m, 4H, 2 x H_1, 2 x H_2), 2.15 – 2.28 (m, 1H, H_{3A}), 2.49 (m, 1H, H_{10A}), 3.14 – 3.23 (m, 2H, H_{10}, H_{3B}), 3.30 (d, *J* = 14.2 Hz, 1H, H_{5A}), 3.82 (s, 6H, 2 x OCH_3), 4.02 (d, *J* = 14.2 Hz, 1H, H_{5B}), 5.12 (dd, *J* = 12.0, 10.3 Hz, 1H, -C$\underline{H}$=CH-OSi), 6.34 (d, *J* = 12.0 Hz, 1H, -CH=C$\underline{H}$-OSi), 6.51 (s, 1H, H_6), 6.59 (s, 1H, H_9); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = -5.2 (Si($\underline{C}H_3)_2C(CH_3)_3$), 18.3 ($Si(CH_3)_2\underline{C}(CH_3)_3$), 21.9 ($C_1$/$C_2$), 25.7 ($Si(CH_3)_2C(\underline{C}H_3)_3$), 26.7 ($C_1$/$C_2$), 41.5 ($C_{10}$), 55.2 ($C_3$), 55.7, 55.8 (2 x OCH_3), 55.9 (C_5), 63.9 (C_{10A}), 109.0 (C_6), 112.4 (C_9), 113.6 (-$\underline{C}$H=CH-OSi), 126.4 (C_{9A}), 130.6 (C_{5A}), 140.6 (-CH=$\underline{C}$H-OSi), 147.3, 147.4 (C_7, C_8). **MS (MALDI):** (*m/z*) 391 (28); 390 (MH^+, 100); 389 (20); 388 (78); 386 (15). **HRMS (MALDI):** Calculated for $C_{22}H_{36}NO_3Si$ (MH^+): 390.2464. Found: 390.2455. **$[\alpha]_D^{20}$:** +69.4 (c = 1.0 g/L, CH_2Cl_2).

Synthesis of 2-((10*S*,10*aS*)-7,8-dimethoxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-10-yl)ethanol (79)



To a solution of former mixture of silyl enol ether diastereomers **78** (50.00 mg, 0.13 mmol) in dry THF (5 mL), a solution 1.0 M of KF (37.30 mg, 0.64 mmol) in dry MeOH (0.64 mL) was added *via* canula under an inert atmosphere. The reaction was stirred for 24 h and additional KF (37.30 mg, 0.64 mmol) was added to the mixture. The course of the reaction was followed by TLC and when the conversion was completed, extractive workup was performed. The mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 20 mL). Combined organic phases were dried over anhydrous Na_2SO_4, extracted and evaporated to dryness. The crude was used without further purification in the following reduction reaction due to the lack of stability of the aldehyde

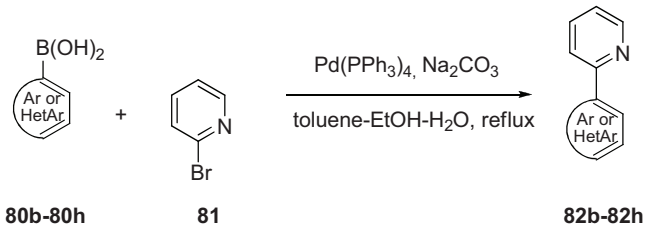
intermediate. The so-obtained aldehyde (35.30 mg, 0.13 mmol) was dissolved in dry MeOH (5 mL) and $NaBH_4$ (9.70 mg, 0.26 mmol) was added portionwise at 0 ºC. The ice bath was removed and the mixture was allowed to reach room temperature for 30 min. The crude was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, extracted and evaporated to dryness. The crude was subjected to flash chromatography (silica gel, EtOAc/MeOH 9/1) obtaining product **79** as a brown oil (21.70 mg, 0.08 mmol, 61% yield over two steps).

IR (ATR): 3328 cm^{-1} (brs, O-H st), 2930 cm^{-1} (C-H_{aliph} st); **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 1.69 – 1.79 (m, 1H, -C$\underline{H}_{1A}$-H_{1B}-CH_{2A}-H_{2B}-OH), 1.79 – 2.10 (m, 4H, 2 x H_1, 2 x H_2), 2.17 – 2.26 (m, 1H, -CH_{1A}-$\underline{H}_{1B}$-CH_{2A}-H_{2B}-OH), 2.27 – 2.36 (m, 1H, H_{3A}), 2.55 – 2.64 (m, 1H, H_{10A}), 2.89 – 2.95 (m, 1H, -CH_{1A}-H_{1B}-C$\underline{H}_{2A}$-H_{2B}-OH), 3.18 - 3.21 (m, 1H, H_{10}), 3.25 – 3.32 (m, 2H, H_{3B}, -CH_{1A}-H_{1B}-CH_{2A}-$\underline{H}_{2B}$-OH), 3.37 (d, *J* = 14.3 Hz, 1H, H_{5A}), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.11 (d, *J* = 14.3 Hz, 1H, H_{5B}), 6.53 (s, 1H, H_6), 6.58 (s, 1H, H_9); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 21.3 (C_2), 25.5 (C_1), 33.0 (-$\underline{C}H_{1A}$-H_{1B}-CH_{2A}-H_{2B}-OH), 39.7 (C_{10}), 54.6 (C_3), 55.5 (C_5), 55.8, 55.9 (2 x OCH_3), 56.9 (-CH_{1A}-H_{1B}-$\underline{C}H_{2A}$-H_{2B}-OH), 62.6 (C_{10A}), 108.9 (C_6), 111.4 (C_9), 126.7 (C_{5A}), 128.7 (C_{9A}), 147.6, 147.9 (C_7, C_8). **MS (ESI$^+$):** (*m/z*) 279 (14); 278 (MH^+, 100). **HRMS (ESI$^+$):** Calculated for $C_{16}H_{24}NO_3$ (MH^+): 278.1756. Found: 278.1760. **$[\alpha]_D^{20}$:** +66.9 (c = 1.0 g/L, CH_2Cl_2).

6.9. Rh(III)-catalyzed ortho-directed nucleophilic addition to polar unsaturated bonds via C-H bond activation

6.9.1. Synthesis of 2-(hetero)arylpyridines 82b-82h and [1,2,3]-benzoxathiazine-2,2-dioxides 85a-85f

General procedure for synthesis of functionalized aryl- and heteroarylpyridines 82b-82h[35]

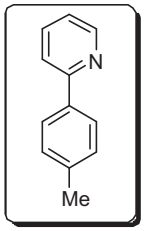


80b-80h **81** **82b-82h**

Boronic acid **80b-80h** (1.3 mmol), Na_2CO_3 (7.5 mmol) and $Pd(PPh_3)_4$ catalyst (3 mol%) were diluted in a mixture of toluene (12 mL), EtOH (3 mL) and H_2O (12 mL) under an inert atmosphere. Subsequently, bromopyridine **81** (1.0 mmol) was added and the system was heated to reflux for 16 h. When the reaction was completed, a saturated solution of NH_4Cl was added to the reaction and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. The crude was purified through flash chromatography (silica gel, hexane/EtOAc) obtaining product **82b-82h**.

[35] Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 1251.

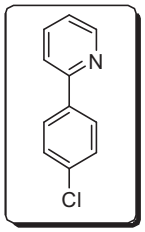
Synthesis of 2-(4-methylphenyl)pyridine (82b)[36]



Prepared from boronic acid **80b** (0.34 g, 2.50 mmol), 2-bromopyridine (**81**) (0.30 g, 1.90 mmol), Na_2CO_3 (1.49 g, 14.06 mmol) as base and $Pd(PPh_3)_4$ as catalyst (0.06 g, 0.06 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **82b** as a white solid (0.27 g, 1.61 mmol, 85% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 2.50 (s, 3H), 7.20 – 7.33 (m, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.75 – 7.90 (m, 2H), 7.92 – 8.00 (m, 2H), 8.71 (m, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 22.3, 121.2, 122.4, 127.9, 130.5, 137.3, 139.5, 139.6, 150.4, 158.0.

Synthesis of 2-(4-chlorophenyl)pyridine (82c)[37]

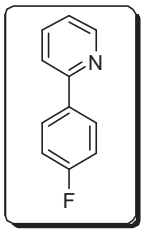


Prepared from boronic acid **80c** (0.39 g, 2.49 mmol), 2-bromopyridine (**81**) (0.30 g, 1.90 mmol), Na_2CO_3 (1.49 g, 14.06 mmol) as base and $Pd(PPh_3)_4$ as catalyst (0.06 g, 0.06 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **82c** as a white solid (0.28 g, 1.49 mmol, 79% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 7.03 – 7.16 (m, 3H), 7.52 – 7.66 (m, 2H), 7.87 – 8.00 (m, 2H), 8.62 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 115.2, 115.5, 119.9, 121.8, 128.4, 135.2, 136.5, 149.4, 156.0.

[36] Ackermann, L.; Kapdi, A. R.; Fenner, S.; Kornhaaß, C.; Schulzke, C. *Chem. Eur. J.* **2011**, *17*, 2965.
[37] Kitamura, K.; Sako, S.; Tsutsui, A.; Monguchi, Y.; Maegawa, T.; Kitade, Y.; Sajikia, Y. *Adv. Synth. Catal.* **2010**, *352*, 718.

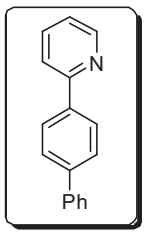
Synthesis of 2-(4-fluorophenyl)pyridine (82d)[38]



Prepared from boronic acid **80d** (0.35 g, 2.50 mmol), 2-bromopyridine (**81**) (0.30 g, 1.90 mmol), Na_2CO_3 (1.49 g, 14.06 mmol) as base and $Pd(PPh_3)_4$ as catalyst (0.06 g, 0.06 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9.5/0.5) obtaining product **82d** as a white solid (0.31 g, 1.76 mmol, 93% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 7.09 – 7.15 (m, 1H), 7.32 – 7.38 (m, 2H), 7.52 – 7.63 (m, 2H), 7.85 – 7.89 (m, 2H), 8.61 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 119.9, 122.0, 127.9, 128.6, 134.7, 136.5, 137.4, 149.4, 155.7.

Synthesis of 2-(biphenyl-4-yl)pyridine (82e)[39]



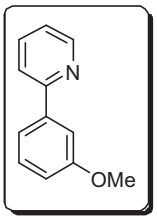
Prepared from boronic acid **80e** (0.81 g, 4.09 mmol), 2-bromopyridine (**81**) (0.50 g, 3.16 mmol), Na_2CO_3 (2.52 g, 23.73 mmol) as base and $Pd(PPh_3)_4$ as catalyst (0.11 g, 0.11 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9.5/0.5) obtaining product **82e** as a white solid (0.45 g, 1.96 mmol, 62% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 7.22 – 7.26 (m, 1H), 7.34 – 7.40 (m, 1H), 7.44 – 7.50 (m, 2H), 7.64 – 7.67 (m, 1H), 7.67 – 7.68 (m, 1H), 7.70 – 7.72 (m, 1H), 7.72 – 7.74 (m, 1H), 7.76 – 7.79 (m, 2H), 8.06 – 8.09 (m, 1H), 8.09 – 8.11 (m,

[38] Ackermann, L.; Potukuchi, H. K.; Kapdi, A. R.; Schulzke, C. *Chem. Eur. J.* **2010**, *16*, 3300.
[39] Kumar, M. R.; Park, K.; Lee, S. *Adv. Synth. Catal.* **2010**, *352*, 3255.

1H), 8.69 – 8.74 (m, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 120.4, 122.1, 127.1, 127.3, 127.4, 127.5, 128.8, 136.7, 138.3, 140.6, 141.7, 149.7, 157.0.

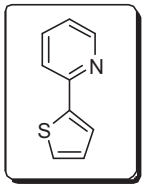
Synthesis of 2-(3-methoxyphenyl)pyridine (82f)[36]



Prepared from boronic acid **80f** (0.38 g, 2.50 mmol), 2-bromopyridine (**81**) (0.30 g, 1.90 mmol), Na_2CO_3 (1.49 g, 14.06 mmol) as base and $Pd(PPh_3)_4$ as catalyst (0.06 g, 0.06 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **82f** as a yellow oil (0.32 g, 1.74 mmol, 92% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 3.80 (s, 3H), 6.93 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 7.09 – 7.15 (m, 1H), 7.30 – 7.36 (m, 1H), 7.53 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H), 7.57– 7.66 (m, 3H), 8.65 (ddd, *J* = 4.8, 1.7, 1.1 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 55.2, 112.1, 115.0, 119.2, 120.6, 122.2, 129.7, 136.7, 140.8, 149.5, 157.0, 160.1.

Synthesis of 2-(thiophen-2-yl)pyridine (82g)[40]

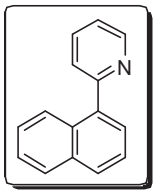


Prepared from boronic acid **80g** (0.32 g, 2.50 mmol), 2-bromopyridine (**81**) (0.30 g, 1.90 mmol), Na_2CO_3 (1.49 g, 14.05 mmol) as base and $Pd(PPh_3)_4$ as catalyst (0.06 g, 0.06 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **82g** as a white solid (55.00 mg, 0.34 mmol, 18% yield).

[40] Fleckenstein, C. A.; Plenio, H. *J. Org. Chem.* **2008**, *73*, 3236.

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 7.01 – 7.08 (m, 2H), 7.31 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.50 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.56 – 7.59 (m, 2H), 8.47 – 8.51 (m, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 118.7, 121.8, 124.4, 127.5, 128.0, 136.5, 144.7, 149.4, 152.5.

Synthesis of 2-(naphthalen-1-yl)pyridine (82h)[41]

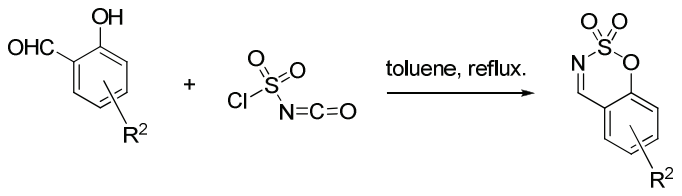


Prepared from boronic acid **80h** (0.71 g, 4.13 mmol), 2-bromopyridine (**81**) (0.50 g, 3.16 mmol), Na_2CO_3 (2.48 g, 23.40 mmol) as base and $Pd(PPh_3)_4$ as catalyst (0.11 g, 0.11 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **82h** as a yellow oil (0.65 g, 3.16 mmol, 100%).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 7.20 (m, *J* = 7.4, 4.9, 0.8 Hz, 1H), 7.43 – 7.53 (m, 3H), 7.53 – 7.59 (m, 1H), 7.61 – 7.71 (m, 2H), 7.86 – 7.96 (m, 2H), 8.19 (dd, *J* = 8.4, 4.1 Hz, 1H), 8.79 – 8.83 (m, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 121.5, 124.5, 124.9, 125.2, 125.4, 126.0, 127.1, 127.9, 128.4, 130.7, 133.5, 135.9, 138.0, 149.0, 158.7.

[41] Li, X.; Zou, D.; Leng, F.; Sun, C.; Li, J.; Wu, Y.; Wu, Y. *Chem. Commun*. **2013**, *49*, 312.

General procedure for cyclic imines 85a-85f[42]

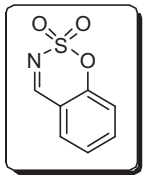


83a-83f **84** **85a-85f**

In a 100 mL two necked round bottom flask provided with a condenser, 2-hydroxybenzaldehyde **83a-83f** (1 mmol) was dissolved in dry toluene (30 mL) under an inert atmosphere. The solution was heated under reflux and chlorosulfonyl isocyanate (**84**) (1 mmol) was added to the former solution *via* siringe. The mixture was heated under reflux for 16 h. The crude was evaporated to dryness, diluted with EtOAc (100 mL) and washed with H_2O (3 x 50 mL), a saturated solution of $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc) obtaining product **85a-85f.**

[42] Kamal, A.; Sattur, P. B. *Synthesis*, **1981**, 272.

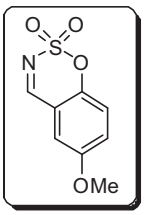
Synthesis of [1,2,3]-benzoxathiazine-2,2-dioxide (85a)[43]



Prepared from 2-hydroxybenzaldehyde **83a** (1.50 g, 12.28 mmol) and chlorosulfonyl isocyanate (**84**) (1.07 mL, 12.28 mmol) in toluene (20 mL). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **85a** as a white solid (1.23 g, 6.72 mmol, 55% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ = 7.22 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.68 – 7.75 (m, 2H), 8.68 (s, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ = 115.0, 118.1, 126.2, 131.0, 137.7, 153.7, 168.1.

Synthesis of 6-methoxy-[1,2,3]-benzoxathiazine-2,2-dioxide (85b)[43]

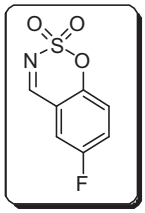


Prepared from 2-hydroxybenzaldehyde **83b** (1.00 g, 6.57 mmol) and chlorosulfonyl isocyanate (**84**) (0.57 mL, 6.57 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **85b** as a yellow solid (0.87 g, 4.08 mmol, 62% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 3.93 (s, 3H), 7.21 (d, *J* = 2.8 Hz, 1H), 7.25 (d, *J* = 9.1 Hz, 1H), 7.34 (dd, *J* = 9.1, 2.9 Hz, 1H), 8.71 (s, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 56.0, 113.1, 115.5, 119.4, 124.6, 147.7, 157.0, 168.0.

[43] Luo, Y.; Carnell, A. J.; Lam, H. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 6762.

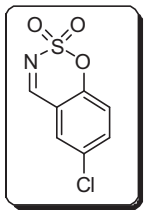
Synthesis of 6-fluoro-[1,2,3]-benzoxathiazine-2,2-dioxide (85c) [44]



Prepared from 2-hydroxybenzaldehyde **83e** (0.30 g, 2.14 mmol) and chlorosulfonyl isocyanate (**84**) (0.19 mL, 2.14 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 8/2) obtaining product **85c** as a white solid (0.24 g, 1.18 mmol, 55% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 7.32 (dd, *J* = 9.1, 4.0 Hz, 1H), 7.39 (dd, *J* = 6.8, 3.0 Hz, 1H), 7.48 (ddd, *J* = 9.1, 7.7, 3.0 Hz, 1H), 8.65 (s, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 115.8 (d, *J* = 7.5 Hz), 116.3 (d, *J* = 24.4 Hz), 120.6 (d, *J* = 7.6 Hz), 124.8 (d, *J* = 24.3 Hz), 150.2 (d, *J* = 2.8 Hz), 159.2 (d, *J* = 249.1 Hz), 166.5 (d, *J* = 1.8 Hz).

Synthesis of 6-chloro-[1,2,3]-benzoxathiazine-2,2-dioxide (85d)[43]

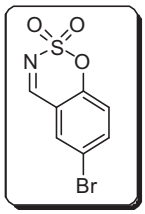


Prepared from 2-hydroxybenzaldehyde **83d** (1.00 g, 6.39 mmol) and chlorosulfonyl isocyanate (**84**) (0.56 mL, 6.39 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **85d** as a yellow solid (0.97 g, 4.46 mmol, 70% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 7.29 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 2.6 Hz, 1H), 7.73 (dd, *J* = 8.7, 2.6 Hz, 1H), 8.70 (s, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 116.5, 120.7, 130.4, 131.9, 137.2, 152.8, 167.0.

[44] Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 8309.

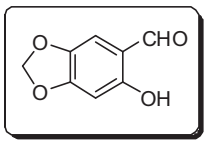
Synthesis of 6-bromo-[1,2,3]-benzoxathiazine-2,2-dioxide (85e)[44]



Prepared from 2-hydroxybenzaldehyde **83c** (1.00 g, 4.97 mmol) and chlorosulfonyl isocyanate (**84**) (0.43 mL, 4.97 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **85e** as a yellow solid (0.79 g, 3.01 mmol, 61% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 7.21 (d, *J* = 8.7 Hz, 1H), 7.85 – 7.90 (m, 2H), 8.72 (s, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 117.1, 119.0, 120.8, 133.4, 140.6, 153.7, 167.0.

Synthesis of 2-hydroxy-4,5-methylenedioxybenzaldehyde (83f)[45]

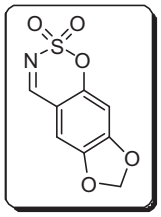


Sesamol (2.70 g, 19.55 mmol) and triethylorthoformate (25 mL, 150.30 mmol) were dissolved in Et_2O (80 mL) at room temperature. $AlCl_3$ (3.91 g, 29.32 mmol) was added to the previous solution portionwise at 0 ºC and the reaction was stirred for 10 min. The crude was quenched with a solution of HCl 5% (20 mL), H_2O was added (20 mL) and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The crude was subjected to column chromatography (silica gel, eluent: hexane/EtOAc 8/2) obtaining product **83f** as a yellow solid (1.42 g, 8.55 mmol, 44% yield).

[45] Maes, D.; Vervisch, S.; Debenedetti, S.; Davio, C.; Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 2505.

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 6.00 (s, 2H), 6.45 (s, 1H), 6.84 (s, 1H), 9.60 (s, 1H), 11.77 (s, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 98.28, 102.12, 109.29, 113.58, 141.27, 155.11, 161.45, 193.64.

Synthesis of 1,3,5-trioxa-6-thia-7-azacyclopenta[*b*]naphthalene 6,6-dioxide (85f)[43]

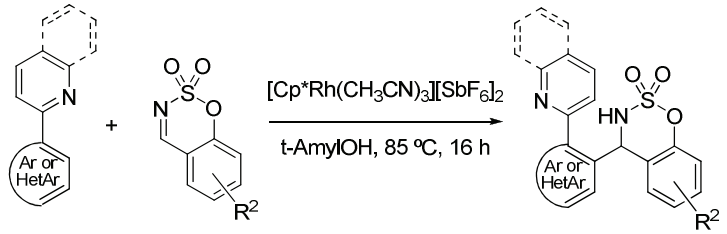


Prepared from 2-hydroxybenzaldehyde **83f** (0.50 g, 3.01 mmol) and chlorosulfonyl isocyanate (**84**) (0.26 mL, 3.01 mmol). After extractive work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 8/2) obtaining product **85f** as a yellow solid (0.46 g, 2.02 mmol, 67% yield).

^{1}H NMR ($CDCl_3$, 25 ºC): δ (ppm) = 6.17 (s, 2H), 6.75 (s, 1H), 6.97 (s, 1H), 8.43 (s, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 100.0, 103.5, 107.3, 109.4, 145.8, 152.7, 155.4, 166.5.

6.9.2. Rh(III)-catalyzed *ortho*-directed nucleophilic addition of 2-(hetero)arylpyridines 82a-82j to cyclic imines 85a-85f. Synthesis of dihydrobenzo[*e*][1,2,3]oxathiazine-2,2-dioxide derivatives 86a-86n

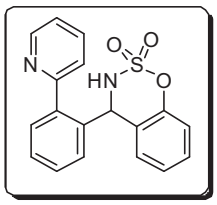
General procedure for the *ortho*-directed Rh(III)-catalyzed C-H additions of 2-(hetero)arylpyridines 82a-82j to cyclic imines 85a-85f[46]



A Schlenk tube (20 mL) was charged with differently functionalized aryl- or heteroarylpyridine **82a-82j** (1 mmol), cyclic imine **85a-85f (**1.1 mmol) and $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol%). Then, *t*-amyl alcohol (3.0 mL), was added *via* a syringe, and the reaction mixture was stirred at 85 ºC for 16 h. When the reaction was completed, the mixture was cooled to room temperature and diluted with CH_2Cl_2 (10 mL). The resulting mixture was filtered through a celite pad, which was then eluted with CH_2Cl_2 (3 x 20 mL). The combined filtrate was concentrated to dryness and the crude was purified through flash chromatography (silica gel, hexane/EtOAc) obtaining the product **86a-86n**.

[46] Parthasarathy, K.; Azcargorta, A. R.; Cheng, Y.; Bolm, C. *Org. Lett*. **2014**, *16*, 2538.

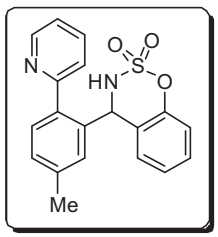
Synthesis of 4-[2-(pyridin-2-yl)phenyl]-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (86a)[46]



Prepared from phenylpyridine **82a** (80.00 mg, 0.52 mmol), cyclic imine **85a** (104.00 mg, 0.57 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (21.70 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **86b** as a white solid (153.00 mg, 0.45 mmol, 88% yield).

m.p.: 165-167 ºC; **IR (ATR)** (cm^{-1}): 3017, 2919, 1590, 1453; **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.92 (s, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.73 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.7 Hz, 1H), 7.00 – 7.14 (m, 2H), 7.38 – 7.47 (m, 1H), 7.47 – 7.61 (m, 3H), 7.62 – 7.71 (m, 1H), 8.47 (d, *J* = 4.7 Hz, 1H), 9.65 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 63.4, 117.9, 122.0, 122.4, 124.1, 124.3, 126.9, 128.9, 129.6, 129.9, 132.0, 133.1, 136.6, 137.7, 140.7, 147.3, 151.1, 159.3. **MS (EI):** *m/z* = 338 (M^+, 9), 274 (84), 260 (1), 182 (10), 181 (77), 155 (100), 78 (12). **HRMS (EI):** Calculated for $C_{18}H_{14}N_2O_3S$ ($[M+Na]^+$): 361.0623. Found: 361.0624.

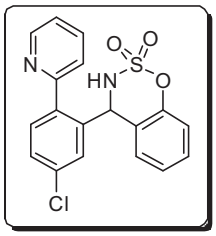
Synthesis of 4-[5-methyl-2-(pyridin-2-yl)phenyl]-3,4-dihydrobenzo[*e*][1,2,3] oxathiazine 2,2-dioxide (86b)[46]



Prepared from arylpyridine **82b** (50.00 mg, 0.30 mmol), cyclic imine **85a** (59.50 mg, 0.33 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (12.50 mg, 0.02 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **86b** as a white solid (98.70 mg, 0.28 mmol, 95% yield).

m.p.: 203-205 ºC; **IR (ATR)** (cm^{-1}): 3017, 2919, 1590, 1453; **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 2.49 (s, 3H), 5.87 (s, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.72 (t, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 6.99 – 7.10 (m, 2H), 7.31 – 7.38 (m, 2H), 7.45 – 7.53 (m, 2H), 8.44 (d, *J* = 4.3 Hz, 1H), 9.77 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 21.0, 29.6 (grease), 63.4, 117.7, 121.9, 122.0, 123.9, 124.0, 126.8, 128.7, 130.2, 131.9, 133.8, 136.2, 137.4, 137.7, 139.5, 147.1, 150.9, 159.2. **MS (EI):** (*m/z*) 352 (M^+, 2), 288 (100), 274 (1), 210 (45), 182 (5), 181 (29), 79 (1), 78 (5). **HRMS (EI):** Calculated for $C_{19}H_{16}N_2O_3S$ (MH^+): 353.0960. Found: 353.0946.

Synthesis of 4-[5-chloro-2-(pyridin-2-yl)phenyl]-3,4-dihydrobenzo[*e*][1,2,3] oxathiazine 2,2-dioxide (86c)[46]

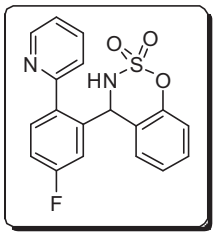


Prepared from arylpyridine **82c** (94.00 mg, 0.50 mmol), cyclic imine **85a** (99.90 mg, 0.55 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (20.90 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **86c** as a white solid (146.00 mg, 0.39 mmol, 79% yield).

m.p.: 195-197 ºC; **IR (ATR)** (cm^{-1}): 3064, 2924, 1726, 1591, 1454; **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.87 (s, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 6.75 (t, *J* = 7.4 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 7.03 – 7.12 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.48 – 7.58 (m, 2H), 7.69 (s, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 9.57 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 62.8, 117.9, 121.2, 122.5, 123.9, 124.2, 126.5, 129.0, 129.7, 132.9, 133.1, 135.3, 137.6, 138.1, 139.0, 147.4, 150.9, 158.0. **MS (EI):** (*m/z*) 372 (M^+, 2), 230 (76), 201 (46), 189 (45), 91 (2), 78

(8). **HRMS (EI):** Calculated for $C_{18}H_{13}ClN_2O_3S$ (MH^+): 373.0414. Found: 373.0390.

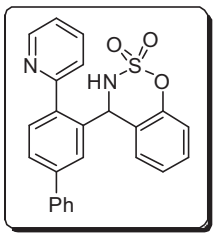
Synthesis of 4-[5-fluoro-2-(pyridin-2-yl)phenyl]-3,4-dihydrobenzo[*e*][1,2,3] oxathiazine 2,2-dioxide (86d)[46]



Prepared from arylpyridine **82d** (85.00 mg, 0.49 mmol), cyclic imine **85a** (98.90 mg, 0.54 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (20.40 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **86d** as a white solid (146.00 mg, 0.41 mmol, 83% yield).

m.p.: 218-220 ºC; **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.87 (s, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 7.02 – 7.14 (m, 2H), 7.20 – 7.29 (m, 1H), 7.36 – 7.47 (m, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 8.47 (d, *J* = 4.3 Hz, 1H), 9.64 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 63.0, 116.5, 116.7, 118.1, 121.4, 122.5, 124.1, 124.4, 126.8, 129.2, 133.8 (d, $J_{C\text{-}F}$ = 8.2 Hz), 136.9 (d, $J_{C\text{-}F}$ = 3.5 Hz), 137.8, 138.9 (d, $J_{C\text{-}F}$ = 7.3 Hz), 147.5, 151.1, 158.3, 161.6, 164.1. **MS (EI):** (*m/z)* 357 (M^+, 2), 292 (50), 277 (1), 173 (100), 172 (41), 79 (2), 78 (13). **HRMS (EI):** Calculated for $C_{18}H_{13}FN_2O_3S$ (MH^+): 357.0709. Found: 357.0704.

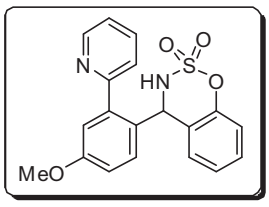
Synthesis of 4-[5-fluoro-2-(pyridin-2-yl)phenyl]-3,4-dihydrobenzo[*e*][1,2,3] oxathiazine 2,2-dioxide (86e)[46]



Prepared from arylpyridine **82e** (49.50 mg, 0.21 mmol), cyclic imine **85a** (43.10 mg, 0.24 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (9.00 mg, 0.01 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **86e** as a pale yellow solid (63.70 mg, 0.15 mmol, 72% yield).

m.p.: 202-204 ºC; **IR (ATR)** (cm^{-1}): 3063, 1591, 1498; **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 6.01 (s, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 6.74 (t, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 7.07 (dd, *J* = 7.0, 5.3 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.48 – 7.58 (m, 4H), 7.71 (d, *J* = 7.4 Hz, 2H), 7.78 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.91 (s, 1H), 8.49 (d, *J* = 4.4 Hz, 1H), 9.82 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 63.5, 117.8, 121.8, 122.2, 123.9, 124.1, 126.7, 127.1, 128.1, 128.1, 128.8, 129.0, 131.8, 132.4, 136.9, 137.5, 139.2, 139.2, 139.3, 142.3, 147.3, 151.0, 158.8. **MS (EI):** (*m/z*) 350 (87), 272 (81), 231 (100), 230 (48), 79 (2), 78 (8). **HRMS (EI):** Calculated for $C_{24}H_{18}N_2O_3S$ (MH^+): 415.1116, Found: 415.1107.

Synthesis of 4-[4-methoxy-2-(pyridin-2-yl)phenyl]-3,4-dihydrobenzo[*e*][1,2,3] oxathiazine 2,2-dioxide (86f)[46]

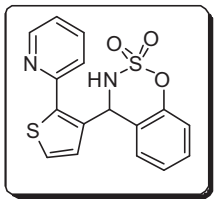


Prepared from arylpyridine **82f** (93.00 mg, 0.50 mmol), cyclic imine **85a** (101.20 mg, 0.55 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (20.90 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1)

obtaining product **86f** as a white solid (150.00 mg, 0.41 mmol, 81% yield).

m.p.: 213-215 ºC; **IR (ATR)** (cm^{-1}): 2969, 2941, 1567, 1478. **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 3.88 (s, 3H), 5.87 (s, 1H), 6.54 (d, *J* = 7.8Hz, 1H), 6.63 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.73 (td, *J* = 7.6, 1.1 Hz, 1H), 6.90 – 6.98 (m, 2H), 7.00 – 7.10 (m, 3H), 7.46 – 7.53 (m, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 8.41 – 8.52 (m, 1H), 9.49 (brs, 1H). **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 55.5, 62.7, 113.5, 117.7, 118.1, 122.2, 122.3, 123.9, 124.1, 126.9, 128.6, 128.7, 134.3, 137.5, 141.9, 147.2, 150.8, 159.0, 160.2. **MS (EI):** (*m/z*) 304 (75), 290 (1), 226 (100), 184 (64), 79 (2), 78 (10). **HRMS (EI):** Calculated for $C_{19}H_{16}N_2O_4S$ (MH^+): 369.0909. Found: 369.0892.

Synthesis of 4-[2-(Pyridin-2-yl)thiophen-3-yl]-3,4-dihydrobenzo[*e*][1,2,3] oxathiazine 2,2-dioxide (86g)[46]

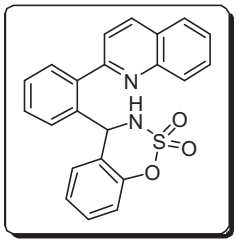


Prepared from thienylpyridine **82g** (80.00 mg, 0.50 mmol), cyclic imine **85a** (100.00 mg, 0.55 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (20.90 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **86g** as a white solid (166.00 mg, 0.48 mmol, 97% yield).

m.p.: 171-173 ºC; **IR (ATR)** (cm^{-1}): 3102, 2926, 2692, 1723, 1586, 1473. **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 6.16 (s, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.77 - 6.83 (m, 1H), 6.85 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.03 -7.12 (m, 2H), 7.28 (d, *J* = 5.1 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 5.1Hz, 1H), 7.61 (td, *J* = 7.8, 1.7 Hz, 1H), 8.40 (d, *J* = 4.7 Hz, 1H), 9.70 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 56.8, 117.8, 122.2, 122.4, 122.9, 124.3, 126.2, 126.6, 129.0, 132.6, 136.9, 137.8, 140.34, 147.9, 151.4, 151.5. **MS (EI):** (*m/z*) 344 (M^+, 4), 280 (63), 265 (2), 161

(100), 160 (22), 82 (1), 79 (4), 78 (30). **HRMS (EI):** Calculated for $C_{16}H_{12}N_2O_3S_2$ (MH^+): 345.0368. Found: 345.0344.

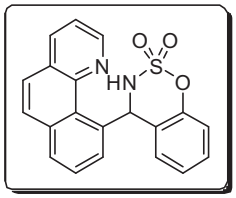
Synthesis of 4-[2-(quinolin-2-yl)phenyl]-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (86i)[46]



Prepared from phenylquinoline **82i** (102.00 mg, 0.50 mmol), cyclic imine **85a** (100.10 mg, 0.55 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (20.80 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 7/3) obtaining product **86i** as a pale yellow solid (108.00 mg, 0.28 mmol, 56% yield).

m.p.: 224-226 ºC; **IR (ATR)** (cm^{-1}): 2923, 2854, 1727, 1598, 1453. **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.98 (s, 1H), 6.28 (d, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 7.5 Hz, 1H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.77 (t, *J* = 7.3Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.56 – 7.64 (m, 3H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.81 (m, 2H), 7.97 (d, *J* = 8.4Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 10.25 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 29.6 (grease), 63.4, 117.4, 121.5, 121.8, 123.9, 126.2, 126.3, 127.1, 127.2, 128.5, 128.6, 129.6, 129.7, 130.7, 132.3, 133.2, 136.9, 137.6, 140.8, 145.6, 151.0, 159.0. **MS (EI):** (*m/*z) 388 (M^+, 6), 324 (100), 231 (28), 205 (38), 204 (36), 128 (5). **HRMS (EI):** Calculated for $C_{22}H_{16}N_2O_3S$ (MH^+): 389.0960. Found: 389.0935.

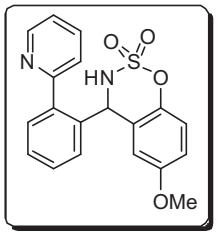
Synthesis of 4-(benzo[*h*]quinolin-10-yl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (86j)[46]



Prepared from benzo[*h*]quinolone (**82j**) (90.00 mg, 0.50 mmol), cyclic imine **85a** (101.20 mg, 0.55 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (20.90 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 95/5) obtaining product **86j** as a white solid (49.00 mg, 0.14 mmol, 27% yield).

m.p.: 236-238 ºC; **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 6.16 (d, *J* = 7.8 Hz, 1H), 6.39 (d, *J* = 10.6 Hz, 1H), 6.53 – 6.60 (m, 1H), 6.99 – 7.07 (m, 2H), 7.42 (dd, *J* = 8.0, 4.4 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.79 – 7.85 (m, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.98 (d, *J* = 6.5 Hz, 1H), 8.11 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.71 (dd, *J* = 4.4, 1.8 Hz, 1H), 9.90 (d, *J* = 10.7 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 29.6 (grease), 66.1, 117.7, 121.8, 124.1, 124.2, 125.2, 126.1, 127.9, 128.3, 128.4, 129.4, 129.5, 131.2, 133.8, 134.6, 136.6, 137.0, 144.7, 146.4, 151.6. **MS (EI):** (*m/z*) 362 (M+, 12), 298 (100), 185 (1), 179 (48), 178 (21). **HRMS (EI):** Calculated for $C_{20}H_{14}N_2O_3S$ (MH^+): 363.0803. Found 363.0789.

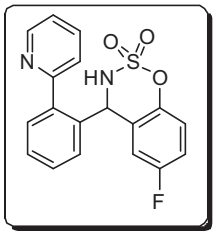
Synthesis of 6-methoxy-4-(2-(pyridin-2-yl)phenyl)-3,4-dihydrobenzo[*e*][1,2,3] oxathiazine 2,2-dioxide (86k)[46]



Prepared from phenylpyridine **82a** (78.00 mg, 0.50 mmol), cyclic imine **85b** (117.90 mg, 0.55 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (20.90 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **86k** as a pale yellow solid (128.00 mg, 0.35 mmol, 69% yield).

m.p.: 186-188 ºC; **IR (ATR)** (cm^{-1}): 2970, 1738, 1591, 1486; **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 3.51 (s, 3H), 5.87 (s, 1H), 6.01 (s, 1H), 6.50 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.59 (d, *J* = 9.0 Hz, 1H), 7.04 – 7.15 (m, 2H), 7.41 – 7.47 (m, 1H), 7.49 – 7.58 (m, 3H), 7.61– 7.68 (m, 1H), 8.47 (d, *J* = 4.4 Hz, 1H), 9.53 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 55.6, 63.4, 111.9, 114.0, 118.6, 122.2, 122.6, 123.9, 129.4, 129.7, 131.8, 133.0, 136.2, 137.6, 140.6, 144.9, 147.3, 155.7, 159.1. **MS (EI):** (*m/z*) 368 (M^+, 2), 290 (4), 214 (4), 154 (54), 153 (100), 79 (2), 78 (9). **HRMS (EI):** Calculated for $C_{19}H_{16}N_2O_4S$ (MH^+): 369.0909. Found: 369.0896.

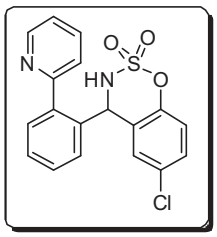
Synthesis of 6-fluoro-4-[2-(pyridin-2-yl)phenyl]-3,4-dihydrobenzo[*e*][1,2,3] oxathiazine 2,2-dioxide (86l)[46]



Prepared from phenylpyridine **82a** (77.00 mg, 0.50 mmol), cyclic imine **85c** (119.80 mg, 0.55 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (20.90 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **86l** as a pale yellow solid (130.00 mg, 0.36 mmol, 74% yield).

m.p.: 135-137 ºC; **IR (ATR)** (cm^{-1}): 3018, 1739, 1592, 1482; **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.87 (s, 1H), 6.23 (d, *J* = 8.4 Hz, 1H), 6.58 – 6.71 (m, 2H), 7.05 – 7.20 (m, 2H), 7.44 – 7.51 (m, 1H), 7.51 – 7.62 (m, 3H), 7.66 (d, *J* = 7.6 Hz, 1H), 8.47 (d, *J* = 4.3 Hz, 1H), 9.68 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 63.2, 113.1, 113.2, 115.6, 115.7, 119.2 (d, $J_{C\text{-}F}$ = 8.2 Hz), 122.4, 123.9, 130.0, 132.0, 133.0, 135.6, 137.8, 140.4, 146.8, 147.2, 157.6, 158.9, 159.2. **MS (EI):** (*m/z*) 292 (5), 291 (6), 166 (22), 154 (84), 152 (100), 79 (1), 78 (9). **HRMS (EI):** Calculated for $C_{18}H_{13}FN_2O_3S$ (MH^+): 357.0709. Found: 357.0693.

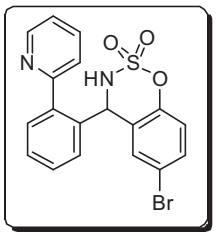
Synthesis of 6-chloro-4-[2-(pyridin-2-yl)phenyl]-3,4-dihydrobenzo[*e*][1,2,3] oxathiazine 2,2-dioxide (86m)[46]



Prepared from phenylpyridine **82a** (77.00 mg, 0.50 mmol), cyclic imine **85d** (119.00 mg, 0.55 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (20.90 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 9/1) obtaining product **86m** as a pale yellow solid (150.00 mg, 0.40 mmol, 81% yield).

m.p.: 169-171 ºC; **IR (ATR)** (cm^{-1}): 2917, 2849, 1739, 1589, 1565; **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.88 (s,1H), 6.49 (d, *J* = 1.1 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 6.92 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.05 – 7.12 (m, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.49 (m, 1H), 7.55 – 7.63 (m, 3H), 7.65 - 7.68 (m, 1H), 8.46 (d, *J* = 4.9 Hz, 1H), 9.66 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 29.7 (grease), 63.1, 119.2, 122.4, 123.5, 124.0, 126.5, 128.7, 129.2, 129.6, 130.1, 132.0, 133.1, 135.5, 137.8, 140.4, 147.3, 149.5, 159.0. **MS (EI):** (*m/z*) 305 (1), 216 (1), 178 (27), 154 (94), 152 (100), 79 (1), 78 (7). **HRMS (EI):** Calculated for $C_{18}H_{13}ClN_2O_3S$ (MH^+): 373.0414. Found: 373.0408.

Synthesis of 6-bromo-4-[2-(pyridin-2-yl)phenyl]-3,4-dihydrobenzo[*e*][1,2,3] oxathiazine 2,2-dioxide (86n)[46]



Prepared from phenylpyridine **82a** (77.00 mg, 0.50 mmol), cyclic imine **85e** (143.00 mg, 0.55 mmol) and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ as catalyst (20.90 mg, 0.03 mmol). After work-up, the crude was purified through flash chromatography (silica gel, hexane/EtOAc 85/15) obtaining product **86n** as a pale yellow solid (171.00 mg, 0.41 mmol, 83% yield).

m.p.: 182-183 ºC; **^{1}H NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 5.89 (s,1H), 6.55 (d, *J* = 8.7 Hz, 1H), 6.63 (s, 1H), 7.08 (m, 2H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.53 (m, 1H), 7.51 – 7.62 (m, 3H), 7.67 (d, *J* = 8.2 Hz, 1H), 8.46 (d, *J* = 4.4 Hz, 1H), 9.62 (brs, 1H); **^{13}C NMR** ($CDCl_3$, 25 ºC): δ (ppm) = 63.1, 116.8, 119.7, 122.6, 124.1, 124.2, 129.6, 129.8, 130.2, 131.8, 132.2, 133.3, 135.6, 137.9, 140.5, 147.5, 150.2, 159.2. **MS (EI):** (*m/z*) 415 (M^+, 2), 352 (100), 337 (4), 273 (41), 179 (39), 155 (5), 78 (1). **HRMS (EI):** Calculated for $C_{18}H_{13}BrN_2O_3S$ (MH^+): 416.9909, Found 416.9915.

6.10. X-Ray Analysis of pyrroloisoquinolines 75a, 75b

The structure of both pyrroloisoquinolines was unambiguously confirmed by single-crystal X-ray analysis. Both pyrroloisoquinolines **75a**, **75b** were recrystallized from chloroform. CCDC 1062658 contains supplementary crystallographic data for the structure **75a**, while CCDC 1062659 contains data for the structure **75b**.

Intensity data were collected on an Agilent Technologies Super-Nova diffractometer, which was equipped with monochromated Cu kα radiation (λ = 1.54184 Å) and Atlas CCD detector. Measurement was carried out at 100.00(10) K with the help of an Oxford Cryostream 700 PLUS temperature device. Data frames were processed (united cell determination, analytical absorption correction with face indexing, intensity data integration and correction for Lorentz and polarization effects) using the Crysalis software package.[47] The structure was solved using Olex2[48] and refined by full-matrix least-squares with SHELXL-97.[49] Final geometrical calculations were carried out with Mercury[50] and PLATON[51] as integrated in WinGX.[52]

[47] CrysAlisPro, Agilent Technologies,Version 1.171.37.31 (release 14-01-2014 CrysAlis171.NET) (compiled Jan 14 2014,18:38:05).
[48] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *J. Appl. Cryst*. **2009**, *42*, 339.
[49] Sheldrick, G. M. Acta Cryst. **2008**, *64*, 112.
[50] Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J.; Wood, P. A. *J. Appl. Cryst.* **2008**, *41*, 466.
[51] a) A. L. Spek (2010) PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands. B) Spek, A.L. *J. Appl. Cryst.* **2003**, *36*, 7.
[52] Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837.

6.10.1. Crystal data for (10*S*,10a*S*)-7,8-dimethoxy-10-vinyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (75a)

Empirical formula: $C_{16}H_{21}NO_2$, M_r = 259.34, T = 100 (1) K, λ (CuKα) = 1.54184 Å, monoclinic, $P2_1$ (No.4), a = 8.8603 (2) Å, b = 8.9830 (2) Å, c = 8.9649 (2) Å, α = γ = 90°, β = 95.796 (2)º, V = 709.89 (3) $Å^3$, Z = 2, D_x = 1.213 $g.cm^{-3}$, μ (CuKα) = 0.630 mm^{-1}, F (000) = 280. Crystal size 0.13 × 0.23 × 0.31 mm, collected reflections = 7725, independent reflections ($R_{int.}$) = 2678 (0.023), observed reflections [I > 2σ(I)] = 2627, R(F) (I>2σI, all data) = 0.0277, 0.0285; $R_w(F^2)$ (I>2σI, all data) = 0.0708, 0.0714.

An ORTEP plot with thermal ellipsoids at 50% probability of compound **75a** with atomic nomenclature used is shown in *Figure 6.1*. For full details, refer to CCDC 1062658.

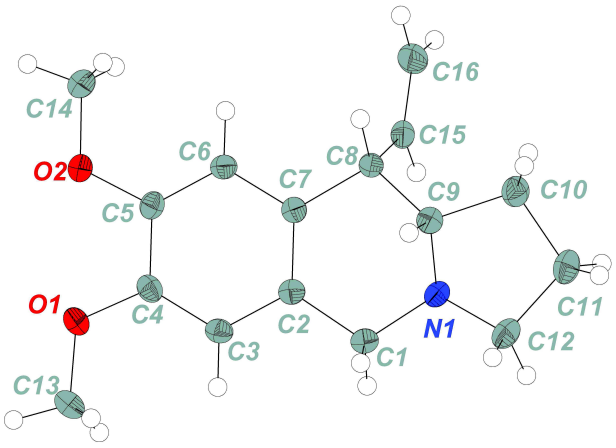


*Figure 6.1. ORTEP plot of compound **75a** with thermal ellipsoids at the 50% probability level with the atomic nomenclature used.*

6.10.2. Crystal data for (10*R*,10a*S*)-7,8-dimethoxy-10-vinyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (75b)

Empirical formula: $C_{16}H_{21}NO_2$, M_r = 259.34, T= 100 (10) K, λ (CuKα) = 1.54184 Å, monoclinic, $P2_1$ (No.4), a = 10.37540 (10) Å, b = 6.38350 (10) Å, c = 10.85090 (10) Å, α = γ = 90°, β = 100.6290 (10)º, V = 706.334 (14) $Å^3$, Z = 2, D_x = 1.219 $g.cm^{-3}$, μ (CuKα) = 0.632 mm^{-1}, F (000) = 280. Crystal size 0.08 × 0.22 × 0.41 mm, collected reflections = 13115, independent reflections ($R_{int.}$) = 2663 (0.025), observed reflections [I > 2σ(I)] = 2630, R(F) (I>2σ_I, all data) = 0.0263, 0.0268; $R_w(F^2)$ (I>2σ_I, all data) = 0.0692, 0.0697.

An ORTEP plot with thermal ellipsoids at 50% probability of compound **75b** with atomic nomenclature used is shown in *Figure 6.2*. For full details, refer to CCDC 1062659.

