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Transition metal-catalyzed reactions. Cascade reactions and chiral ligand synthesis

MEMORIA PRESENTADA POR

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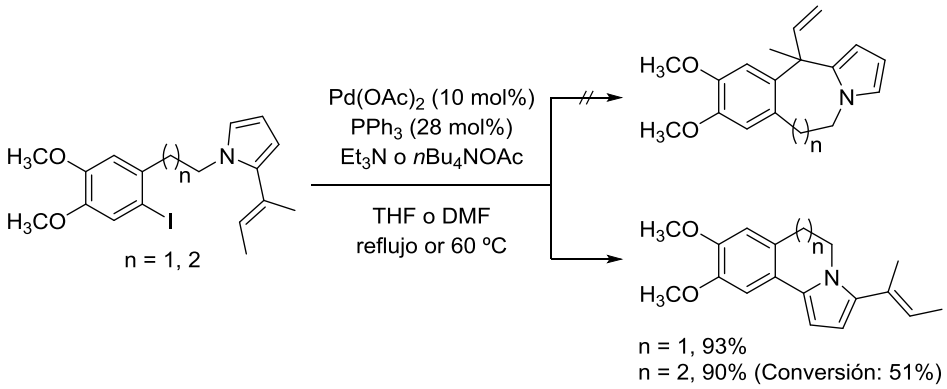
Resumen

El trabajo de investigación que se recoge en la presente memoria se centra, por una parte, en el desarrollo de nuevos métodos sintéticos basados en el empleo de reacciones tipo Heck catalizadas por Pd(0) para la formación de enlaces carbono-carbono, orientados a la preparación de heterociclos nitrogenados con un centro cuaternario. Asimismo, se estudia la síntesis de una nueva familia de ligandos quirales híbridos guanidina/amina, con el objetivo de formar complejos con distintos metales de transición, tales como Cu(I), para promover enantioselectividad en reacciones de adición conjugada y Henry. Asimismo, durante una estancia predoctoral en la Universidad de Illinois en Chicago, bajo la supervisión de la Dr. Laura Anderson, se ha estudiado la síntesis y reactividad de *N*-alquenilnitronas.

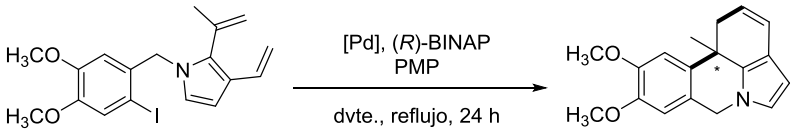
En el primer capítulo, se ha extendido el estudio de la reacción de Mizoroki-Heck intramolecular, puesto a punto en nuestro grupo de investigación para la síntesis de pirrolo[1,2-*b*]isoquinolinas, a la construcción de anillos medianos de siete y ocho miembros. Así, se ha investigado la posibilidad de generar un centro cuaternario de manera estereocontrolada mediante la reacción de Mizoroki-Heck intramolecular asimétrica sobre *N*-(*o*-yodoarilalquil)pirroles 2-alquenil sustituidos. Sin embargo, se ha demostrado que existe una competencia entre la reacción de Mizoroki-Heck y arilación directa cuando se realizan acoplamientos catalizados por paladio sobre *N*-(*o*-yodoarilalquil)pirroles 2-alquenil sustituidos, no habiendo sido posible controlar la quimioselectividad de la reacción. De hecho, bajo todas las condiciones ensayadas, las reacciones muestran una preferencia clara para rendir los productos de reacción de arilación directa sobre el anillo de pirrol y, por tanto, no ha sido posible la síntesis asimétrica de pirrolo[1,2-*a*]benzazepinas ni pirrolo[1,2-*a*]benzazocinas *vía* reacción de Mizoroki-Heck intramolecular. En su lugar, se han obtenido de modo completamente quimioselectivo las correspondientes pirrolo[2,1-*a*]isoquinolinas y pirrolo[2,1-*a*]benzazepinas**,** a través de la reacción de activación de enlace C-H o arilación directa sobre el C-2 del anillo de pirrol (Esquema 1).



Esquema 1

Por otra parte, durante el presente trabajo se ha estudiado la generación de centros cuaternarios a través de distintos procesos en cascada catalizados por Pd(0). Para ello, se han diseñado los sustratos adecuados para estudiar reacciones en cascada de tipo Heck/captura aniónica o Heck seguida de otra reacción de acoplamiento.

Así, la segunda parte del capítulo se centra en el uso de un modelo quimioinformático diseñado en colaboración con el Prof. Humberto González Díaz (Ikerbasque Research Professor, UPV/EHU) capaz de predecir el exceso enantiomérico y el rendimiento de la reacción Heck/Heck en cascada de *N*-bencil-2,3-dialquenilpirroles previamente estudiada en nuestro grupo de investigación. Así, se han probado las condiciones de reacción que predicen mejor valor de *ee* para la construcción del esqueleto tetracíclico del Licorano, las cuales implican el empleo de $Pd(dba)_2$ como catalizador en EtOH como disolvente (Esquema 2). Si bien las distintas condiciones de reacción no han mejorado el exceso enantiomérico obtenido bajo las condiciones optimizadas experimentalmente (Esquema 2, Condiciones a), se ha conseguido sintetizar el esqueleto tetracíclico del Licorano con resultados comparables en términos de enantioselectividad y mayor rendimiento (hasta 88%), reduciendo considerablemente la carga de precatalizador de paladio y ligando (Esquema 2, Condiciones b).



Condiciones a. *Predicción.* 54%, 79% *ee*
Experimental. 66%, 70% *ee*
Condiciones b. *Experimental.* 71%, 64% *ee*

Condiciones a. $Pd(dba)_2$ (10 mol%), (*R*)-BINAP (28 mol%), PMP (2 equiv.), EtOH
Condiciones b. $Pd(OAc)_2$ (2.5 mol%), (*R*)-BINAP (15 mol%), PMP (7.5 equiv.), CH_3CN

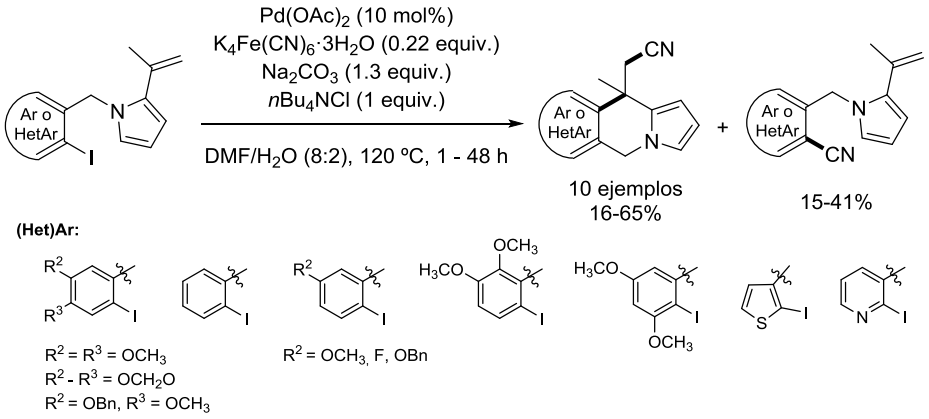
Esquema 2

Asimismo, el modelo computacional incluye el estudio del efecto de la estructura del ligando en la enantioselectividad de la reacción Heck-Heck en cascada, así como una predicción de los ligandos quirales que darían lugar a un mayor valor de exceso enantiomérico. Así, si bien se han ensayado alguno de estos ligandos, como (*S*)-P-Phos, únicamente se ha conseguido un pequeño aumento en el valor de exceso enantiomérico con respecto a las condiciones optimizadas experimentalmente (-73% *ee* vs. 70% *ee*).

Finalmente, se ha demostrado que los *N*-(*o*-yodobencil)pirroles 2-alquenil sustituidos son sustratos adecuados para la generación de pirrolo[1,2-*b*]isoquinolinas C-10 disustituidas con un centro cuaternario, ya que una reacción de tipo Heck intramolecular da lugar un intermedio σ-alquilpaladio, tras un proceso inicial de ciclación 6-*exo*, el cual puede bien ser atrapado por un nucleófilo bien participar en una segunda reacción de acoplamiento.