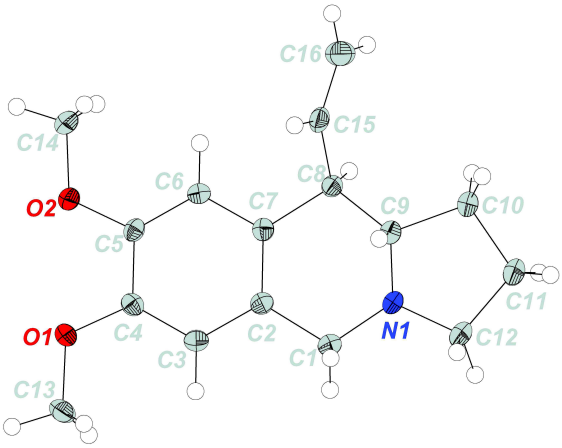
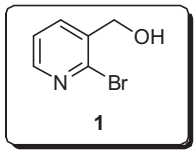


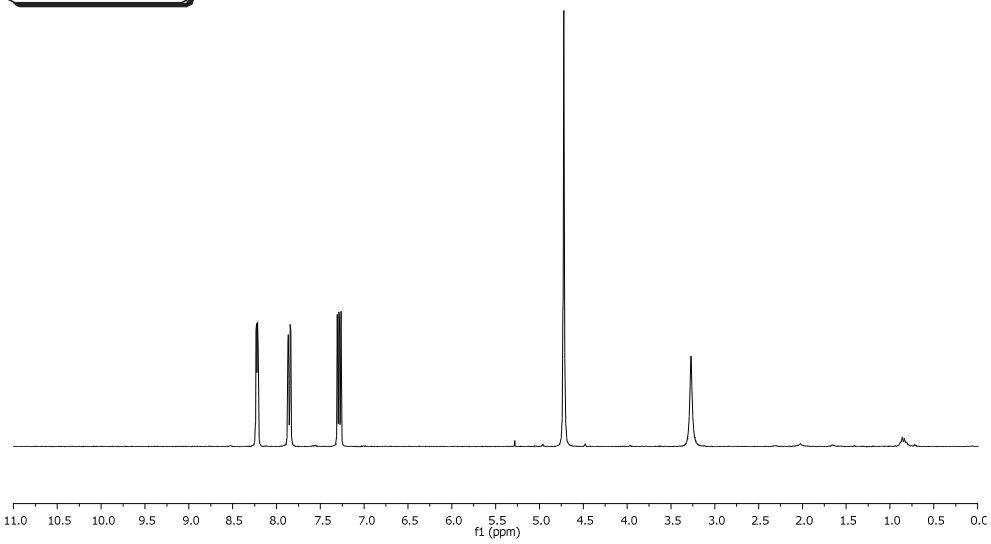
*Figure 6.2. ORTEP plot of compound **75b** with thermal ellipsoids at the 50% probability level with the atomic nomenclature used.*

Appendix

Selected NMR Spectra


OH
N
Br

1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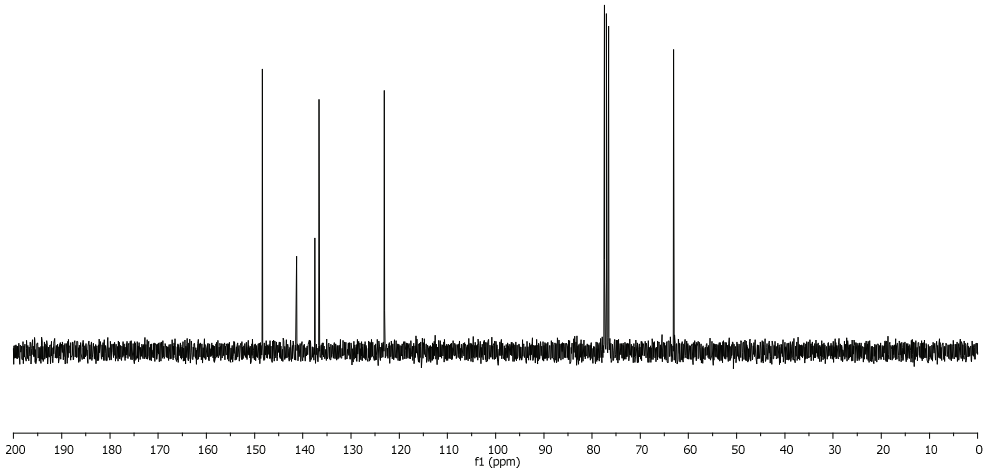
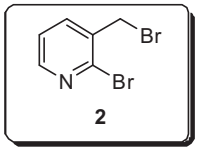
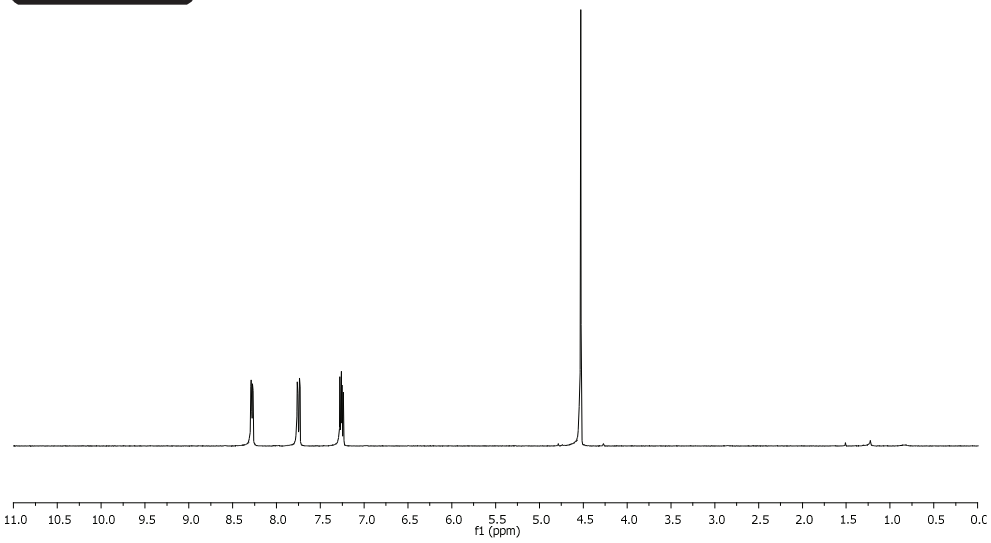
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Br
N
Br

2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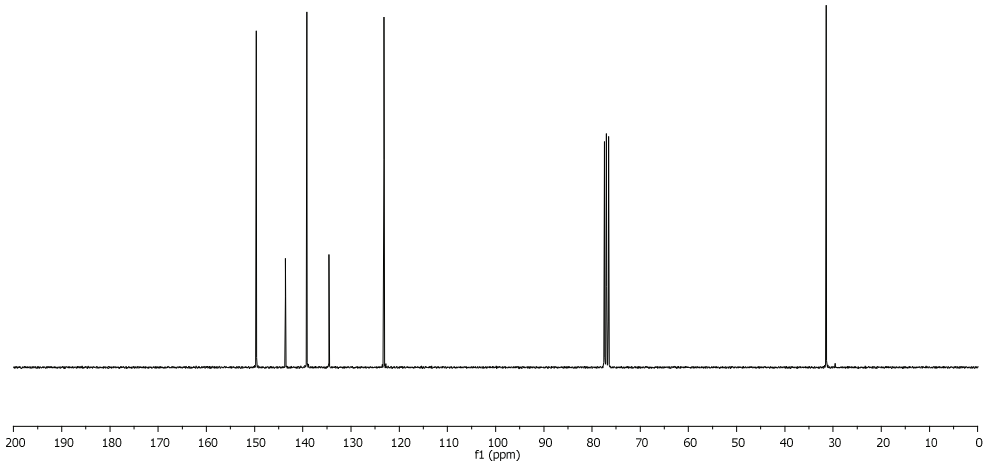
f1 (ppm)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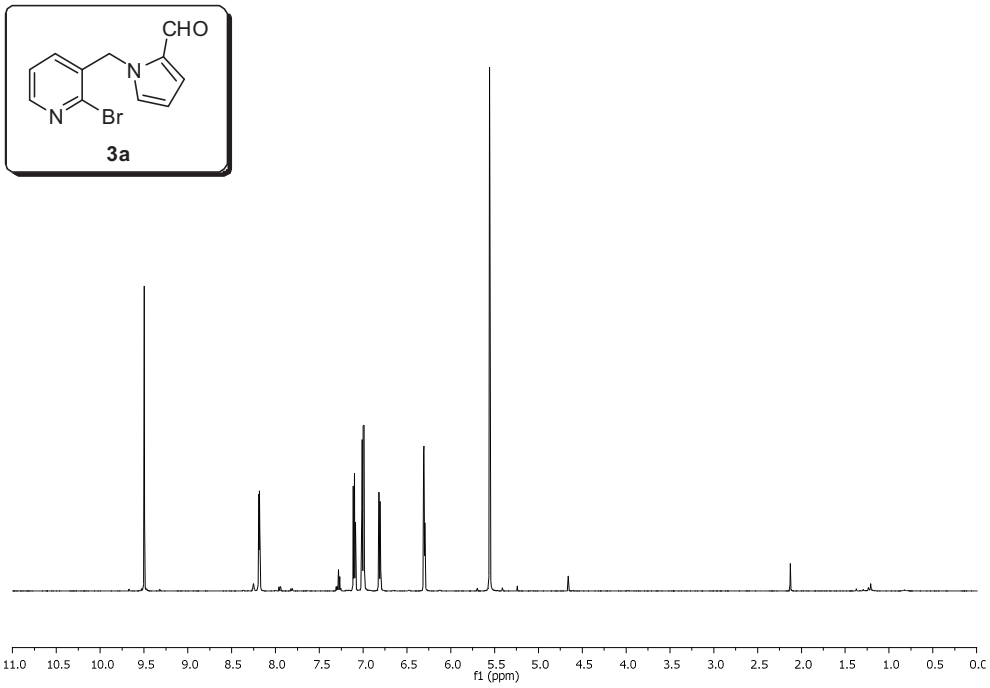
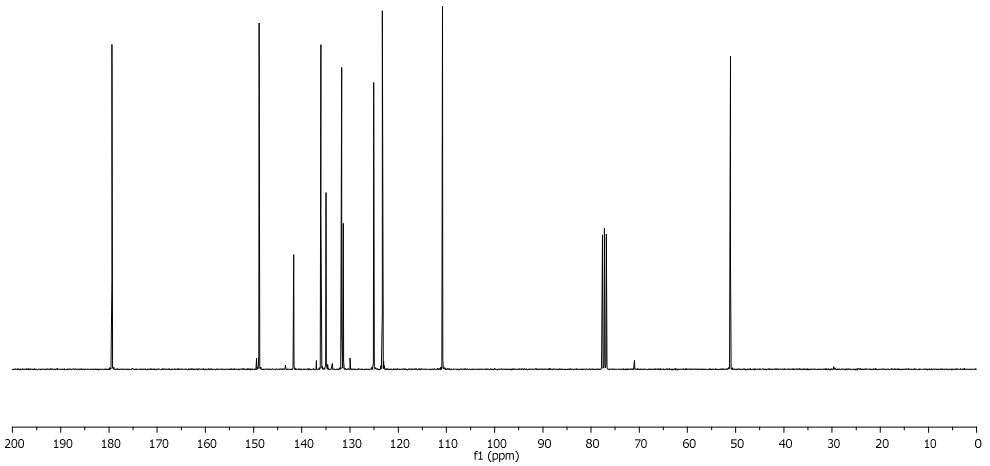
f1 (ppm)


CHO
N
N
Br
3a
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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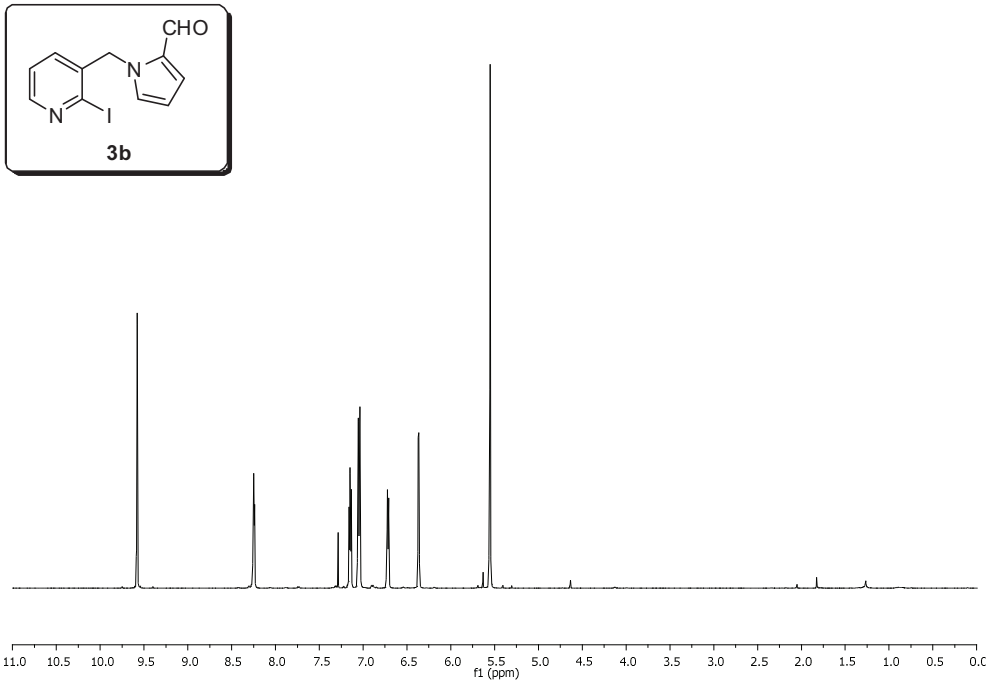
f1 (ppm)


CHO
N
N
I
3b
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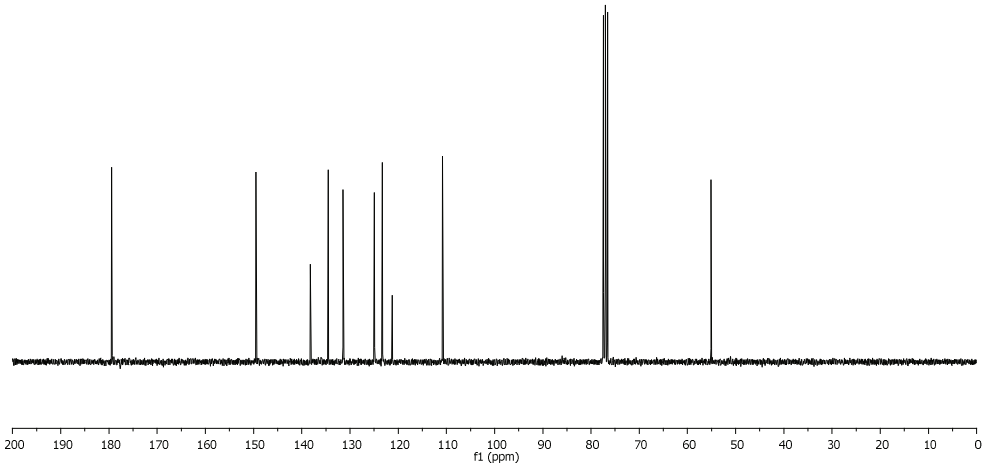
f1 (ppm)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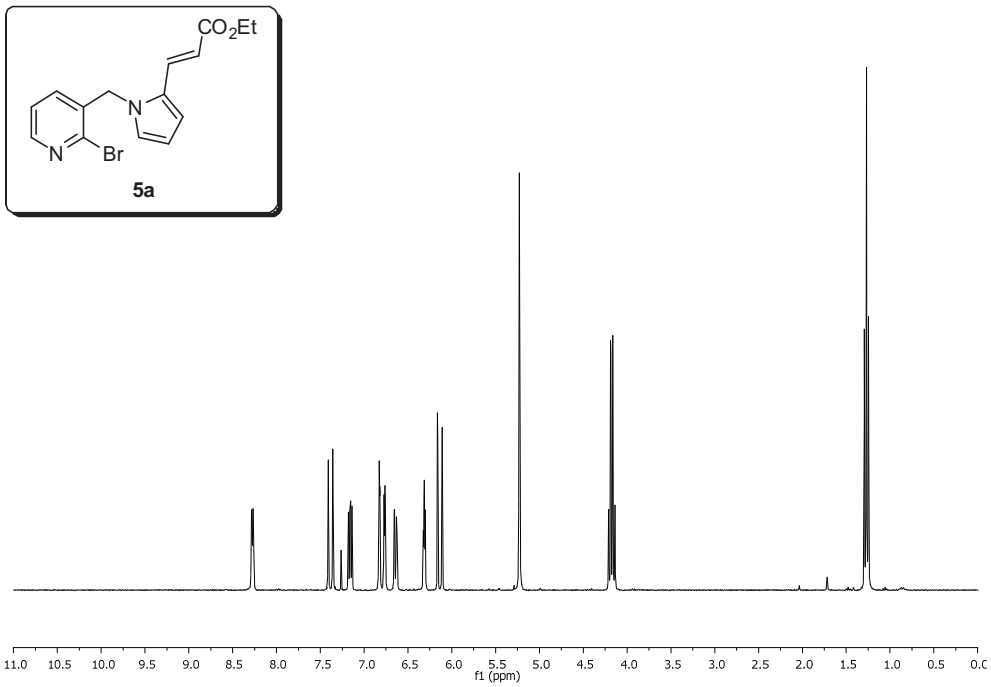
f1 (ppm)


CO2Et
N
N
Br
5a
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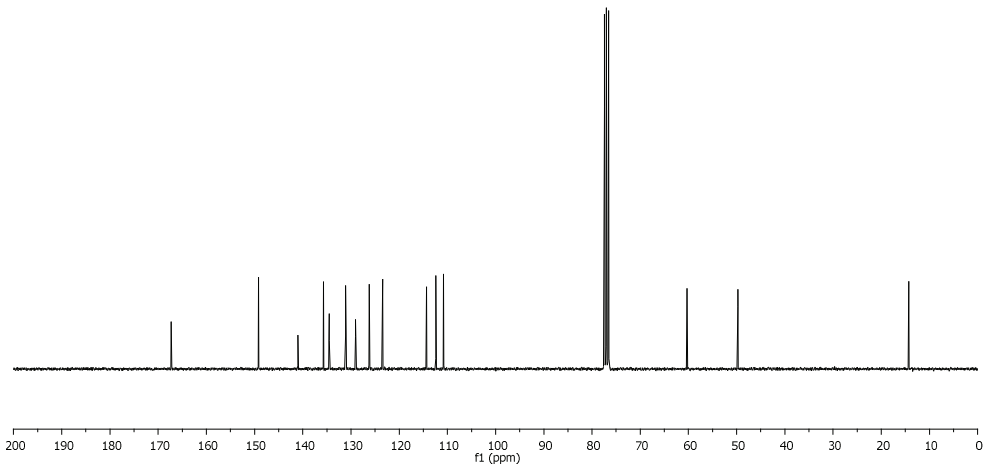
f1 (ppm)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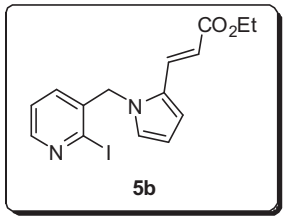
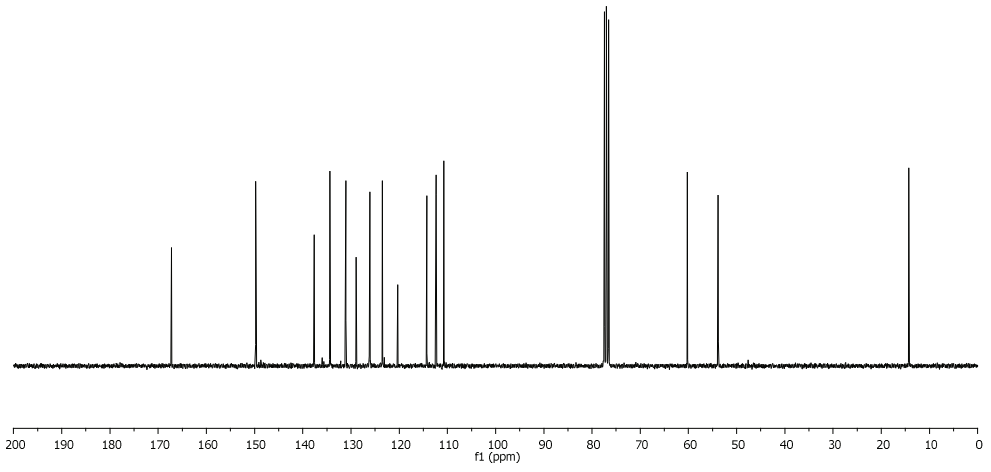
f1 (ppm)


CO2Et
N
N
I

5b

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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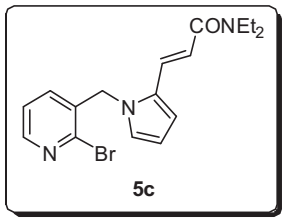
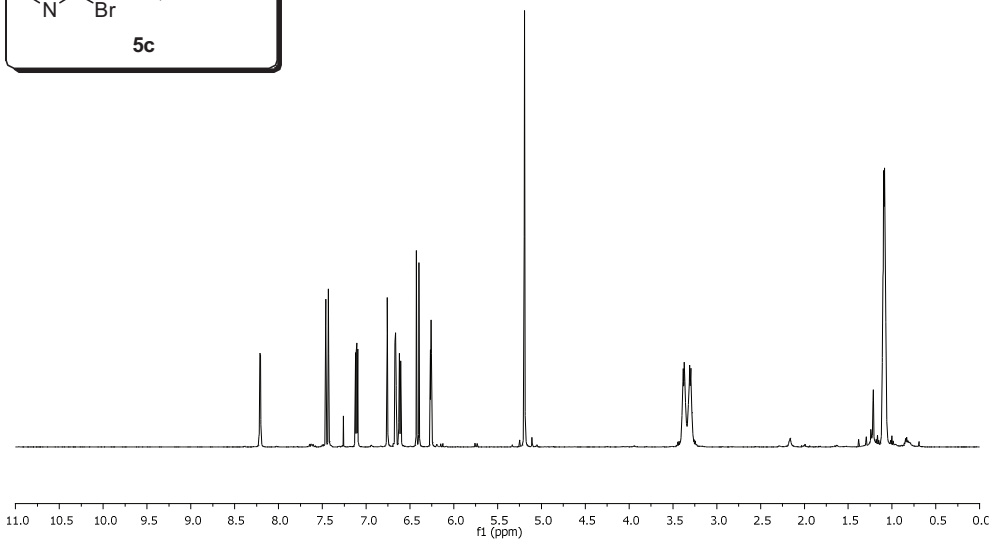
f1 (ppm)


CONEt2
N
N
Br

5c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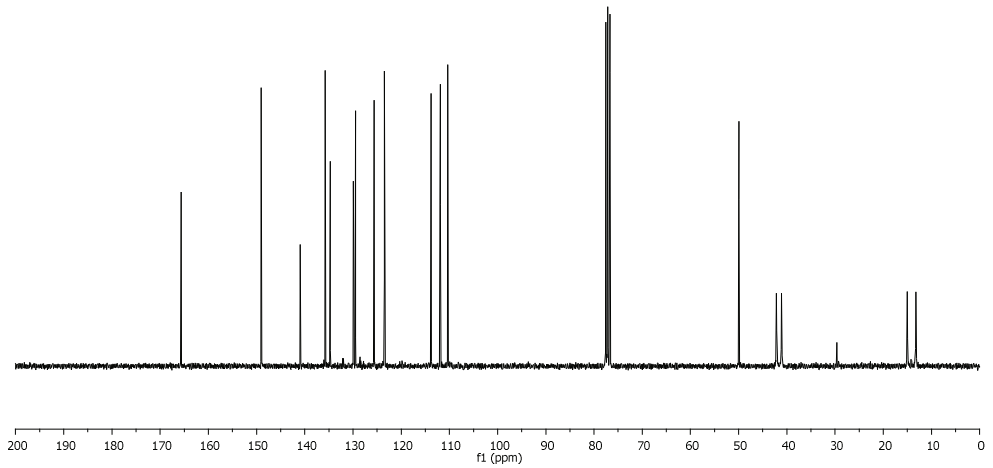
f1 (ppm)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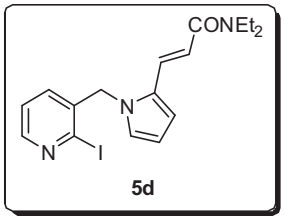
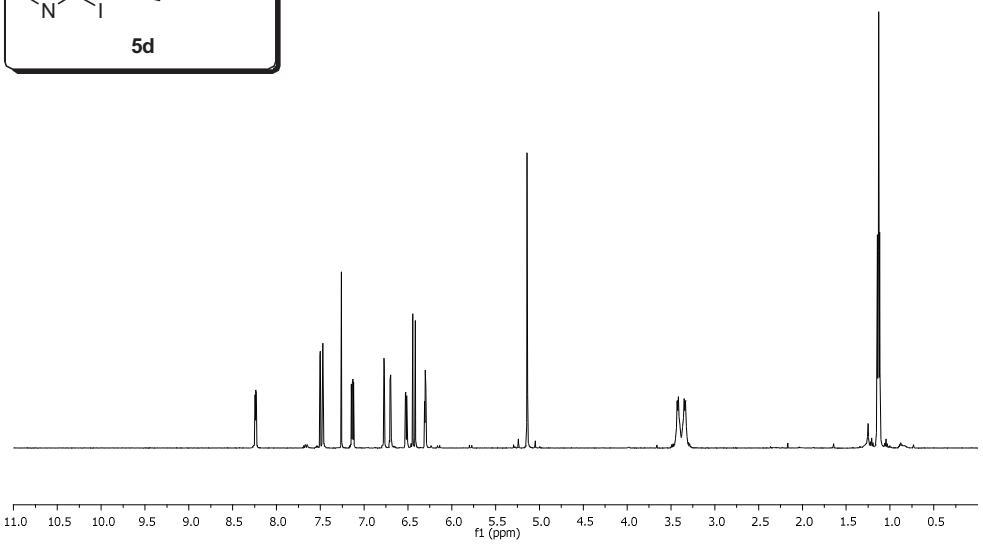
f1 (ppm)


CONEt2
N
N
I

5d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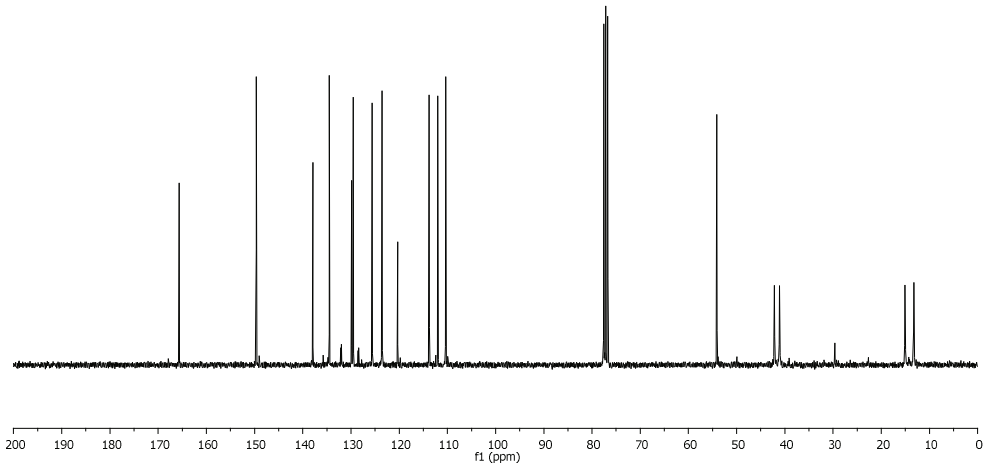
f1 (ppm)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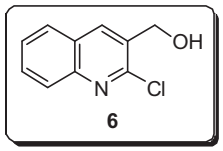
f1 (ppm)


OH
N
Cl

6

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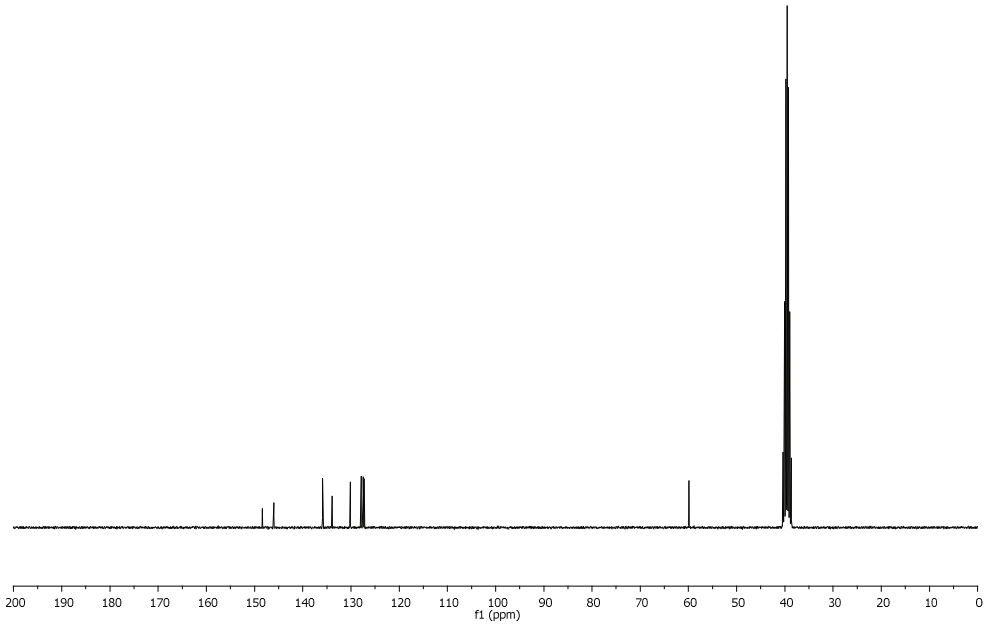
f1 (ppm)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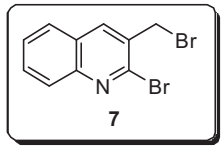
f1 (ppm)


Br
N
Br

7

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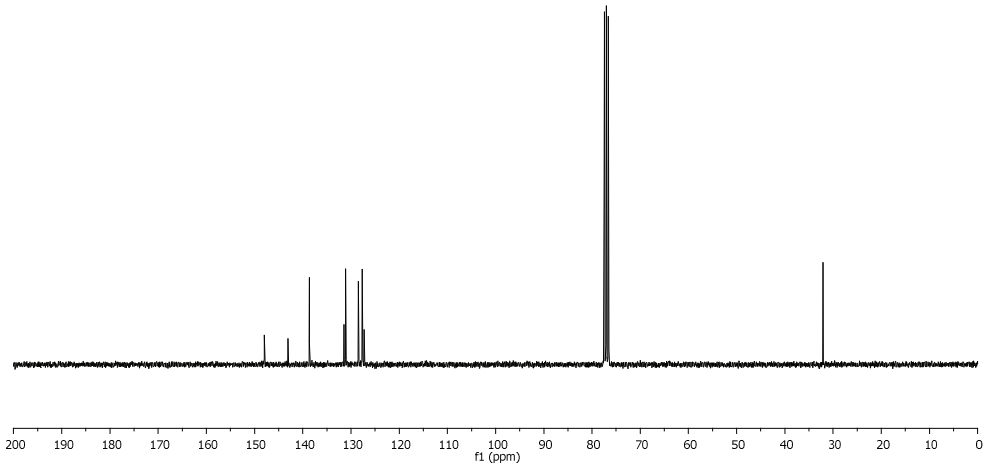
f1 (ppm)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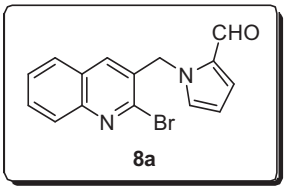
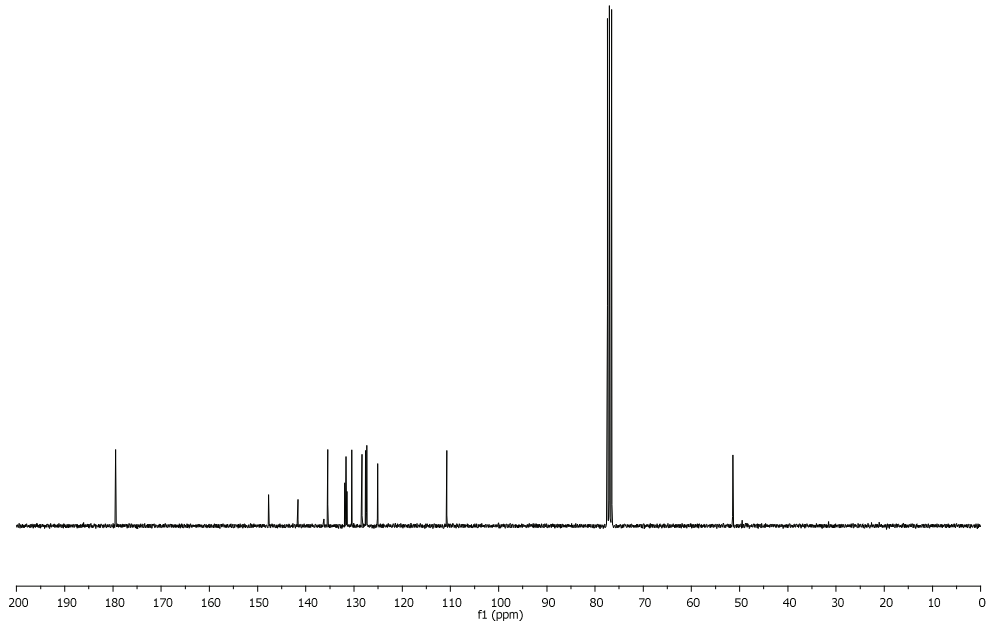
f1 (ppm)


CHO
N
N
Br

8a

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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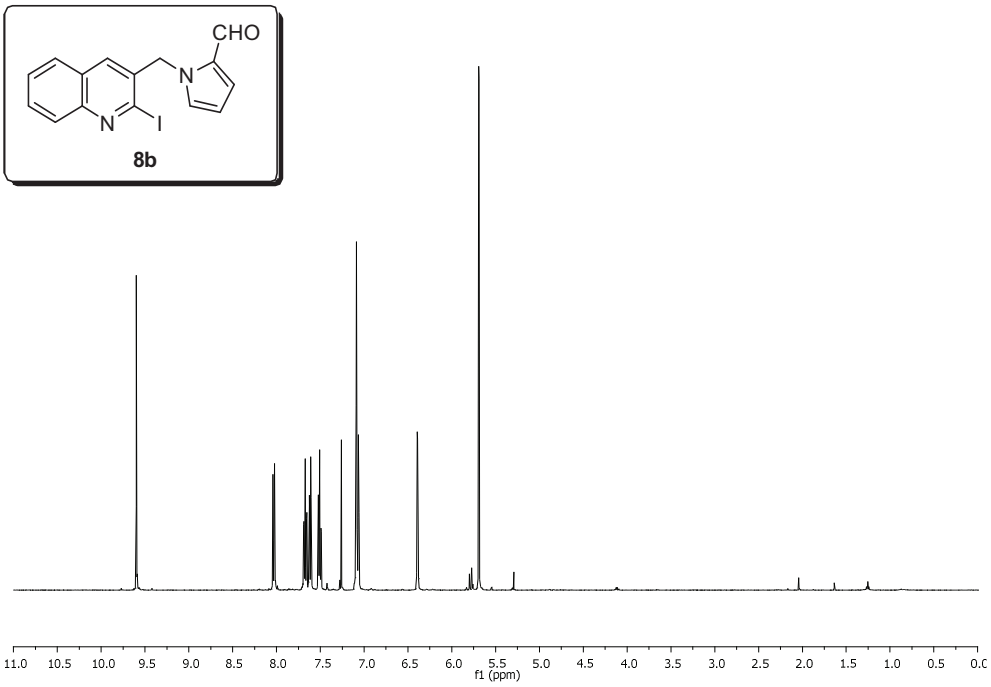
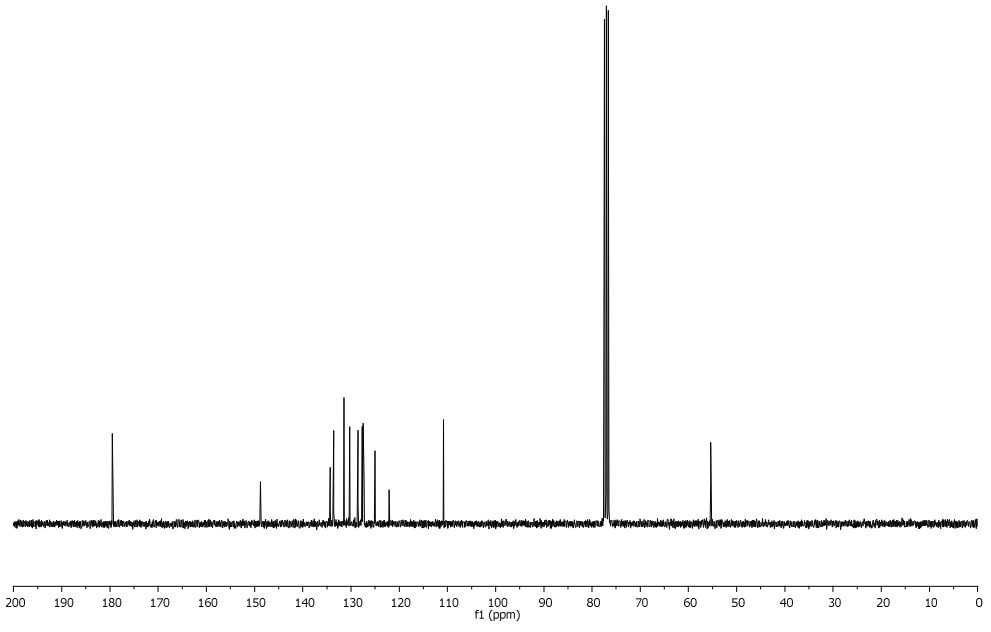
f1 (ppm)


CHO
N
N
I
8b
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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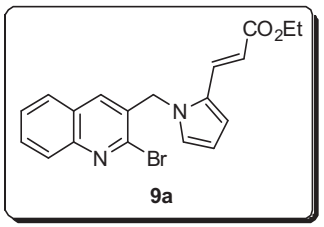
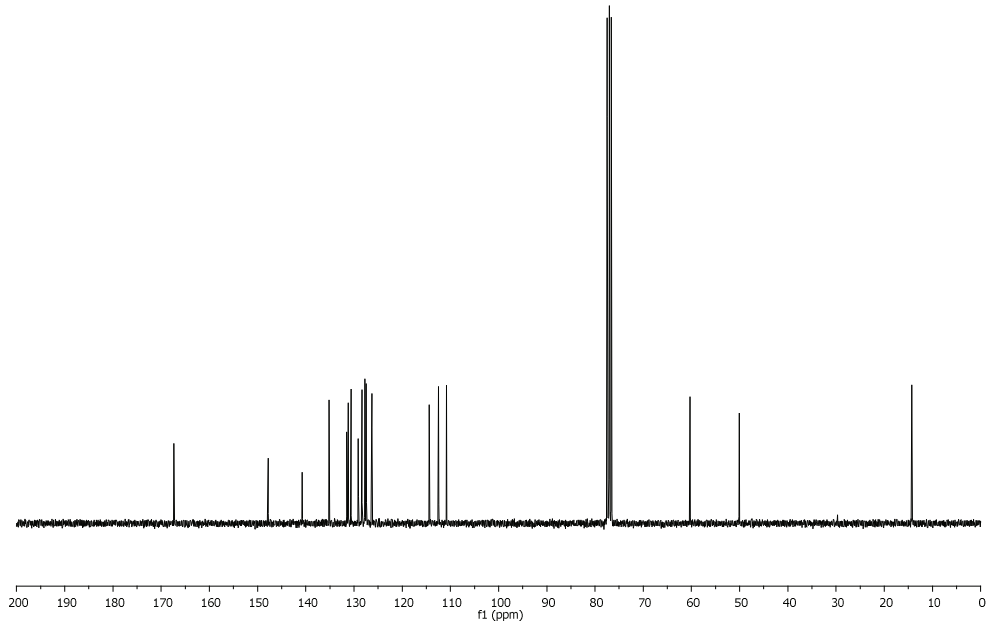
f1 (ppm)


CO2Et
N
N
Br

9a

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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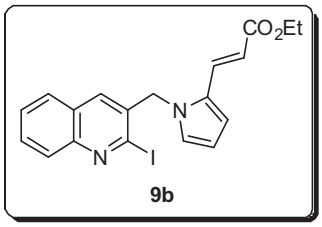
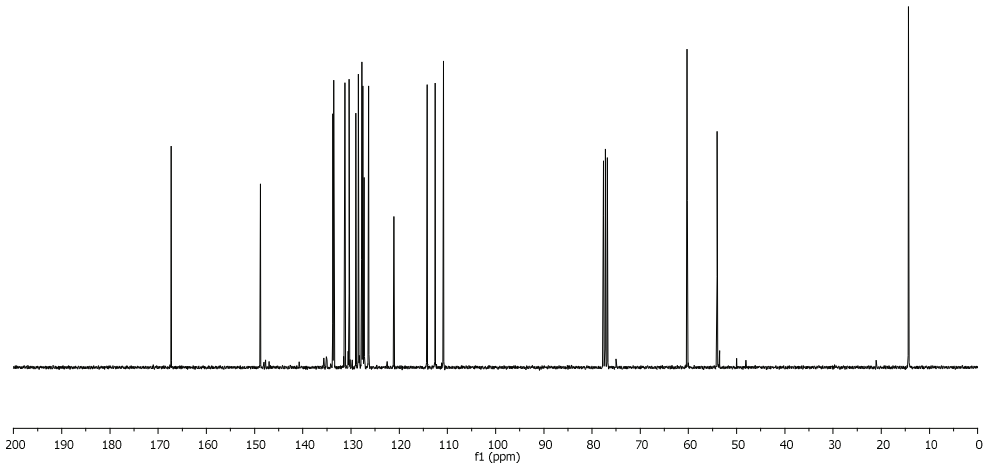
f1 (ppm)


CO2Et
N
N
I

9b

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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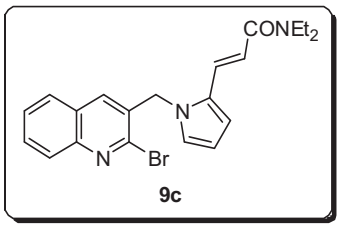
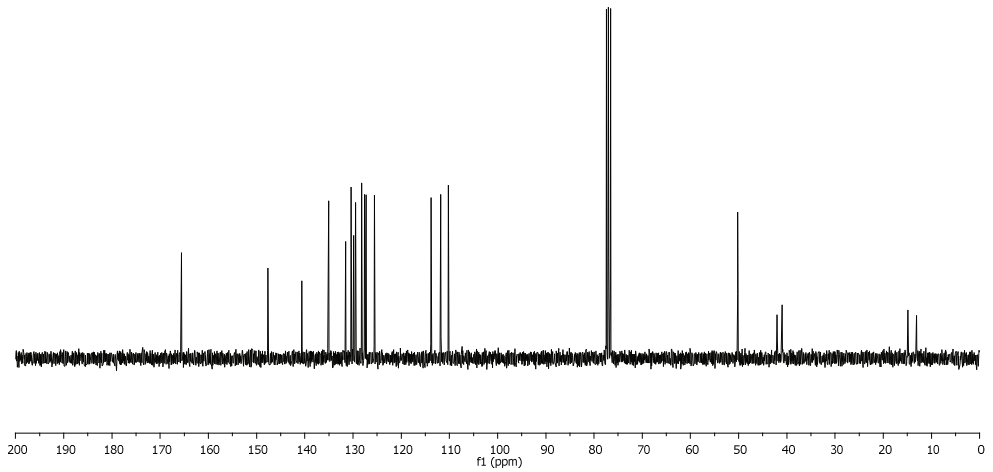
f1 (ppm)


CONEt2
N
N
Br

9c

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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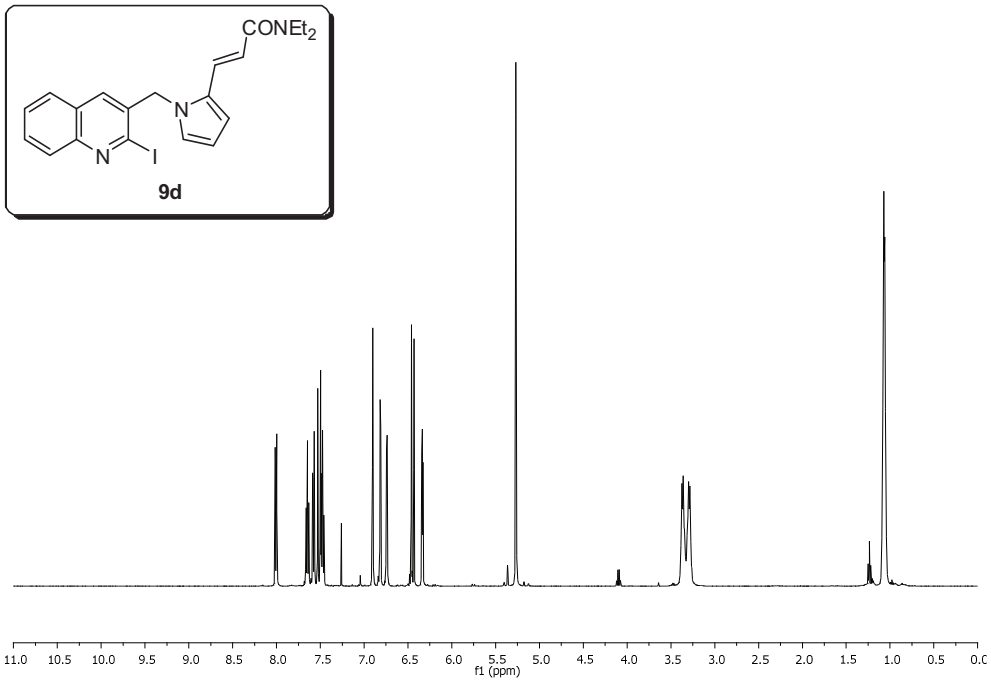
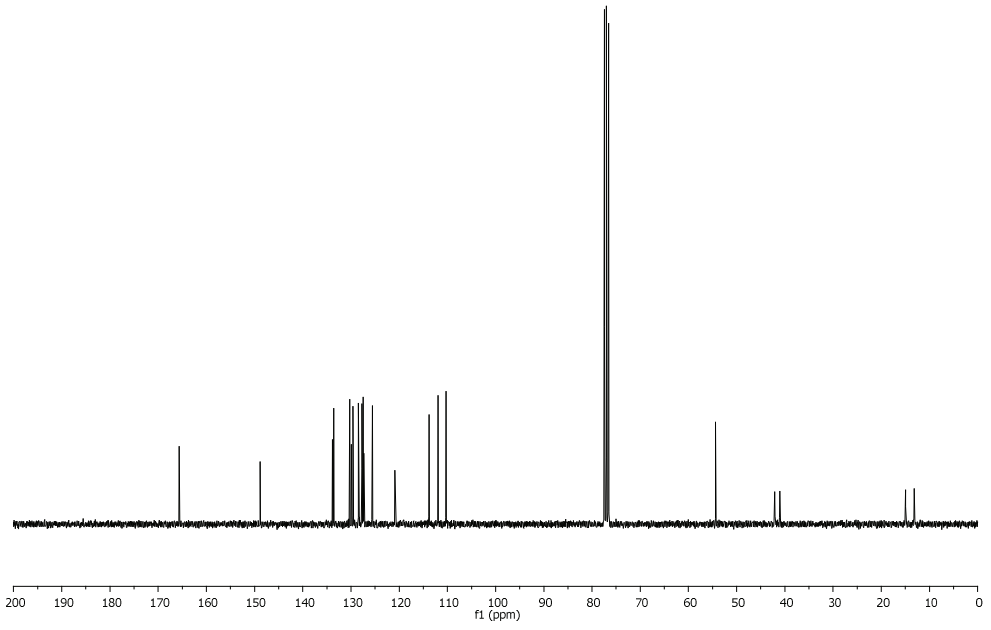
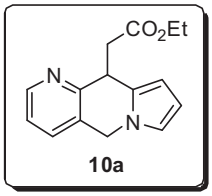
f1 (ppm)