Así, en la tercera parte del capítulo, se ha estudiado la captura del intermedio σ-alquilpaladio formado tras la carbopaladación con una fuente de iones cianuro como nucleófilo. Así, se ha conseguido la formación secuencial de un enlace C-C y un enlace C-CN usando un sistema catalítico en ausencia de ligandos fosfano. De hecho, se ha demostrado el uso de ligandos no tiene un efecto beneficioso en la secuencia Heck/cianación, mientras que el empleo de nBu$_4$NCl como aditivo y agua como co-disolvente resultaron cruciales. Así, la secuencia Heck/cianación se ha podido extender a una amplia variedad de sustratos con distinto patrón de sustitución en el anillo aromático, si bien las pirrolo[1,2-*b*]isoquinolinas se obtuvieron únicamente con rendimientos de bajos a

moderados, ya que el proceso de cianación directa resultó ser siempre competitivo (Esquema 3).

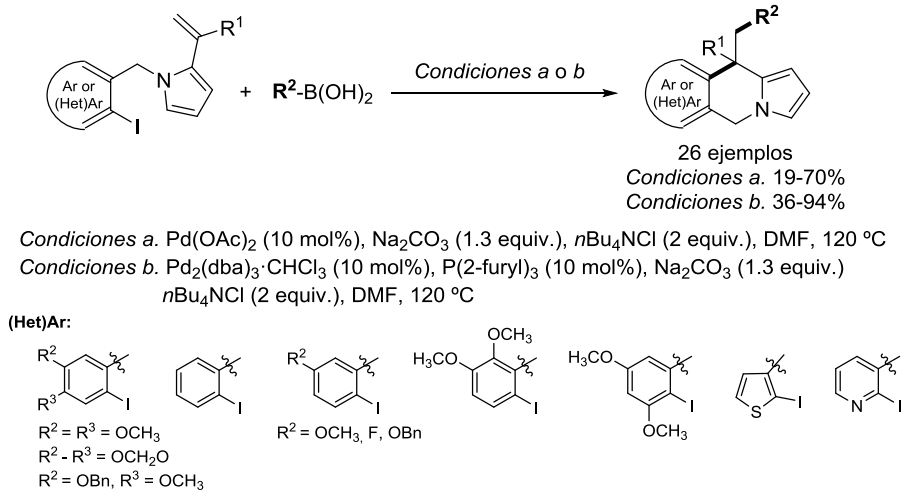


Esquema 3

Finalmente, el grupo ciano de las pirrolo[1,2-*b*]isoquinolinas obtenidas mediante la reacción Heck/cianación se ha derivatizado de manera eficiente a distintos grupos funcionales como aldehído, amida y amina, demostrando así la gran versatilidad del procedimiento.

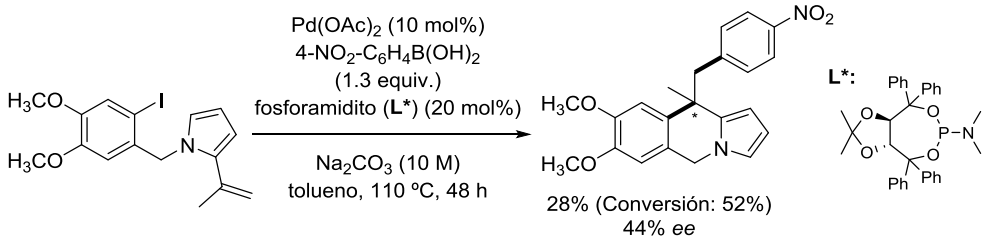
En la última parte del primer capítulo, se ha comprobado que los 2-alquenil *N*-(o-yodobencil)pirroles pueden dar lugar también a una reacción Heck/Suzuki en cascada a través de una carbopaladación inicial catalizada por paladio(0) seguida de una reacción de acoplamiento cruzado con ácidos borónicos. Así, se han podido usar ácidos arilborónicos ricos y deficientes en electrones en la reacción dominó Heck/Suzuki, así como ácidos alquenil- o heteroarílicos, obteniéndose las correspondientes pirrolo[1,2-*b*]isoquinolinas con rendimientos de moderados a buenos usando un sistema catalítico en ausencia de ligandos fosfano. Asimismo, la secuencia carbopaladación/Suzuki se ha podido extender a una variedad de 2-alquenil *N*-(o-yodobencil)pirroles con distinto patrón de sustitución en el alqueno y el anillo aromático, si bien los rendimientos de las pirroloisoquinolinas resultaron moderados (hasta 70%) (Esquema 4, Condiciones a).

Por otra parte, si bien el sistema catalítico en ausencia de ligandos empleado favorecía la reacción de carbopaladación con respecto al acoplamiento cruzado directo, el proceso 7-*endo* fue siempre competitivo. Sin embargo, se ha comprobado que el uso de ligandos fosfano, tales como tri(furan-2-il)fosfano en presencia de $Pd_2(dba)_3 \cdot CHCl_3$, permitía la supresión de la ruta 7-*endo*, además de provocar un aumento significativo del rendimiento de la reacción en la mayoría de los casos (hasta 94%) (Esquema 4, Condiciones b).



Esquema 4

Finalmente, se ha estudiado la versión asimétrica de la secuencia Heck/Suzuki. Para ello, se han analizado distintos sistemas catalíticos y condiciones de reacción, pudiéndose obtener únicamente enantioselectividades moderadas (hasta 44% *ee*) empleando $Pd(OAc)_2$ como catalizador y un fosforamidito quiral como ligando (Esquema 5).



Esquema 5

Adicionalmente, se ha evaluado la actividad antileishmanicida, así como la citotoxicidad, de alguna de las pirrolo[1,2-*b*]isoquinolinas sintetizadas frente a las formas de Leishmaniasis visceral (*L. donovani*) y cutánea (*L. amazonensis*) mediante ensayos biológicos realizados por la Dr. M. A. Dea de la Universidad CEU Cardenal Herrera (Valencia). Así, los ensayos *in vitro* con promastigotes han revelado que las pirroloisoquinolinas son más activas y menos tóxicas que el fármaco de referencia, Miltefosina, para el tratamiento de la leishmaniasis cutánea. Asimismo, se ha observado que los derivados C-10 bencil sustituidos presentan mayor actividad que los compuestos que presentan un grupo cianometilo en C-10. Además, se ha podido concluir que la presencia de sustituyentes electron-dadores en el anillo aromático del esqueleto de pirroloisoquinolina tiene un impacto positivo en la actividad antileishmanicida. Por otra parte, los compuestos más activos de los ensayos con promastigotes se analizaron con amastigotes de *L. amazonensis* y *L. donovani*. Así, las pirroloisoquinolinas analizadas han resultado ser menos activas que la Miltefosina para el tratamiento de la leishmaniasis visceral, si bien presentan un IC_{50} similar o incluso mejor el fármaco de referencia, así como un SI elevado.

Por otra parte, en el segundo capítulo se ha llevado a cabo la síntesis de una nueva familia de ligandos quirales híbridos guanidina/amina con la estructura adecuada para la formación de complejos mononucleares en reacciones catalizadas por Cu(I) a partir de aminoácidos comerciales, tales como D-valina, D-fenilglicina y D-alanina (Figura 1). Así, los aminoácidos se han transformado eficazmente en los correspondientes alcoholes a través de una reacción de *N*-formilación y posterior reducción. A continuación, la reacción de condensación entre los aminoalcoholes *O*-protegidos y Boc-glicina permitió alcanzar las correspondientes diaminas enantioméricamente puras con buenos rendimientos, las cuales dieron lugar a los ligandos quirales recogidos en la Figura 1 mediante reacción de alquilación con la sal de imidazolio adecuada.