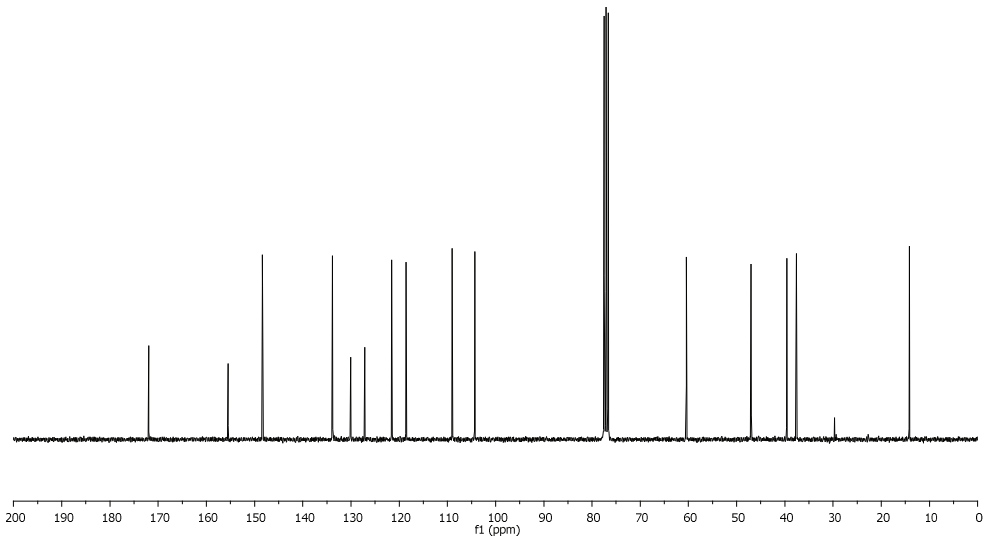

CONEt2
N
N
I
9d
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CO2Et
N
N

10a

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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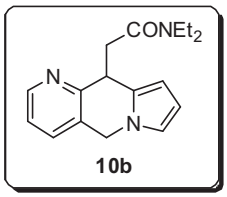
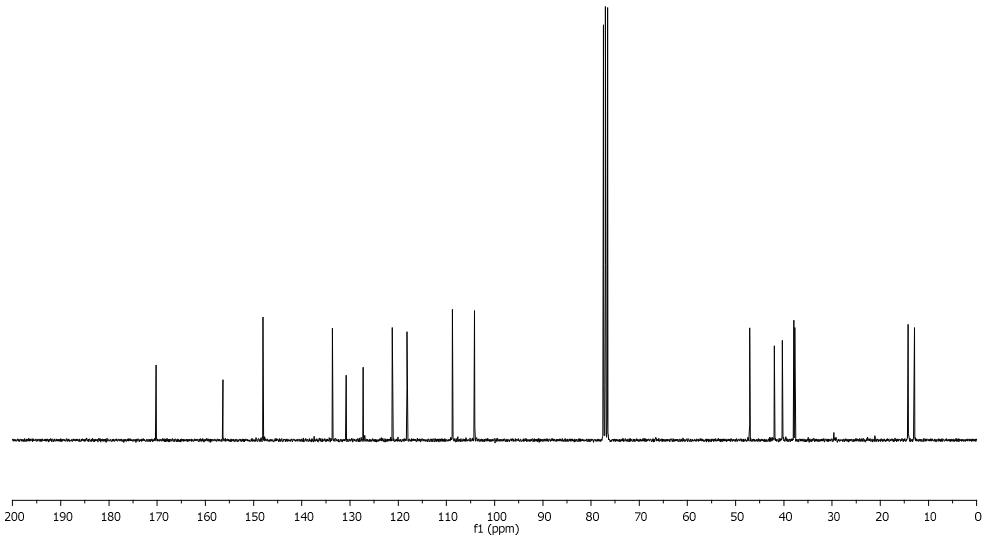
f1 (ppm)


CONEt2
N
N

10b

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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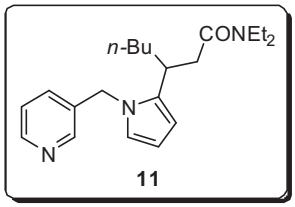
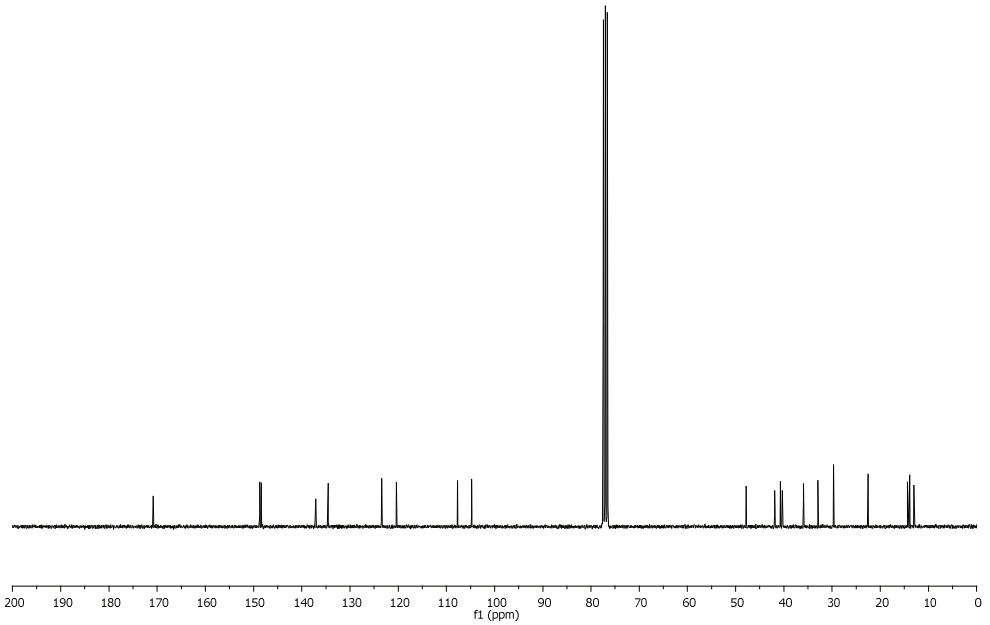
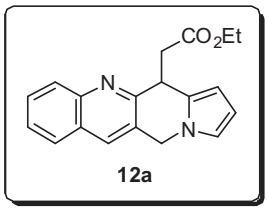
f1 (ppm)


n-Bu
CONEt2
N
N

11

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CO2Et
N
N

12a

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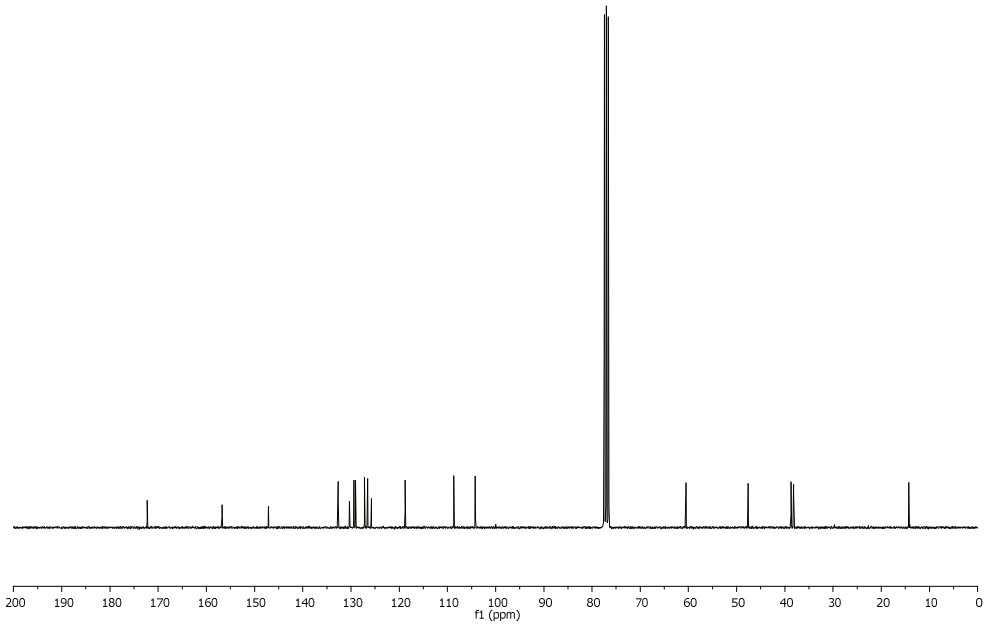
f1 (ppm)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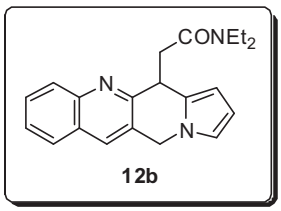
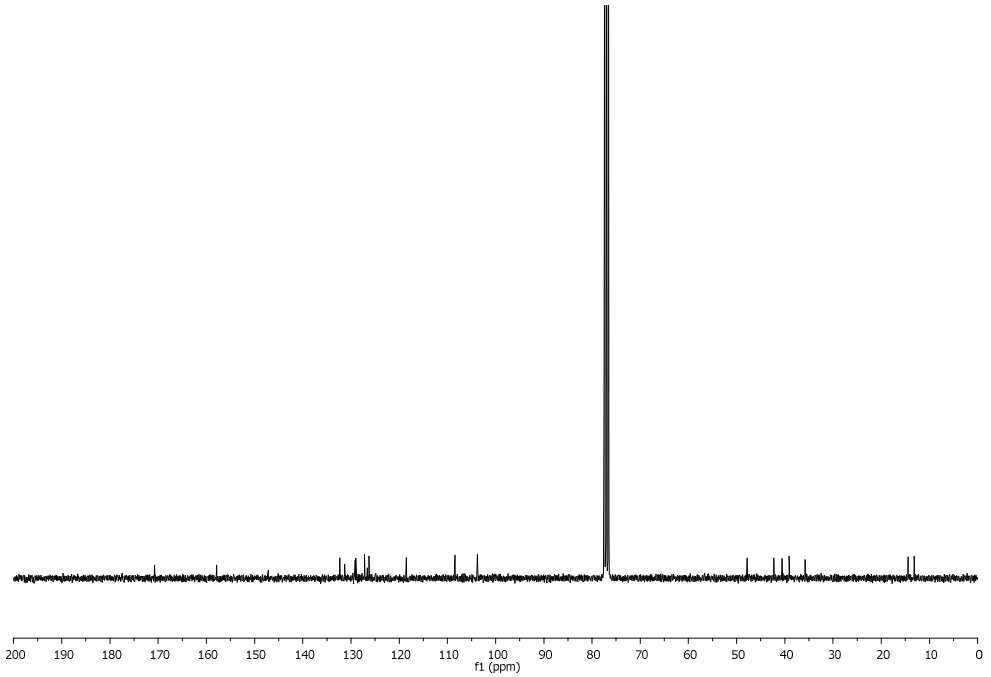
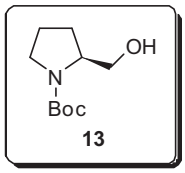
f1 (ppm)


CONEt2
N
N

12b

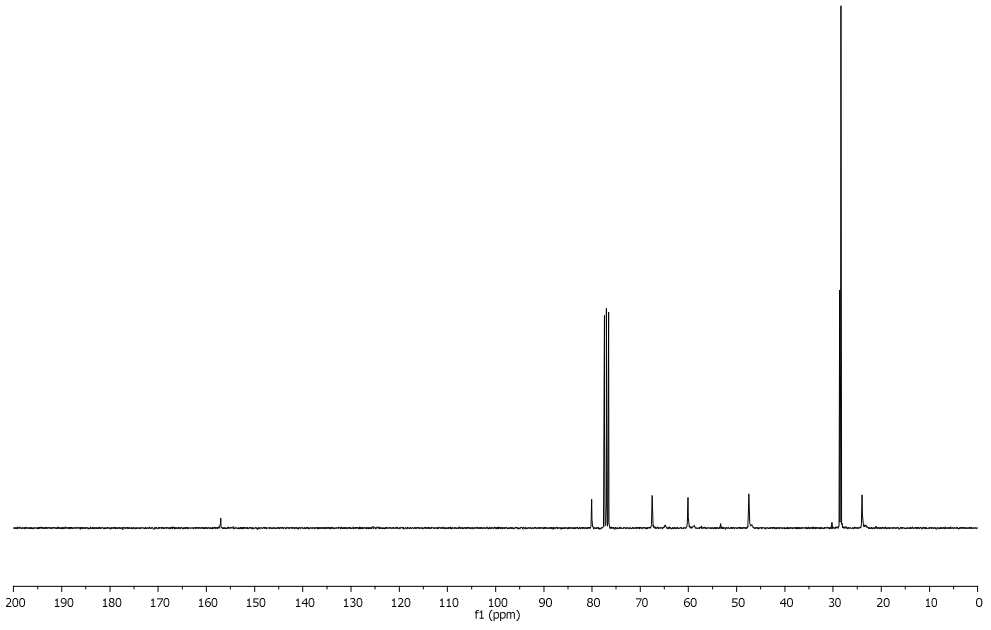
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
N
Boc

13

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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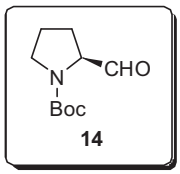
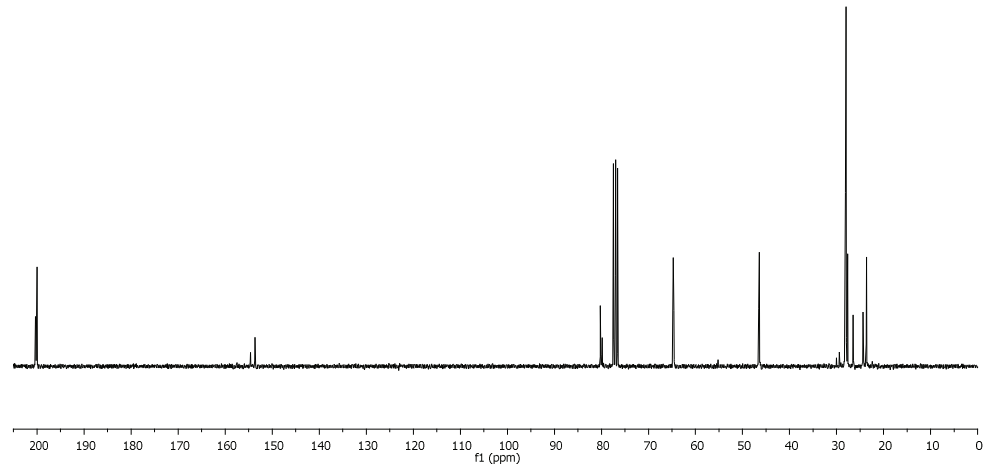
f1 (ppm)


CHO
N
Boc

14

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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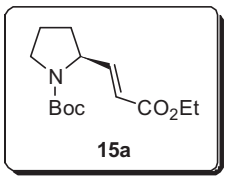
f1 (ppm)


N
Boc
CO_2Et

15a

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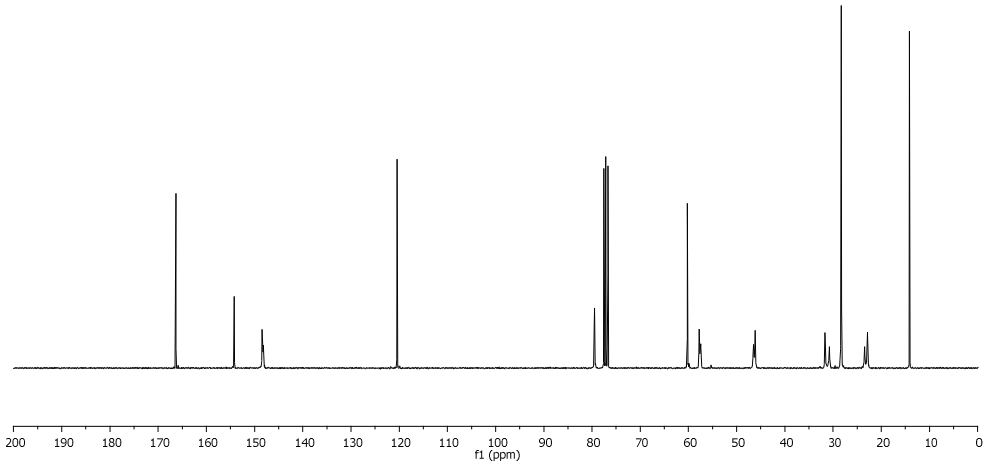
f1 (ppm)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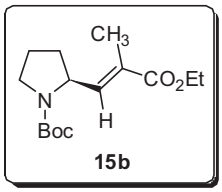
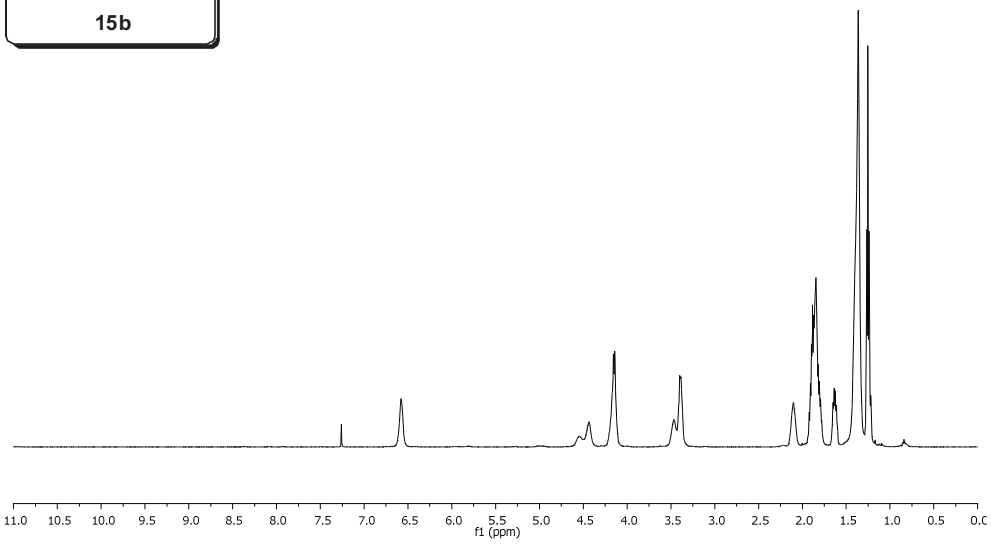
f1 (ppm)


CH3
CO2Et
N
Boc
H

15b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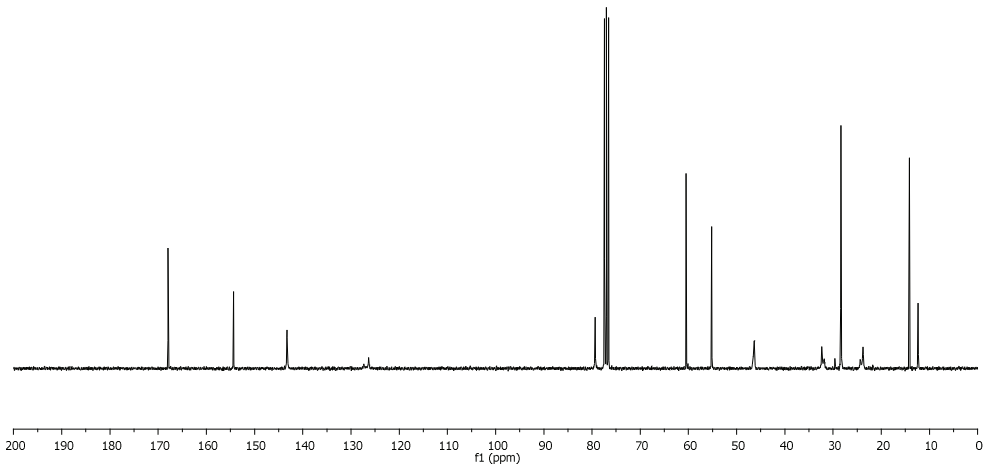
f1 (ppm)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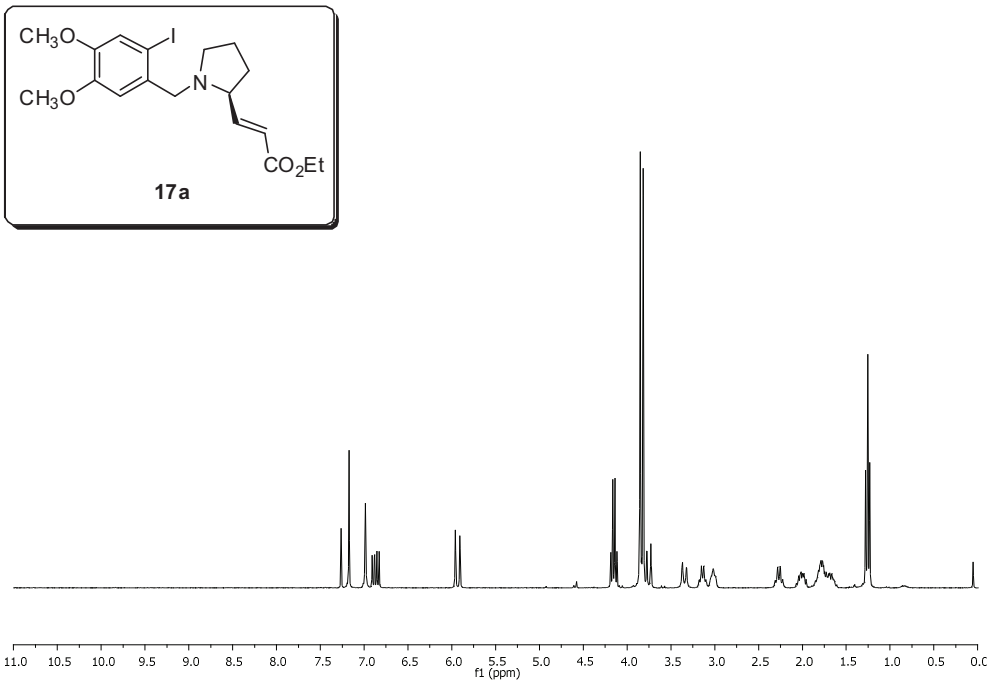
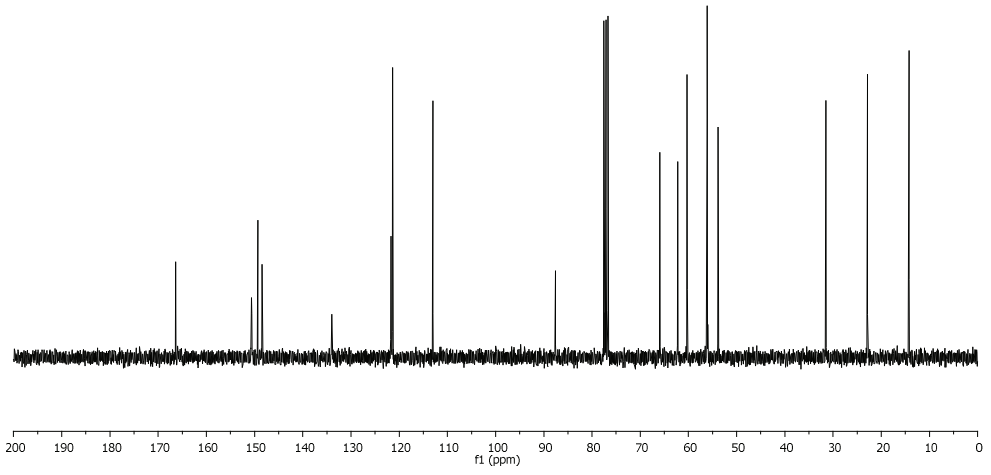
f1 (ppm)


CH3O
CH3O
I
N
CO2Et
17a
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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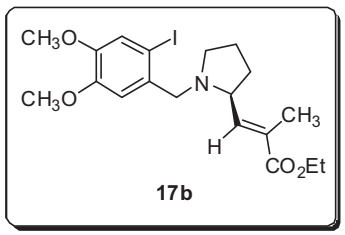
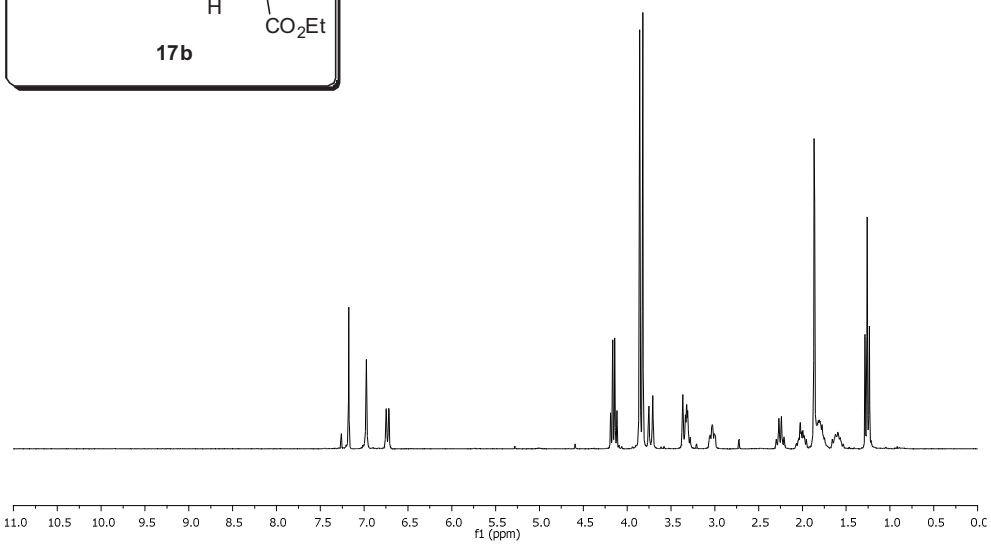
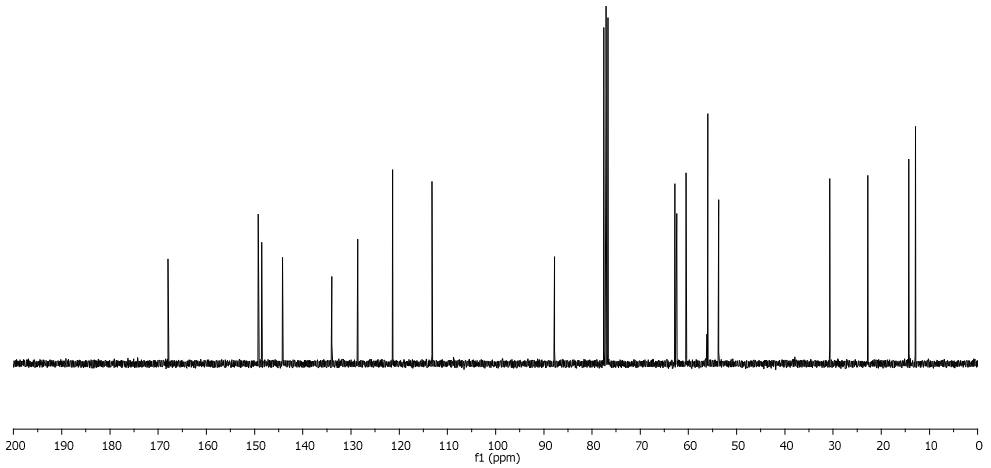
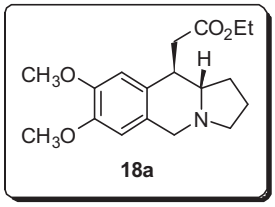
f1 (ppm)


CH3O
I
CH3O
N
CH3
H
CO2Et

17b


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CO2Et
H
CH3O
CH3O
N

18a

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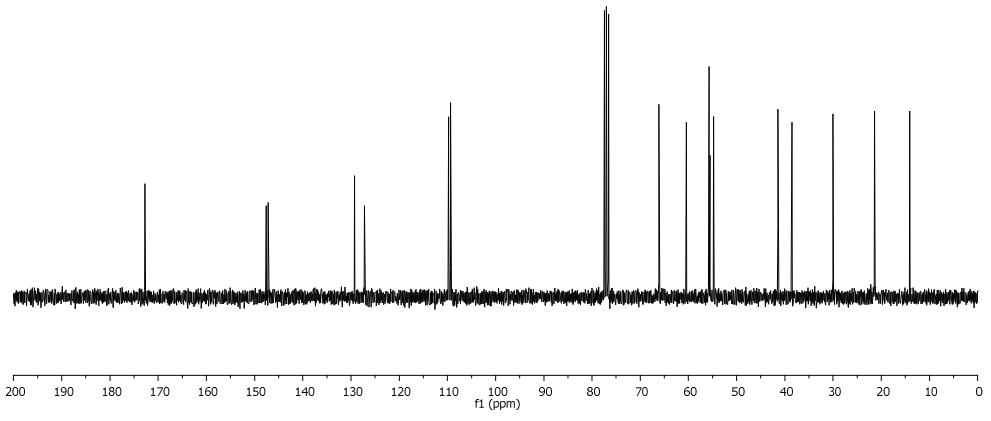
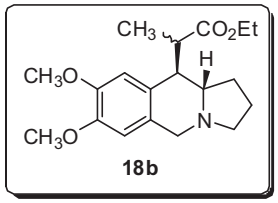
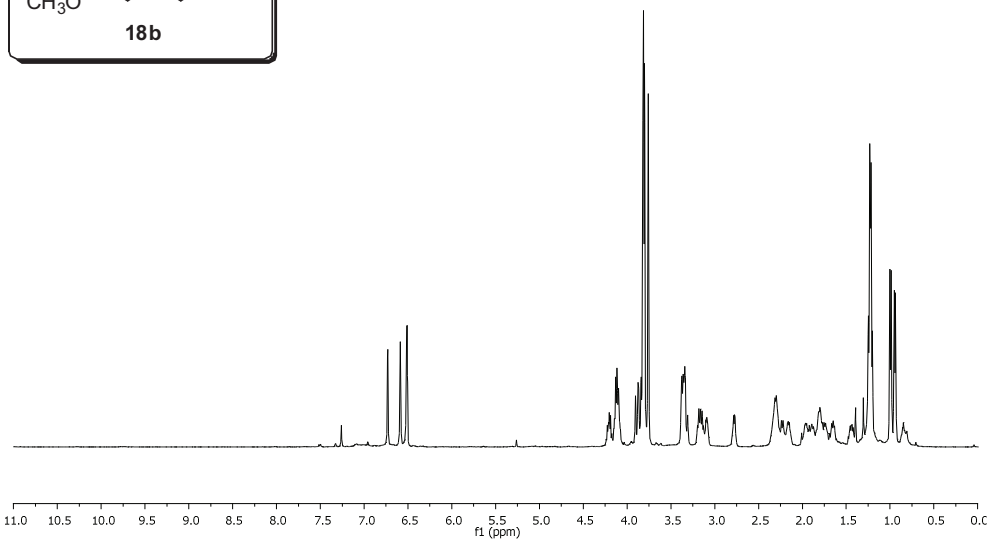
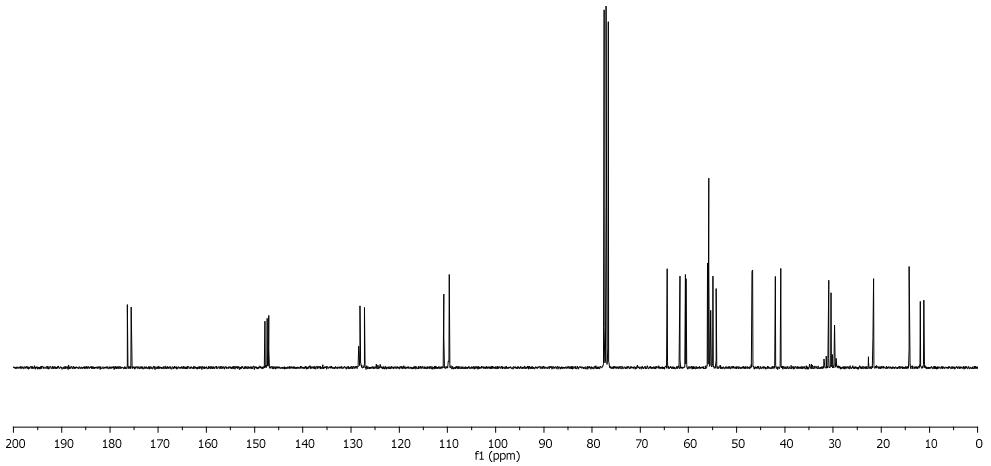
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3
CO2Et
H
CH3O
CH3O
N

18b


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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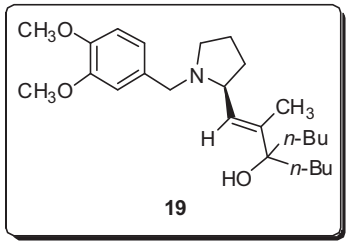
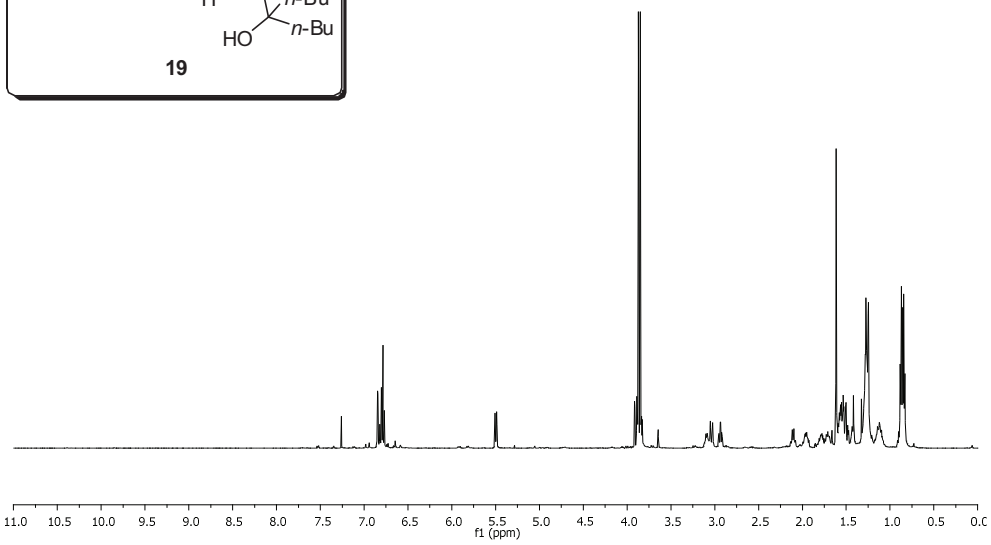
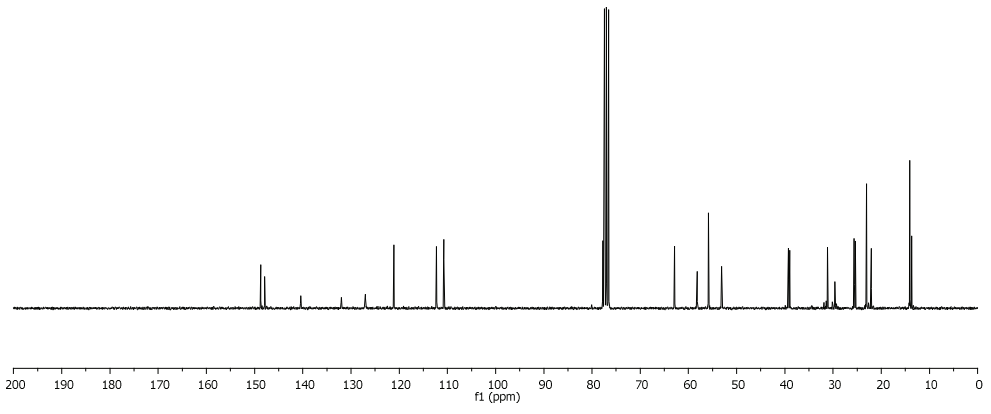
f1 (ppm)


CH3O
CH3O
N
CH3
H
n-Bu
HO
n-Bu

19


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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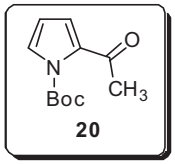
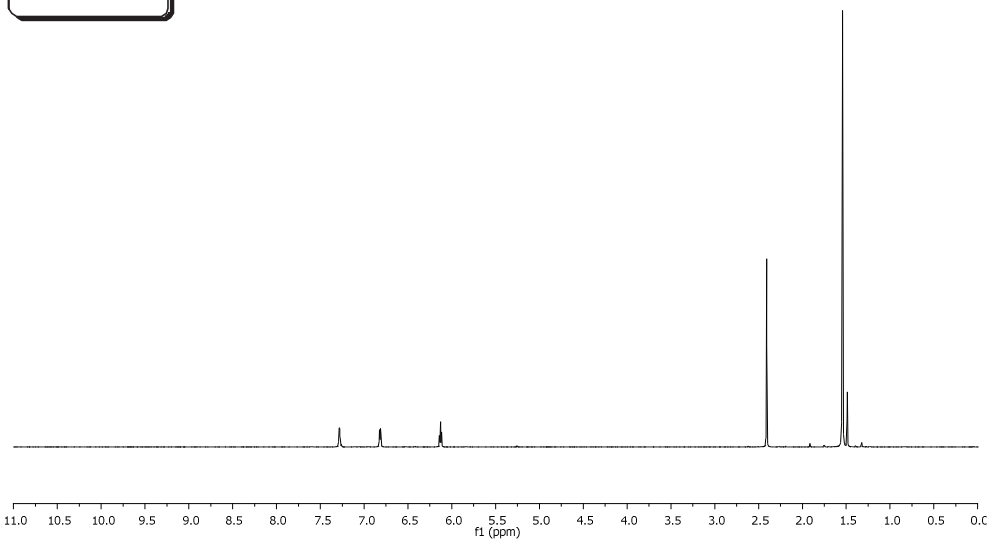
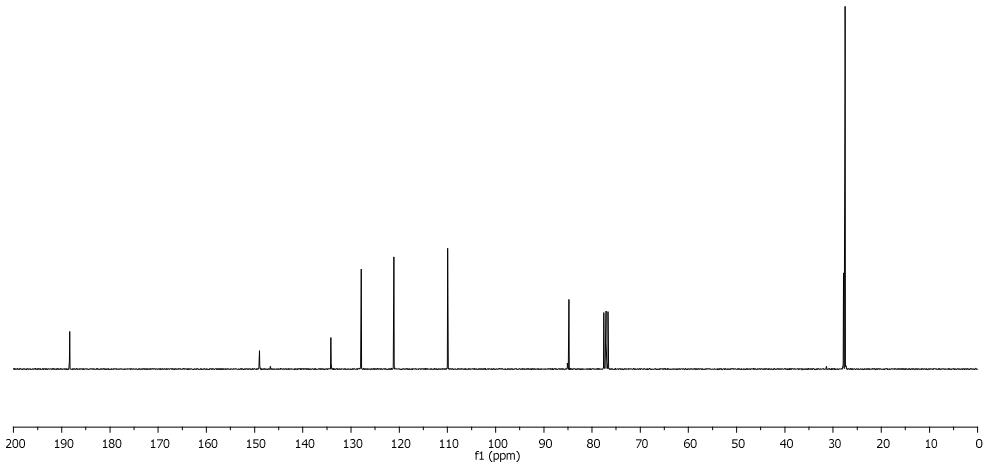
f1 (ppm)


O
N
Boc
CH3

20


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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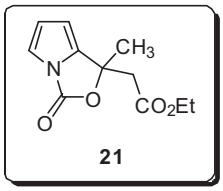
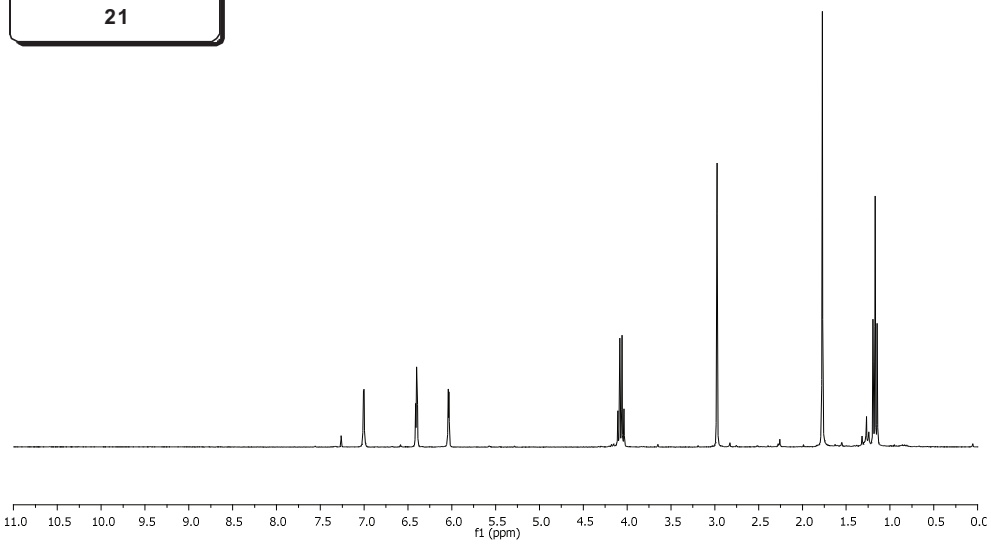
f1 (ppm)


CH3
N
O
O
CO2Et

21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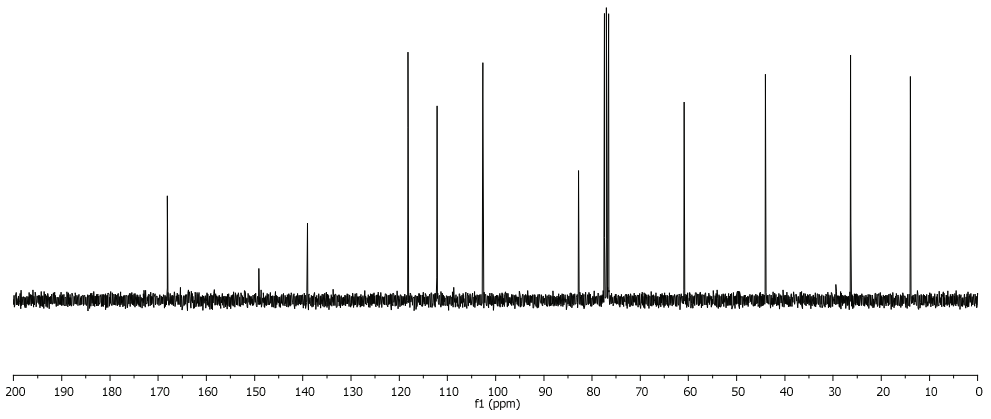
f1 (ppm)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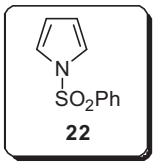
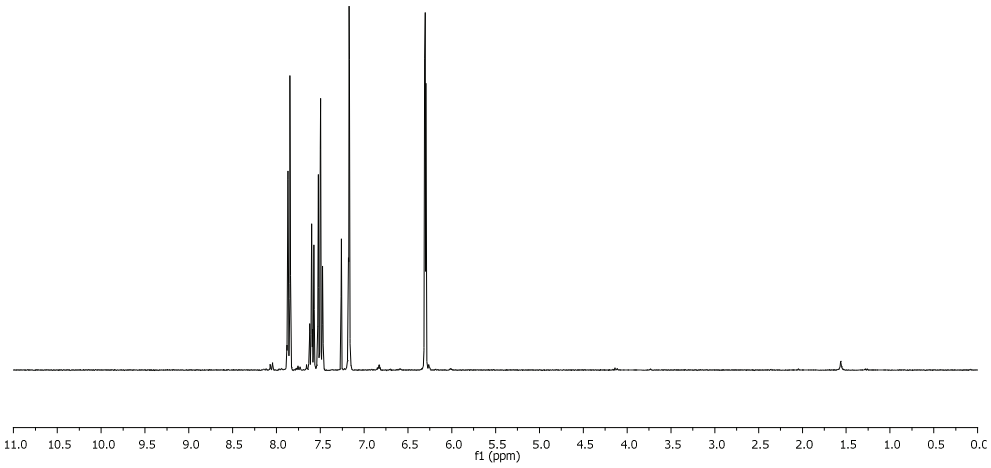
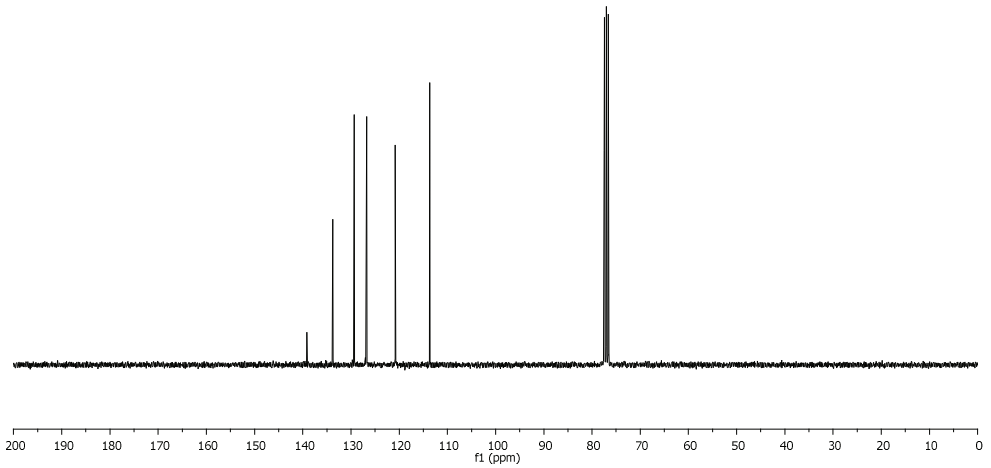
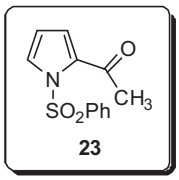
f1 (ppm)


N
SO2Ph

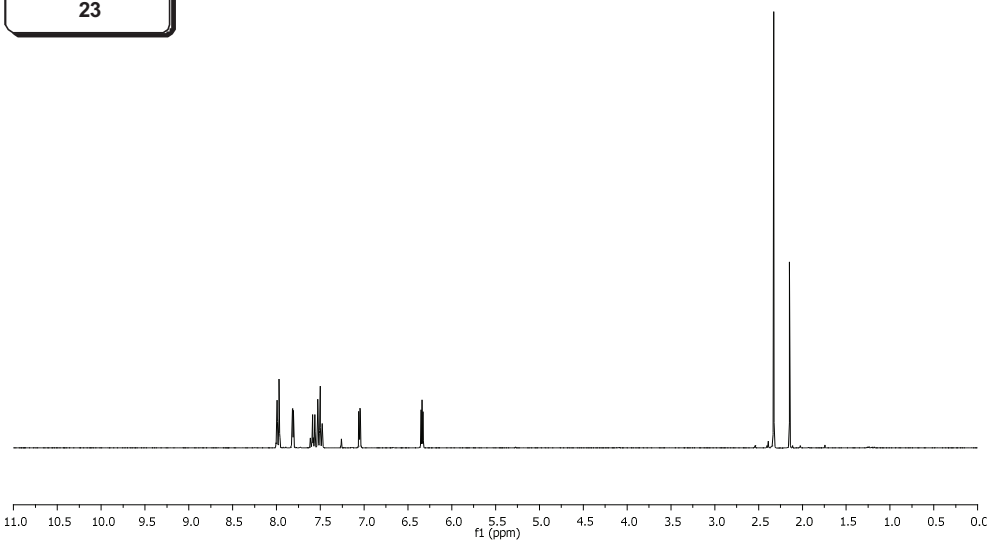
22

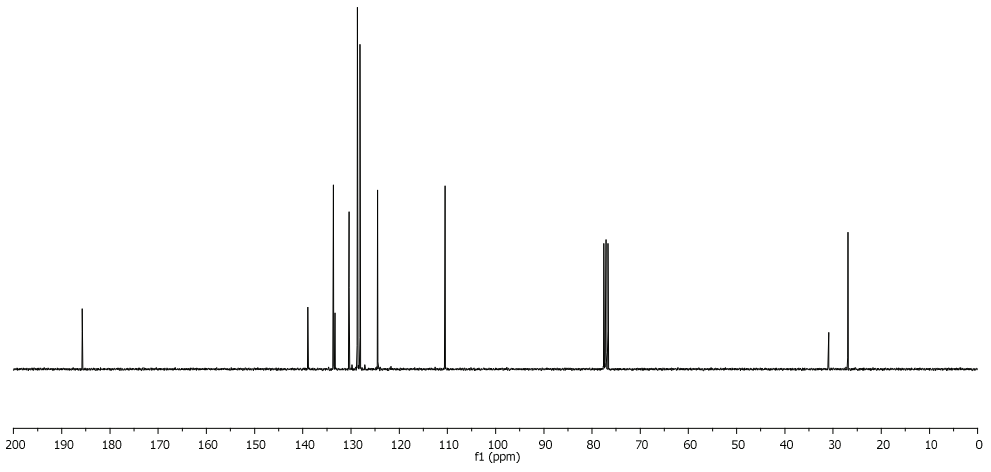

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
N
CH3
SO2Ph

23


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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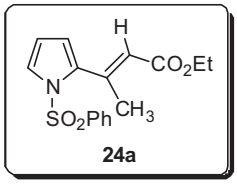
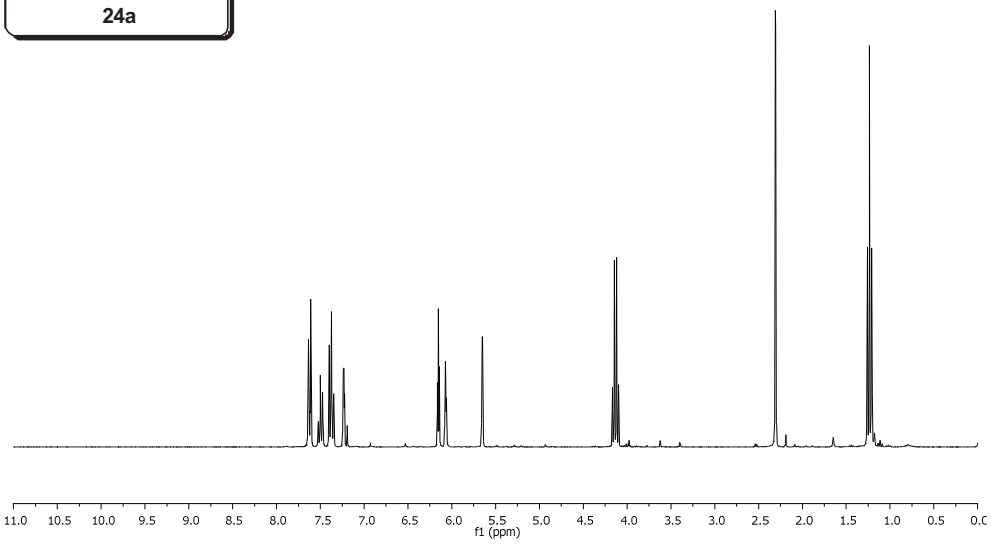
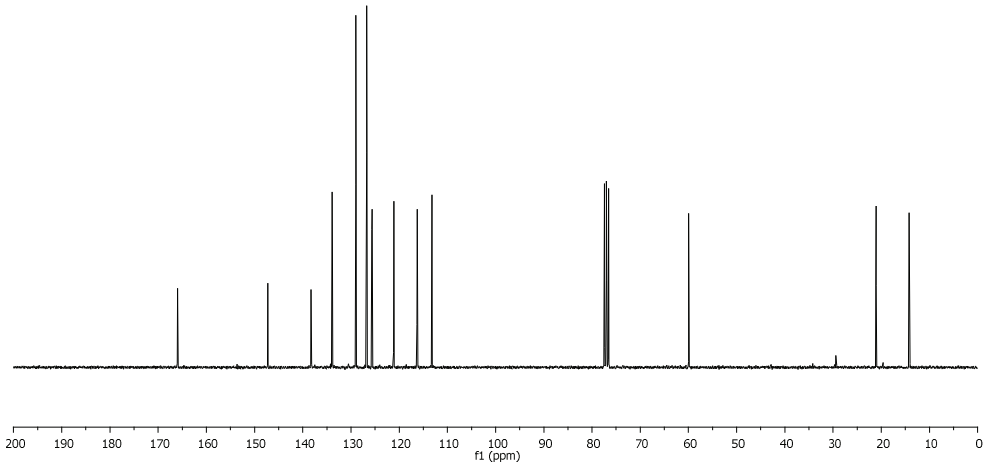
f1 (ppm)