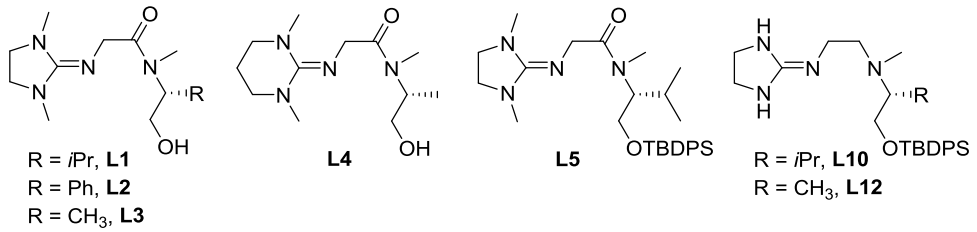
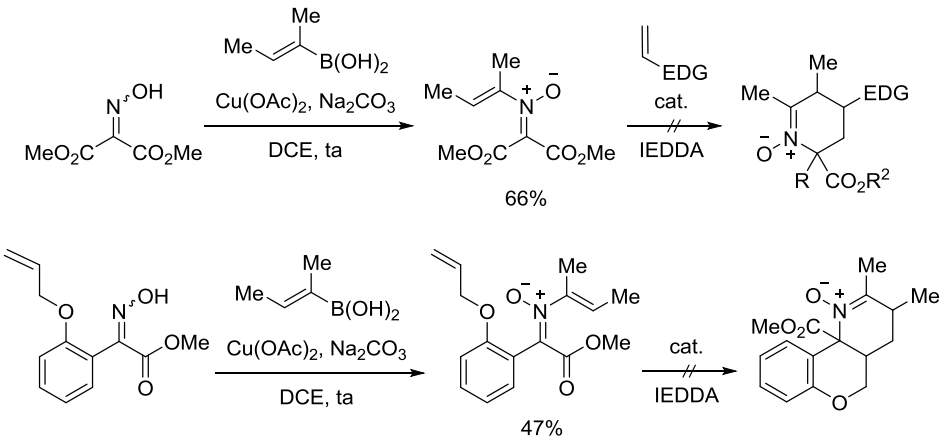


Figura 1.

Asimismo, se ha evaluado la capacidad de los complejos formados entre los ligandos sintetizados y distintas sales de cobre para inducir regio- y enantiocontrol en las reacciones de adición de reactivos organometálicos a enonas acíclicas y la reacción de Henry entre *p*-nitrobenzaldehído y nitrometano, obteniéndose buenos rendimientos, pero enantioselectividades bajas.

Finalmente, el tercer capítulo describe el trabajo desarrollado durante una estancia predoctoral en el Departamento de Química de la Universidad de Illinois en Chicago bajo la supervisión de la Dr. Laura Anderson, el cual se centra en el empleo de *N*-alquenilnitronas en las versiones inter- e intramolecular de la reacción de Diels-Alder con demanda electrónica inversa.

En este contexto, se ha logrado la síntesis de distintas *N*-alquenilnitronas a través de la reacción de acoplamiento de Chan-Lam catalizada por cobre (Esquema 6). Una vez sintetizadas, se ha llevado a cabo el estudio de su reactividad como azadienos pobres en electrones en la reacción intermolecular de Diels-Alder con demanda electrónica inversa con distintos dienófilos ricos en electrones. Para ello, se han empleado distintos catalizadores metálicos (complejos tipo BINOL-Ln(III) y bis(oxazolina)-cobre), así como organocatalizadores (tioureas, escuaramidas y ácidos fosfóricos). Desafortunadamente, se observó que la reacción de cicloadición no tenía lugar independientemente del tipo de catálisis empleado y, por tanto, no ha sido posible la formación de los *N*-óxidos de tetrahidropiridina (Esquema 6).


Me
Me
B(OH)2
Cu(OAc)2, Na2CO3
DCE, ta
N
OH
MeO2C
CO2Me
Me
Me
N
O
MeO2C
CO2Me
66%
EDG
cat.
IEDDA
Me
Me
EDG
N
O
R
CO2R2
O
N
OH
OMe
O
Me
Me
B(OH)2
Cu(OAc)2, Na2CO3
DCE, ta
O
N
Me
Me
O
OMe
47%
cat.
IEDDA
Me
O
N
Me
MeO2C
O

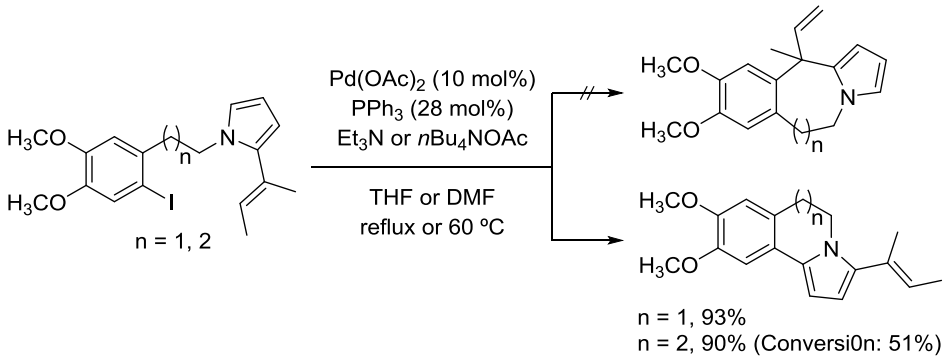
Esquema 6

Summary

The research work described in this thesis is focused on the development of new synthetic methods based on the use of Pd(0) catalyzed Heck-type reactions for the formation of carbon-carbon bonds, oriented to the preparation of nitrogenated heterocycles with a quaternary stereocenter. Moreover, the synthesis of a new family of chiral hybrid guanidine/amine ligands has been performed, which could form complexes with different transition-metals, such as Cu(I), to promote enantioselectivity in conjugate addition and Henry reactions. Furthermore, during a research stay at the University of Illinois at Chicago, under the supervision of Prof. Laura L. Anderson, the synthesis and reactivity of *N*-alkenylnitrones has been investigated.

In the first chapter, the intramolecular Mizoroki-Heck reaction, developed in our group for the synthesis of pyrrolo[1,2-*b*]isoquinolines, has been extended to the construction of seven- and eight-membered rings. Thus, the possibility of generating a quaternary center in a stereocontrolled fashion through an asymmetric intramolecular Miroroki-Heck reaction over 2-alkenyl *N*-(*o*-iodoarylalkyl)pyrroles has been investigated.

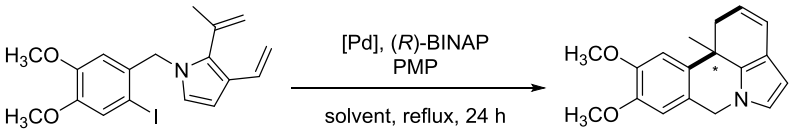
However, it has been demonstrated that a clear competition exists between the Mizoroki-Heck and direct arylation reactions when palladium catalyzed couplings are carried out on 2-alkenyl substituted *N*-(*o*-iodoarylalkyl)pirroles, so it was not possible to control the chemoselectivity of the reaction. In fact, the direct arylation onto the pyrrole nucleus emerges as the predominant process under all the conditions tested and, therefore, the asymmetric synthesis of neither pyrrolo[1,2-*a*]benzazepines nor pyrrolo[1,2-*a*]benzazocines has been possible through intramolecular Mizoroki-Heck reaction. Instead, the corresponding pyrrolo[2,1-*a*]isoquinolines and pyrrolo[2,1-*a*]benzazepines has been obtained with complete chemoselectivity *via* C-H activation or direct arylation reaction onto the C-2 of the pyrrole nucleus (Scheme 1).



Esquema 1

On the other hand, the generation of quaternary stereocenters through different Pd(0) catalyzed cascade processes has also been studied. For that purpose, adequate substrates have been designed for the study of Heck/anionic capture cascade or Heck followed by other cross-coupling reactions.

Thus, the second part of the chapter is focused on the use of a chemoinformatic model, designed in collaboration with Prof. Humberto González Díaz (Ikerbasque Research Professor, UPV/EHU), able to predict the enantiomeric excess and the yield of the Heck/Heck cascade reaction of *N*-benzyl-2,3-dialkenylpyrroles previously studied in our research group. This way, conditions that predict best value of *ee* have been attempted for the construction of the tetracyclic framework of the Licorane, which are based on changes in catalyst, ligand and base loadings. Although the different reaction conditions have not improved the enantiomeric excess obtained under experimentally optimized conditions, the synthesis of the tetracyclic core of Licorane has been possible with similar results in terms of enantioselectivity and better yield (up to 88%), decreasing considerably the palladium preacatalyst and additive loadings (Scheme 2).