H
CO2Et
N
SO2Ph
CH3

24a


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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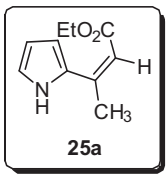
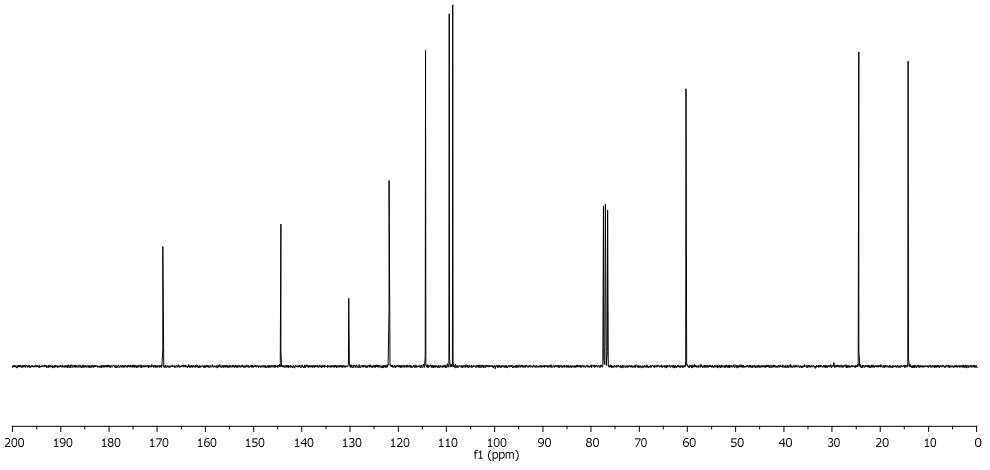
f1 (ppm)


EtO2C
H
N
H
CH3

25a

14.5 13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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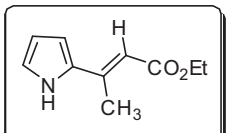
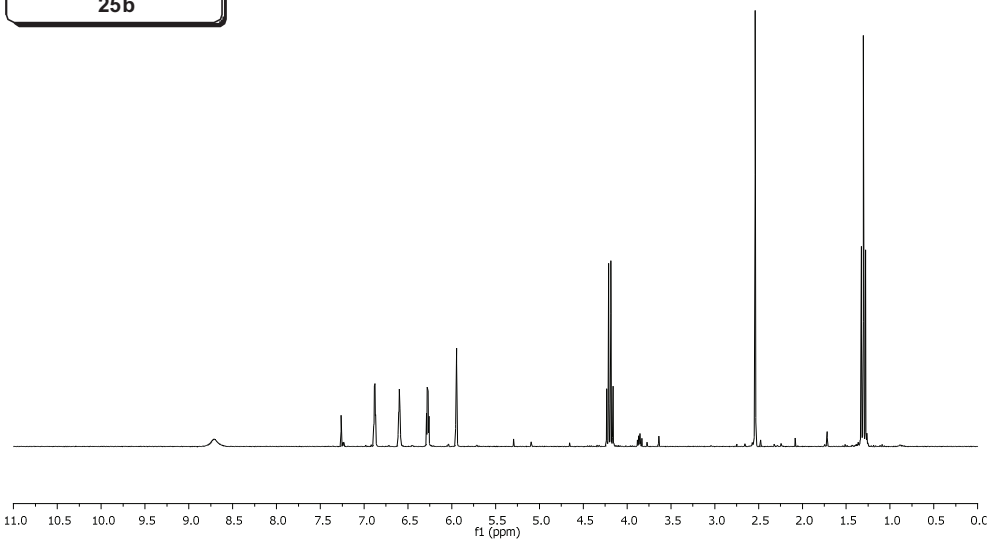
f1 (ppm)


H
CO2Et
N
H
CH3

25b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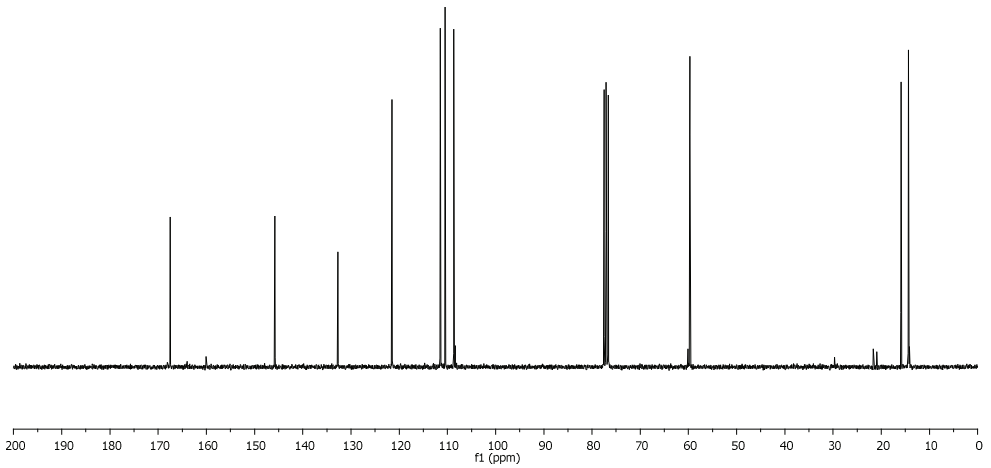
f1 (ppm)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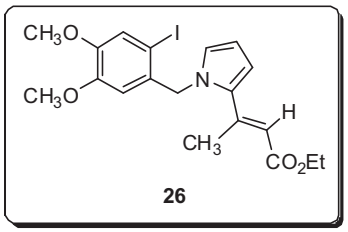
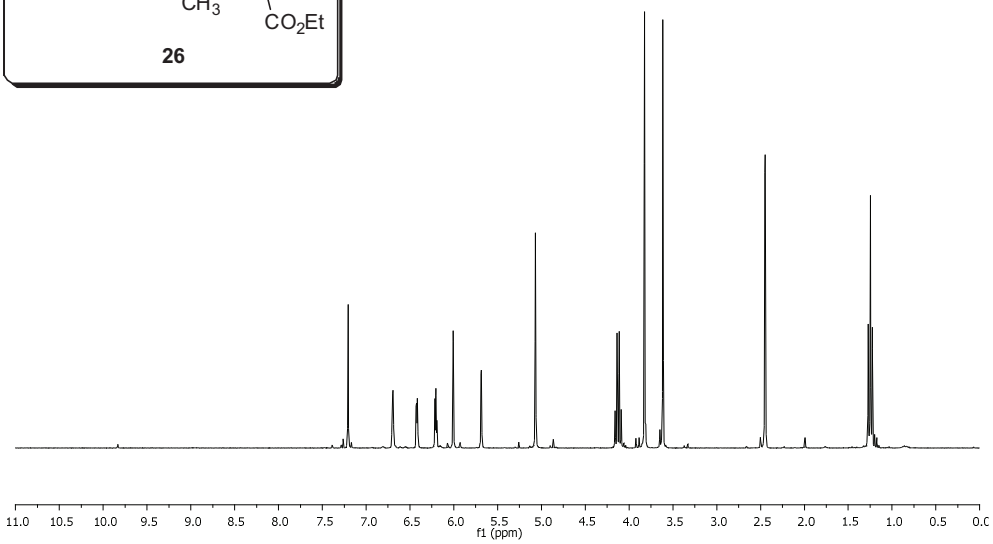
f1 (ppm)


CH3O
I
CH3O
N
H
CH3
CO2Et

26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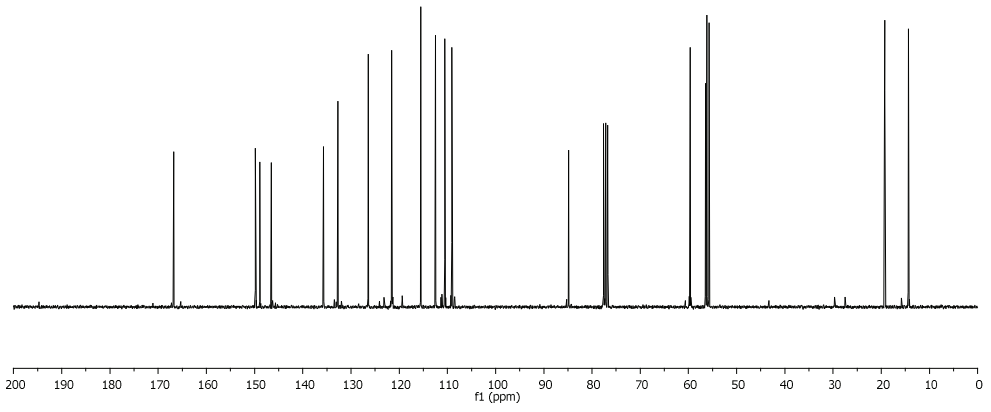
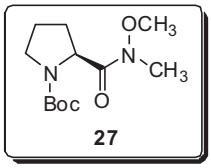
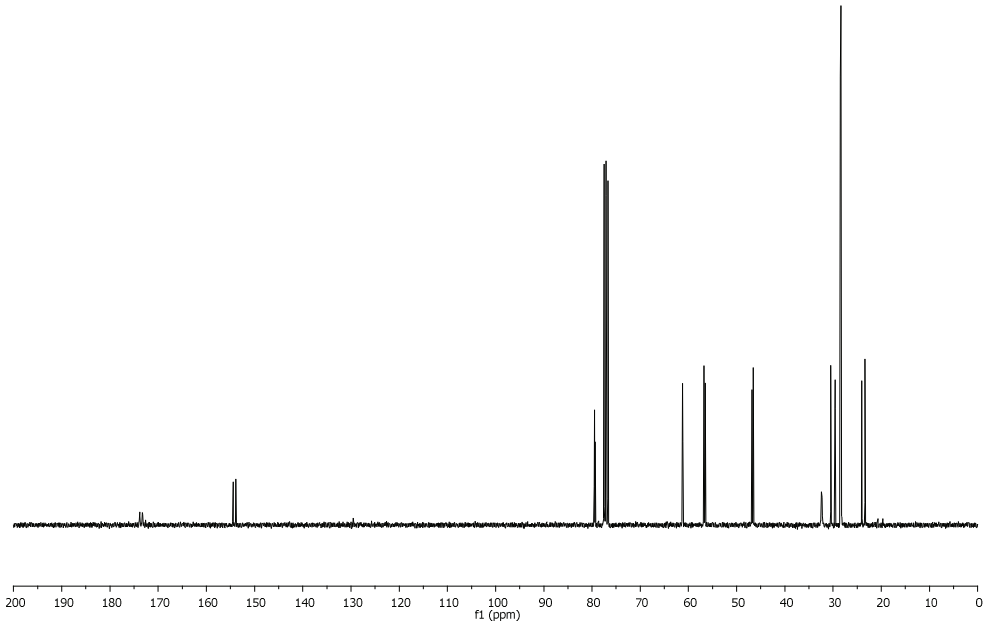
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OCH3
N
CH3
N
Boc
O

27

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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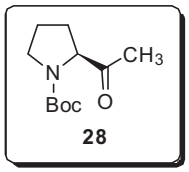
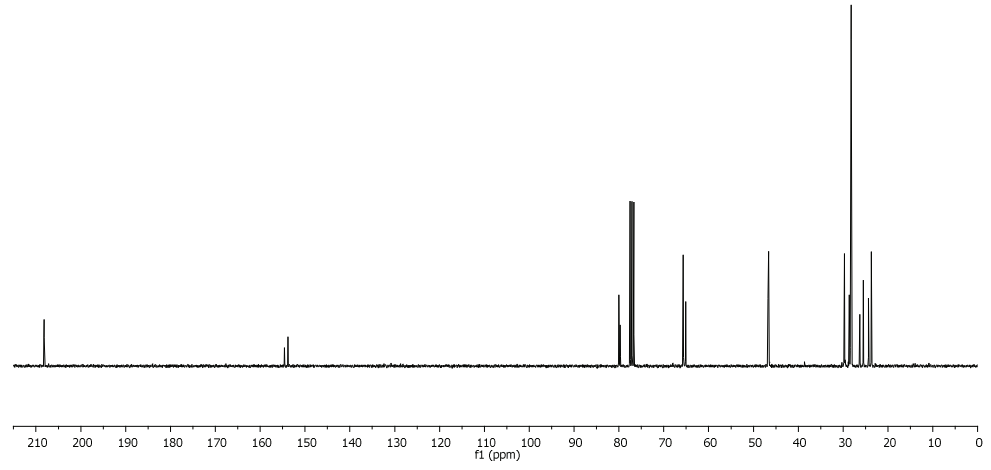
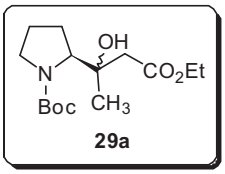
f1 (ppm)


CH3
N
Boc
O

28

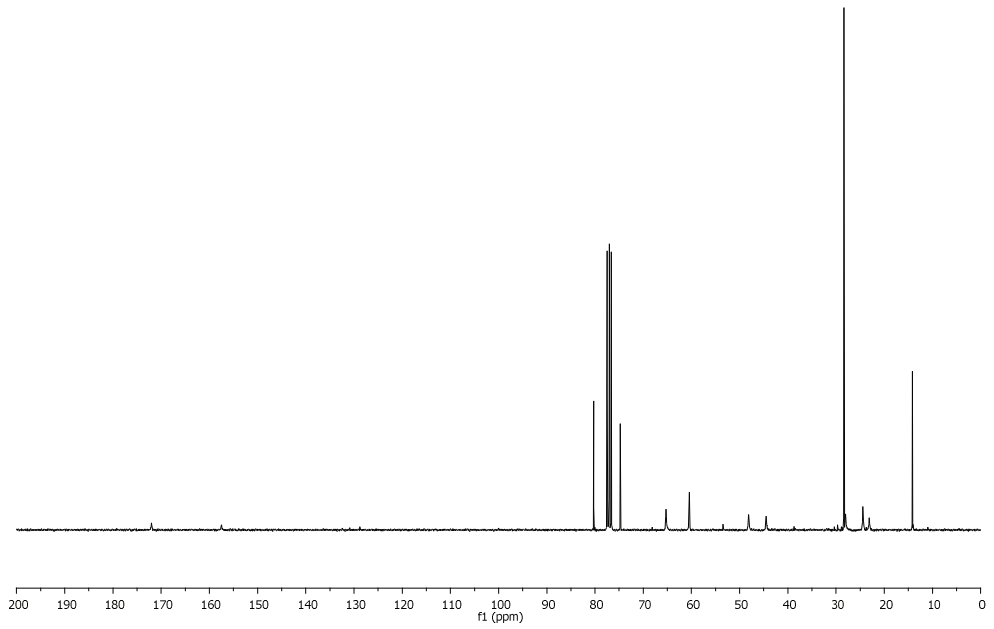
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
N
CO2Et
Boc
CH3

29a

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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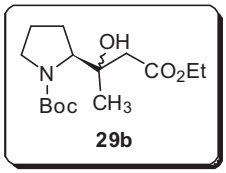
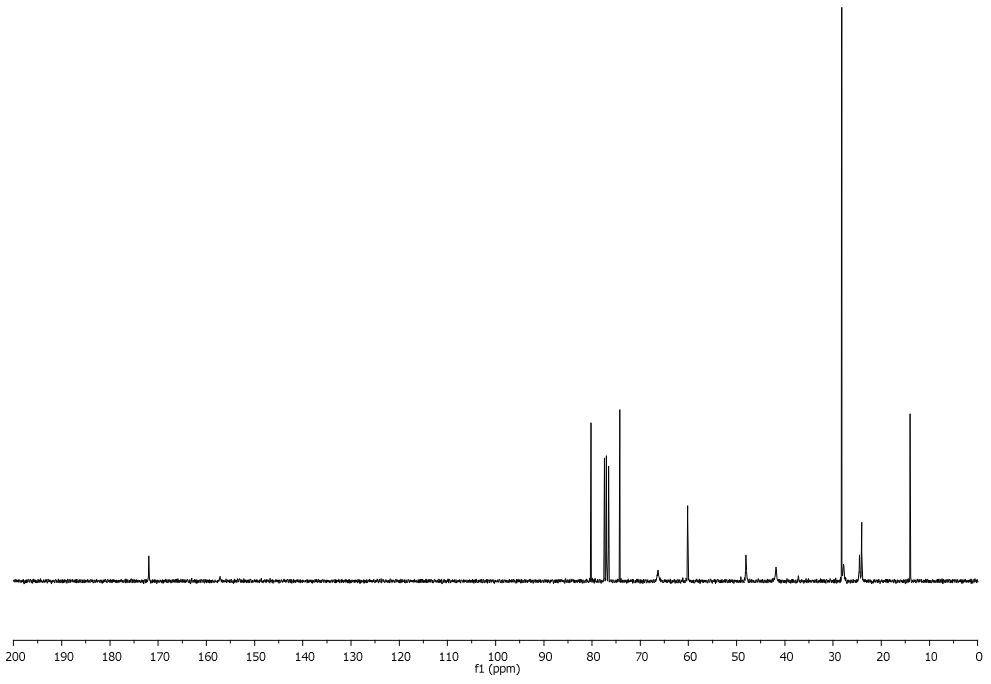
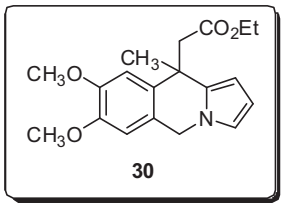
f1 (ppm)


OH
N
CO2Et
Boc
CH3

29b

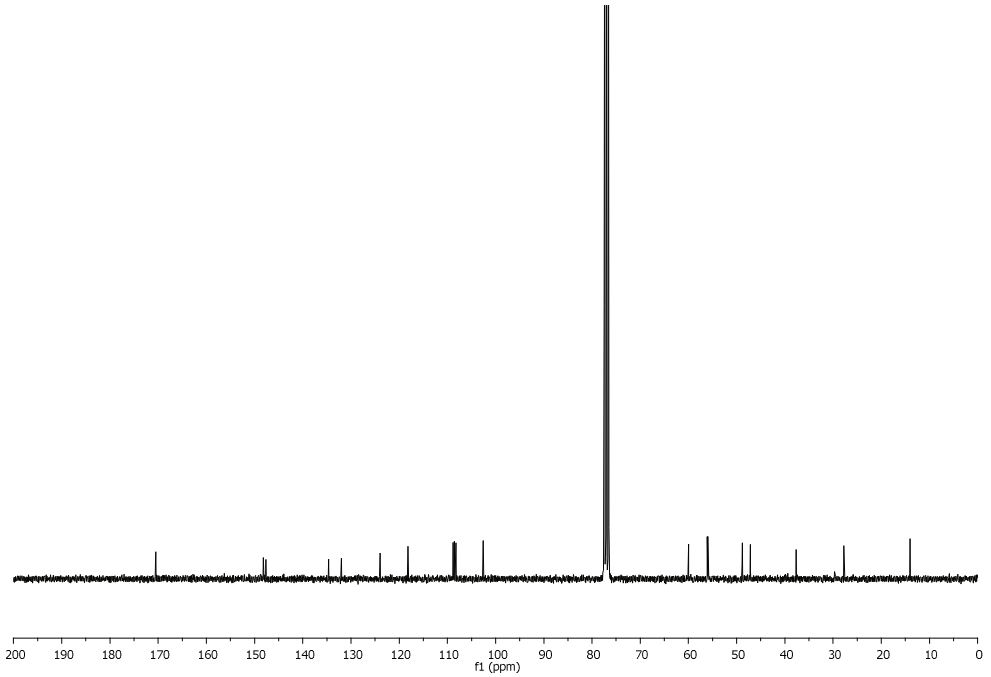
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

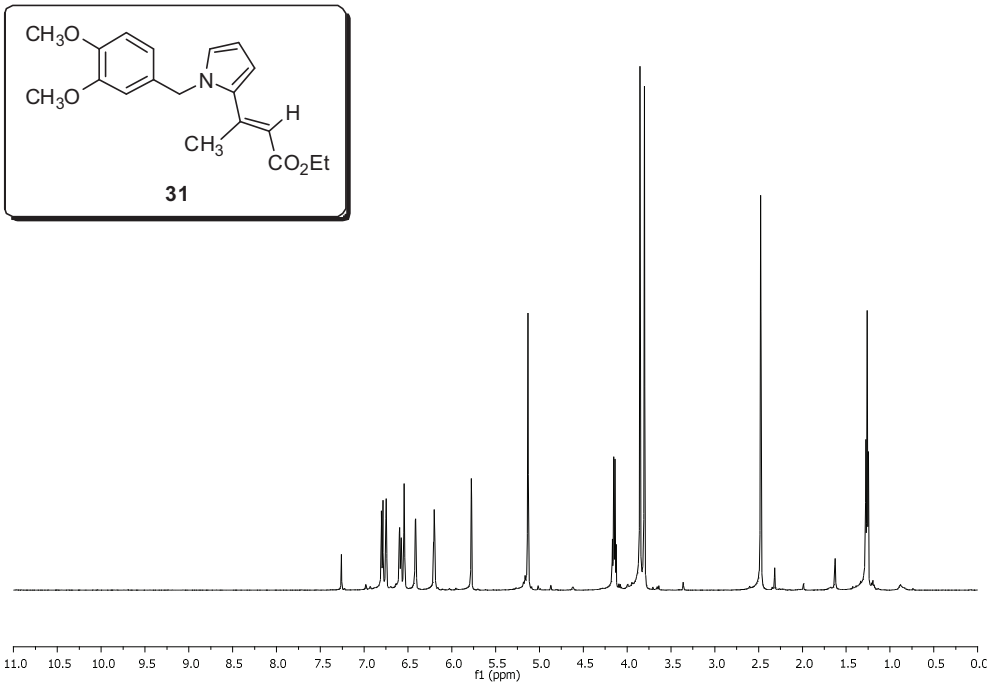

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

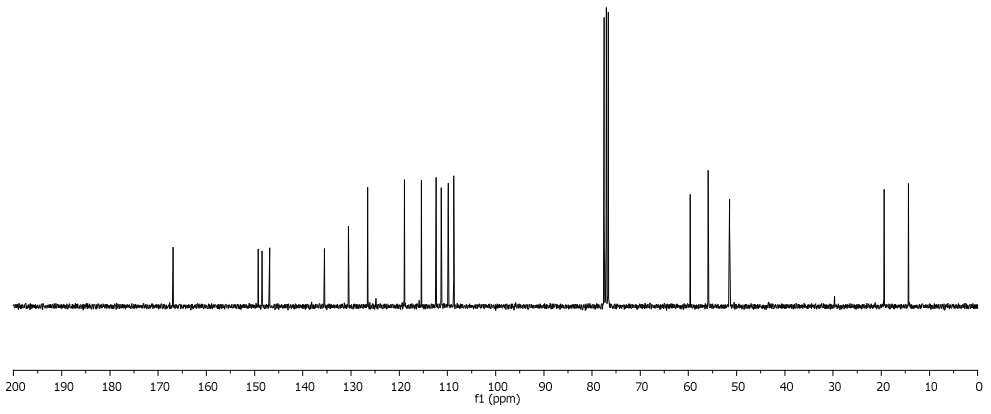

CO2Et
CH3
CH3O
CH3O
N

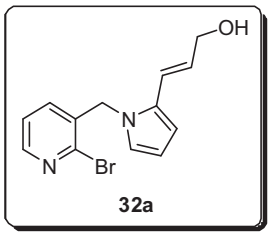
30

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

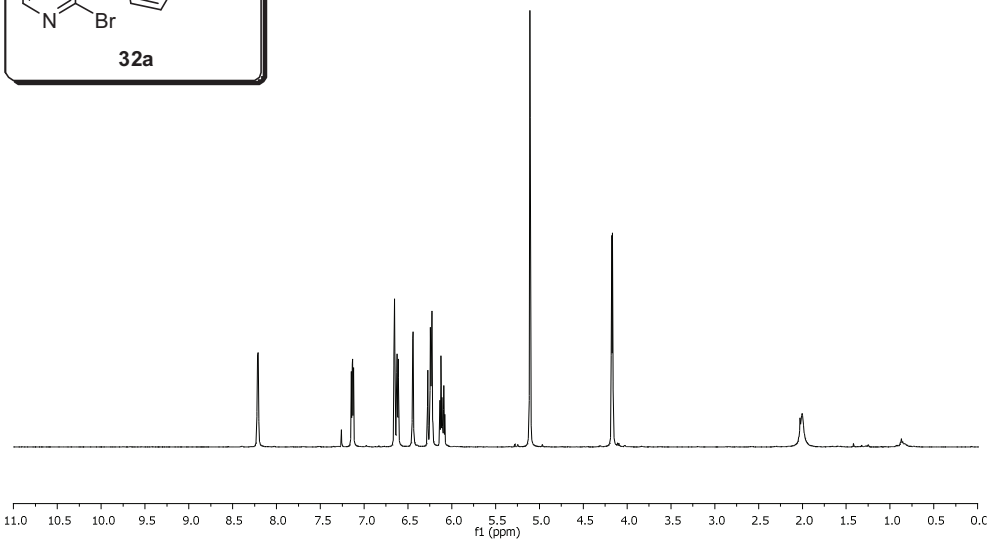

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

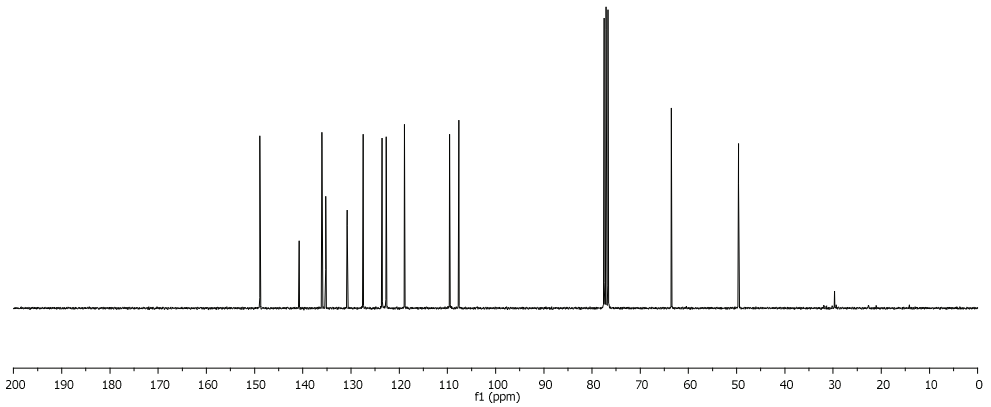

CH3O
CH3O
N
H
CH3
CO2Et
31
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

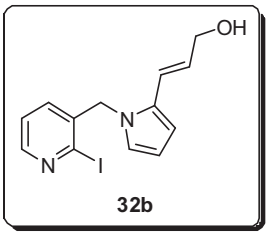

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
N
N
Br

32a

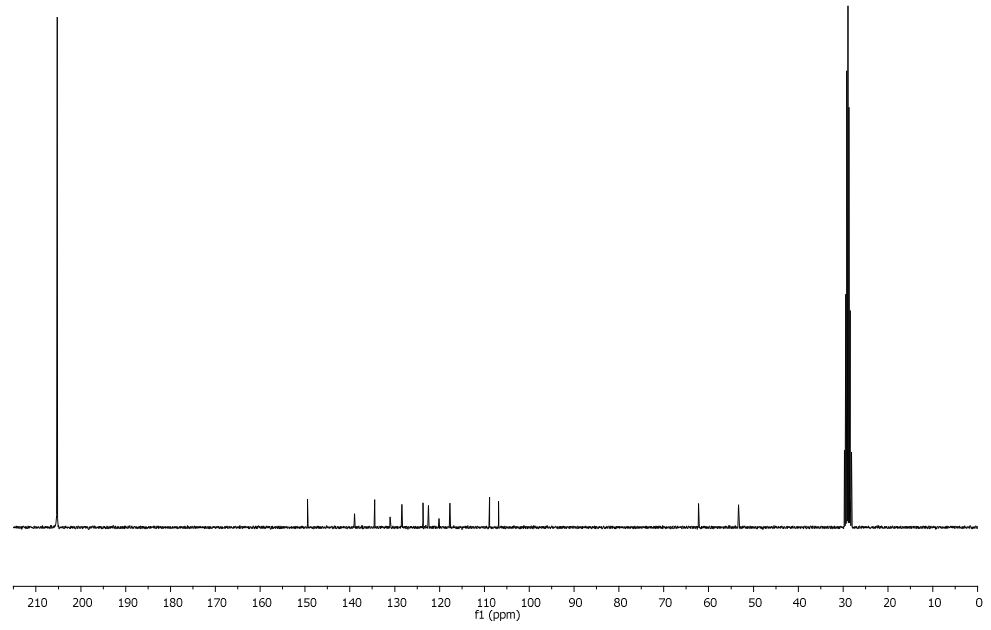

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

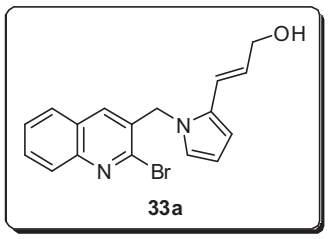

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
N
N
I

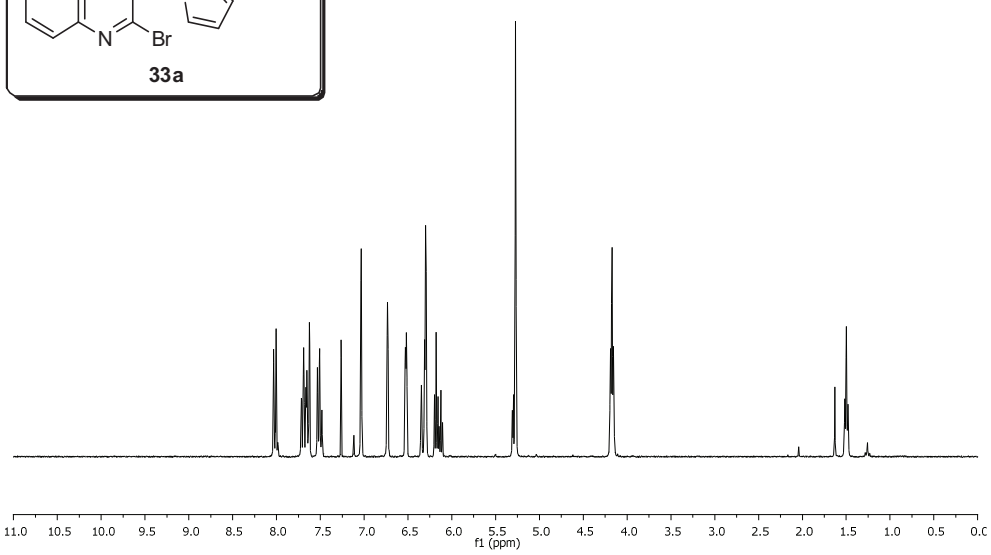
32b

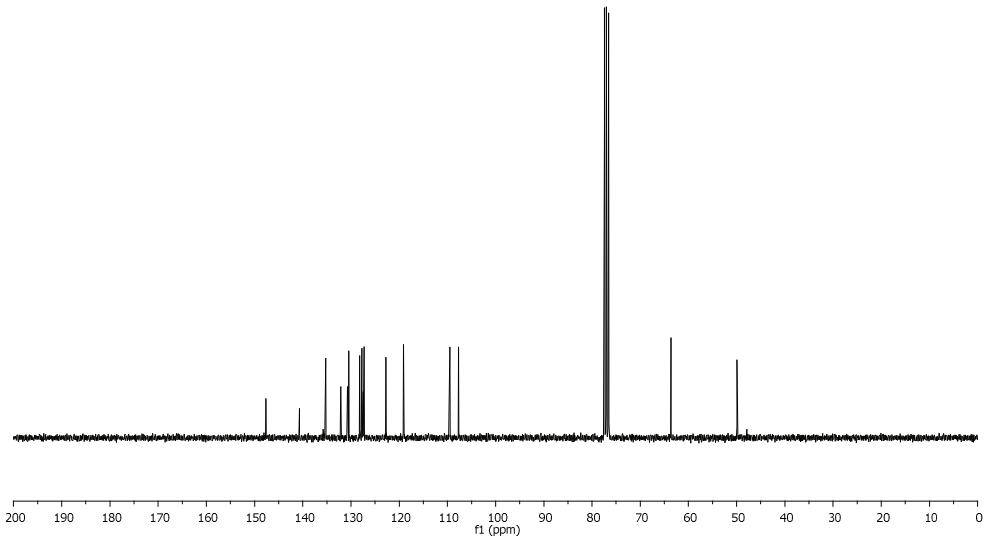
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

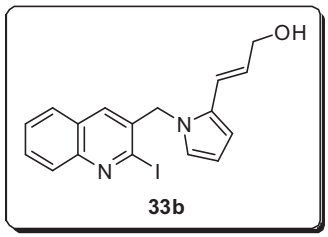

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
N
N
Br

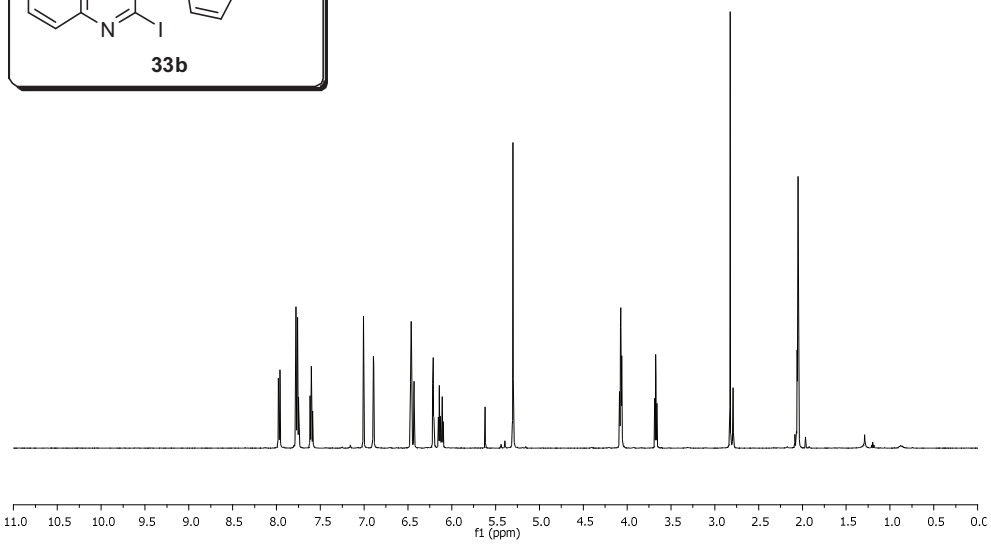
33a


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
N
N
I

33b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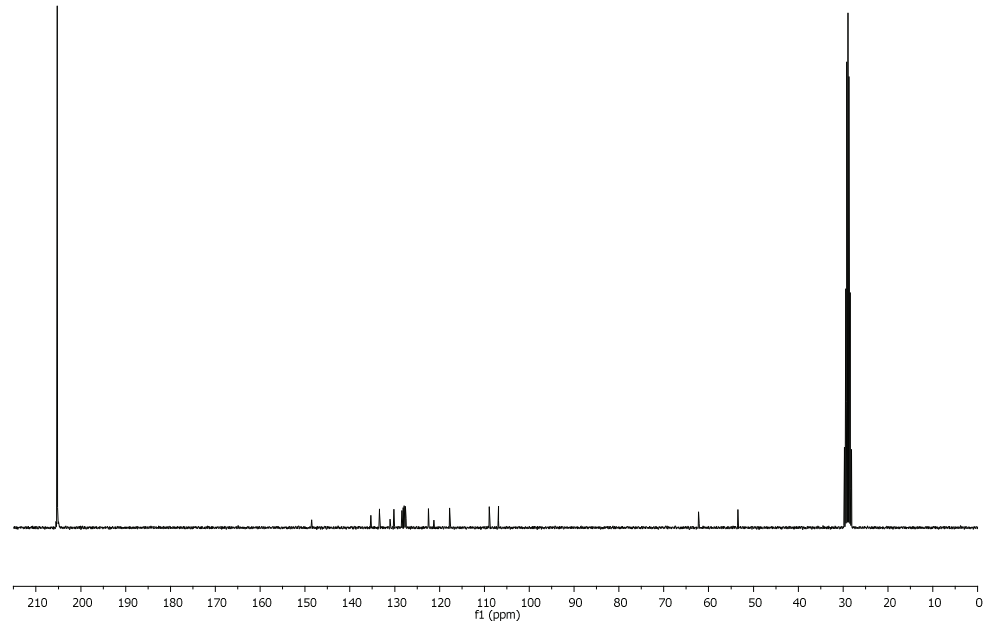
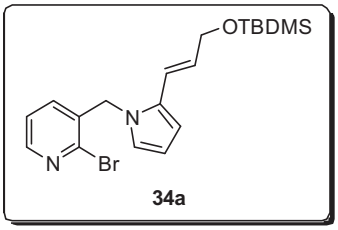
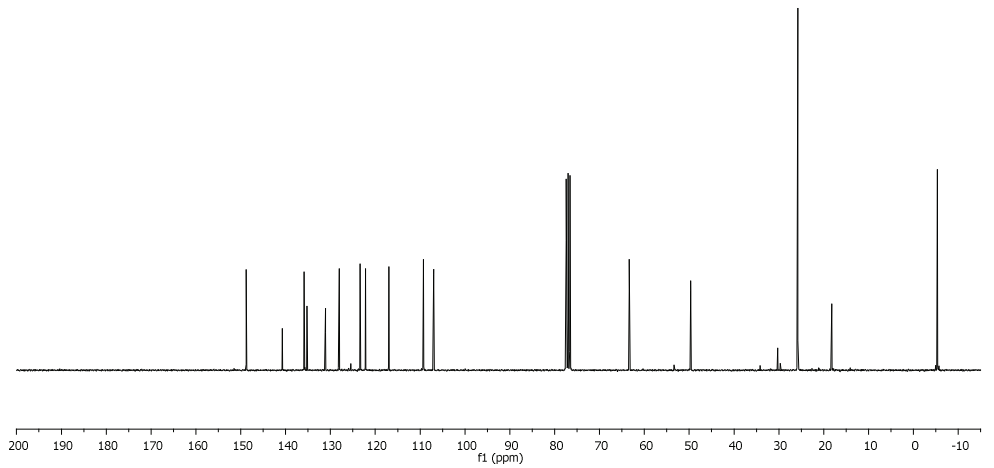
f1 (ppm)

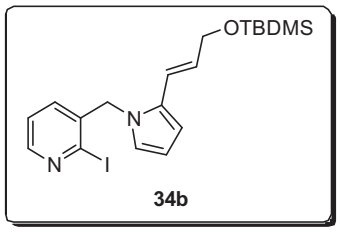

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OTBDMS
N
N
Br

34a

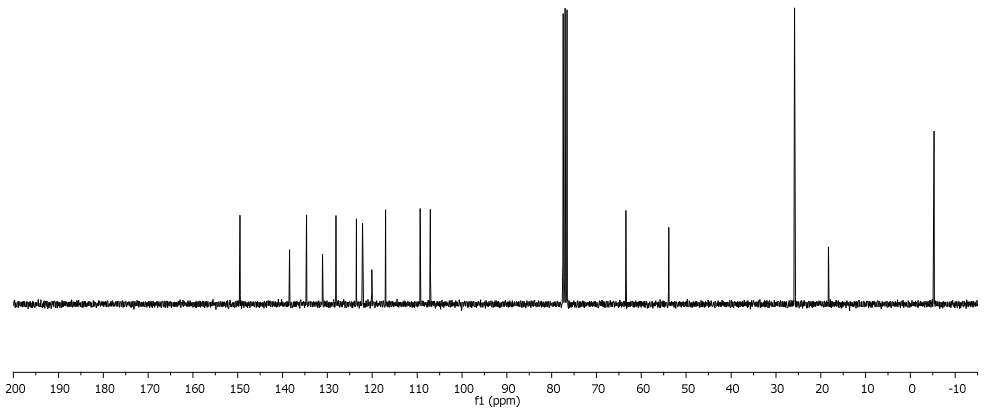
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OTBDMS
N
N
I

34b

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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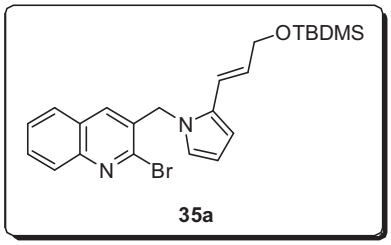
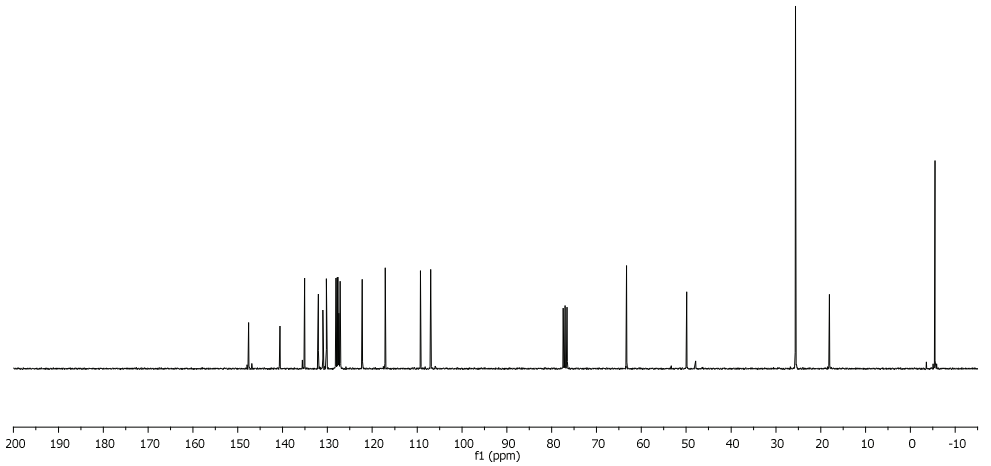
f1 (ppm)


OTBDMS
N
N
Br

35a

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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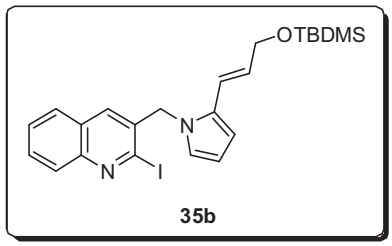
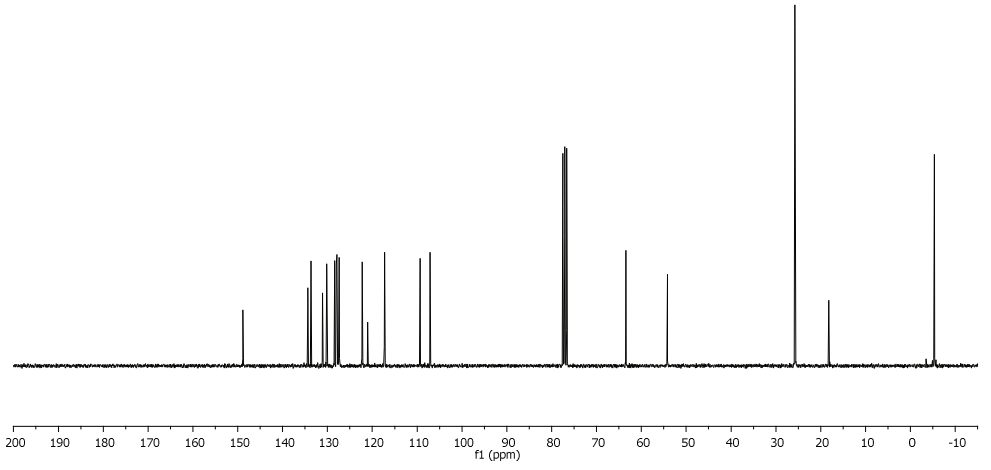
f1 (ppm)


OTBDMS
N
N
I

35b

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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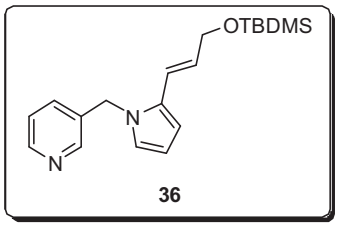
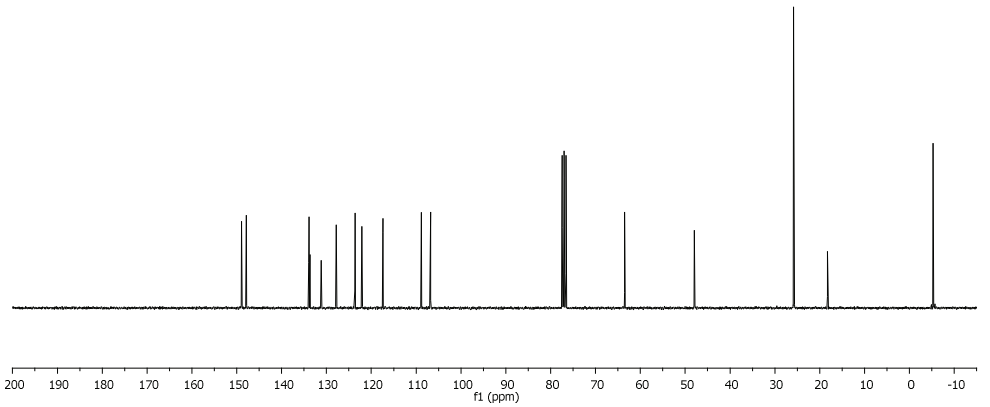
f1 (ppm)


OTBDMS
N
N

36

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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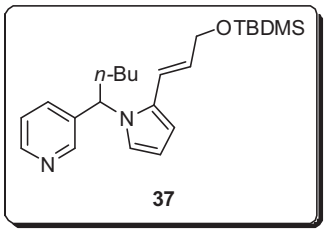
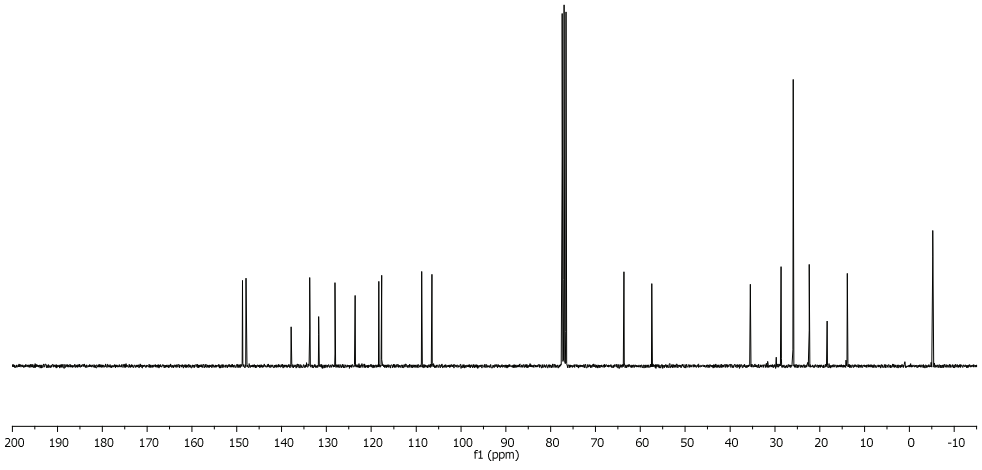
f1 (ppm)


OTBDMS
n-Bu
N
N

37

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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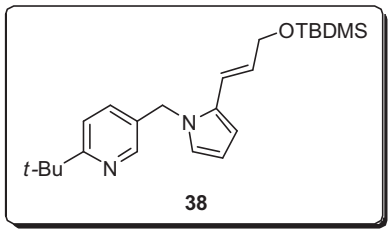
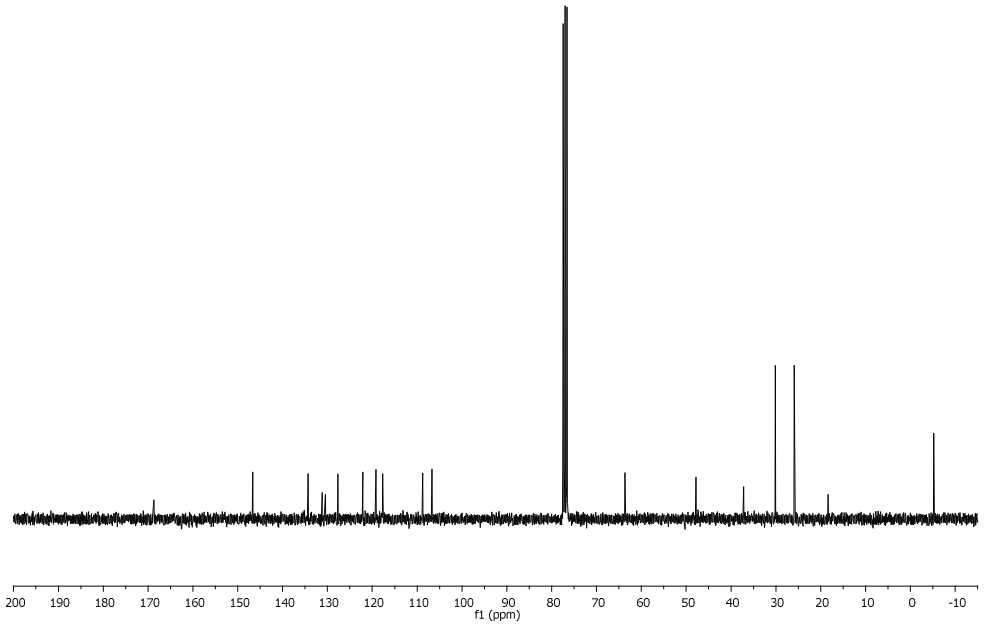
f1 (ppm)


OTBDMS
N
t-Bu
N

38

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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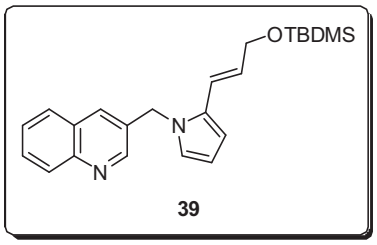
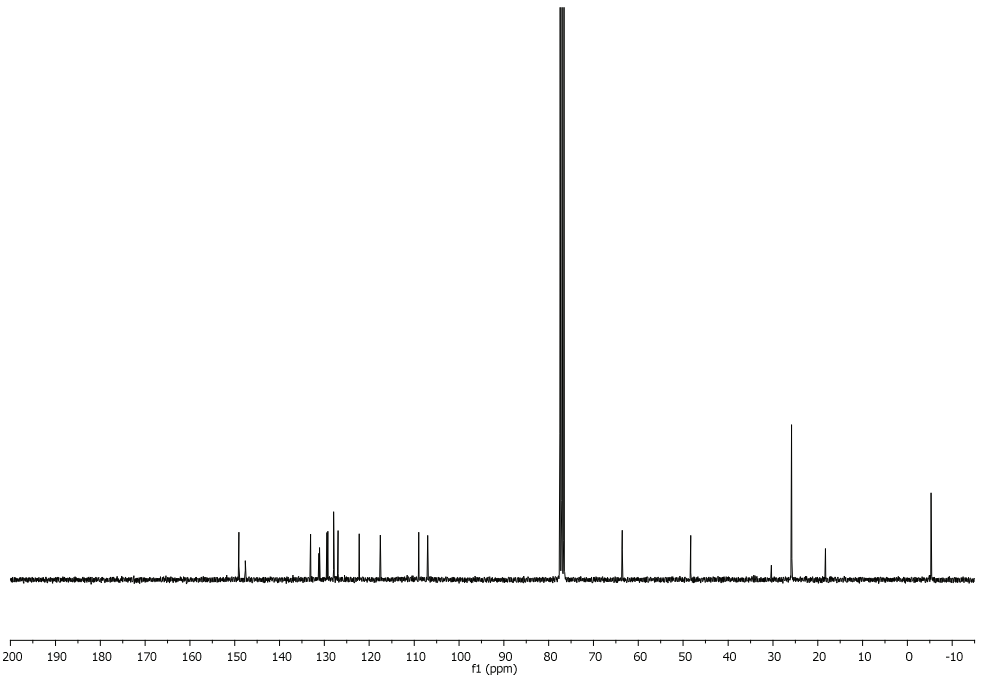
f1 (ppm)


OTBDMS
N
N

39

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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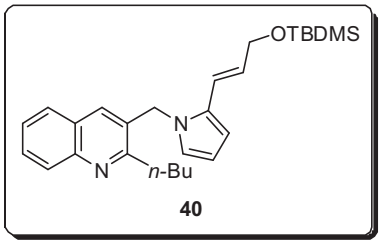
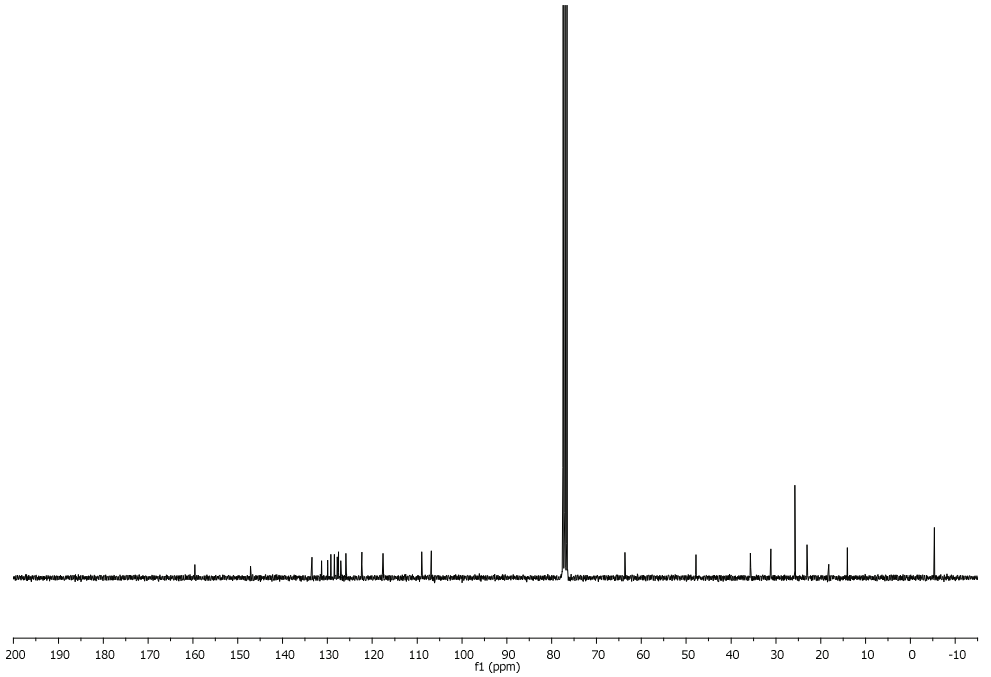
f1 (ppm)


OTBDMS
N
N
n-Bu

40

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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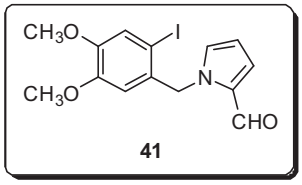
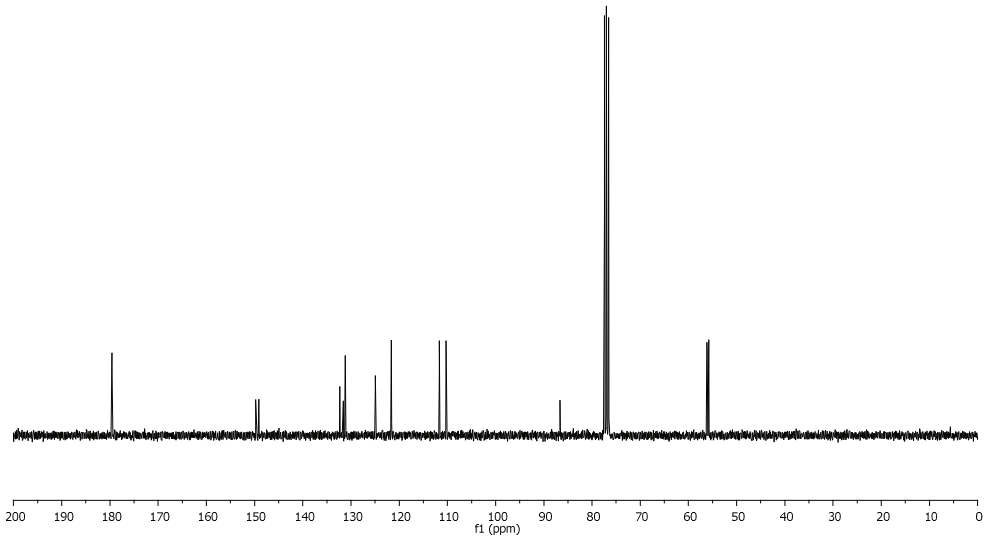
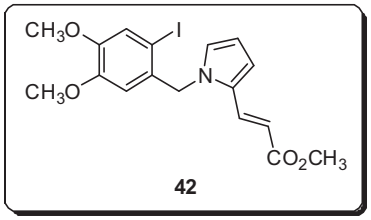
f1 (ppm)


CH3O
I
CH3O
N
CHO

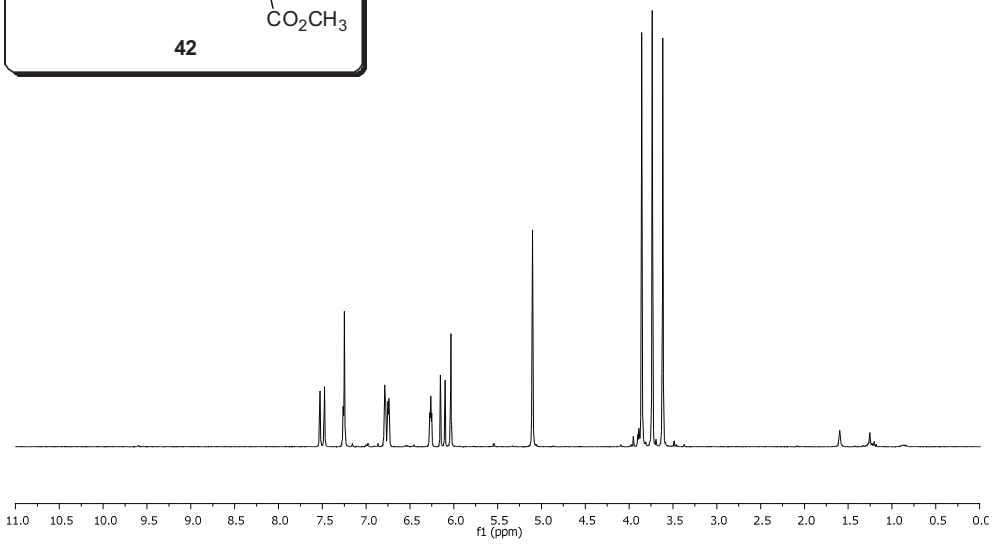
41

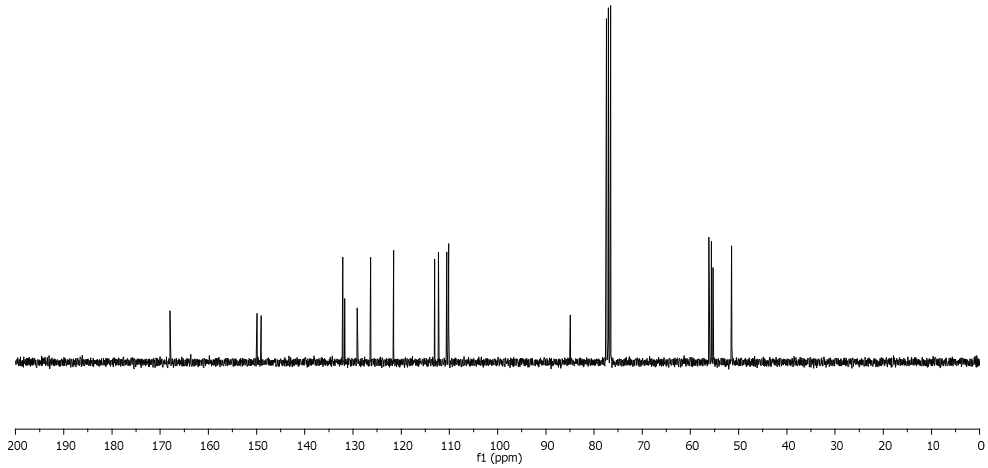
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

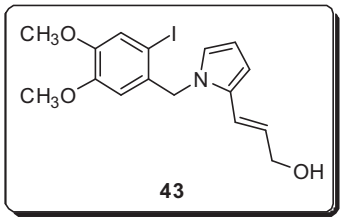

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3O
I
CH3O
N
CO2CH3

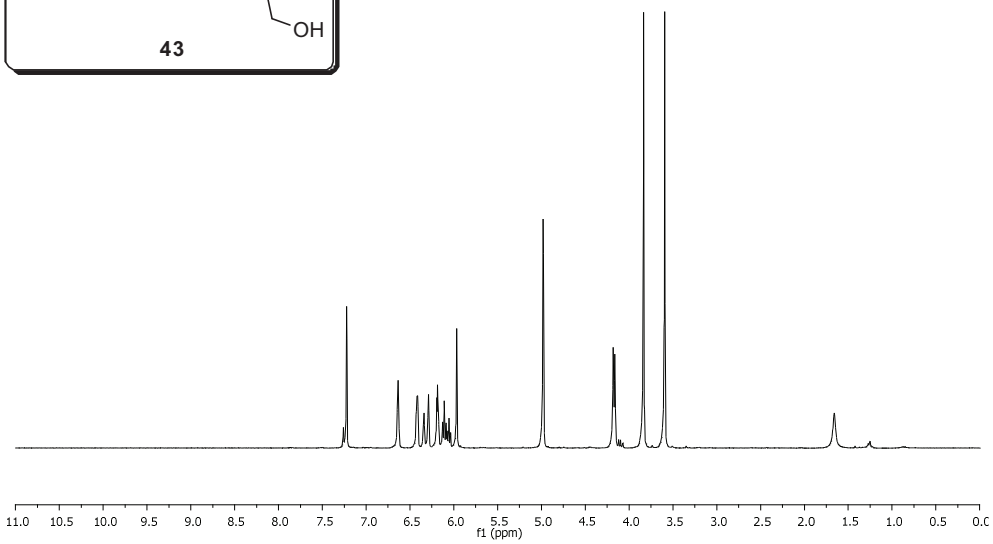
42

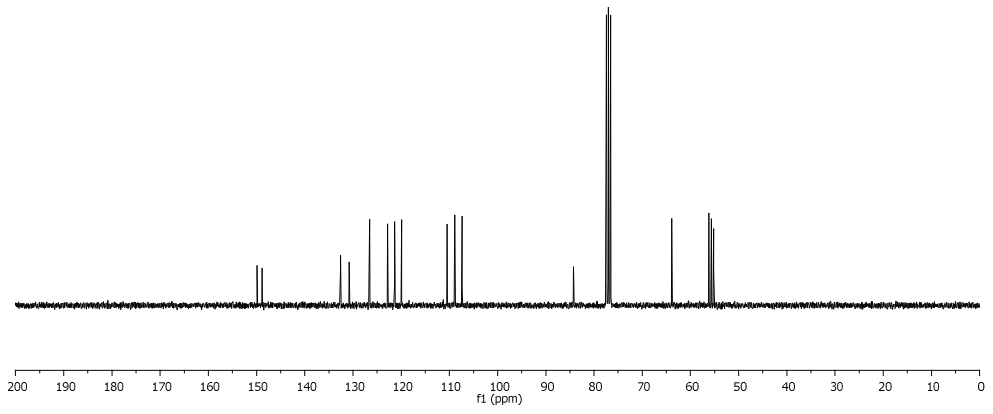

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

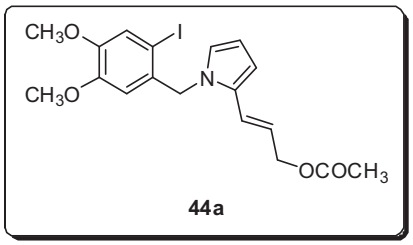

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3O
I
CH3O
N
OH

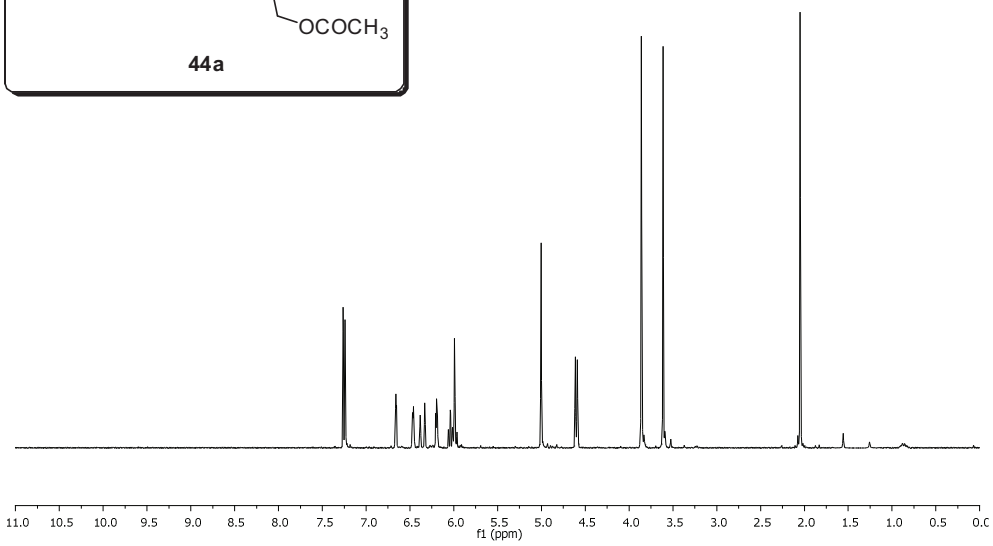
43


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3O
I
CH3O
N
OCOCH3

44a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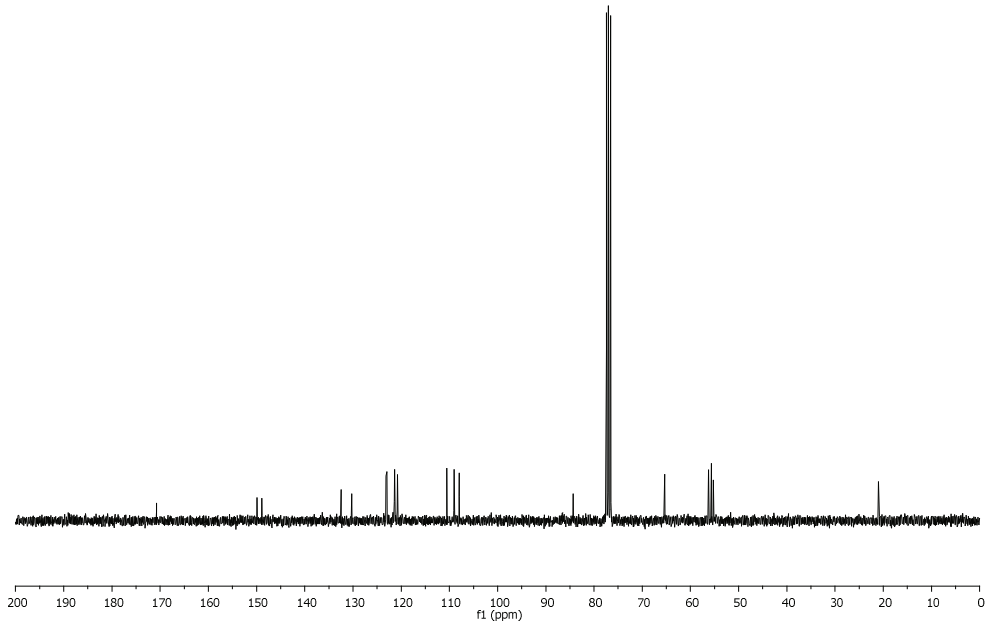
f1 (ppm)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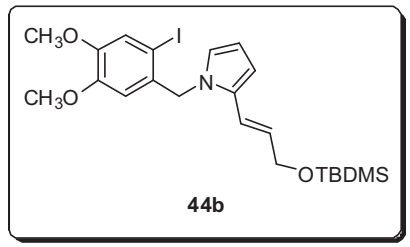
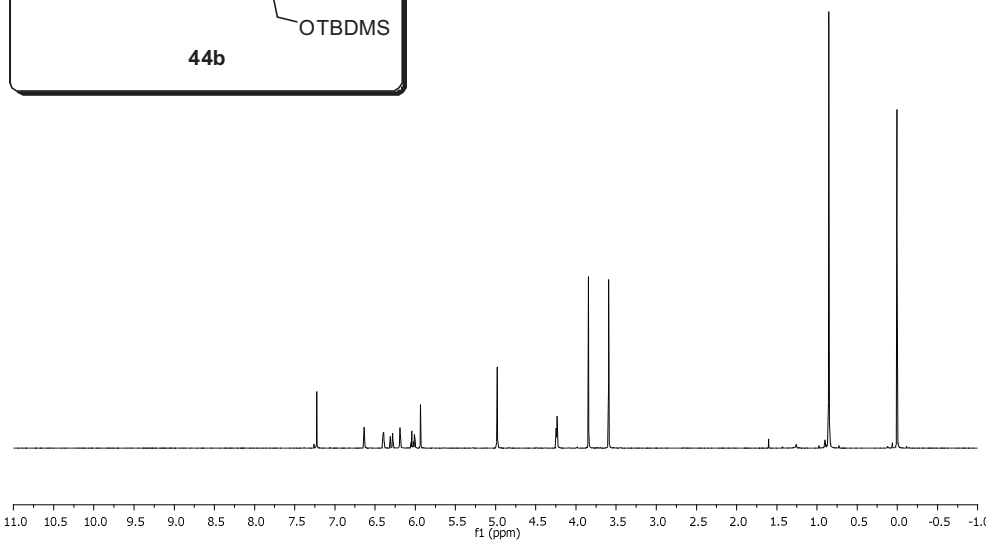
f1 (ppm)


CH3O
I
CH3O
N
OTBDMS

44b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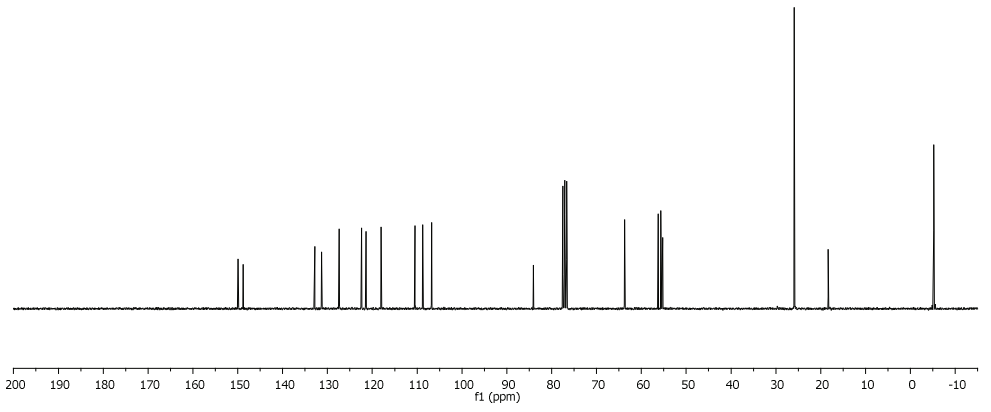
f1 (ppm)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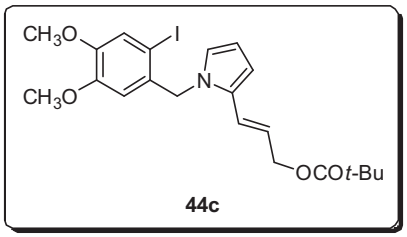
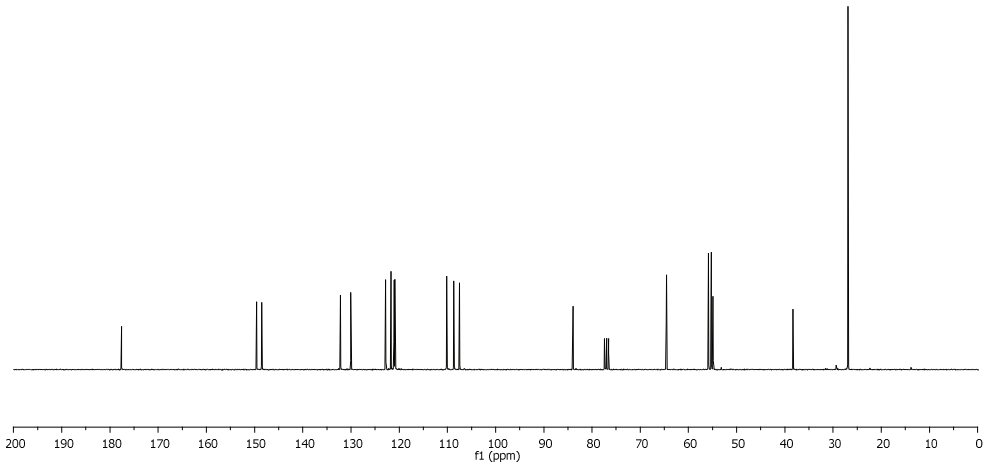
f1 (ppm)


CH3O
CH3O
I
N
OCOt-Bu

44c

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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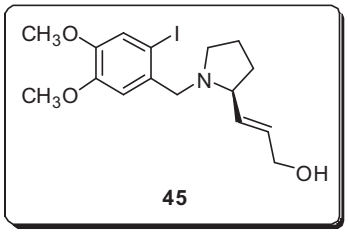
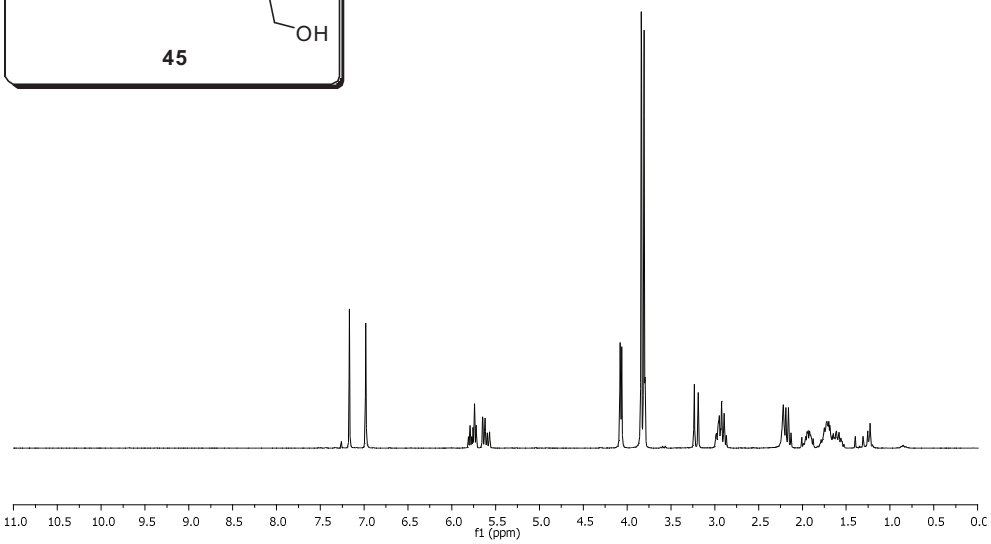
f1 (ppm)


CH3O
CH3O
I
N
OH

45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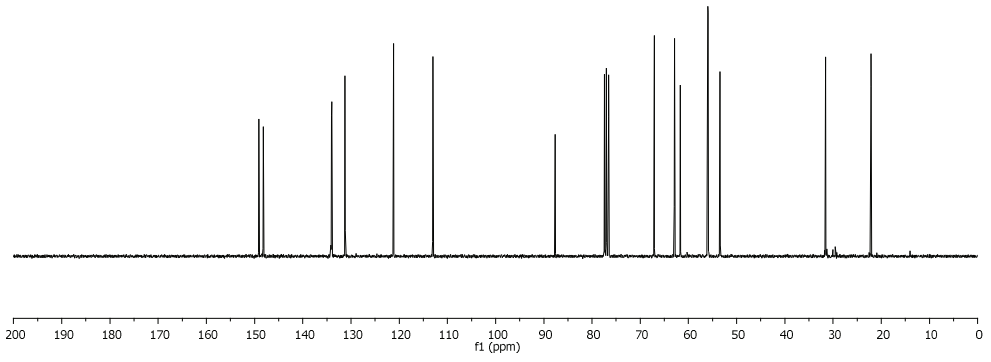
f1 (ppm)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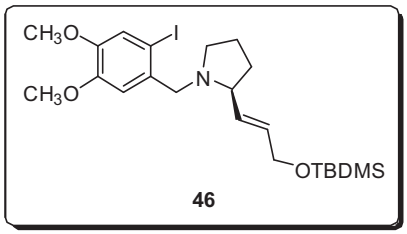
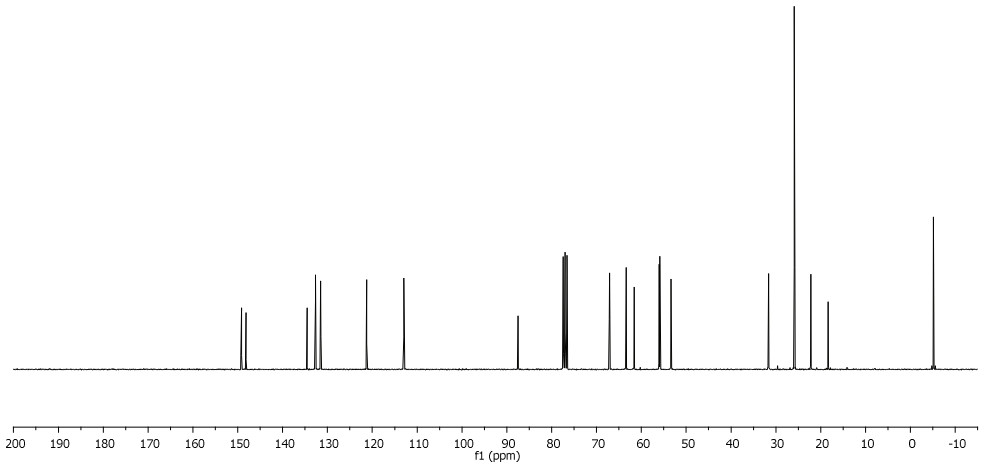
f1 (ppm)


CH3O
I
CH3O
N
OTBDMS

46

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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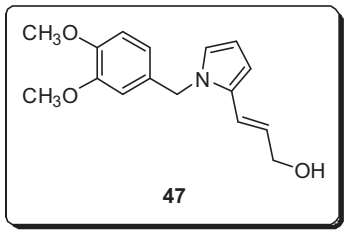
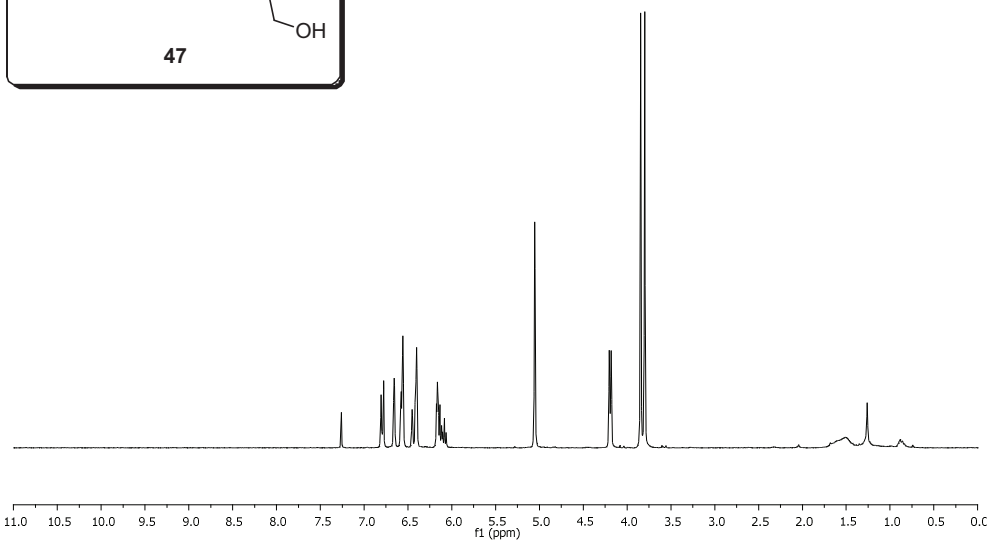
f1 (ppm)


CH3O
CH3O
N
OH

47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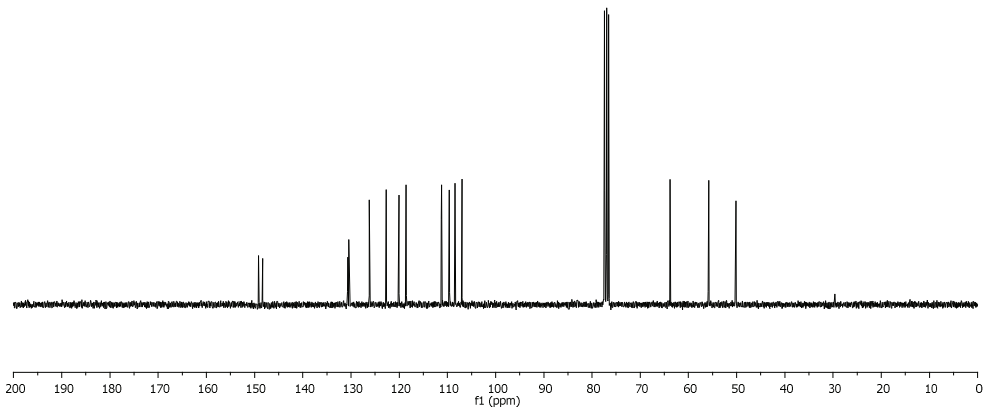
f1 (ppm)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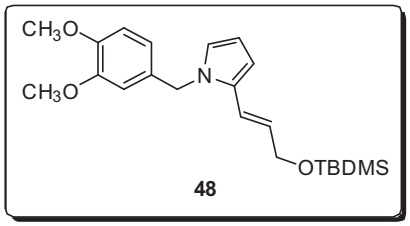
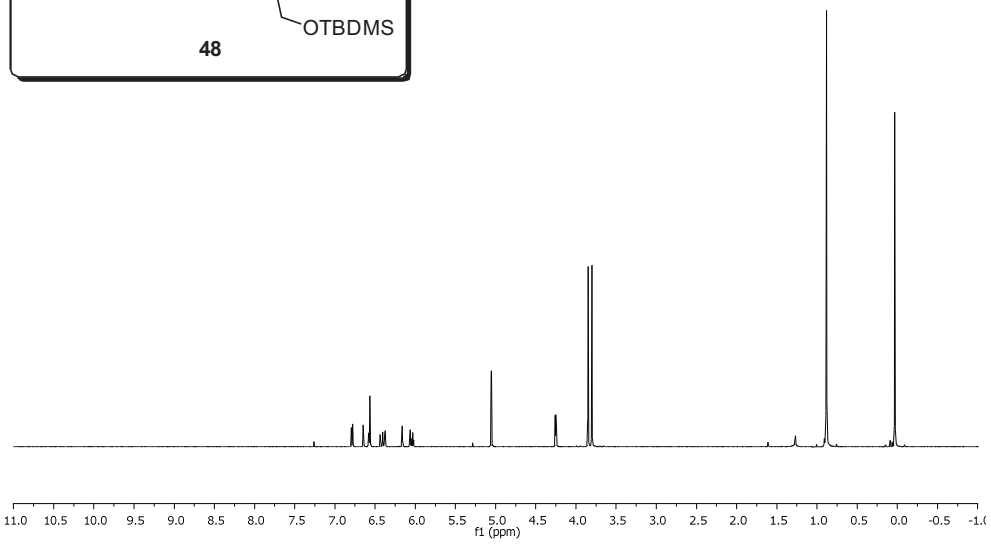
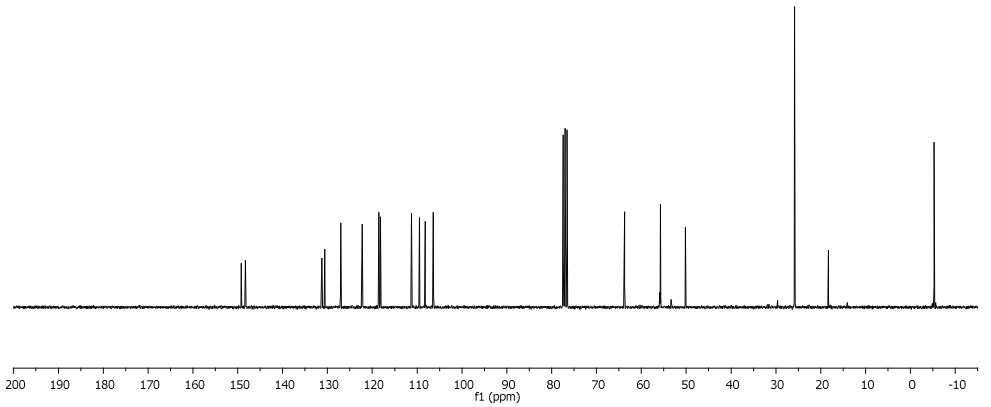
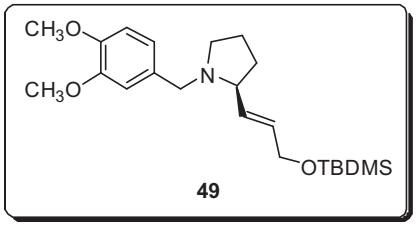
f1 (ppm)


CH3O
CH3O
N
OTBDMS

48

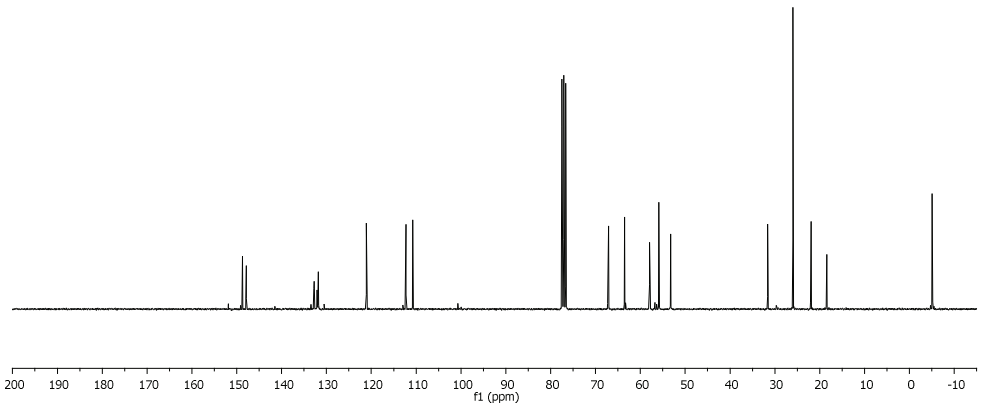

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CH3O
CH3O
N
OTBDMS

49

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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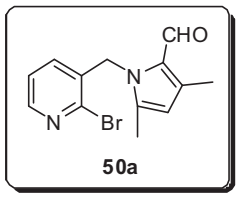
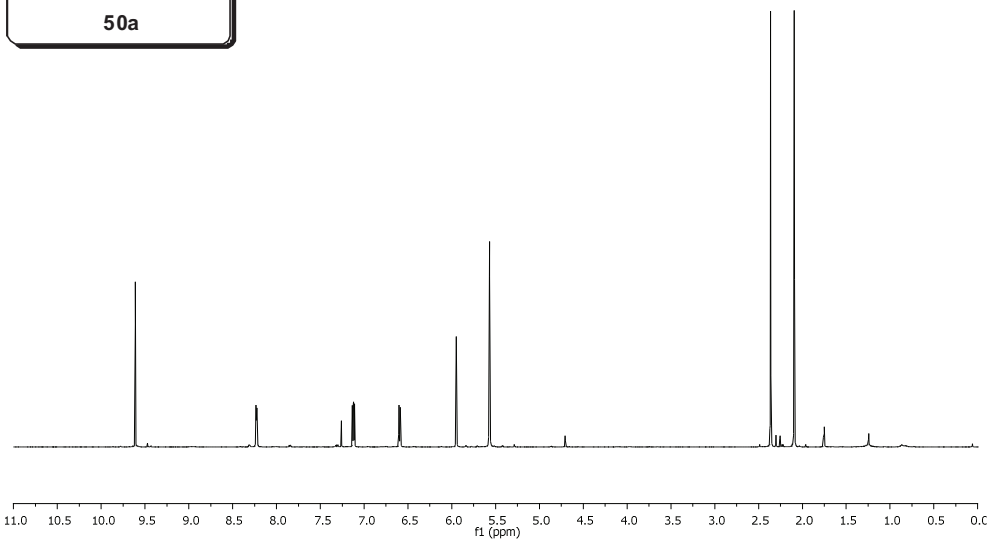
f1 (ppm)


CHO
N
N
Br

50a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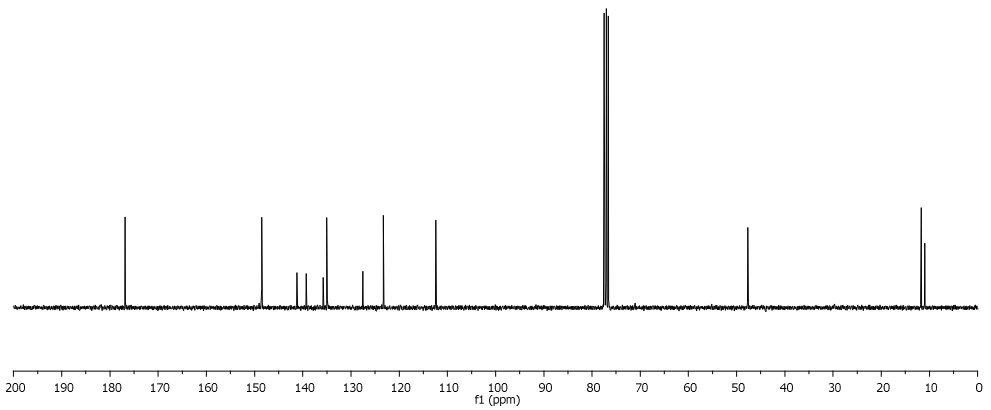
f1 (ppm)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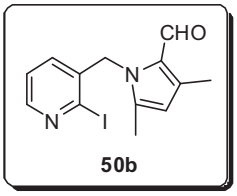
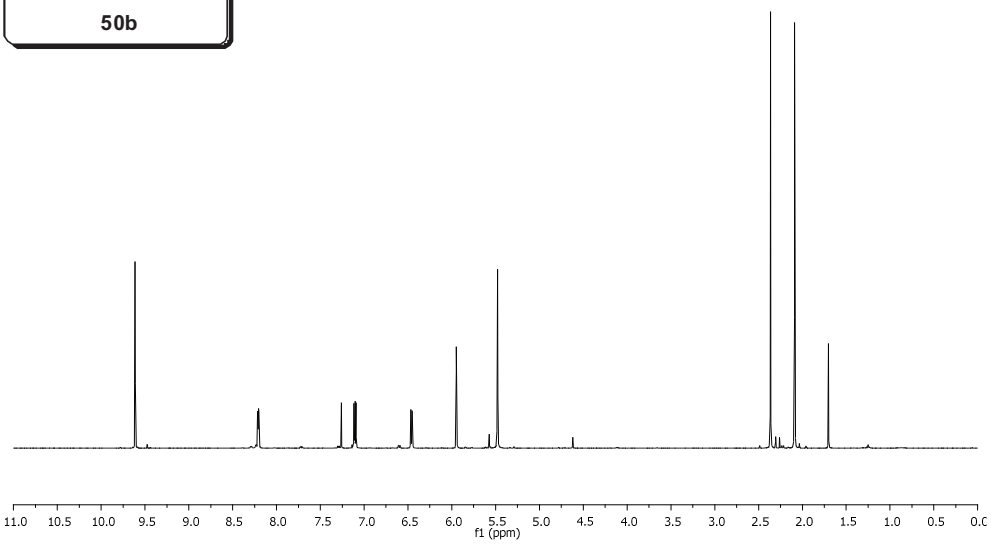
f1 (ppm)


CHO
N
N
I

50b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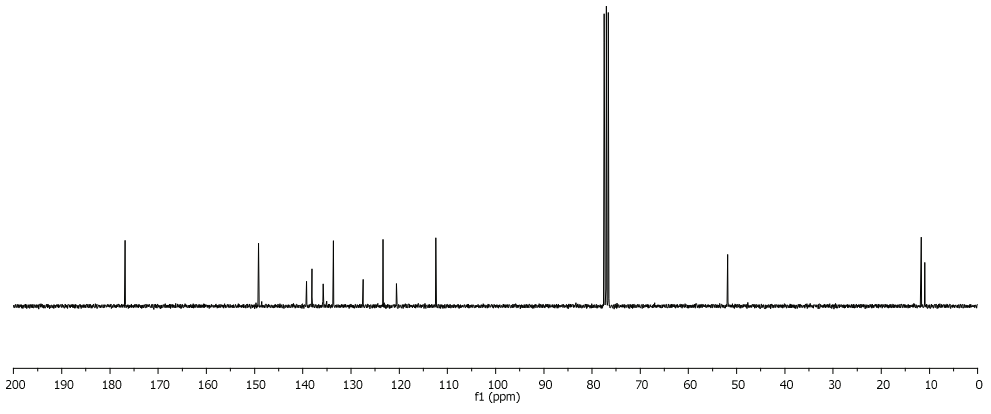
f1 (ppm)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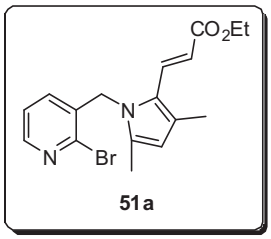
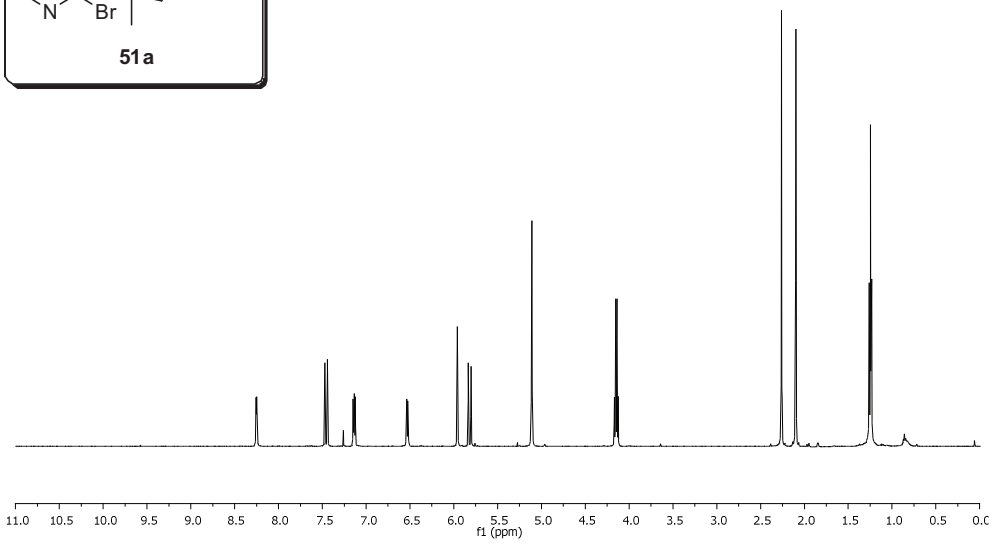
f1 (ppm)