Conditions a. *Predicted.* 54%, 79% *ee*
Experimental. 66%, 70% *ee*
Conditions b. *Experimental.* 71%, 64% *ee*

Conditions a. $Pd(dba)_2$ (10 mol%), (*R*)-BINAP (28 mol%), PMP (2 equiv.), EtOH
Conditions b. $Pd(OAc)_2$ (2.5 mol%), (*R*)-BINAP (15 mol%), PMP (7.5 equiv.), CH_3CN

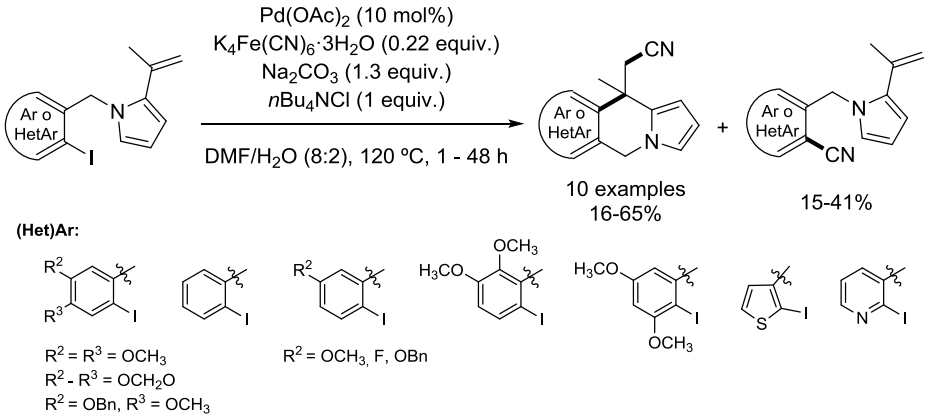
Scheme 2

In addition, the computational model includes the study of the effect of the ligand structure over the enantioselectivity of the Heck-Heck reaction, as well as the prediction of the chiral ligands that would afford higher value of enantiomeric excess. Thus, although some of these ligands have been tested, such as (*S*)-P-Phos, only a slight increase in the enantiomeric excess value has been obtained in relation to experimentally optimized conditions (-73% *ee* vs. 70% *ee*).

In the third and fourth part of the chapter, it has been demonstrated that 2-alkenyl *N*-(*o*-iodobenzyl)pyrroles are adequate substrates for the generation of C-10 disubstituted pyrrolo[1,2-*b*]isoquinolines with a quaternary center, as the intramolecular Heck-type reaction leads to a σ-alkylpalladium intermediate, after an initial 6-*exo* cyclization process, which can be trapped by a nucleophile or participate in a second coupling reaction.

Thus, in the third part, the capture of the σ-alkylpalladium intermediate formed after the carbopalladation with a cyanide source as nucleophile has been studied. This way, the sequential formation of a C-C and a C-CN bond has been achieved, using a catalytic system in absence of phosphane ligands. It has been found that the use of ligands has not a beneficial effect in the Heck/cyanation sequence, while the use of $n Bu_4NCl$ as additive and water as co-solvent were crucial. It has also been possible to extend the Heck/cyanation sequence to a wide variety of substrates with different substitution pattern on the aromatic

ring, although the pyrrolo[1,2-*b*]isoquinolines were isolated only in moderate to good yields, as the direct cyanation process was always competitive (Scheme 3).



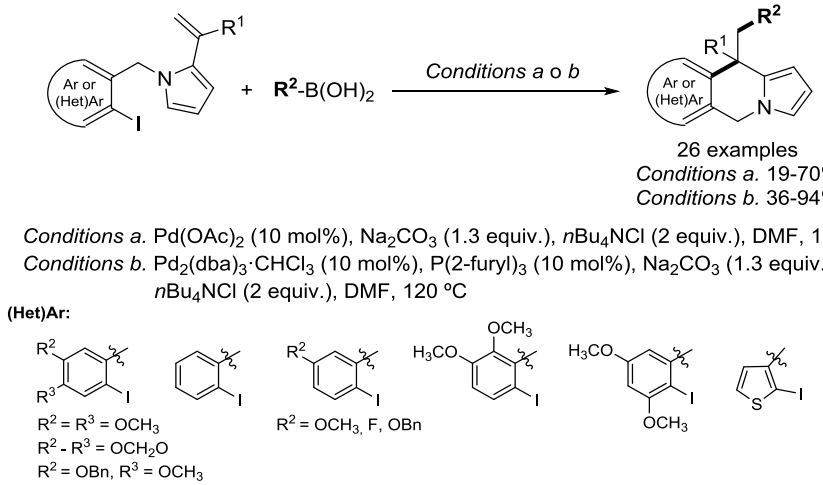
Scheme 3

Finally, the cyano group of the pyrrolo[1,2-*b*]isoquinolines obtained through the Heck/cyanation reaction has been efficiently derivatized to different functional groups, such as aldehyde, amide and amine, showing the versatility of the procedure.

In the last part of the chapter, it has been shown that the 2-alkenyl *N*-(o-iodobenzyl)pirroles can also lead to a Heck/Suzuki cascade reaction through an initial palladium(0) catalyzed carbopalladation followed by a cross-coupling reaction with boronic acids. Thus, electron rich and deficient arylboronic acids have been employed in the Heck/Suzuki sequence, as well as alkenyl- or heteroarylboronic acids, obtaining the corresponding pyrrolo[1,2-*b*]isoquinolines with moderate to good yields using a catalytic system in absence of phosphane ligands. Furthermore, the carbopalladation/Suzuki sequence has also been extended to a variety of 2-alkenyl *N*-(o-iodobenzyl)pyrroles with different substitution pattern in the alkene and on the aromatic ring, although the yields of the pyrroloisoquinolines were moderate (Scheme 4).

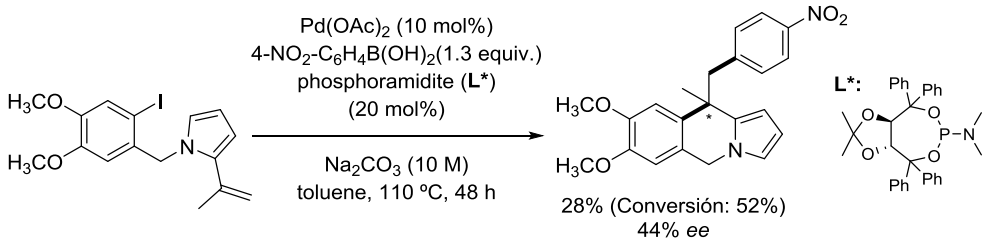
The utilized catalytic system in absence of ligands favoured the carbopalladation reaction over the direct cross-coupling pathway, but the 7-*endo* process was always competitive.

However, it has been found that the use of phosphane ligands, such as tri(furan-2-yl)phosphane in the presence of $Pd_2(dba)_3 \cdot CHCl_3$, allowed the suppression of the 7-*endo* route and afforded in most cases a significant improvement in the Heck/Suzuki reaction yield (up to 94%) (Scheme 4).



Scheme 4

Finally, the asymmetric version of the Heck/Suzuki sequence has been studied. For that purpose, different catalytic systems and reaction conditions have been evaluated, but only moderate enantioselectivities (up to 44% *ee*) have been obtained, using $Pd(OAc)_2$ as catalyst and a chiral phosphoramidite as ligands (Scheme 5).



Scheme 5

Additionally, anti-leishmanicidal activity and cytotoxicity of some of the synthesized pyrrolo[1,2-*b*]isoquinolines against visceral (*L. donovani*) and cutaneous (*L. amazonensis*) leishmaniasis have been evaluated through biological assays carried out by Dr. M. A. Dea from University CEU Cardenal Herrera (Valencia). Thus, *in vitro* assays on promastigotes has revealed that pyrroloisoquinolines are more active and less toxic than the drug of reference, Miltefosine, for the treatment of cutaneous leishmaniasis. Moreover, C-10 benzyl substituted derivatives have been found to have higher activity than the compounds with a cyanomethyl group at C-10. Besides, it has been observed that the presence of electron-donor groups on the aromatic ring of the pyrroloisoquinoline framework enhances the anti-leishmanicidal activity. On the other hand, the more active compounds of the assays on promastigotes were further analyzed with amastigotes from *L. amazonensis* and *L. donovani*. Thus, it has been shown that the evaluated pyrroloisoquinolines are less active than Miltefosine for the treatment of visceral leishmaniasis, although they have similar or even better IC_{50} than the drug of reference, as well as a high SI.