CO2Et
N
N
Br

51a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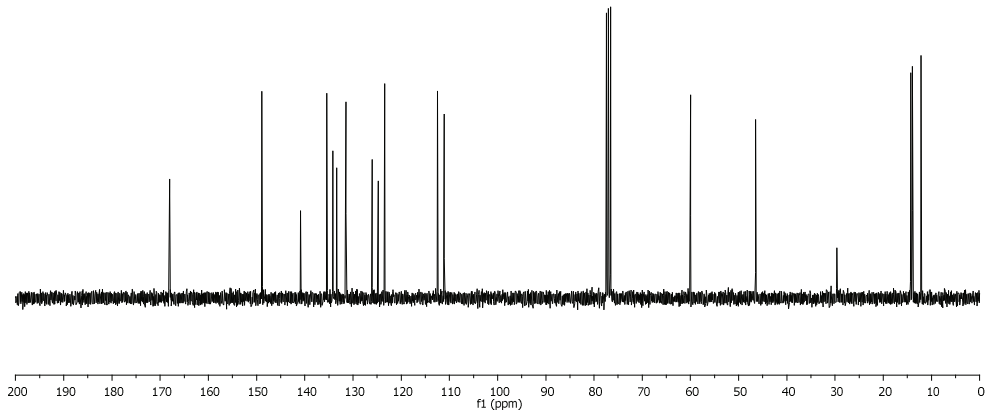
f1 (ppm)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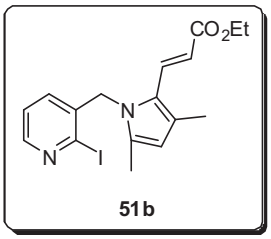
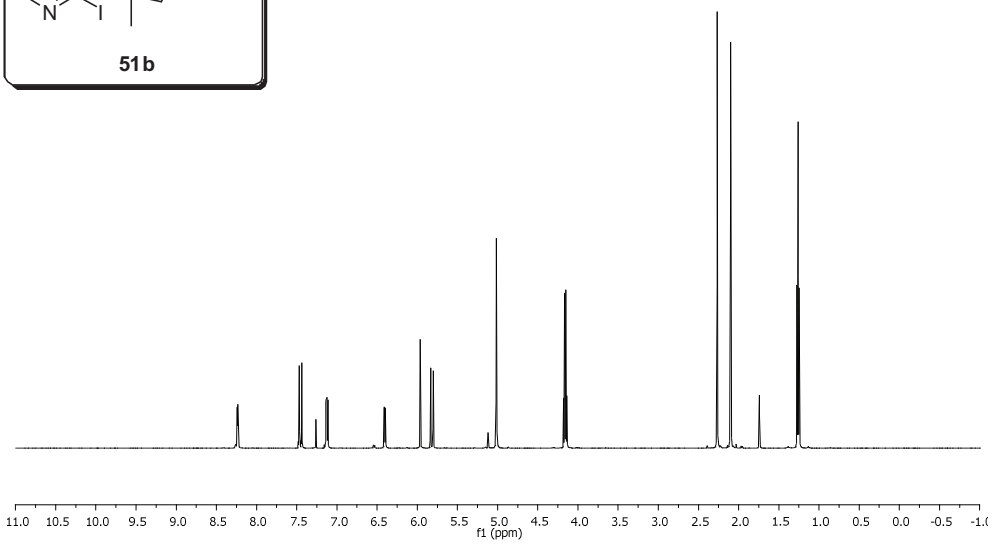
f1 (ppm)


CO2Et
N
N
I

51b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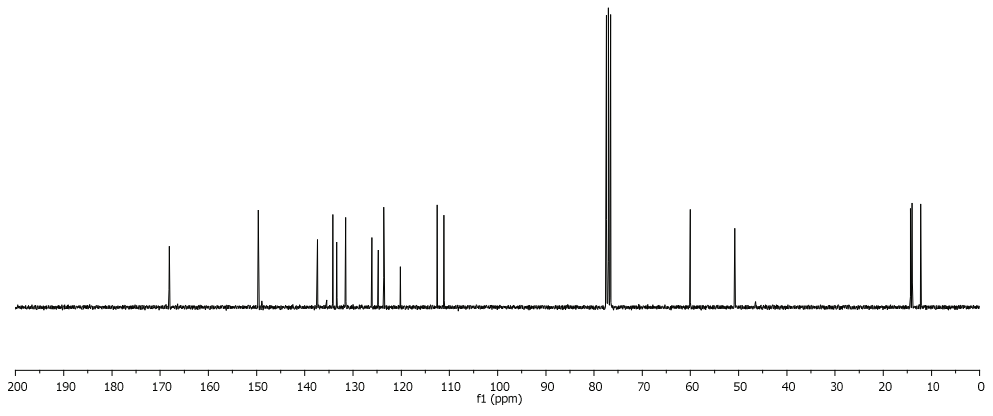
f1 (ppm)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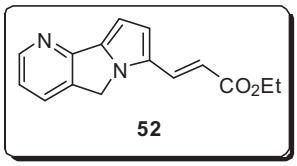
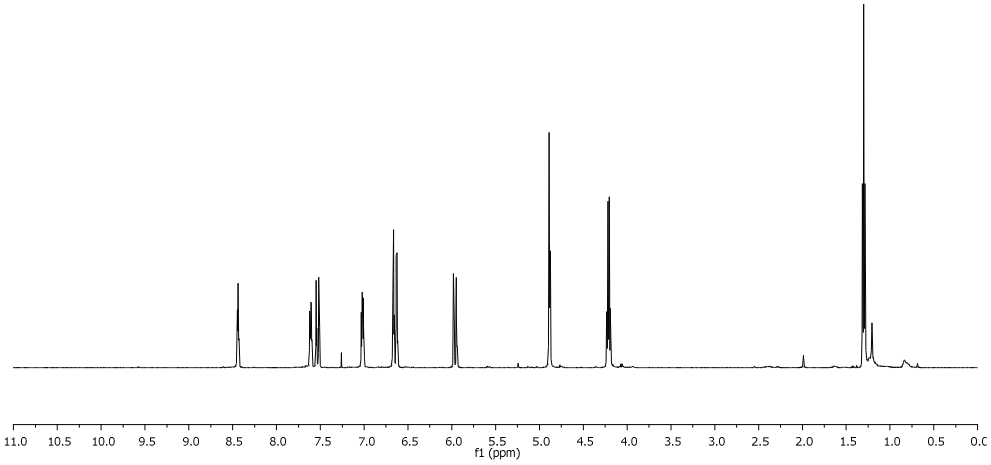
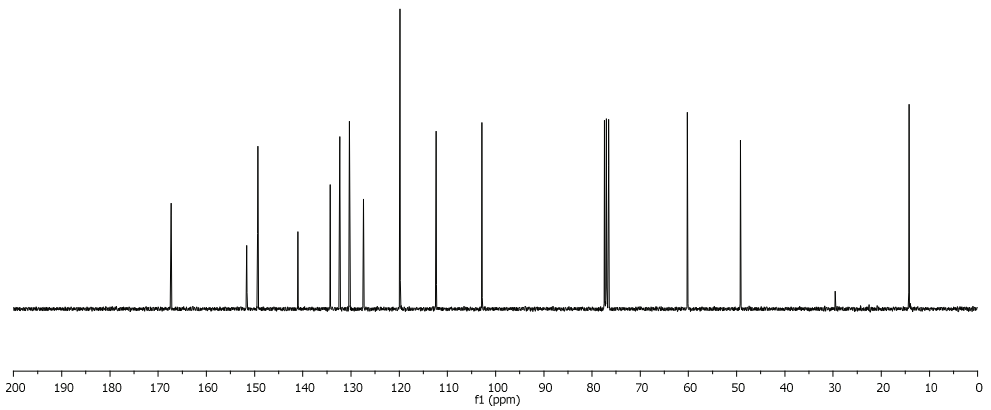
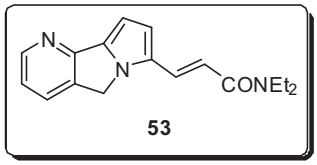
f1 (ppm)


N
N
CO2Et

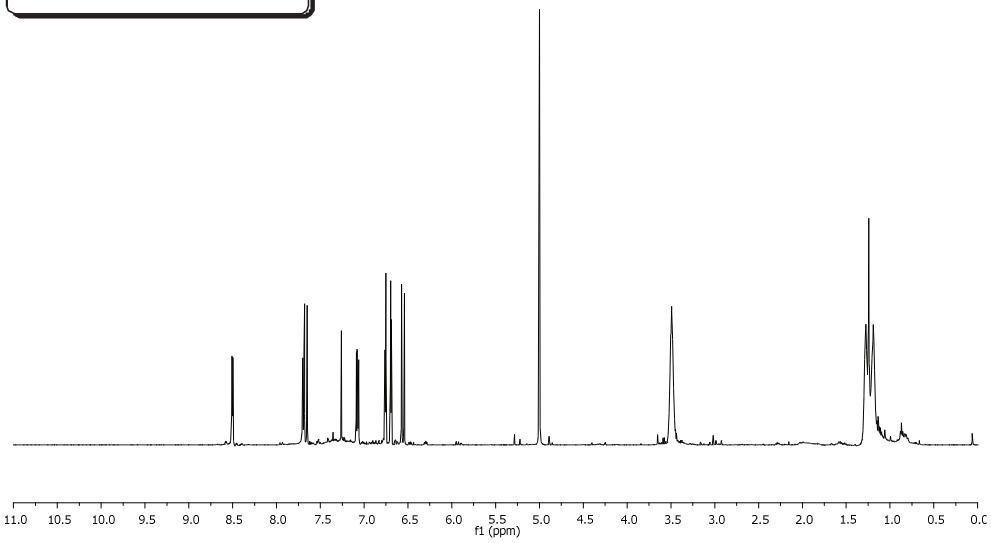
52

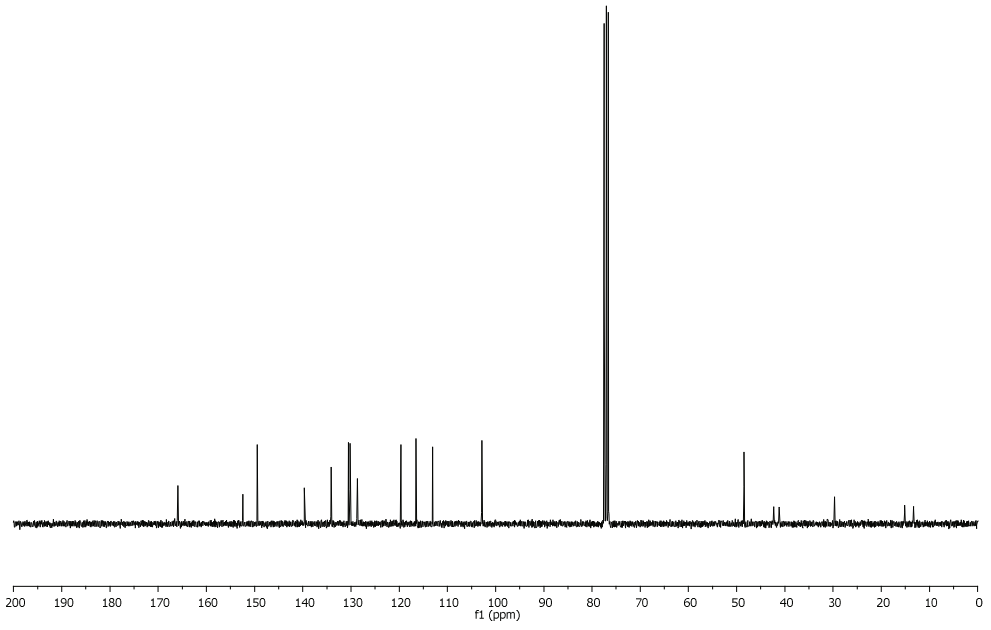

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

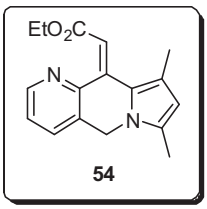

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


N
N
CONEt2

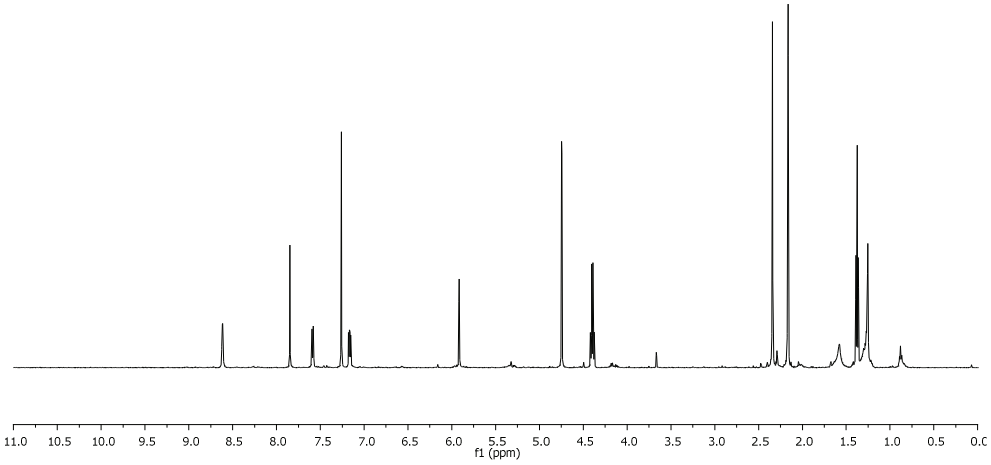
53

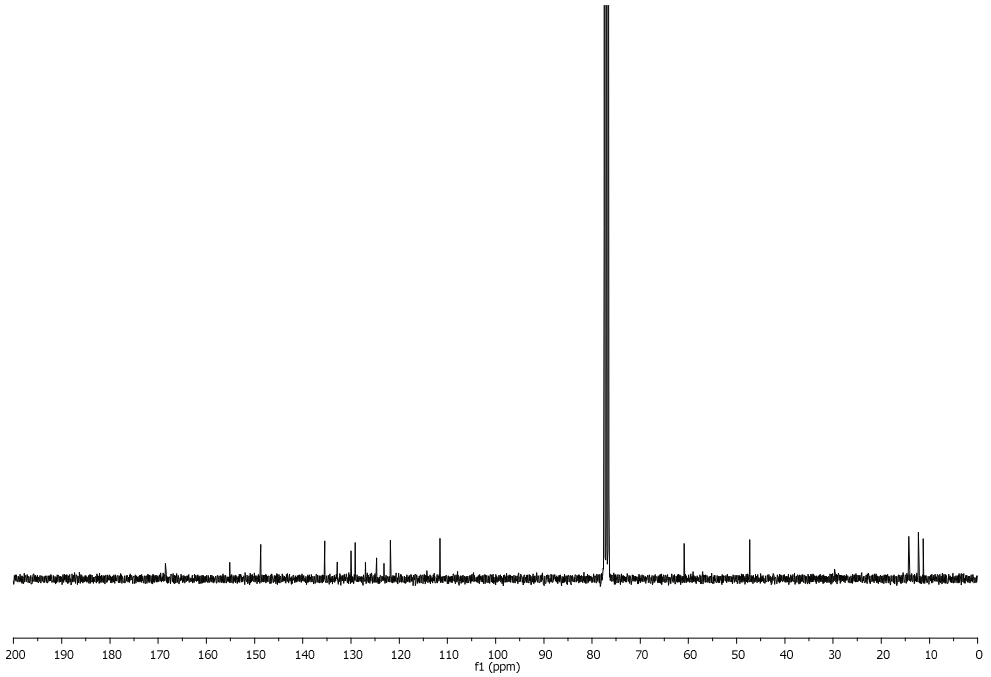

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


EtO2C
N
N

54


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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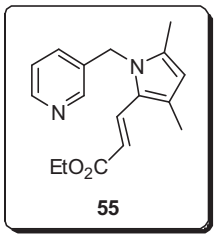
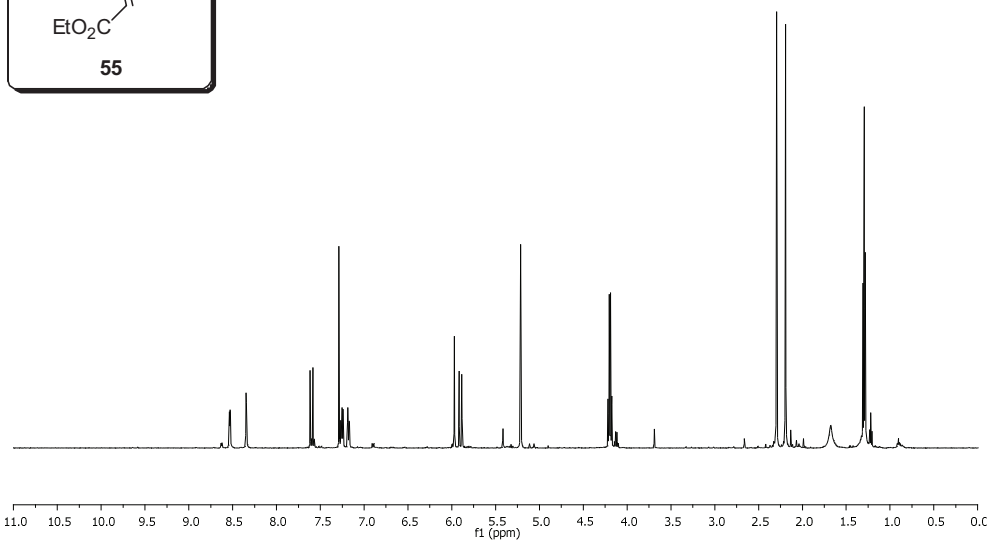
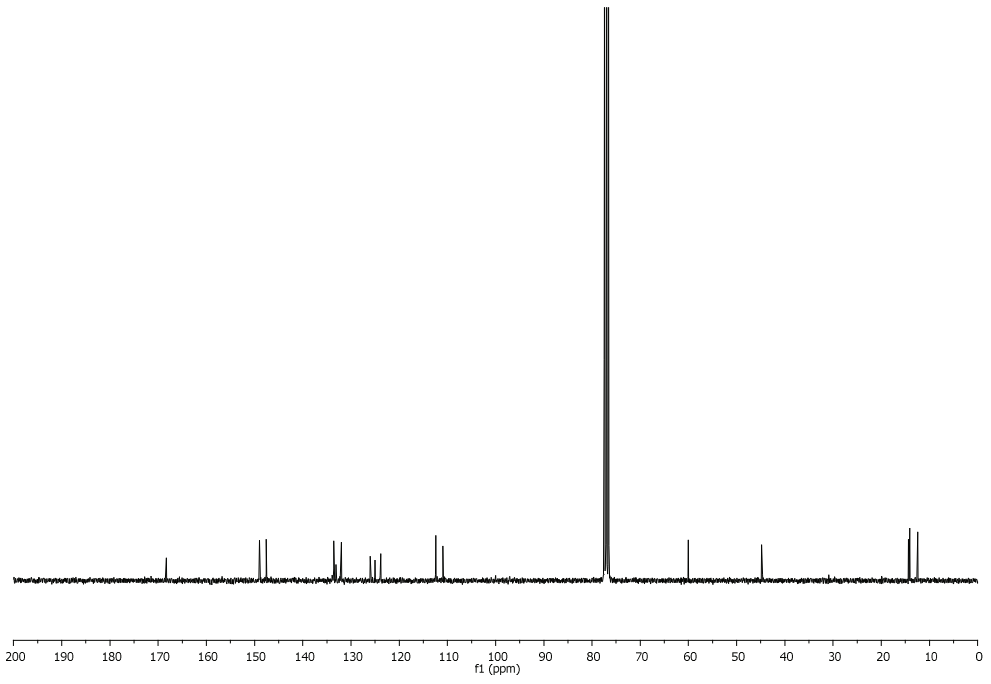
f1 (ppm)


N
N
EtO2C

55


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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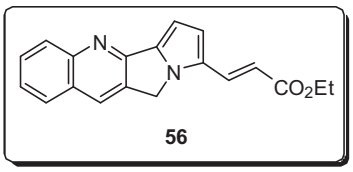
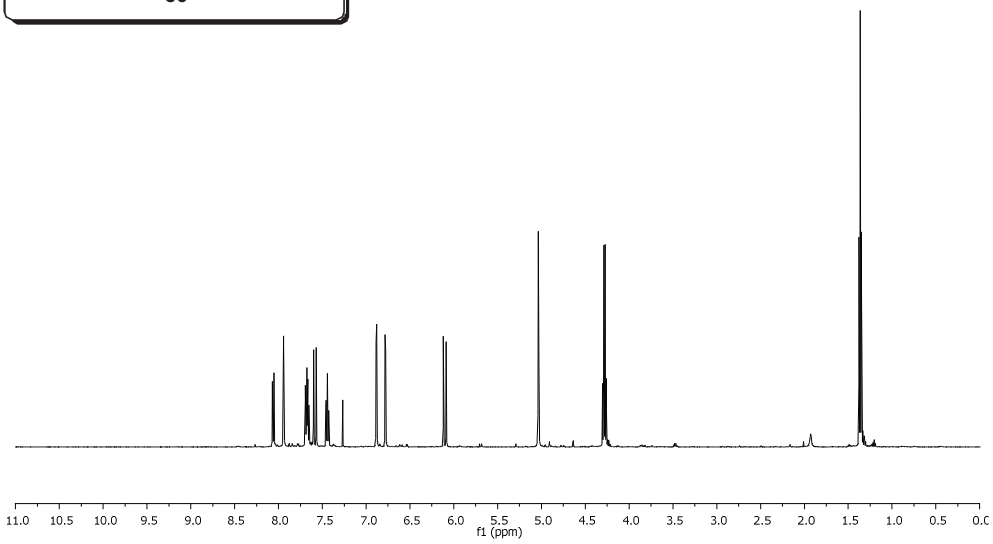
f1 (ppm)


N
N
CO2Et

56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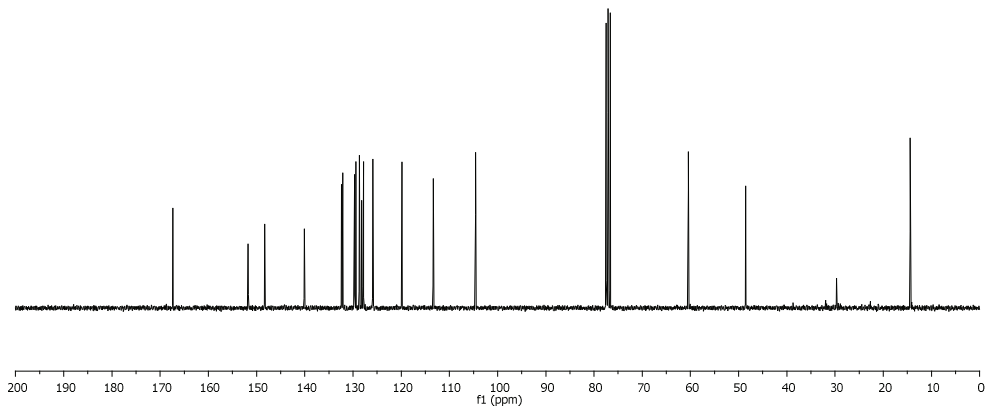
f1 (ppm)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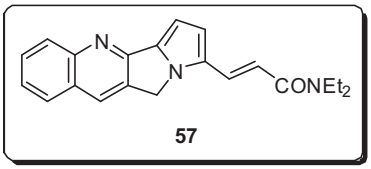
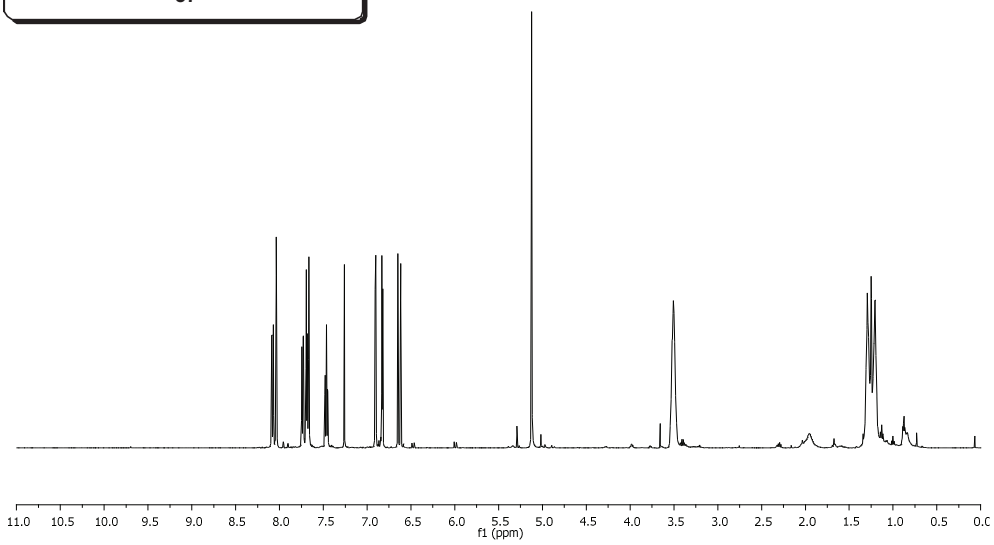
f1 (ppm)


N
N
CONEt2

57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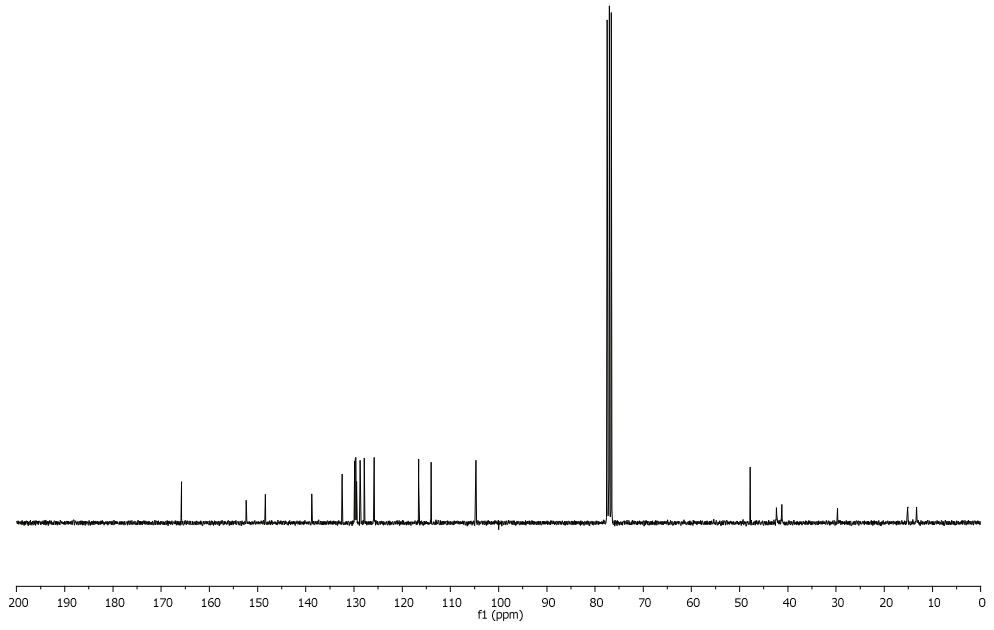
f1 (ppm)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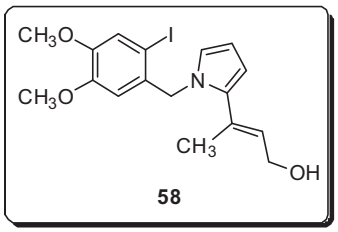
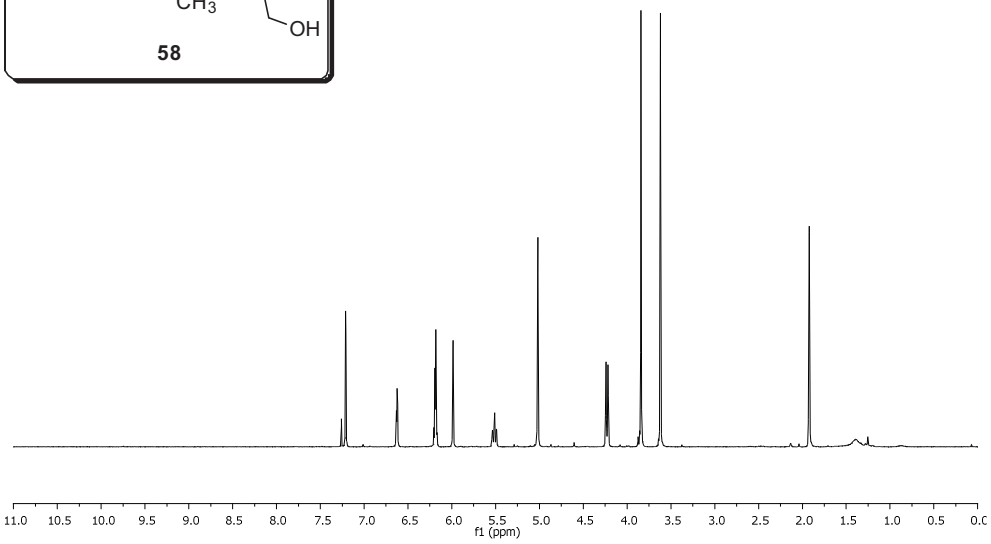
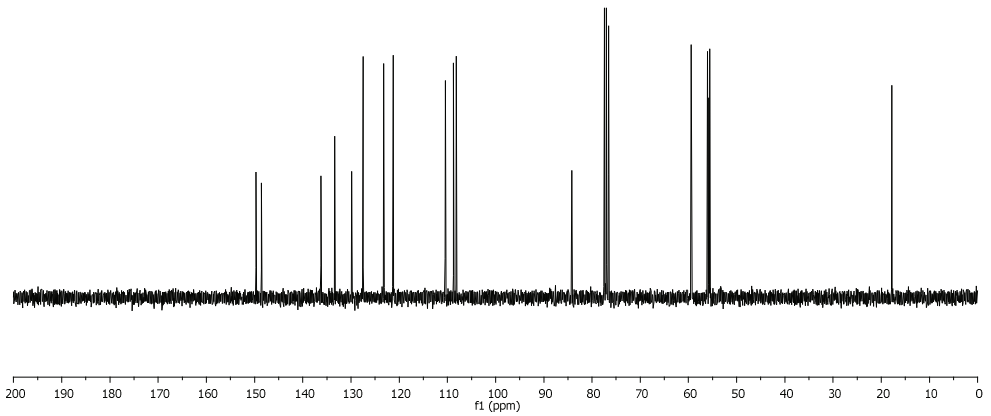
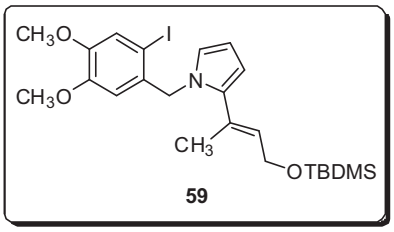
f1 (ppm)


CH3O
I
CH3O
N
CH3
OH

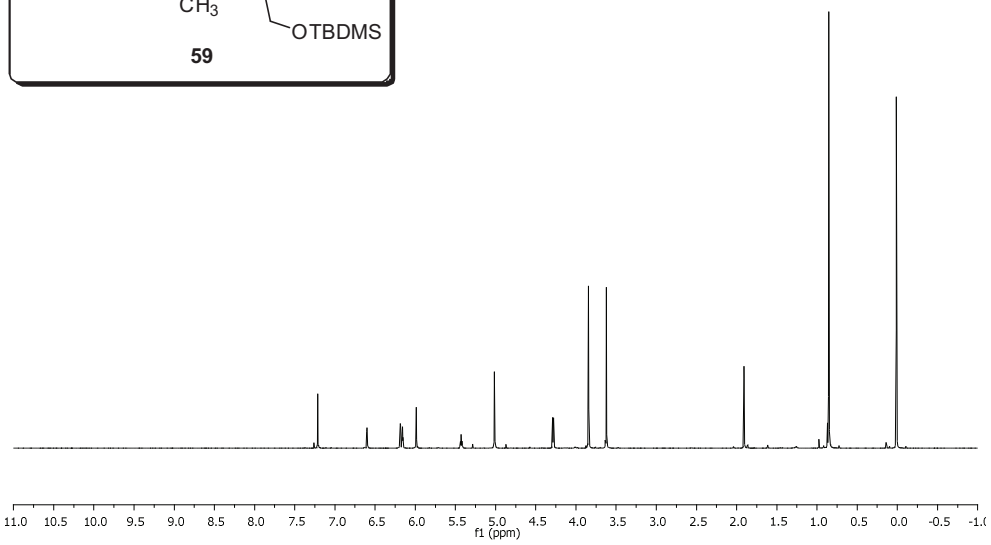
58

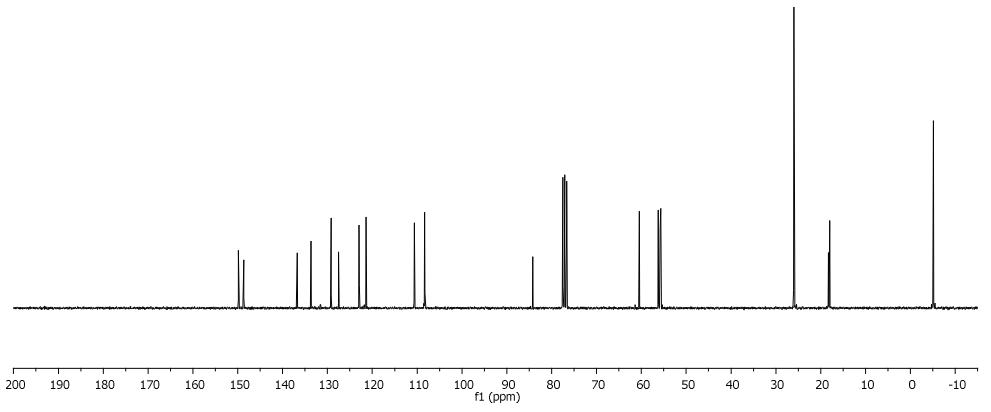

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

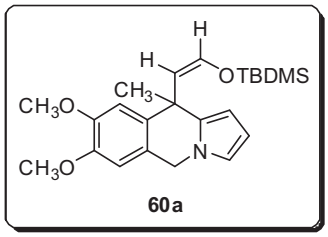

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3O
I
CH3O
N
CH3
OTBDMS

59

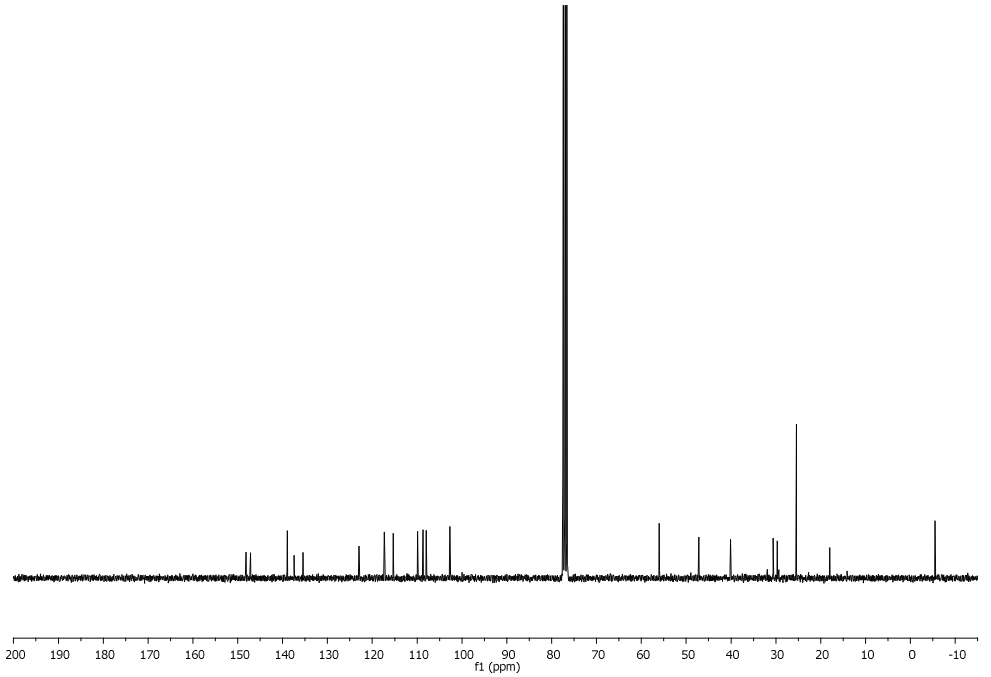

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

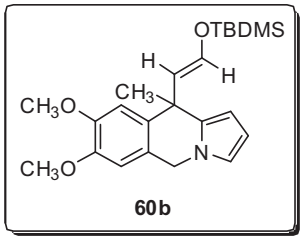

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H
H
OTBDMS
CH3
CH3O
CH3O
N

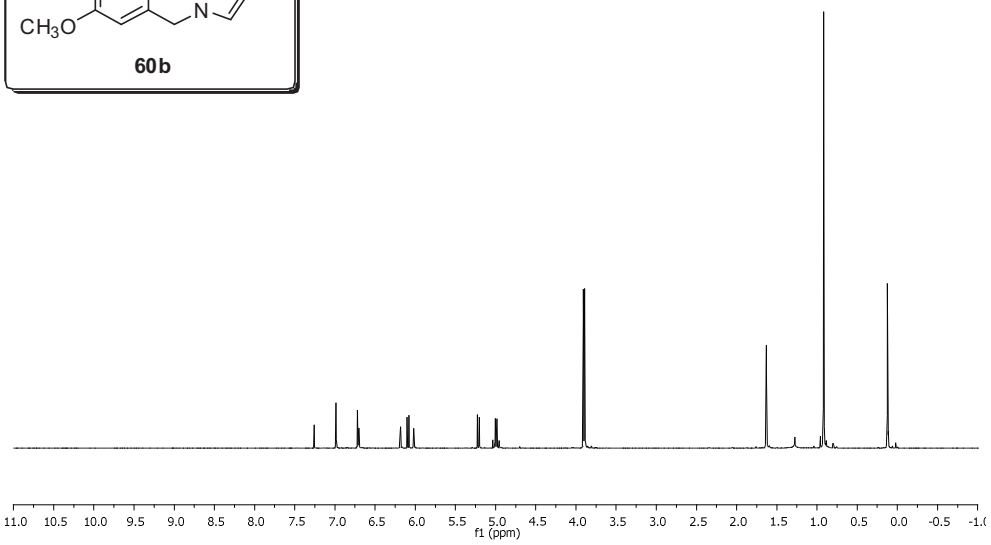
60a

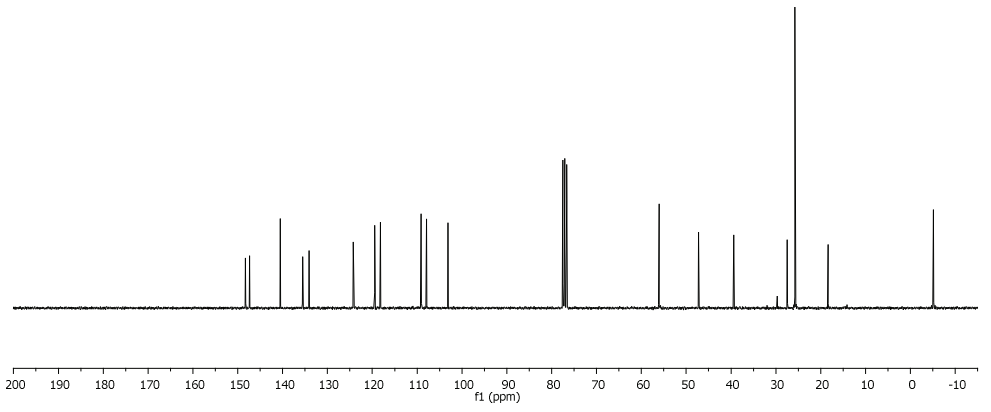
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

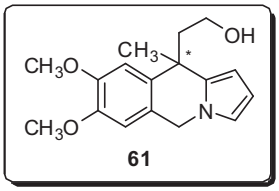

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OTBDMS
H
H
CH3
CH3O
CH3O
N

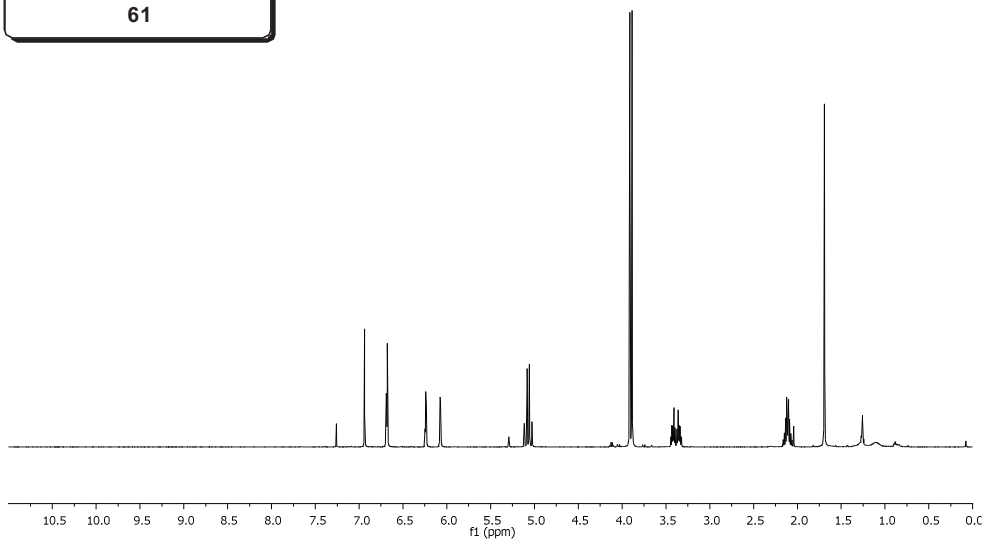
60b

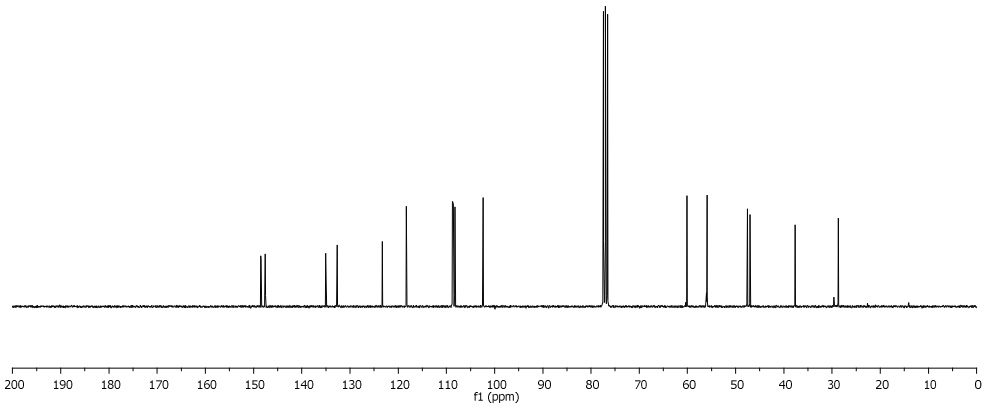

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

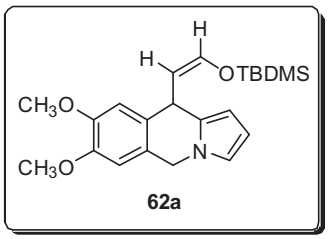

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
CH3
*
CH3O
CH3O
N

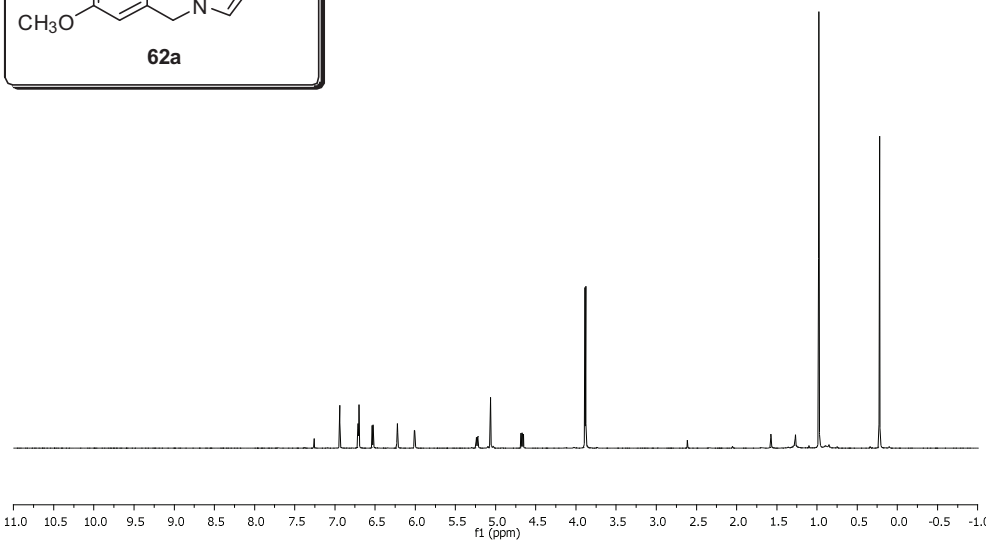
61

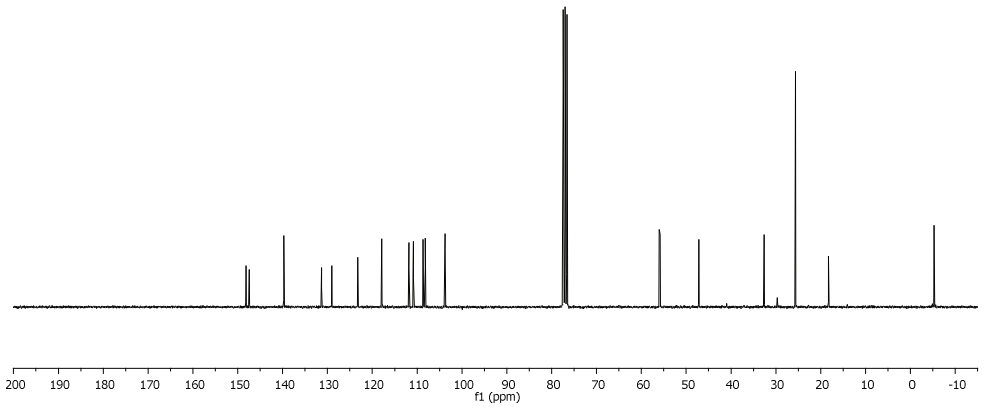

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

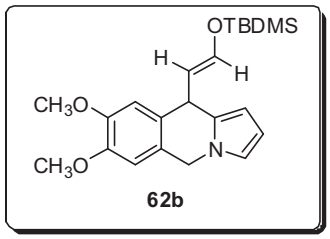

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


H
H
OTBDMS
CH3O
CH3O
N

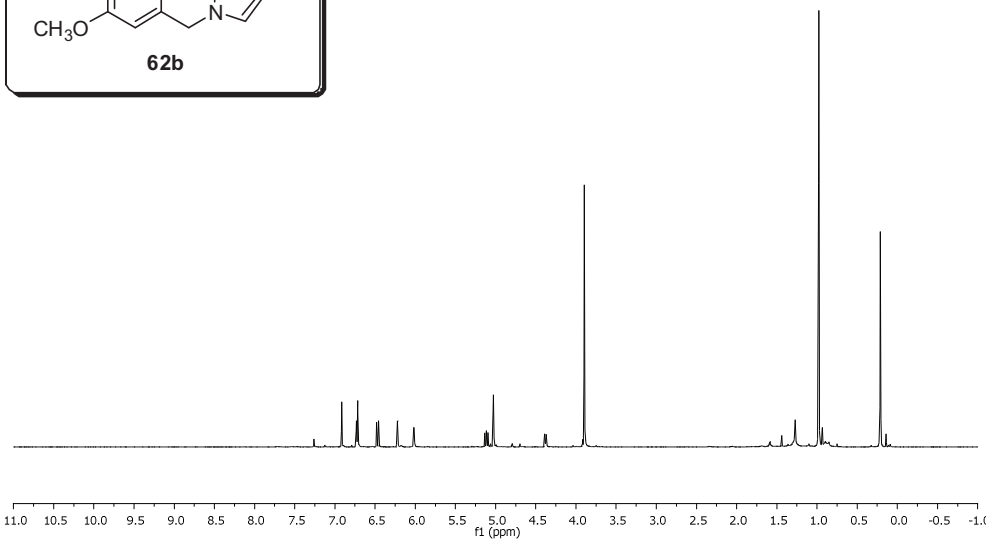
62a

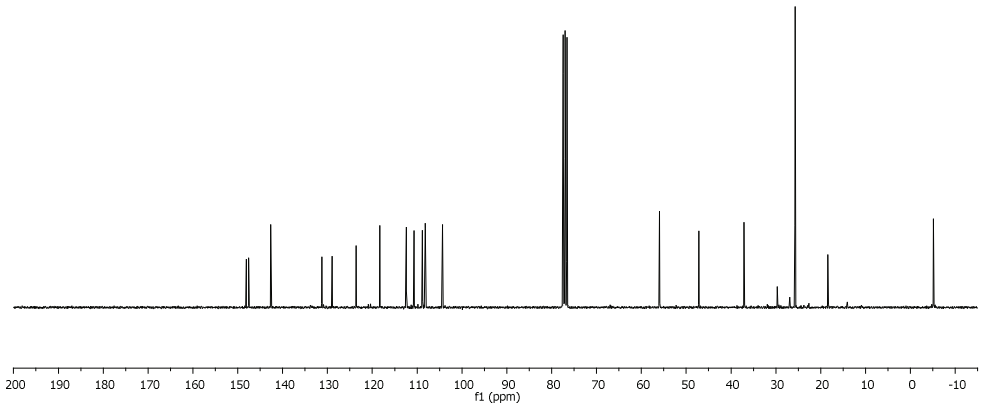

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

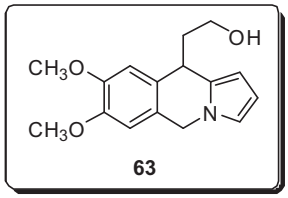

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OTBDMS
H
H
CH3O
CH3O
N

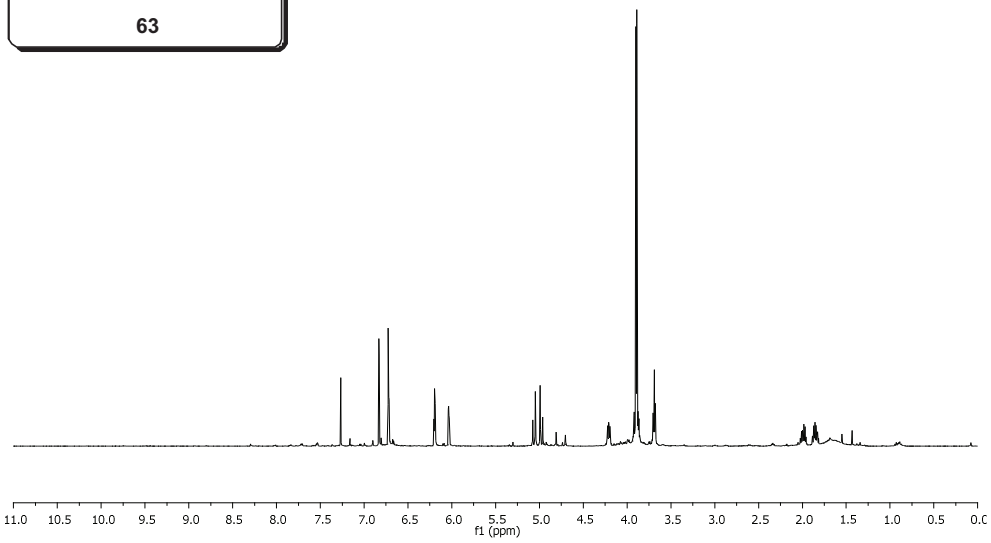
62b

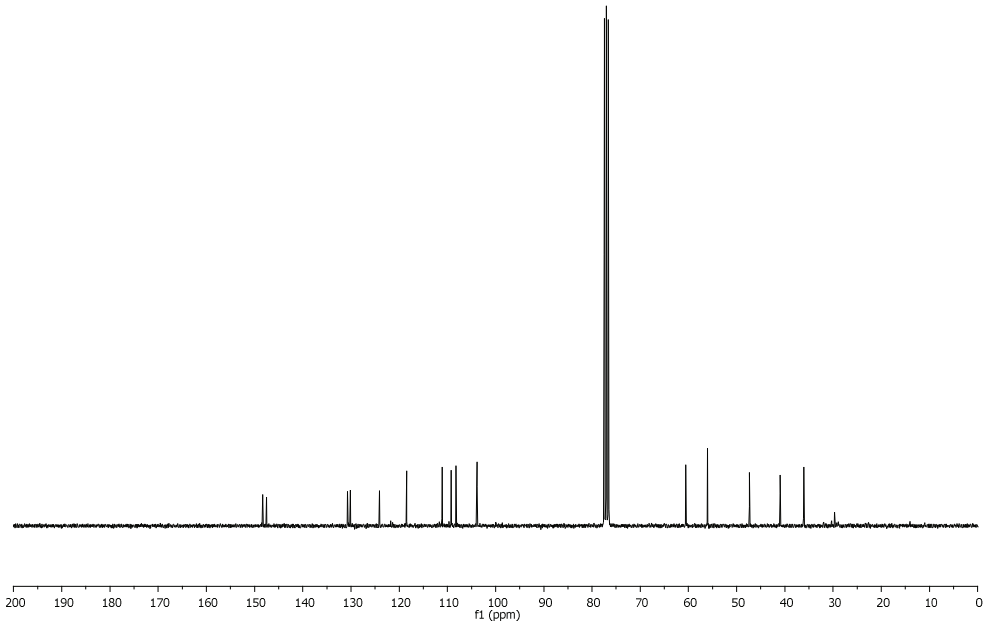

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
CH3O
CH3O
N

63


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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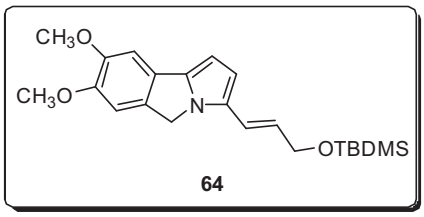
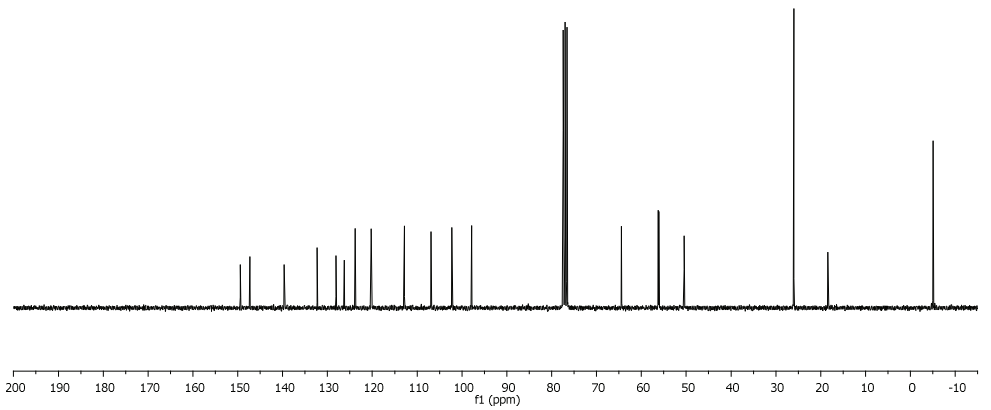
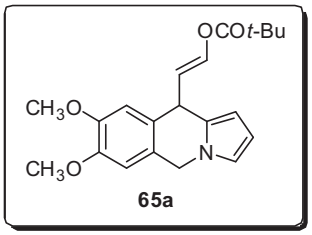
f1 (ppm)