On the other hand, in the second chapter the synthesis of a new family of chiral hybrid guanidine/amine ligands with the appropiate structure for the formation of mononuclear complexes in Cu(I)-catalyzed reactions has been accomplished (Figure 1), starting from commercially available amino acids, such as D-valine, D-phenylglicine and D-alanine. Thus, the amino acids have been efficiently transformed into the corresponding alcohols through *N*-formylation reaction and a subsequent reduction. Next, condensation reaction between *O*-protected amino alcohols and Boc-glycine has allowed the formation of the corresponding enantiomerically pure diamines in high yields, which afforded the chiral hybrid ligands depicted in Figure 1 by alkylation reaction with an adequate imidazolium salt.

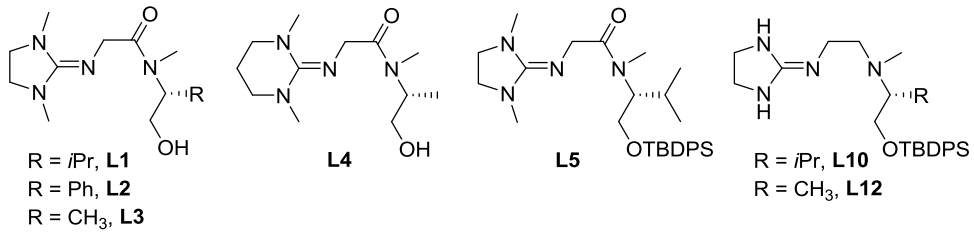
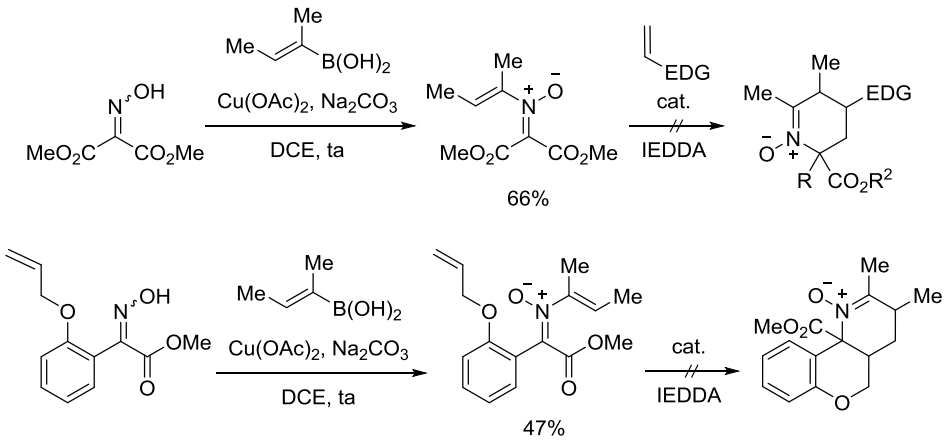


Figure 1

Moreover, the capacity of the complexes formed between the synthesized ligands and different copper salts has been evaluated to induce regio- and enantiocontrol in conjugate addition of organometallic reagents to acyclic enones and Henry reaction between *p*-nitrobenzaldehyde and nitromethane, obtaining good yields, but low to moderate enantioselectivities.

Finally, in the third chapter, the research work developed during a predoctoral stay in the Department of Chemistry at the University of Illinois at Chicago under the supervision of Prof. Laura L. Anderson is described, which is focused on the use of *N*-alkenylnitrones in the inter- e intramolecular versions of the inverse electron demand Diels-Alder reaction.

In this context, the synthesis of different *N*-alkenylnitrones has been achieved through copper-catalyzed Chan-Lam coupling reaction (Scheme 6). Once synthesized, the evaluation of their reactivity as electron poor azadienes in the intermolecular inverse-electron demand Diels-Alder reaction has been carried out with different metallic catalyst (BINOL-Ln(III) and bis(oxazoline)-copper type complexes), as well as organocatalyts (thioureas, squaramides y phosphoric acids). Unfortunately, it was observed that cycloaddition reaction did not take place regardless the type of catalysis employed and, therefore, the formation of tetrahydropyridine *N*-oxides was not been possible (Scheme 6).


Me
Me
B(OH)2
Cu(OAc)2, Na2CO3
DCE, ta
N
OH
MeO2C
CO2Me
66%
EDG
cat.
IEDDA
R
CO2R2
O
OMe
47%

Scheme 6

Index

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Abbreviations, acronyms and symbols

aq.	Aqueous	**δ**	Chemical shift
ATR	Attenuated Total Reflection	**DABCO**	1,4-Diazabicyclo[2.2.2]octane
BARF	Tetrakis[3,5-bis(trifluoro-methyl)phenyl]borate	**dba**	Dibenzylideneacetone
bdmegb	1,2-Bis(dimethylethylene guanidino)benzene	**DBU**	1,8-Diazabicyclo[5.4.0] undec-7-ene
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl	**DCC**	*N,N'*-Dicyclohexyl-carbodiimide
BINOL	1,1′-Binaphthalene-2,2′-diol	**DCE**	Dichloroethane
BITIANP	2,2'-bis(diphenylphosphino)-3,3'-bibenzo[*b*]thiophene	**DEPT**	Distorsionless Enhancement by Polarization Transfer
Boc	*tert*-Butoxycarbonyl	**DIBAL-H**	Diisobutylaluminum hydride
btmgb	1,2-Bis(tetramethylguanidino) benzene	**DIPEA**	*N,N*-Diisopropylethylamine
btmgn	1,8- Bis(tetramethylguanidino) naphthalene	**DMA**	*N,N*-Dimethylacetamide
btmgp	1,3-Bis(tetramethylguanidino) propane	**DMAP**	4-Dimethylaminopyridine
c	Concentration	**DMF**	*N,N*-Dimethylformamide
CC_{50}	Cytotoxic Concentration	**DMSO**	Dimethylsulfoxide
CL	Cutaneous Leishmaniasis	**dppp**	1,3-Bis(diphenylphosphino)propane
CMD	Concerted metalation-deprotonation	***dr***	Diastereomeric ratio
COD	1,5-Cyclooctadiene	**D*t*BPF**	1,1'-bis(di-tertbutylphosphino)ferrocene
COSY	COrrelated SpectroscopY	**Ed(s).**	Editor(s)
CuTC	Copper thiophene carboxylate	***ee***	Enantiomeric excess
		equiv.	Equivalent
		ESI	ElectroSpray Ionization
		MW	Microwave

EWG	Electron Withdrawing Group	**m/z**	Mass to charge ratio
FDA	Food and Drug Administration	**N/A**	No Activity
HetAr	Heteroaryl	**ND**	Not Detected
HMBC	Heteronuclear Multiple Bond Correlation	**NDDS**	Nanoparticle Drug Delivery Systems
HPLC	High Performance Liquid Chromatography	**NMR**	Nuclear Magnetic Resonance
		nOe	Nuclear Overhausser Effect
HRMS	High Resolution Mass Spectrometry	**NOESY**	Nuclear Overhausser Effect Enhancement SpectroscopY
HSQC	Heteronuclear Single Quantum Coherence	**n.r.**	No reaction
		Nu	Nucleophile
IC_{50}	Half maximal inhibitory concentration	**p.**	Page
		***p*-ABSA**	*p*-Acetamidobenzenesulfonyl azide
IEDDA	Inverse Electron Demand Diels-Alder	**[Pd]**	Palladium source
IR	Infrared	**phen**	1,10-Phenanthroline
J	Coupling Constant	**Pin**	Pinacol
L	Ligand	**PM**	Paromomycin
L-AmB	Liposomal amphotericin B	**PMB**	*p*-Methoxybenzyl
LAH	Lithium aluminum hydride	**PMP**	1,2,2,6,6-Pentamethylpiperidine
Lit.	Literature	**Prod.**	Product
M	Metal	**PT**	Perturbation Theory
M^+	Molecular Ion (MS)	**PVM**	Parasitophorous Vacuole Membrane
MCL	Monocutaneous Leishmaniasis		
ML	Machine Learning	**Py**	Pyridine
m.p.	Melting point	**QSRR**	Quantitative Structure-Reactivity Relationship
MS	Molecular Sieves; Mass Spectrometry		
		QTOF	Quadrupole time-of-flight mass spectrometer
MTBE	*tert*-Butyl methyl ether		

rt	Room temperature
SD	Standard deviation
SDP	7,7'-Bis(diphenylphosphino)-1,1'-spirobiindane
SI	Selectivity Index
Subs.	Substrate
T	Temperature
t	Time
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TFP	Tri(2-furyl)phosphine
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl
t_r	Retention time
ttmgb	1,2,4,5-Tetrakis(tetramethyl guanidine)benzene
UPLC	Ultra Performance Liquid Chromatography
UV	Ultraviolet
VL	Visceral Leishmaniasis
vs.	Versus

I

Mizoroki-Heck Reaction for the Generation of Quarternary Centers

1. INTRODUCTION

1.1. Intramolecular Mizoroki-Heck reaction for the generation of stereocenters

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1.1.2. Approaches based on blocking the β-hydride elimination: tetrasubstituted acyclic alkenes as coupling partners

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1. INTRODUCTION

Transition metal-catalyzed cross-coupling reactions are nowadays recognized to be one of the most valuable carbon-carbon bond-forming processes in organic synthesis.[1] In this context, palladium-mediated chemistry[2] occupies an important position, due to its ability to promote many unconventional transformations in excellent yields with a high specificity under reaction conditions that are compatible with a wide range of functionalities.

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 been found to be an extremely powerful and useful tool in organic synthesis.

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[1] a) Beller, M.; Bolm, C. Eds. *Transition Metals for Organic Synthesis*, 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 CrossCoupling 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) Tsuji, J. *Palladium in Organic Synthesis*, 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.

[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.

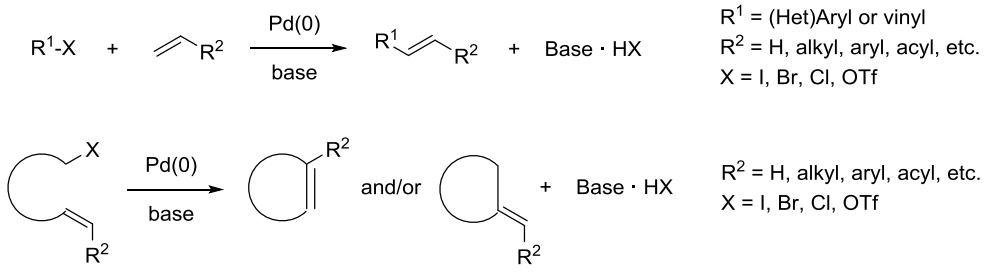
[4] a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.

[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.

The Mizoroki-Heck reaction (M-H) is known since 1968,[9] when Heck described the formation of arylated alkenes obtained by reaction of alkenes with stoichoimetric amounts of aryl palladium compounds, such as [Ar-Pd-Cl] or [Ar-Pd-OAc], generated *in situ* from the combination of ArHgCl with $PdCl_2$ or ArHgOAc with $Pd(OAc)_2$, respectively.

The M-H reaction can be defined as the palladium-catalyzed cross-coupling reaction of (hetero)aryl and vinyl halides or triflates with alkenes, which can be carried out in both an intermolecular or intramolecular fashion (Scheme 1.1). The intramolecular version is a simple and useful method for the synthesis of carbocycles[10] and heterocycles.[11]



Scheme 1.1.

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[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*, 5518; b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *14*, 2320; c) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

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

[11] 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.

As stated before, the versatility of this reaction is an important characteristic, as it tolerates different functional groups. In fact, the M-H reaction has been widely employed for preparation of highly functionalized olefins, dienes or other unsaturated compounds, being also used in polymerization chemistry.

The Heck type reactivity depends on the ability of Pd(0) species to suffer oxidative addition to C-X bonds of aryl halides or triflates and the subsequent addition of the ArPdX intermediates to unsaturated bonds. Thus, under the same reaction conditions, the reactivity order for aryl halides and triflates in M-H reactions is: Ar-I >> Ar-OTf > Ar-Br >> Ar-Cl,[12] which suggests that the oxidative addition step is rate determining for the less reactive aryl halides. On the contrary, limiting step for more reactive aryl halides is thought to be the complexation/insertion process.

The M-H reaction can be performed both in the presence and in absence of ligands. The most commonly used ligands are phosphanes, whose function is to keep the catalyst stable at a (0) oxidation state, by forming species like PdL_4 and PdL_2. However, the use of ligand free M-H reaction is interesting due to economical, environmental and chemical reasons (high toxicity, difficulty to be recovered, high price, etc.). Additionally, fully coordinated palladium complexes present lower reactivity, so, consequentely, an increase of catalyst loading would be needed to obtain reasonable reaction rate.

A wide variety of different palladium complexes may be used as catalyst in M-H reaction. Some palladium sources, such as $Pd(PPh_3)_4$, $Pd(dba)_2$ and $Pd_2(dba)_3$, provide directly catalytically active Pd(0) species. However, Pd(0) species is usually *in situ* generated by reduction of Pd(II) precatalysts, such as $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$, in the presence of ligands.

Since the original work of Mizoroki[13] and Heck,[14] many modifications have been proposed to improve the selectivity and regioselectivity of the reaction. For example, the use of

[12] Jutand, A.; Negri, S.; de Vries, J. G. *Eur. J. Inorg. Chem.* **2002**, 1711.
[13] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

tetraalkylammonium salts in the catalytic system (Jeffery protocol)[15] has been found to improve the reactivity of the M-H reaction. Further improvements in the reaction outcome are based on the addition of either silver[16] or thallium[17] salts. In addition, it has been demonstrated that the efficiency of the catalyst can be increased carrying out the reaction under pressure or microwave assisted conditions.

A wide variety of solvents can be used in Mizoroki-Heck reactions, and high temperatures are frequently necessary. Generally, non-protic polar solvents are used (DMF, DMA, DMSO, etc.), although sometimes a mixture of a organic solvent and water, or even only water, can be employed as reaction medium.[18] Both organic (trialkylamines) and inorganic bases (NaOAc, $NaHCO_3$, etc.) may be employed for the regeneration of catalytic active palladium(0) species.

The M-H reaction has found wide application for the formation of $C(sp^2)$-$C(sp^2)$ bonds. However, it can also be applied for the generation of tertiary and quaternary stereocenters. In the following section, in connection with the objectives of this PhD work, the main strategies towards this goal will be discussed through some selected examples.

1.1. Intramolecular Mizoroki-Heck reaction for the generation of stereocenters

The intramolecular M-H reaction can be an useful strategy for the generation of tertiary and quaternary centers by controlling the β-hydride elimination step. For that purpose, it is necessary to avoid the *syn* β-hydride elimination in the alkylpalladium intermediate formed after the insertion of the arylpalladium to the alkene, so that the elimination takes places in another β'-position and not on the carbon directly involved in bond formation (Scheme 1.2).

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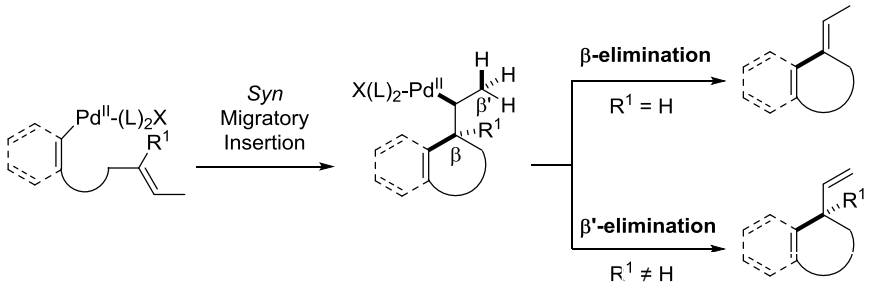
[14] Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.
[15] Jeffery, T. *Tetrahedron* **1996**, *52*, 10113 and references cited therein
[16] Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896.
[17] Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687.
[18] Shaughnessy, K. H.; DeVasher, R. B. *Curr. Org. Chem.* **2005**, *9*, 585.



Scheme 1.2.

The reactions are generally highly diastereoselective and the use of chiral ligands for palladium, such as chiral bidentate phosphines (*e.g.* (*R*)-BINAP), has allowed the development of an enantioselective variant, which has become an important tool in natural product and pharmaceutical syntheses.[2]

Different strategies have been developed to avoid this *syn* β-hydride elimination and, thus, to direct the elimination to another β'-position. First approaches implied blocking the β-hydride elimination on an acyclic alkene ($R^1 \neq H$) (Scheme 1.2), or alternatively, the use of cyclic alkenes, where conformational rigidity and, hence, restricted rotation around the C-C bonds steers β-hydride elimination away from the newly formed C-C bond. Other strategies involved the introduction of a heteroatom in an allylic position of the olefin, either to promote the elimination of a good leaving group or a tautomerization reaction as a thermodynamic driving force in favor of β´-hydride elimination. Finally, cascade reactions, where β-hydride elimination is avoided by involving the alkylpalladium intermediate in another coupling reaction or in an anion capture event, have also been successfully applied for this purpose.