CH3O
CH3O
N
OTBDMS

64

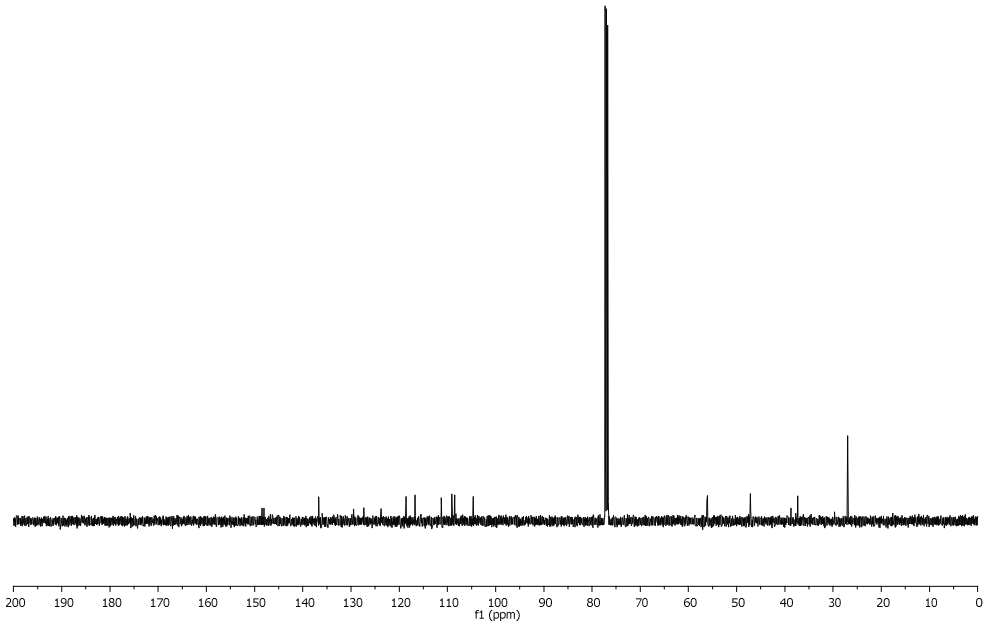
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

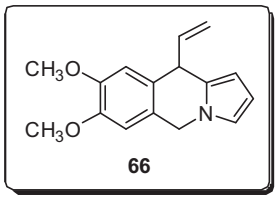

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OCO*t*-Bu
CH_3O
CH_3O
N

65a

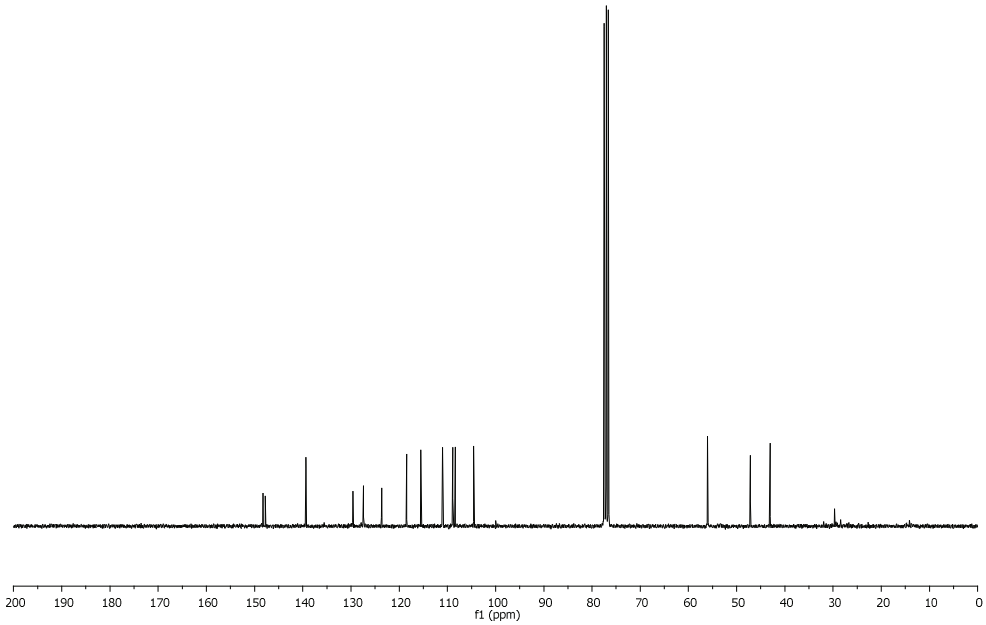
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

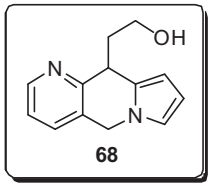

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3O
CH3O
N

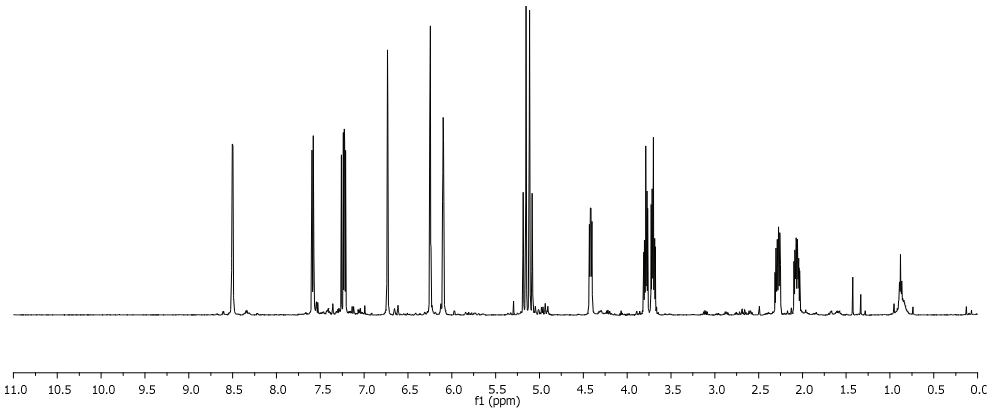
66

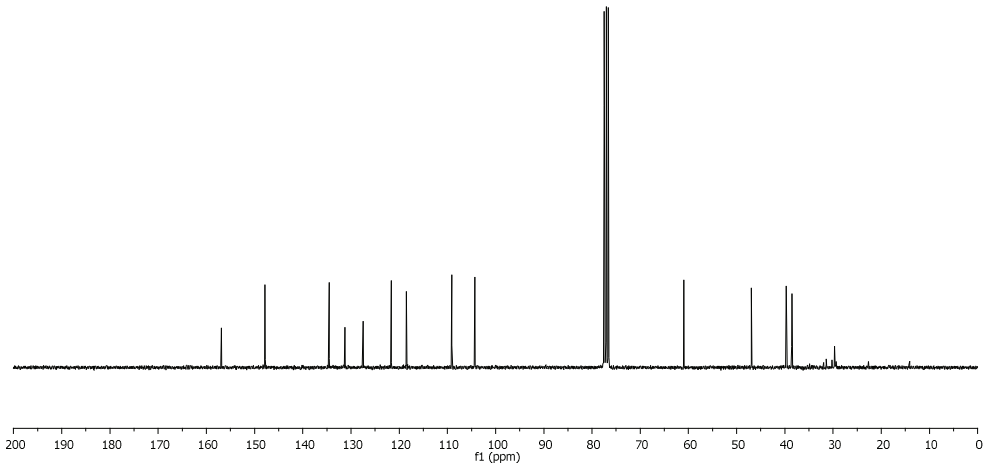
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
N
N

68


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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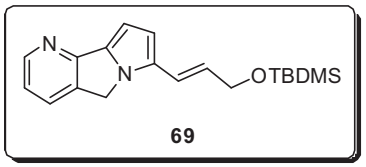
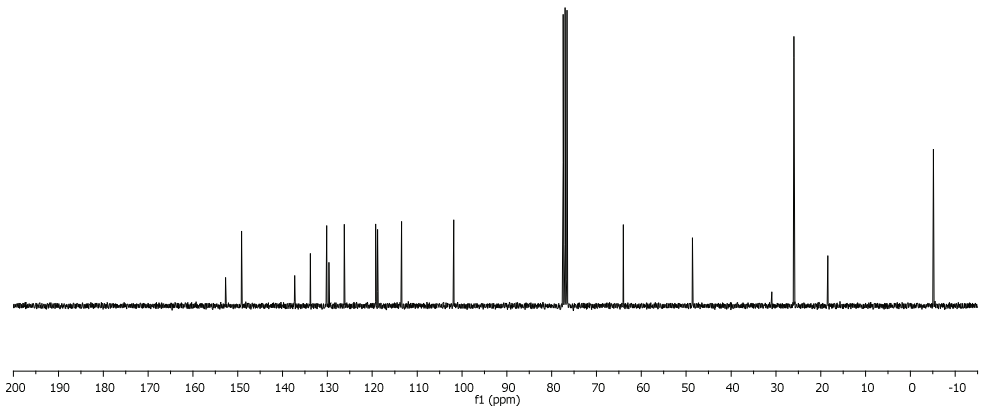
f1 (ppm)


N
N
OTBDMS

69

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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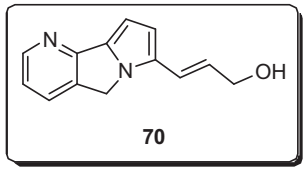
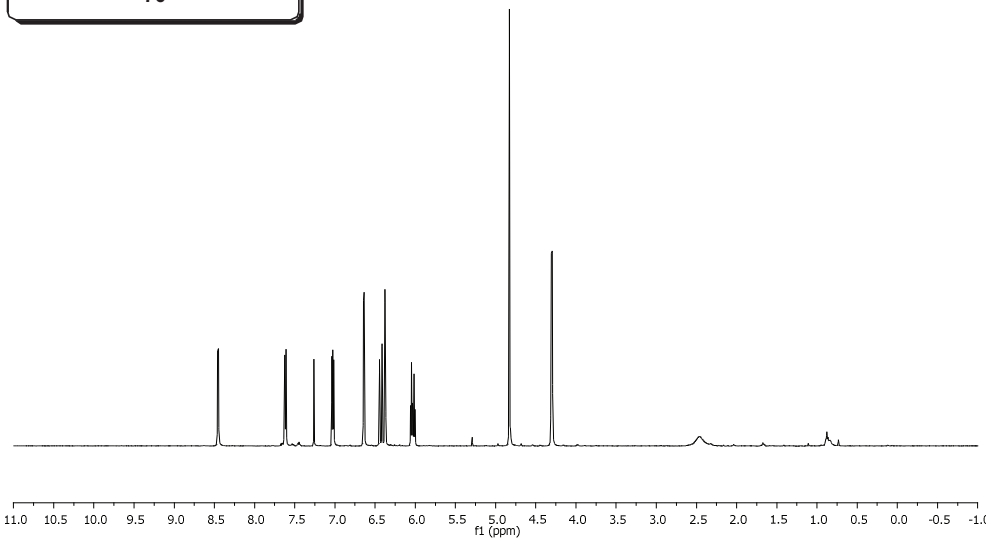
f1 (ppm)


N
N
OH

70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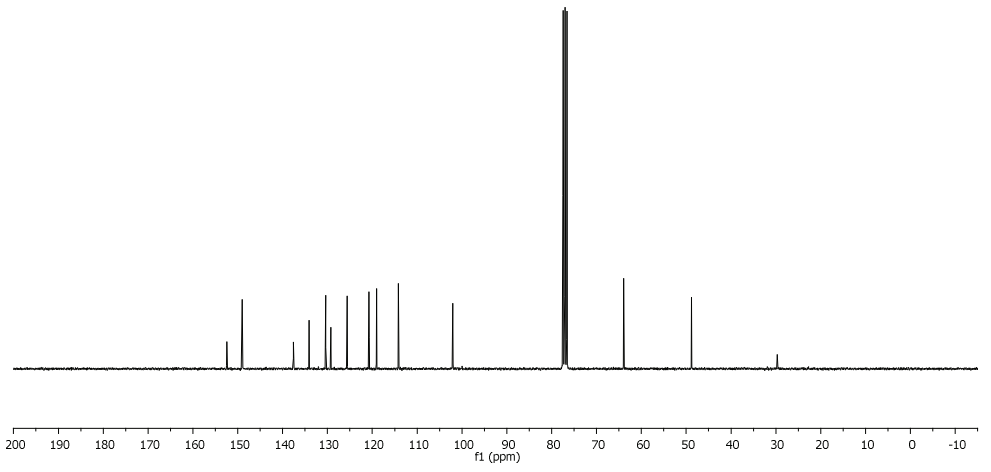
f1 (ppm)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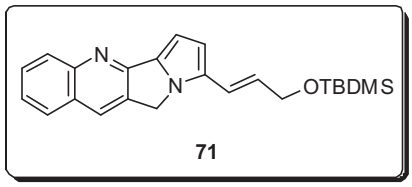
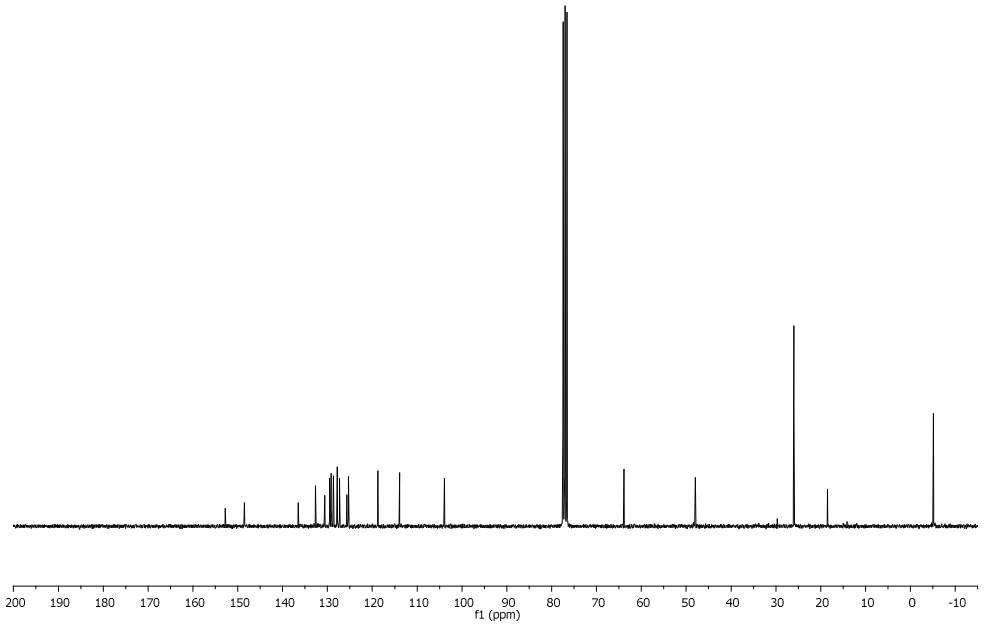
f1 (ppm)


N
N
OTBDMS

71

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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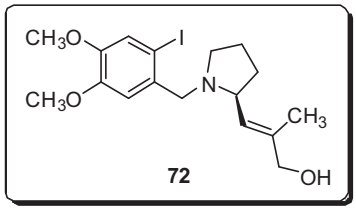
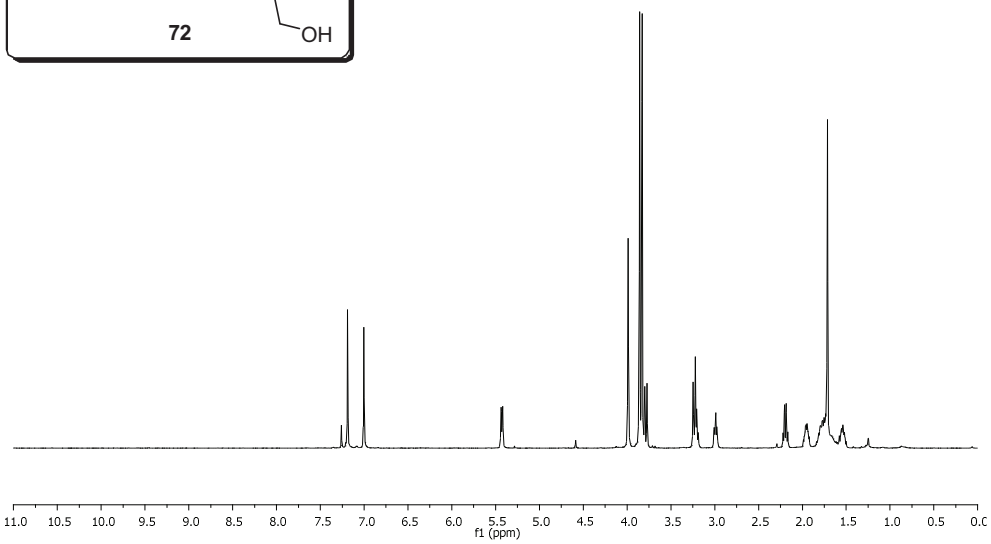
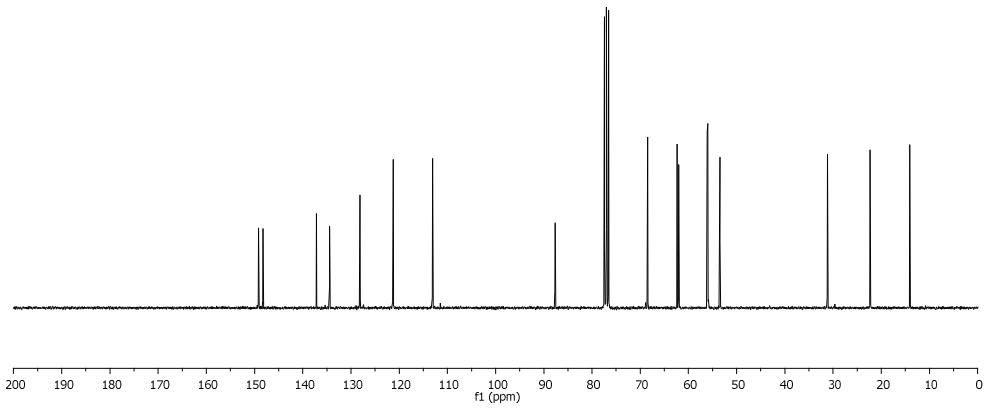
f1 (ppm)


CH3O
I
CH3O
N
CH3
OH

72


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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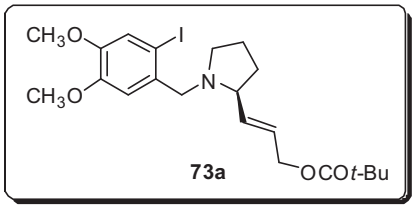
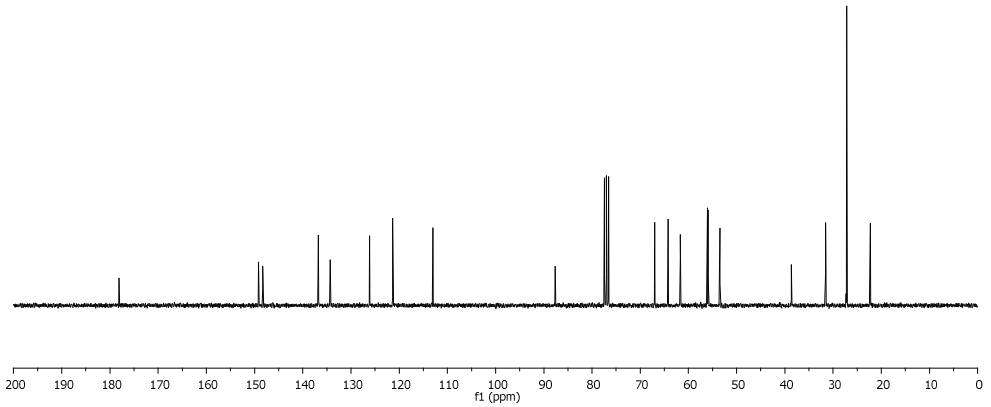
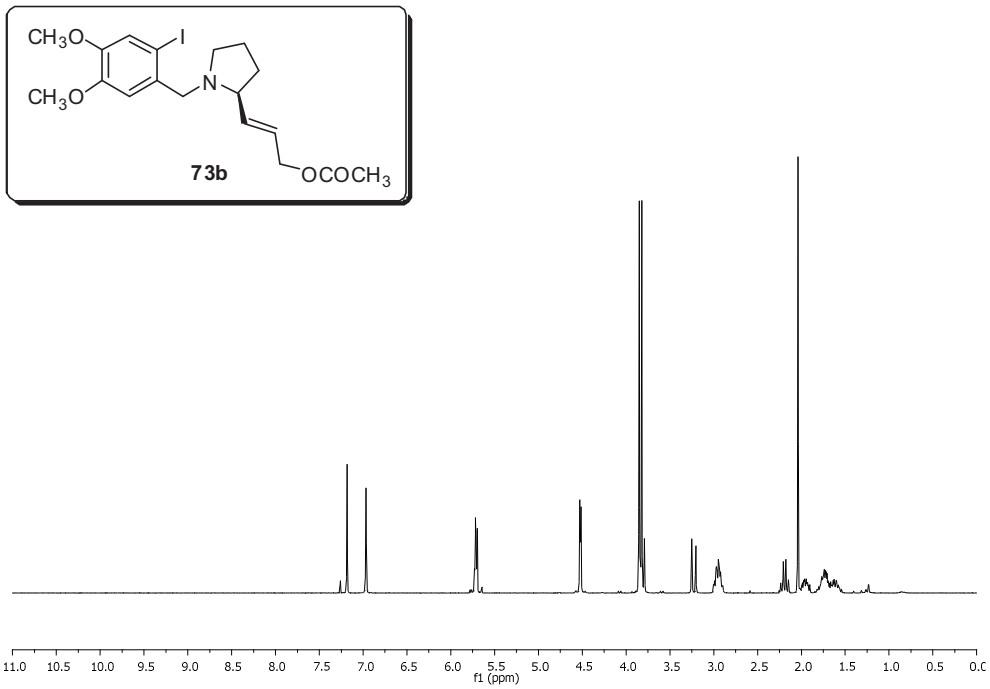
f1 (ppm)

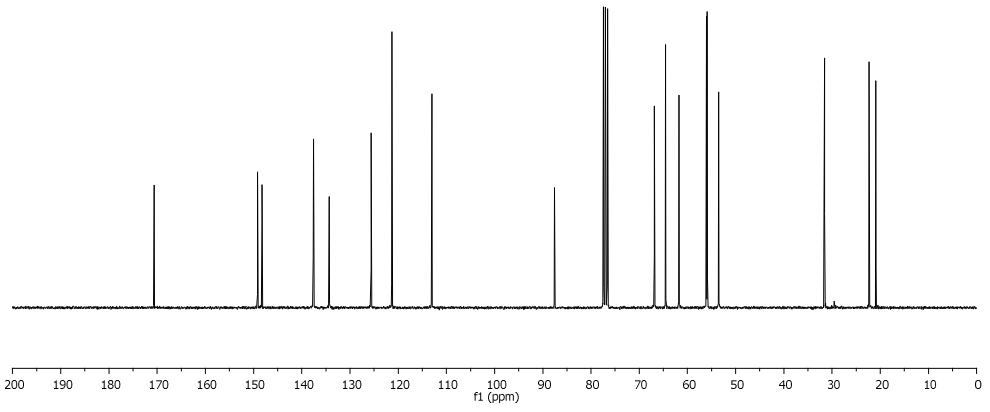

CH3O
I
CH3O
N
OCOt-Bu

73a

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3O
I
CH3O
N
OCOCH3
73b
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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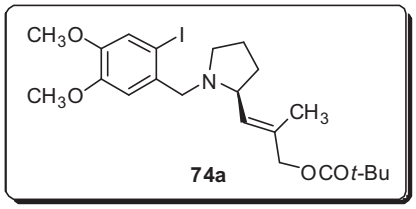
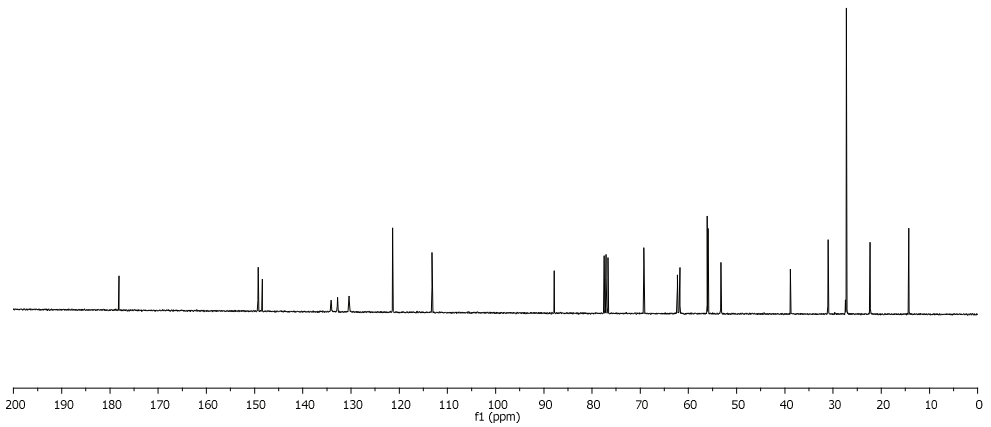
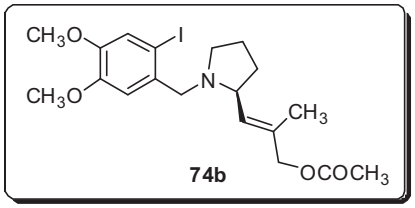
f1 (ppm)


CH3O
I
CH3O
N
CH3
OCOt-Bu

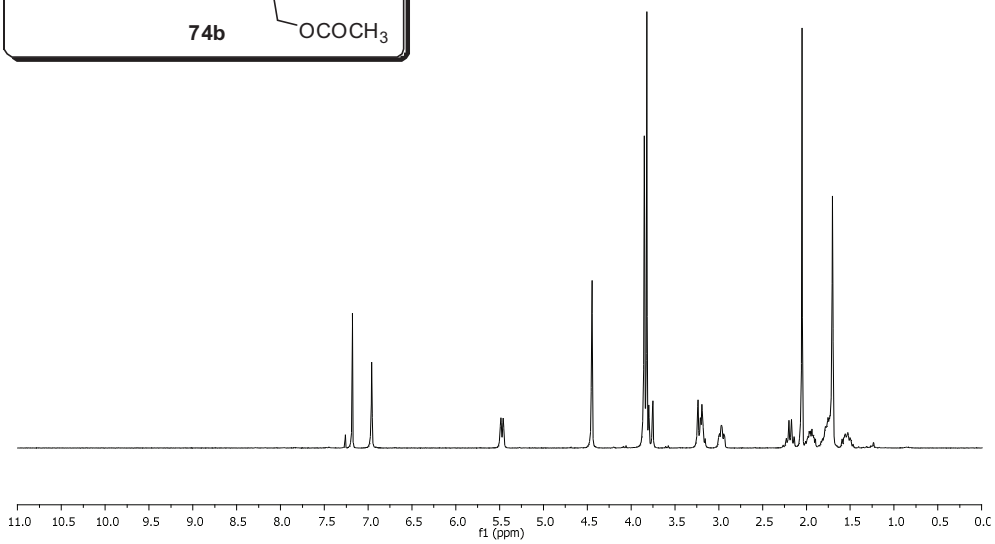
74a

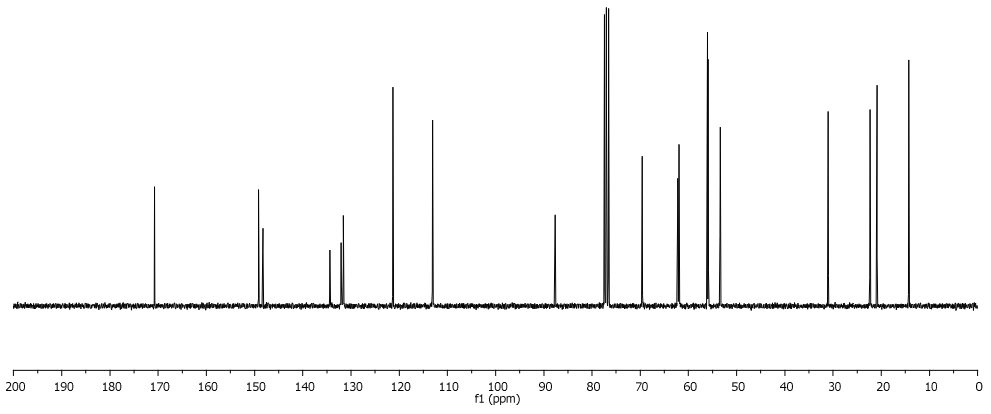
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3O
I
CH3O
N
CH3
OCOCH3

74b


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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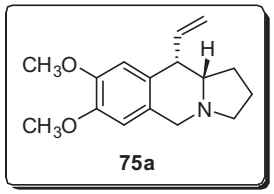
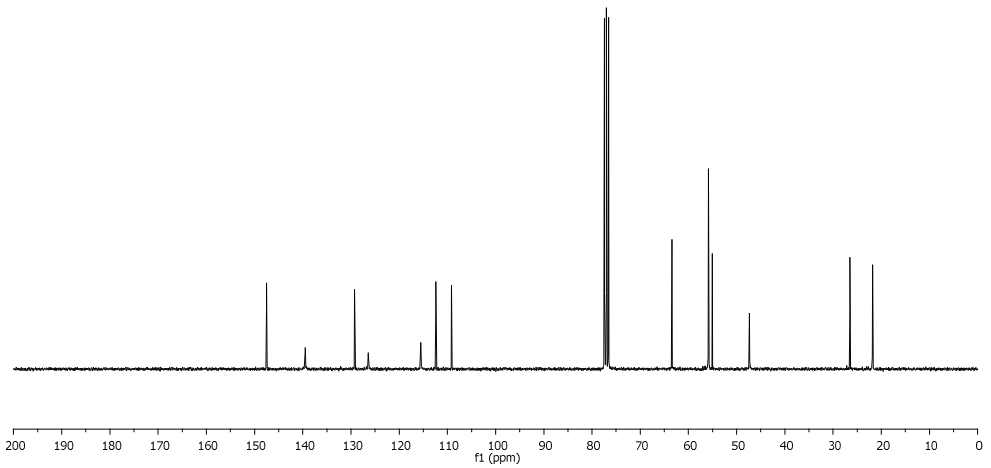
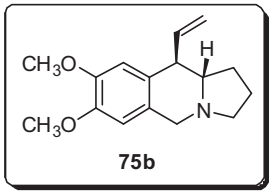
f1 (ppm)


CH3O
CH3O
H
N

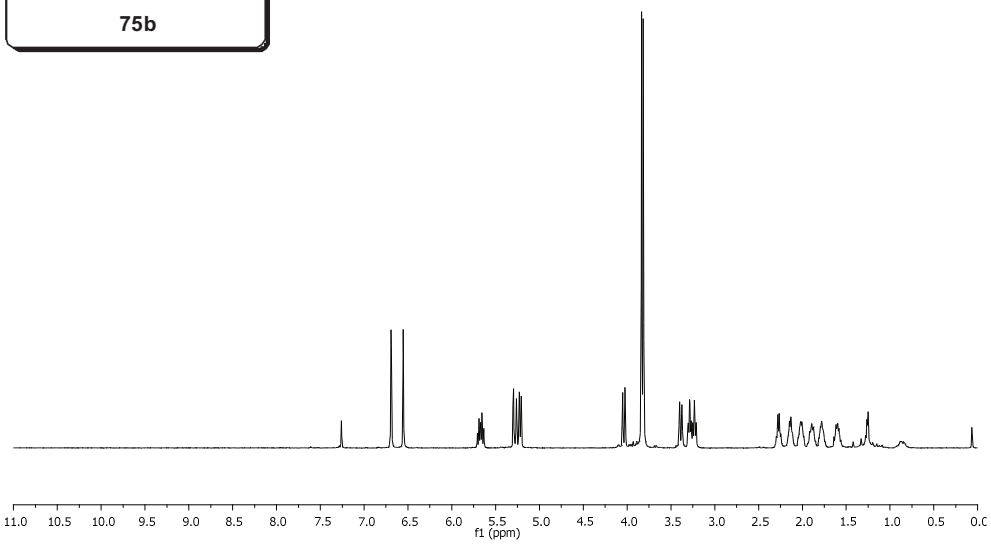
75a

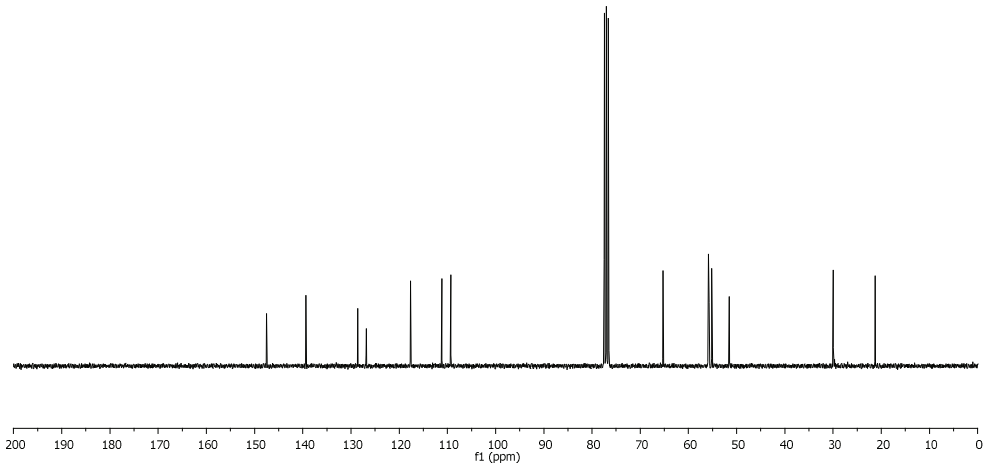
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3O
CH3O
H
N

75b


11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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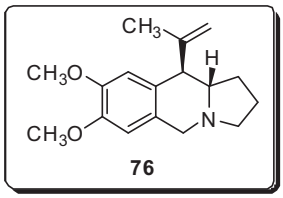
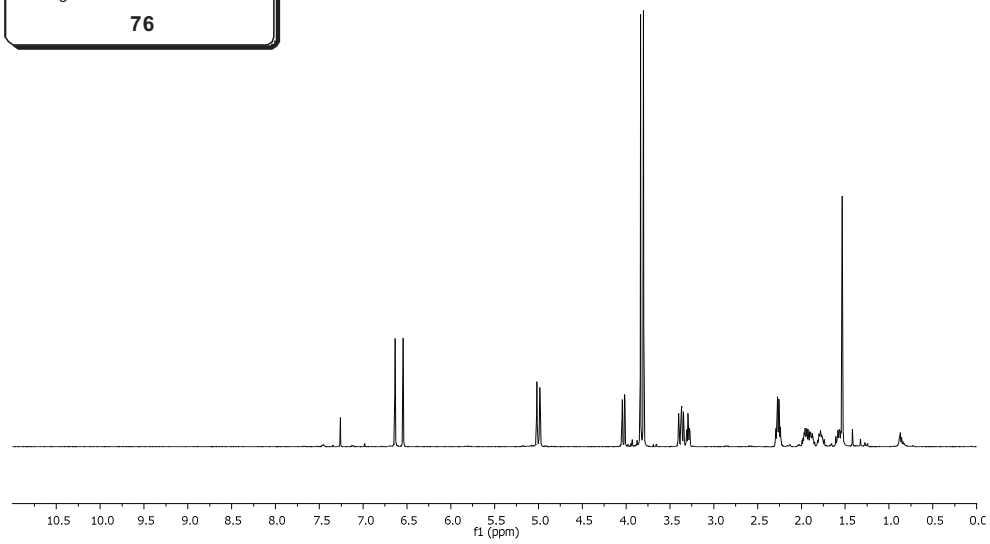
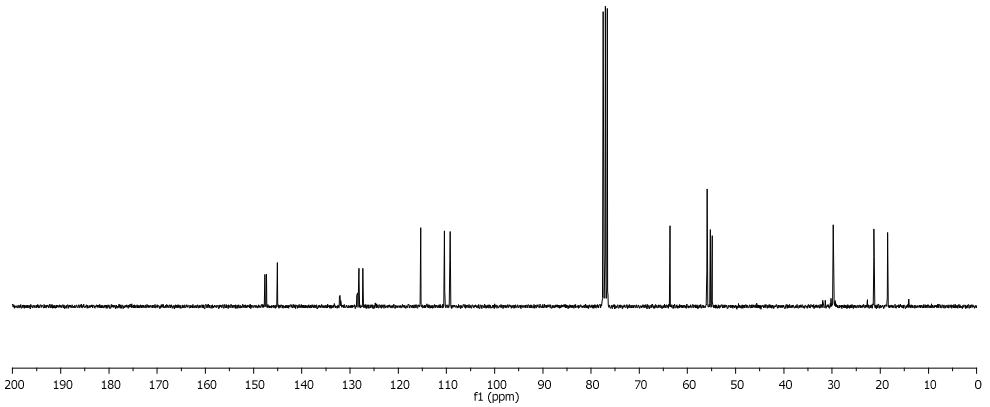
f1 (ppm)


CH3
H
CH3O
CH3O
N

76


10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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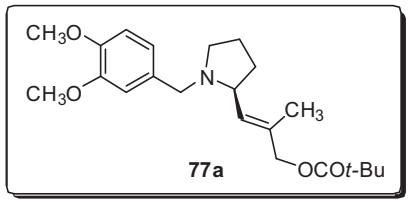
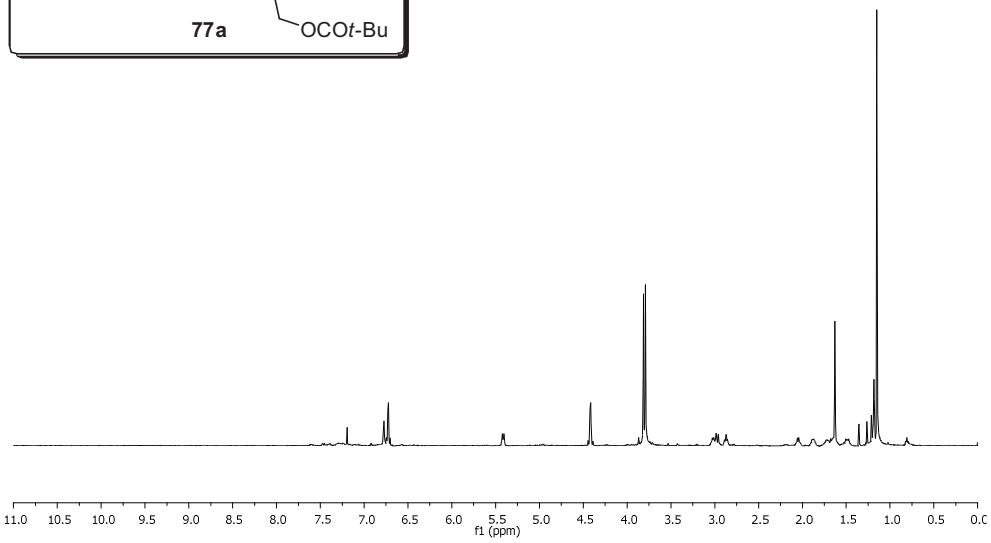
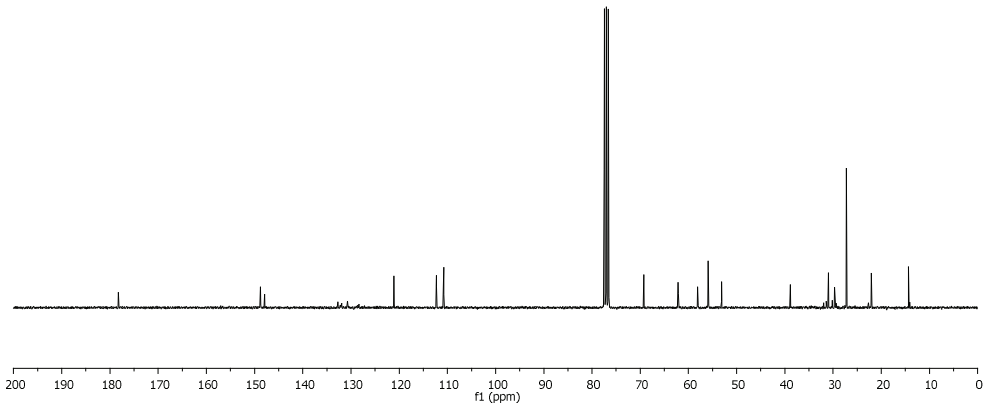
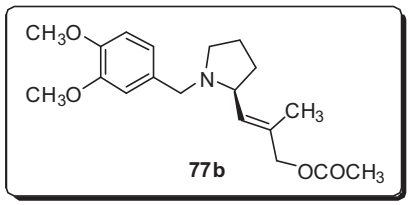
f1 (ppm)


CH3O
CH3O
N
CH3
OCOt-Bu

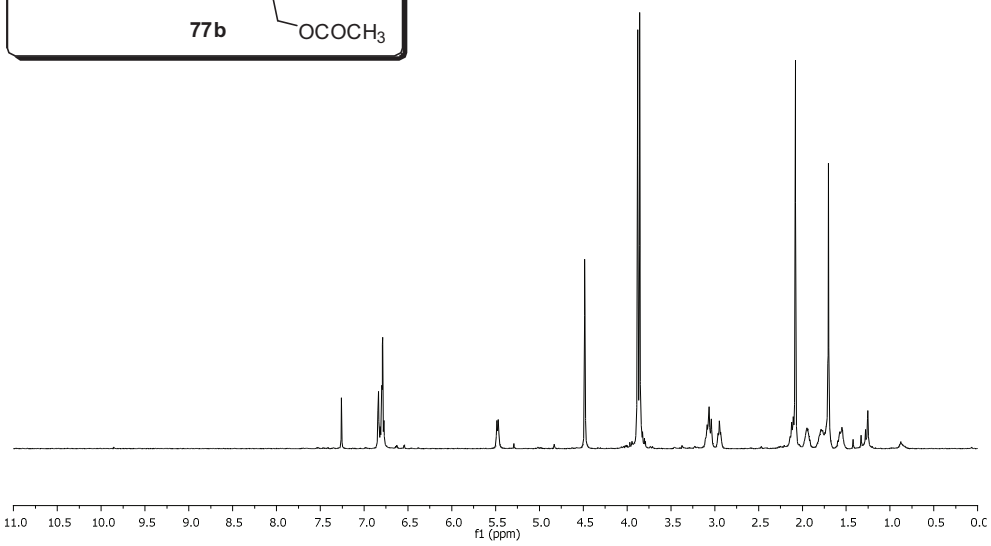
77a

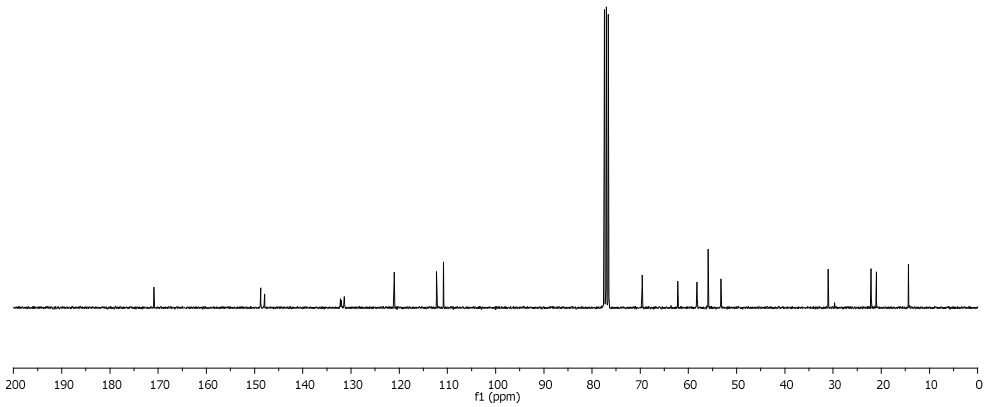

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

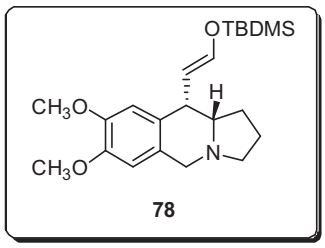

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3O
CH3O
N
CH3
OCOCH3

77b

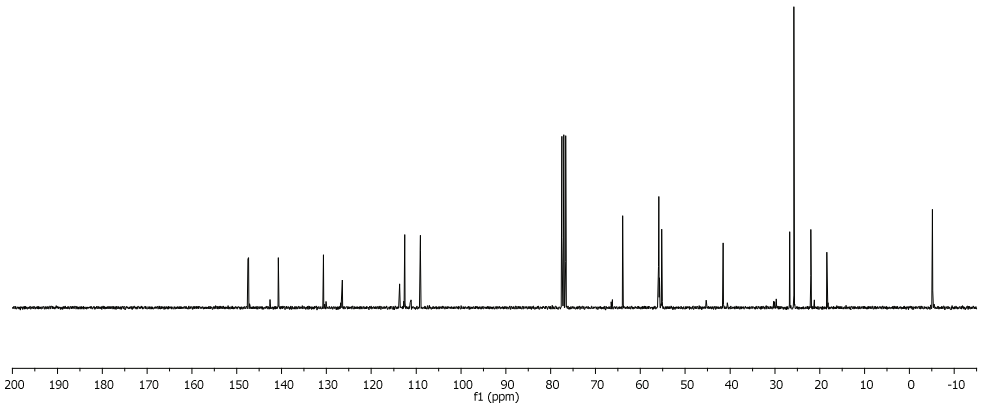

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

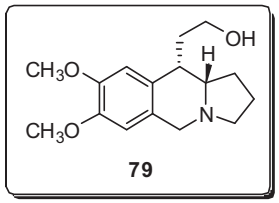

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OTBDMS
H
CH_3O
CH_3O
N

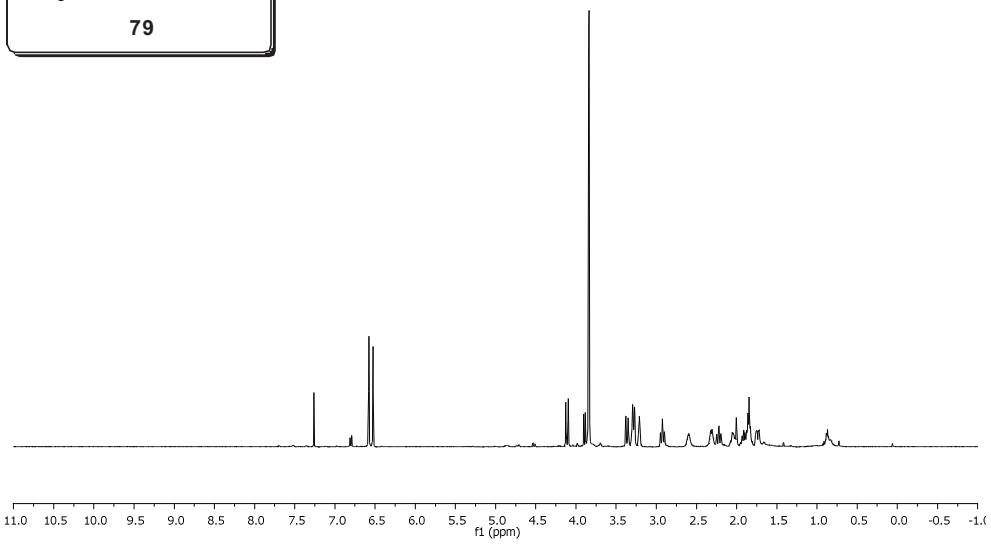
78

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
H
CH3O
CH3O
N

79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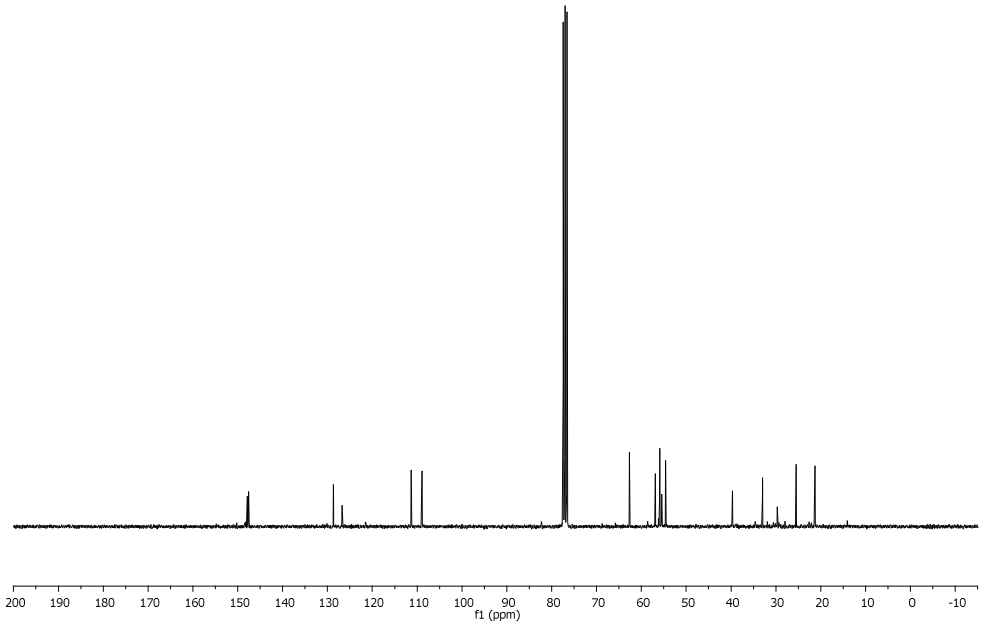
f1 (ppm)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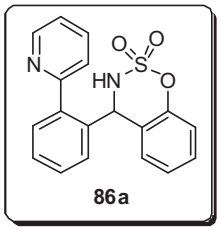
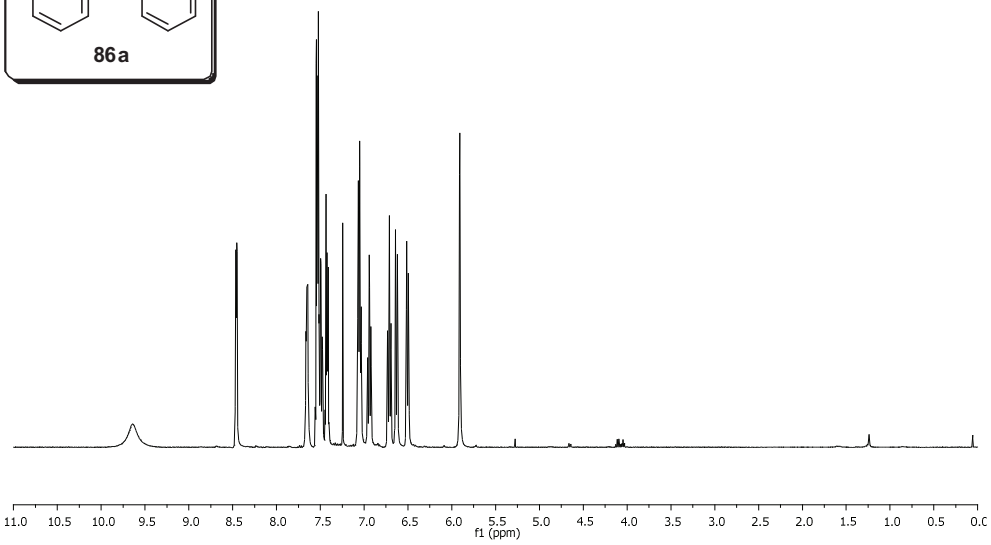
f1 (ppm)


N
O
O
S
HN
O

86a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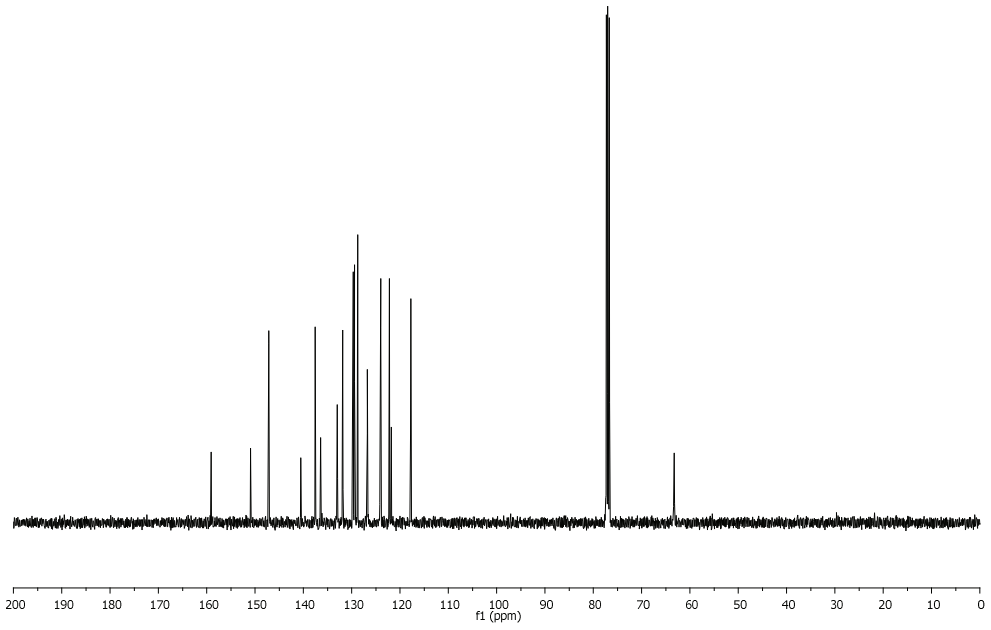
f1 (ppm)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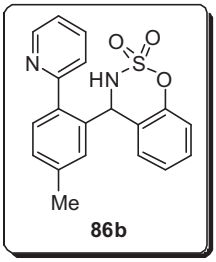
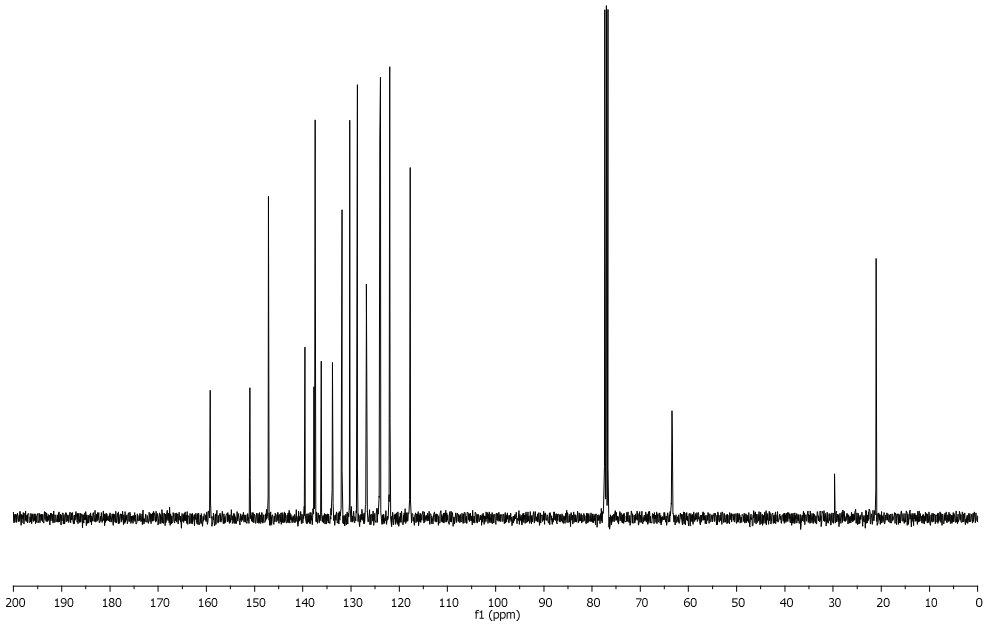
f1 (ppm)


N
O
O
S
HN
O
Me

86b

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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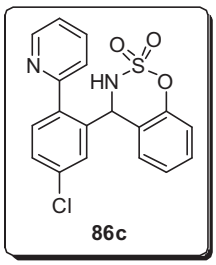
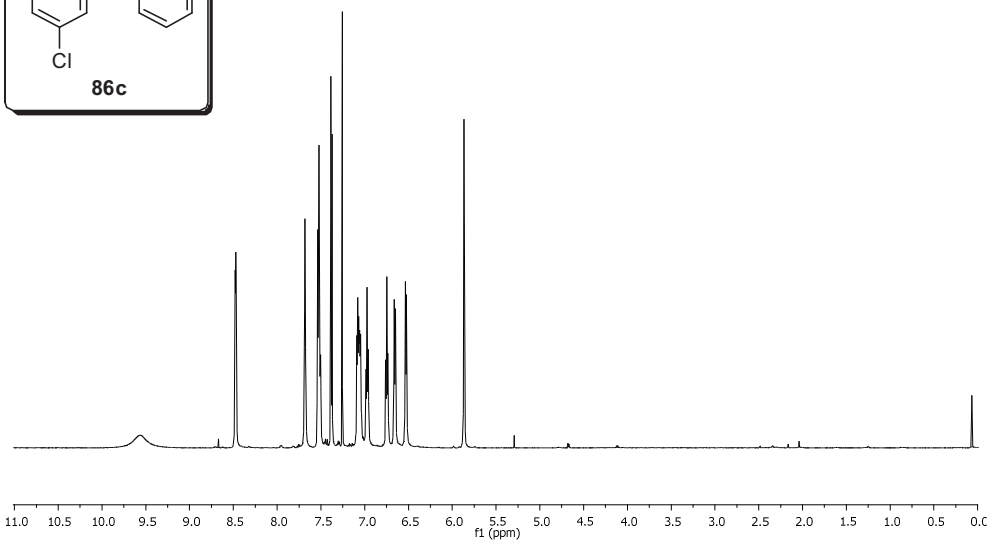
f1 (ppm)


N
O
O
S
HN
O
Cl

86c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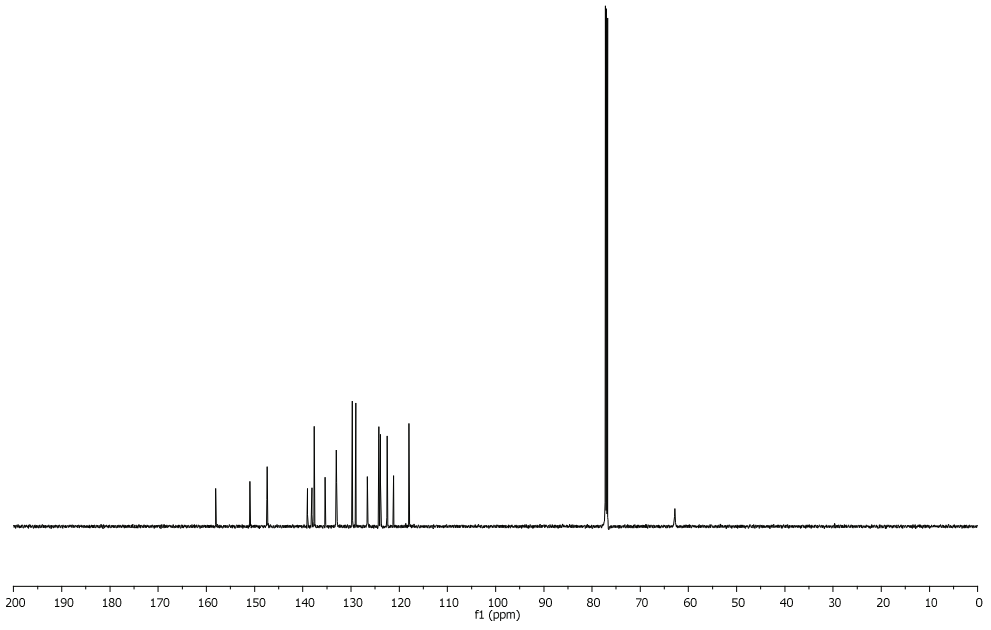
f1 (ppm)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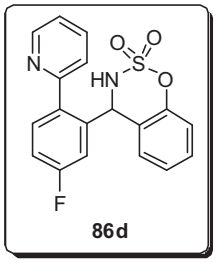
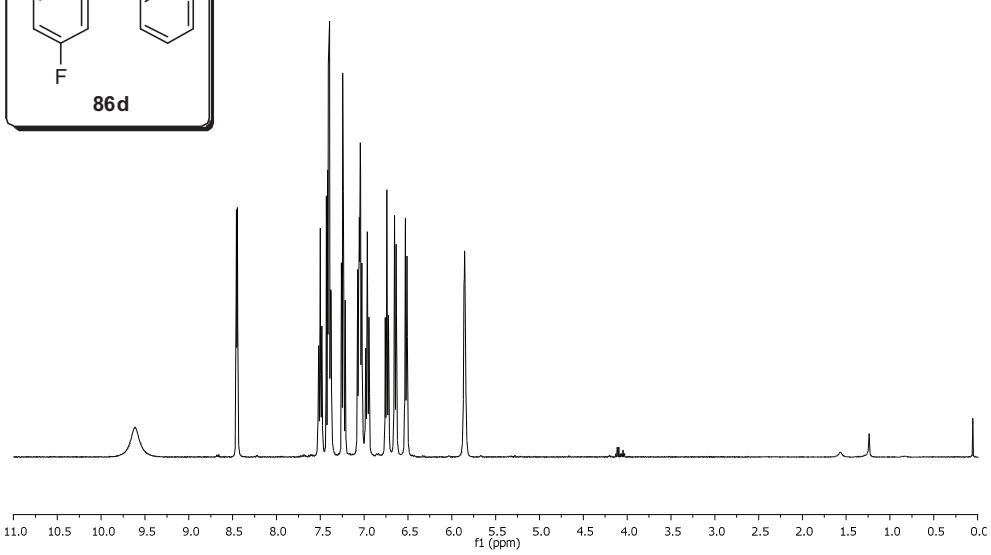
f1 (ppm)


N
O
O
S
HN
O
F

86d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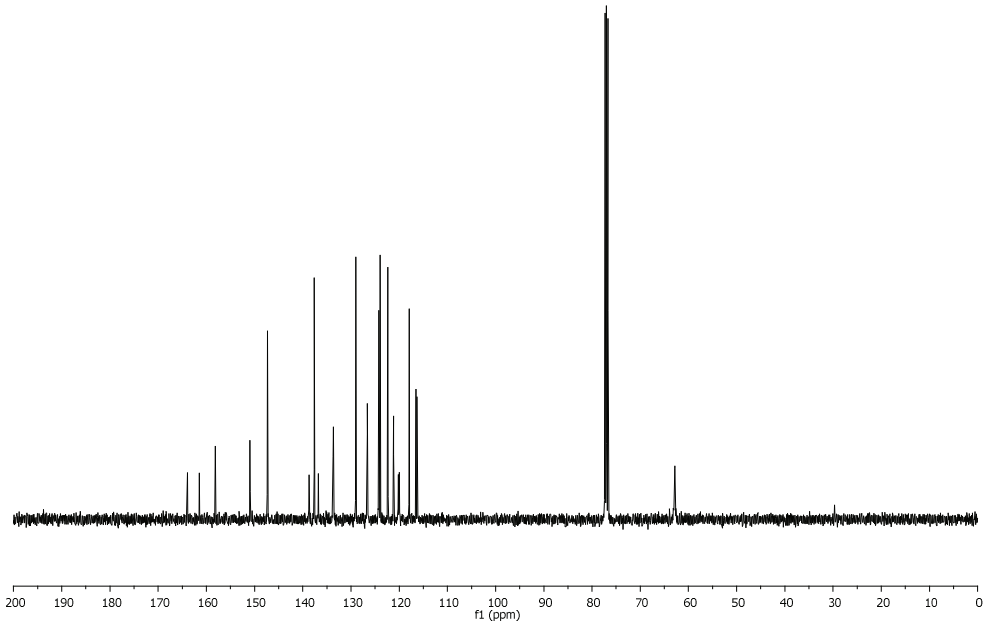
f1 (ppm)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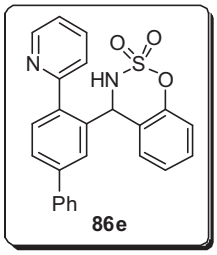
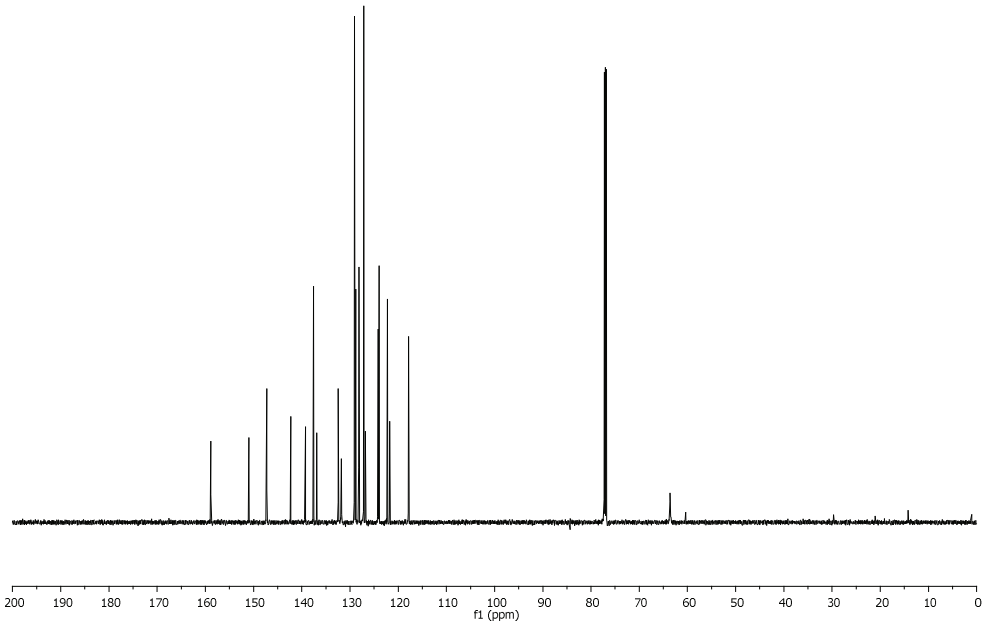
f1 (ppm)


N
O
O
S
HN
O
Ph

86e

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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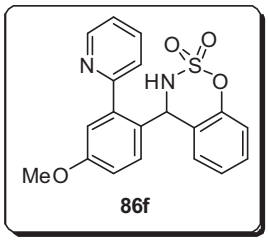
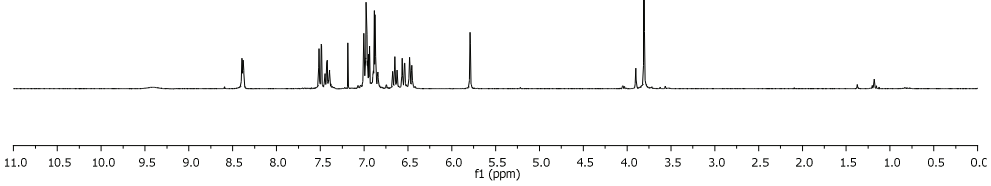
f1 (ppm)


N
O
O
S
HN
O
MeO

86f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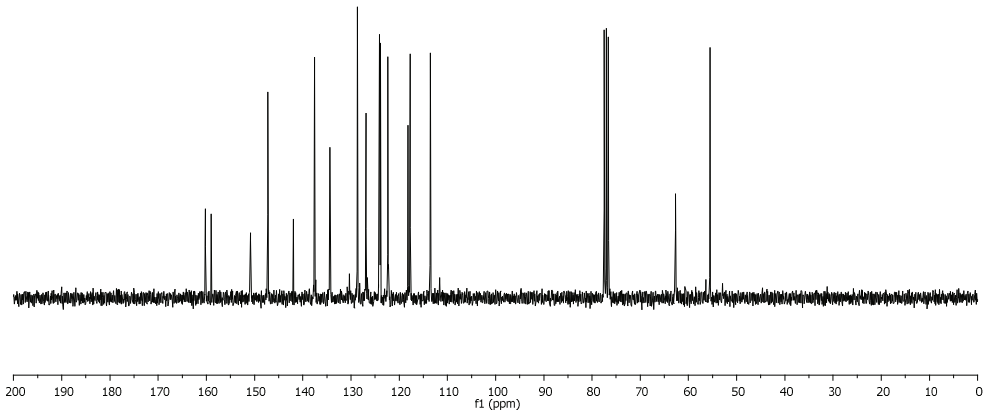
f1 (ppm)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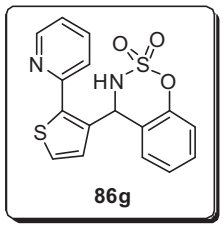
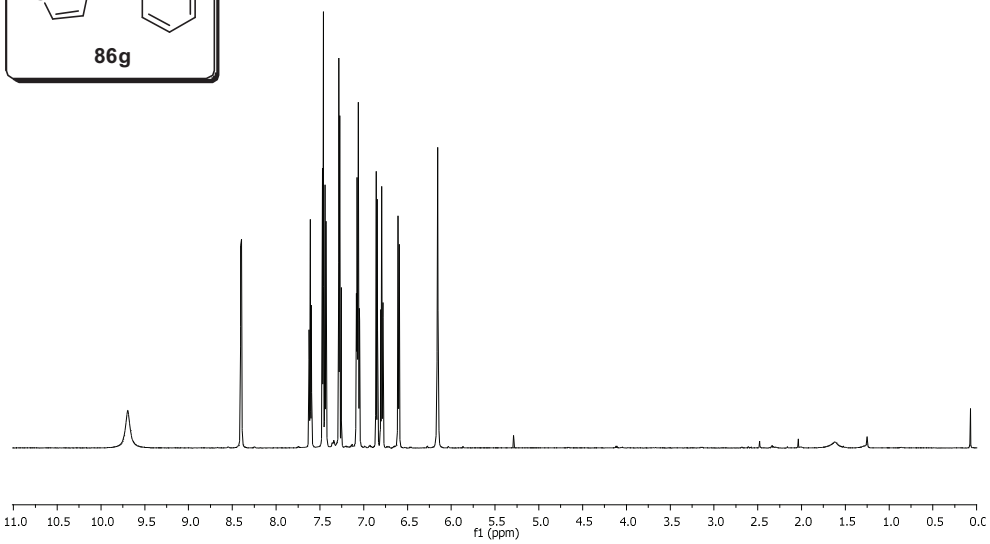
f1 (ppm)


N
O
O
S
HN
O
S

86g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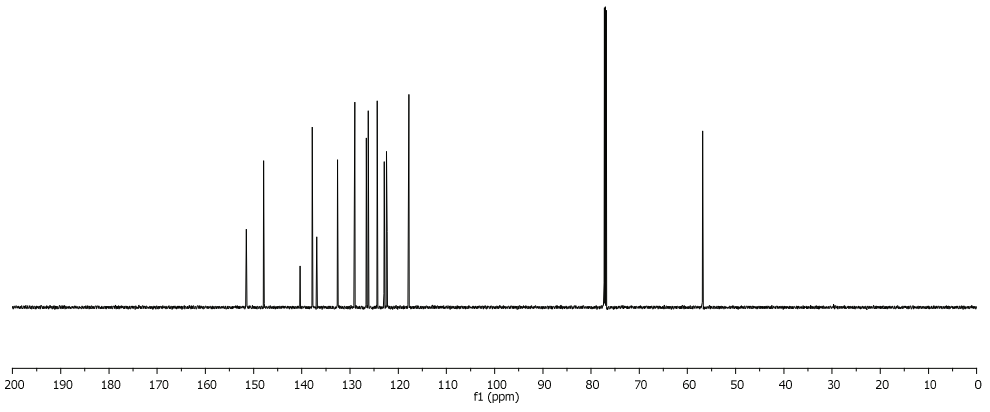
f1 (ppm)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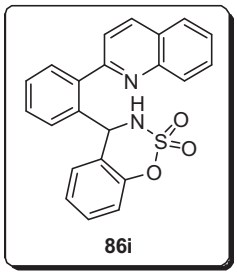
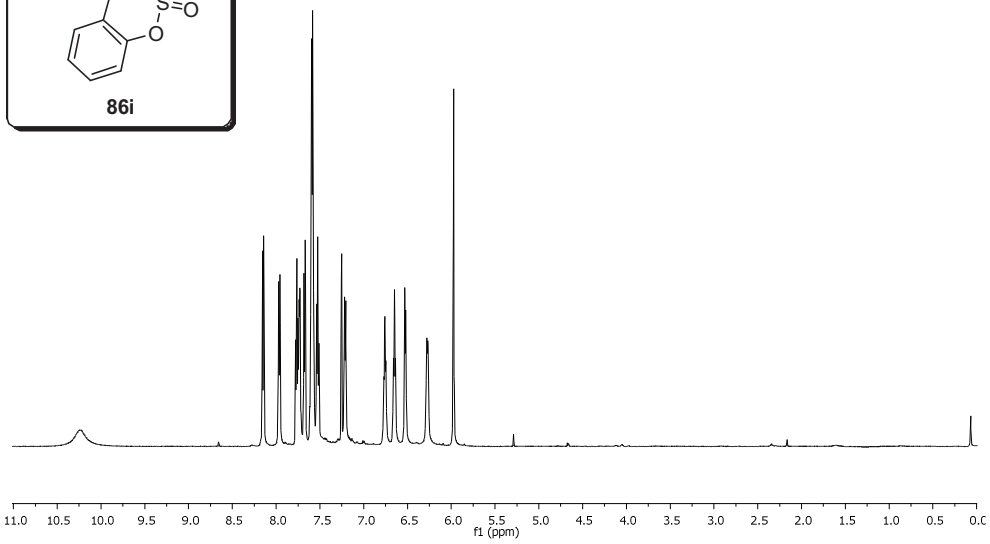
f1 (ppm)


N
H
N
O
S
O
O

86i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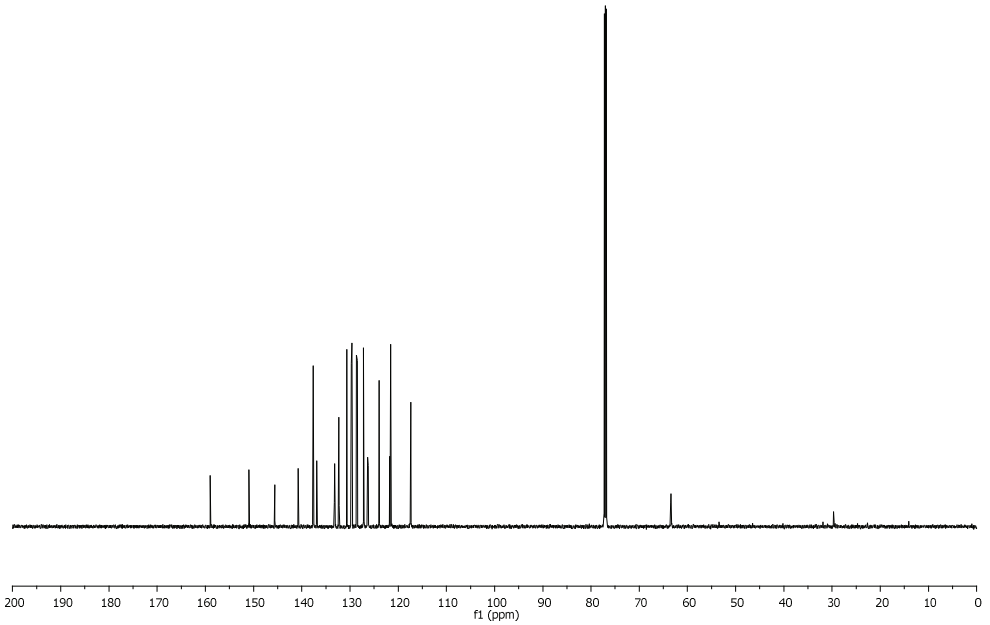
f1 (ppm)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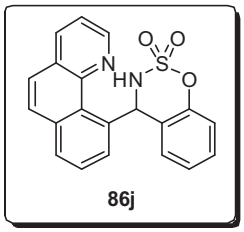
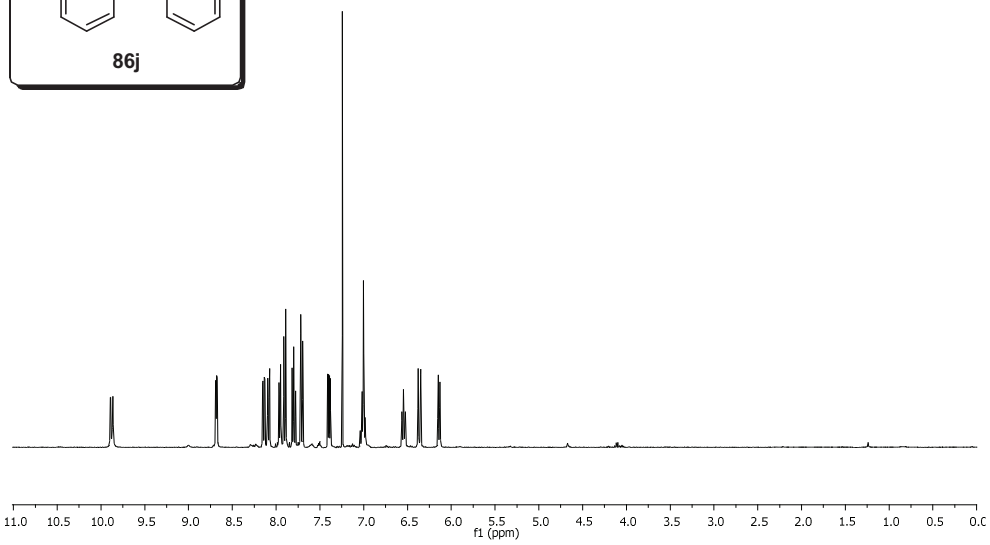
f1 (ppm)


O
O
N
HN
S
O

86j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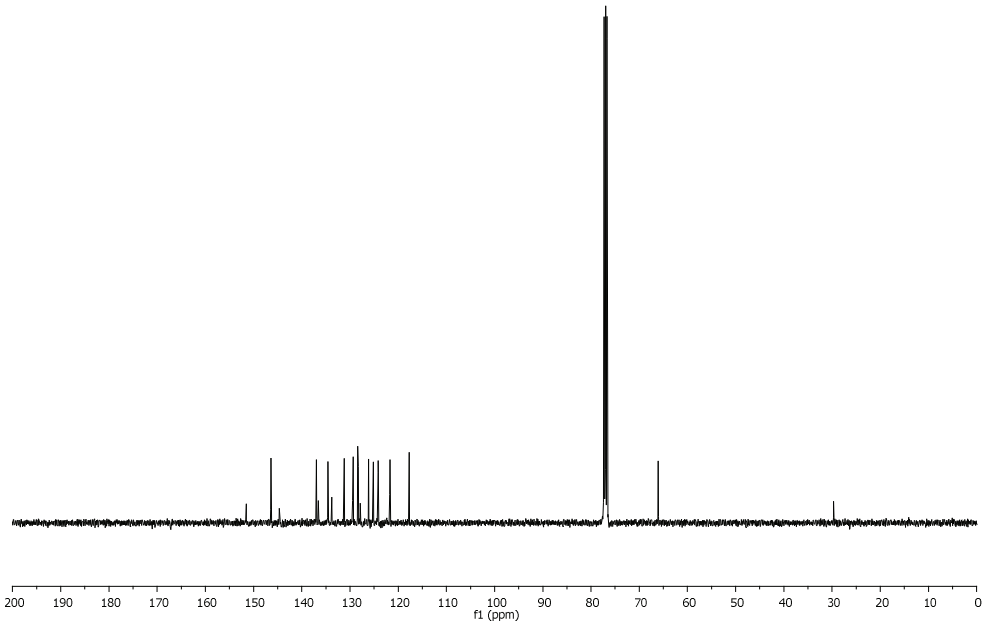
f1 (ppm)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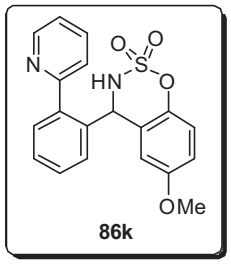
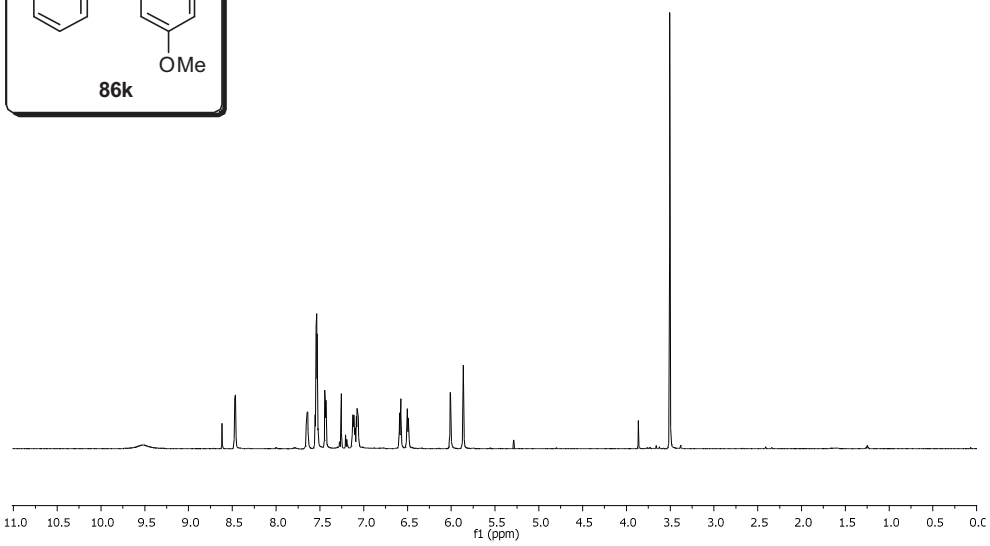
f1 (ppm)


O
O
S
N
HN
O
OMe

86k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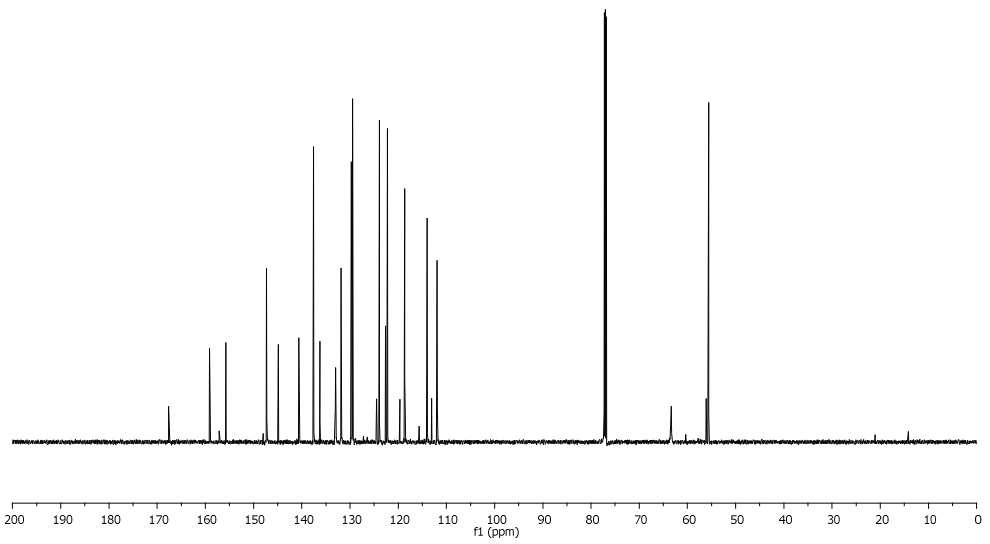
f1 (ppm)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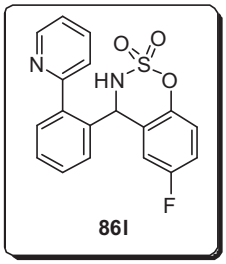
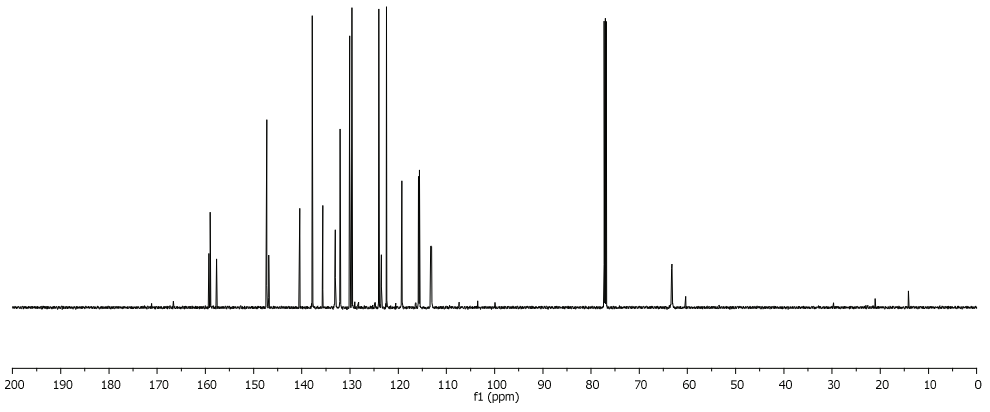
f1 (ppm)


N
O
O
S
HN
O
F

86l

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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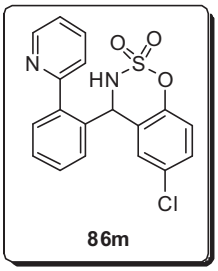
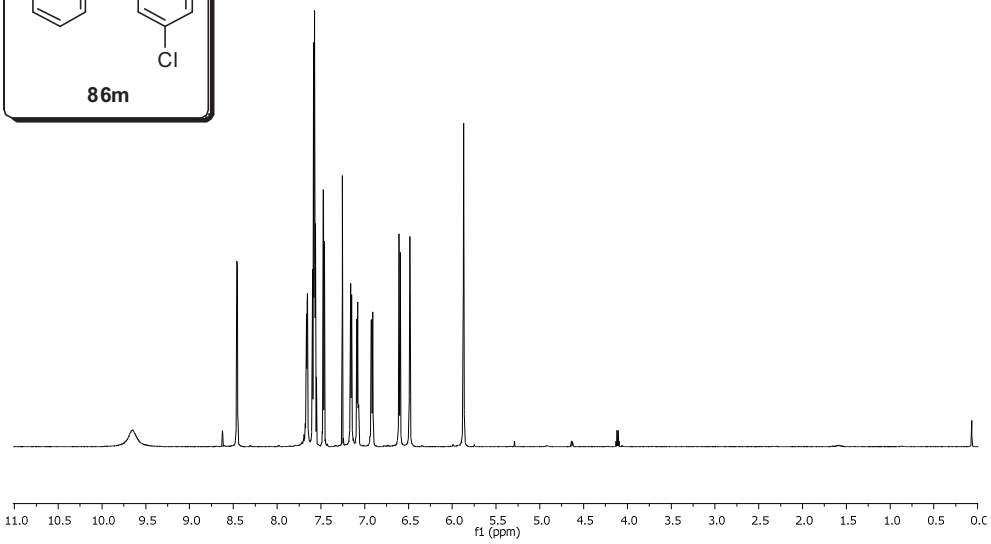
f1 (ppm)


O
O
S
N
HN
O
Cl

86m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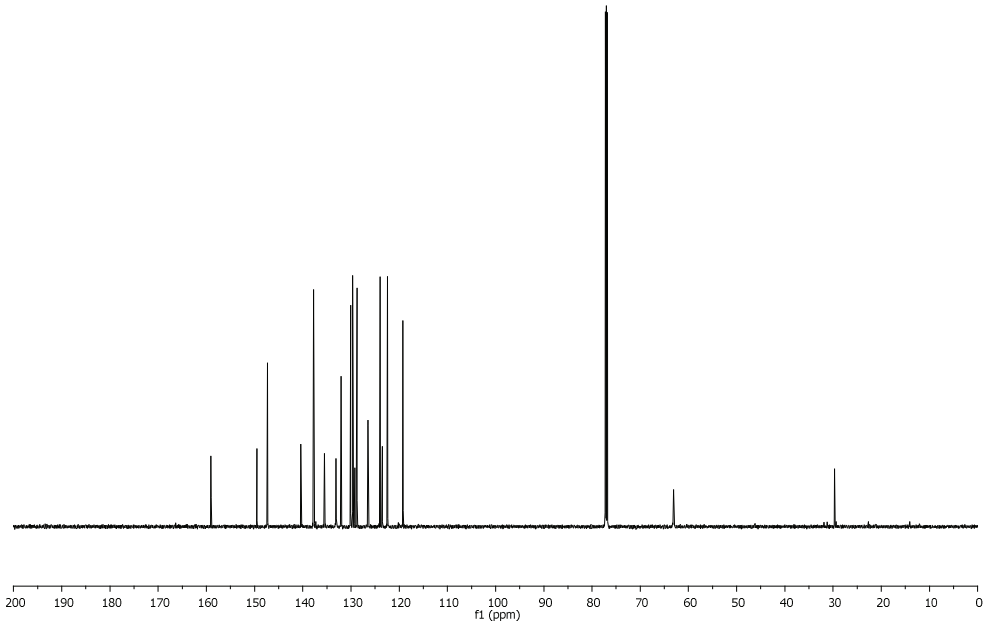
f1 (ppm)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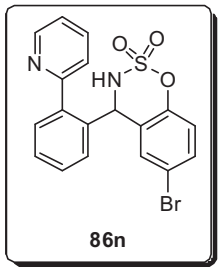
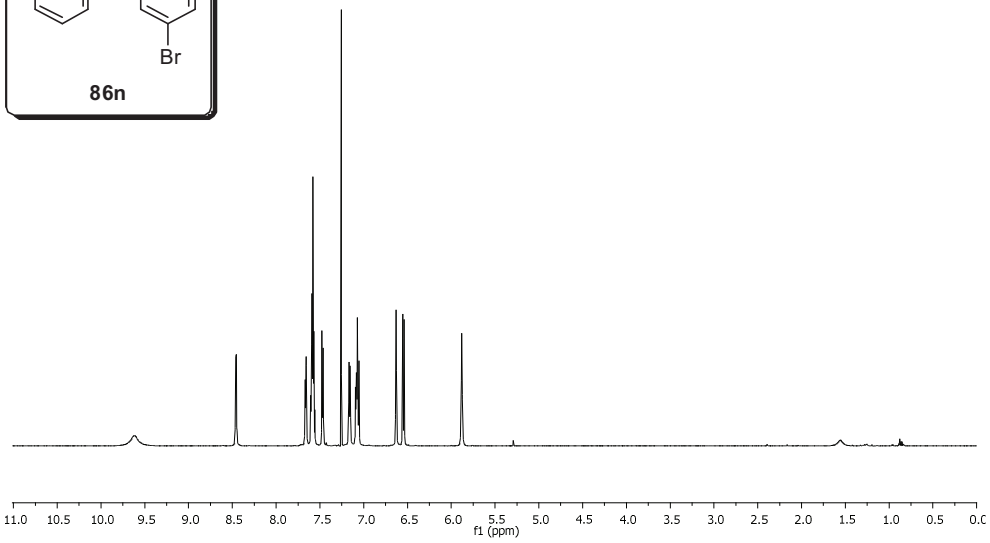
f1 (ppm)


N
HN
O
O
S
O
Br

86n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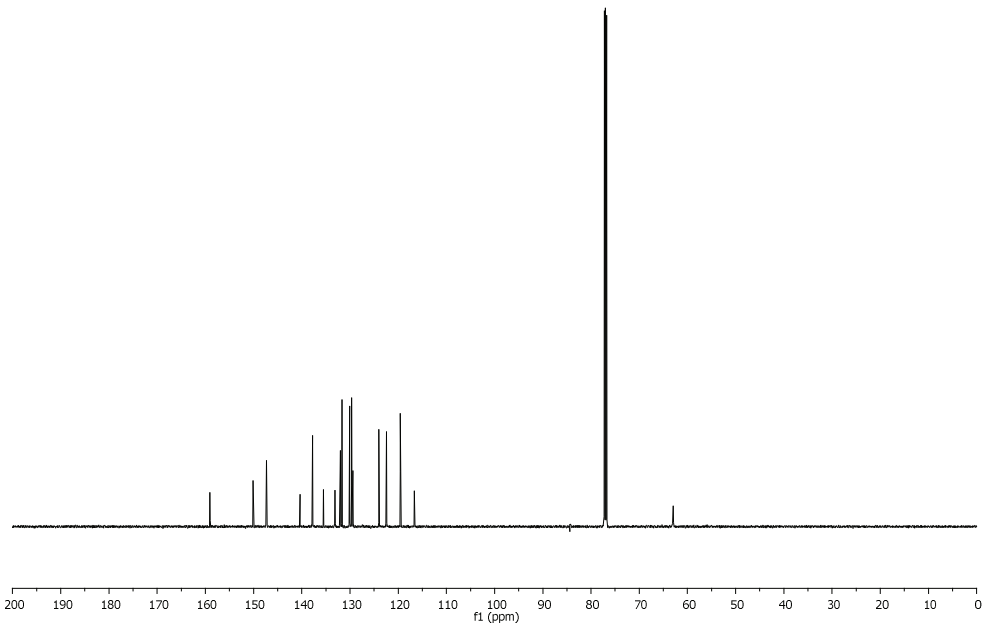
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)