The recent advances in all variants of the M-H reaction have led to a great number of reports[19,20] that focus on different aspects such as enantioselective variants[21] or cascade

[19] For selected reviews on the intramolecular Mizoroki-Heck reaction, see: a) Geoghegan, K.; Evans, P. In *Science of Synthesis. Cross Coupling and Heck-Type Reactions 3. Metal-Catalyzed Heck-Type Reactions and C-H Couplings via C-H Activation*; Larhed, M., Ed., Georg Thieme Verlag: Stuttgart,

reactions.[22] In this section, some examples of the most significant strategies used for the generation of stereocenters in its application to the synthesis of heterocyclic systems are shown.

1.1.1. Approaches based on blocking the β-hydride elimination: cyclic alkenes as coupling partners

The use of cyclic alkenes as coupling partners is one of the first strategies used for the generation of stereocenters. In this case, *syn* β-hydride elimination is avoided, as rotation of the C-C bond of the intermediate alkylpalladium species formed after carbopalladation is not possible. Since the first examples of intramolecular M-H reaction using cyclic alkenes reported by Shibasaki[23] and Overman,[24] this protocol has become an excellent tool for the construction of cyclic frameworks generating tertiary and quaternary stereocenters in the asymmetric synthesis of natural products and pharmaceuticals. In this context, Tietze synthesis of steroids[25] and (–)-cephalotoxine alkaloid[26] for the generation of tertiary stereocenters, or the assembly of spirocyclic oxindoles and the synthesis of mesembrine alkaloids reported by Overman[27] and Evans,[28] respectively, for the formation of quaternary

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2013, p. 391. b) Stwart, S. G. In *Science of Synthesis. Cross Coupling and Heck-Type Reactions 3. Metal-Catalyzed Heck-Type Reactions and C-H Couplings via C-H Activation*; Larhed, M., Ed., Georg Thieme Verlag: Stuttgart, **2013**, p. 441.

[20] Broggini, G.; Borsini, E.; Piarulli; U. In *Science of Synthesis. Cross Coupling and Heck-Type Reactions 3. Metal-Catalyzed Heck-Type Reactions and C-H Couplings via C-H Activation*, Larhed, M., Ed., Georg Thieme Verlag: Stuttgart, **2013**, p. 521.

[21] For selected reviews, see: a) Sibashaki, M.; Boden, C. D. J; Kojima, A. *Tetrahedron*, **1997**, *53*, 7371. b) Dounay, A. N.; Overman, L. *Chem. Rev*. **2003**, *103*, 2945. c) Tietze, L. F.; Ila. H.; Bell, H. P. *Chem. Rev*. **2004**, *104*, 3453. d) Mc Cartney, D.; Guiry, P. J. *Chem. Soc. Rev*. **2011**, *40*, 5122.

[22] a) Ohno, H. *Asian J. Org. Chem*. **2013**, *2*, 18. b) Biemolt, J.; Ruijter, E. *Adv. Synth. Catal*. **2018**, *360*, 3821. c) Blouin, S.; Blond, G.; Donnard, M.; Gulea, M.; Suffert, J. *Synthesis*, **2017**, *49*, 1767. d) Ohno, H.; Inuki, S. *Synthesis*, **2018**, *50*, 700. e) Ping, Y.; Li, Y.; Zhu, J.; Kong, W. *Angew. Chem. Int. Ed*. **2019**, *58*, 1562.

[23] Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738.

[24] Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959.

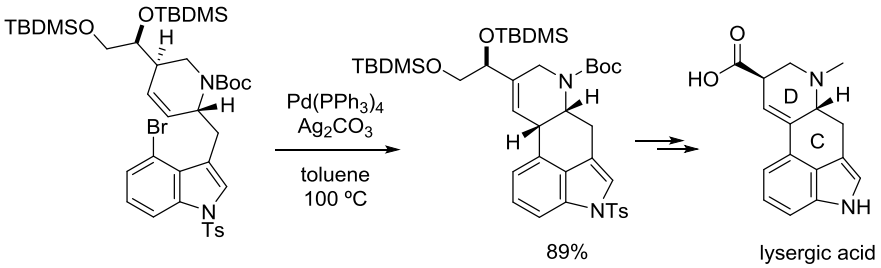
[25] a) Tietze, L. F.; Petersen, S. *Eur. J. Org. Chem.* **2000**, 1827; b) Tietze, L. F.; Petersen, S. *Eur. J. Org. Chem.* **2001**, 1619; c) Tietze, L. F.; Krahnert, W. R. *Chem. Eur. J.* **2002**, *8*, 2116.

[26] Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264.

[27] Overman, L. E. Watson, D. A. *J. Org. Chem.* **2006**, *71*, 2587.

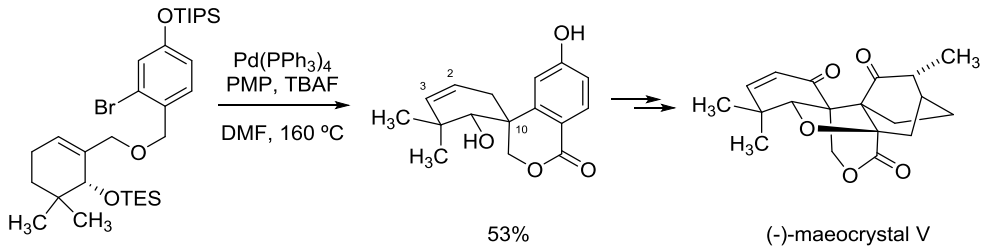
[28] Geoghegan, K.; Evans, P. *J. Org. Chem.* **2013**, *78*, 3410.

stereocenters are relevant examples of the diastereoselective variants of these reactions. More recently, Fukuyama has accomplished a total synthesis of lysergic acid, in which D ring is formed through an intramolecular Heck reaction (Scheme 1.3).[29]



Scheme 1.3.

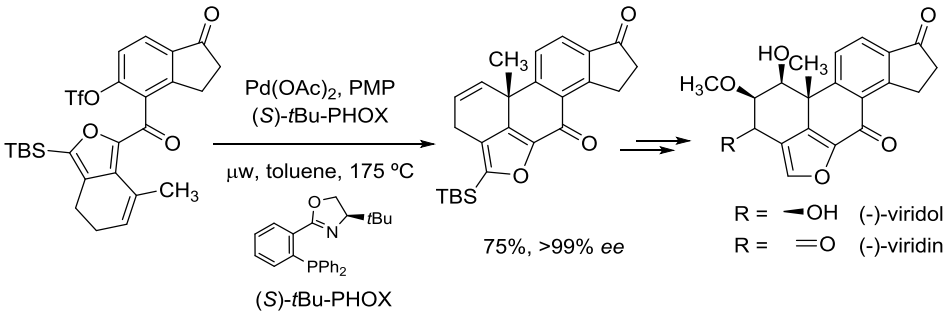
On the other hand, Thomson[30] reported the enantioselective total synthesis of a cytotoxic polycyclic diterpene, (–)-maoecrystal V, where the construction of the critical C-10 spirocyclic quaternary stereocenter was achieved through a completely diastereoselective Heck reaction. Formation of the 2,3-alkene as the major product could be rationalized by olefin isomerization to the more thermodynamically stable isomer by reinsertion of the intermediate Pd−hydride complex formed after initial spirocyclization (Scheme 1.4).



Scheme 1.4.

[29] Umezaki, S.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2013**, *15*, 4230.
[30] Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750.

The enantioselective variant has been employed in the asymmetric synthesis of natural products using chiral ligands for palladium. The development of new chiral ligands has allowed great advances in the area, although some limitations remain because the understanding of how different parameters of a M-H reaction affect the stereochemical outcome is difficult to rationalize. Nevertheless, enantioselective intramolecular M-H reaction using cyclic alkenes is nowadays used as a routine procedure in organic synthesis.[21] In this context, a convergent approach for the synthesis of furanosteroids (-)-viridin and (-)-viridiol has been reported, which employs an enantioselective intramolecular Heck reaction on an aryl triflate to set the absolute stereochemical configuration of the generated quaternary stereocenter. The use of (*S*)-*t*Bu-PHOX ligand and PMP was crucial to achieve high enantioselectivity (Scheme 1.5).[31]



Scheme 1.5.

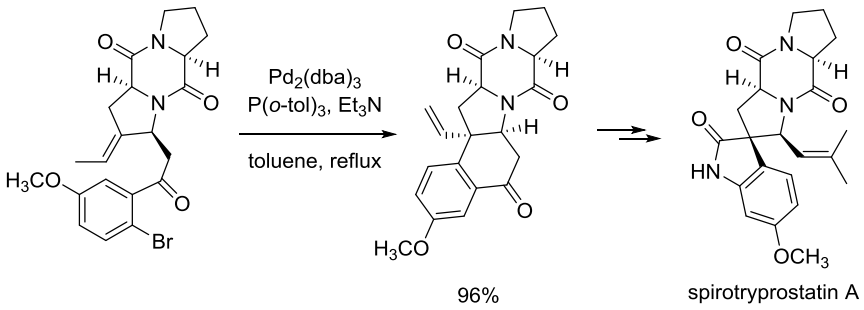
1.1.2. Approaches based on blocking the β-hydride elimination: use of tri- and tetrasubstituted acyclic alkenes as coupling partners

The use of tri- and tetrasubstituted acyclic olefins as coupling partners in intramolecular M-H reactions can lead to the generation of quaternary stereocenters. The introduction of substituents in the carbon atom of the acyclic olefin that suffers directly the coupling drives

[31] Del Bel, M.; Abela, A. R.; Ng, J. D.; Guerrero, C. A. *J. Am. Chem. Soc.* **2017**, *139*, 6819.

the hydride elimination to a contiguous β′-position, even though in some cases steric hindrance could decrease their reactivity leading to low conversions or yields.

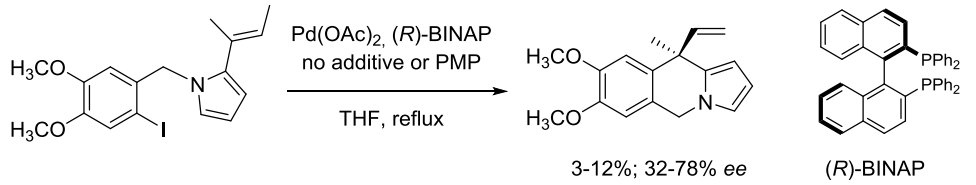
In this context, the pioneering work of Overman[32] showed that the intramolecular Heck reaction of *o*-iodoacrylamides gave oxindoles, generating a quaternary stereocenter in an enantioselective fashion using (*R*)-BINAP as chiral ligand. Depending on the use of Ag_3PO_4 or PMP as halide scavenger, either of the enantiomers of the oxindole could be obtained. The procedure was applied to the synthesis of (+)-asperazine.[33] Later, Curran[34] demonstrated that, when acrylamides with axial chirality were used, the chirality could be efficiently transferred obtaining the oxindoles with a quaternary center with high enantiomeric purity. This strategy has allowed the development of new methodologies for the synthesis of complex natural products as spirotryprostatin A (Scheme 1.6). Thus, Fukuyama[35] achieved the asymmetric synthesis of this alkaloid by using a diastereoselective intramolecular Heck reaction on an aryl bromide to introduce a quaternary center, whose stereochemistry was controlled by the diketopiperazine scaffold.



Scheme 1.6.

[32] Ashimori, A.; Bachand, B.; Calter, M. A.; Overman, L.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477; erratum: Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **2000**, *122*, 192.
[33] Govek, S. P.; Overman, L. E. *Tetrahedron* **2007**, *63*, 8499.
[34] Lapierre, A. J. B.; Geib, S. J.; Curran, D. P. *J. Am Chem. Soc.* **2007**, *129*, 494.
[35] Kitahara, K.; Shimokawa, J.; Fukuyama, T. *Chem. Sci*. **2014**, *5*, 904.

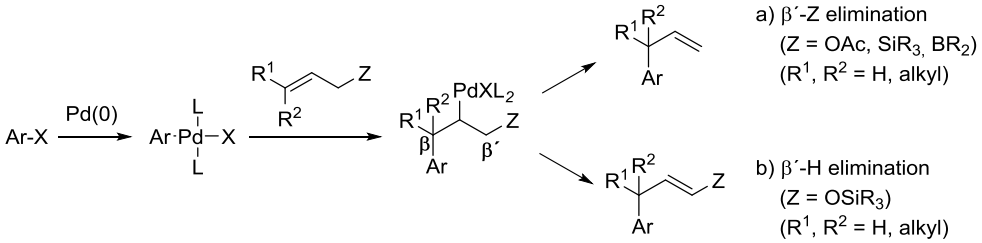
Our group has also studied the generation of a quaternary stereocenter on C-10 of pyrrolo[1,2-*b*]isoquinoline core, starting from 2-alkenyl substituted pyrroles, in which the β-elimination is blocked by a substituent on the alkene.[36] The cyclizations proceeded with moderate to good enantioselectivity (up to 78% *ee*), but low yield (3-12%) when using (*R*)-BINAP as chiral ligand (Scheme 1.7).



Scheme 1.7.

1.1.3. Approaches based on the use of a leaving group: allylsilanes, ethers, esters, and boronates as coupling partners

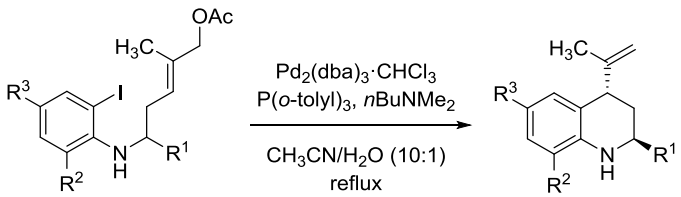
The introduction of a heteroatom in an allylic position of the alkene (Z, Scheme 1.8) can promote the elimination of a good leaving group, instead of β-hydride elimination (Scheme 1.8a). On the contrary, a tautomerization reaction could be the thermodynamic driving force in favor of a β´-hydride elimination (Scheme 1.8b). Thus, allyl esters, allyl silyl ethers, allylsilanes, and allylboronates can be used for the formation of tertiary and quaternary stereocenters.



Scheme 1.8.

[36] Rebolledo-Azcargorta, A.; Coya, E.; Barbolla, I.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2016**, 2054.

Although the intermolecular M-H coupling of aryl halides or triflates with allyl esters (acetates, carbonates) has been widely used,[37] the intramolecular variant has been less explored. Lautens reported a representative example in the intramolecular M-H reaction of aryl iodides for the synthesis of *trans*-2,4-disubstituted 1,2,3,4-tetrahydroquinolines (Scheme 1.9).[38] In this approach, the generation of the tertiary stereocenter at C-4 of the isoquinoline framework *via* elimination of β´-acetoxy group took place with complete diastereoslectivity to afford the *trans* diastereomers. The reaction was extended to the construction of five- to seven-membered carbo- and heterocycles with the same catalytic system using carbonates as leaving groups and microwave-assisted conditions.



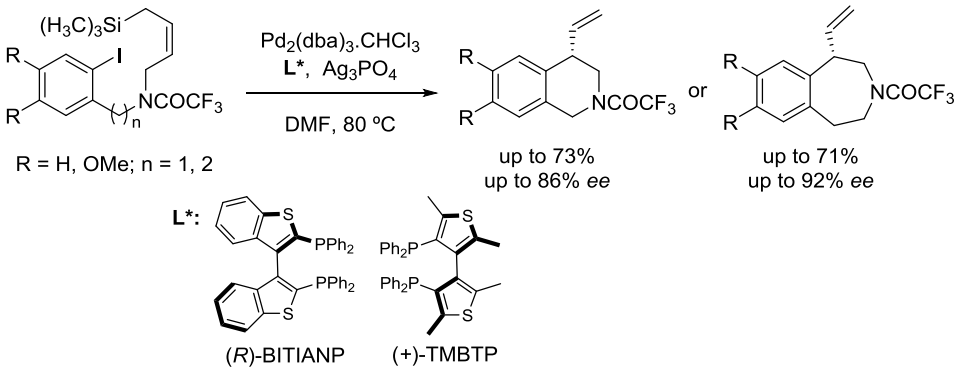
R^1 = Ph, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, COO-Cy
R^2 = H, Me, OMe; R^3 = H, Me, Cl

73-88%

Scheme 1.9.

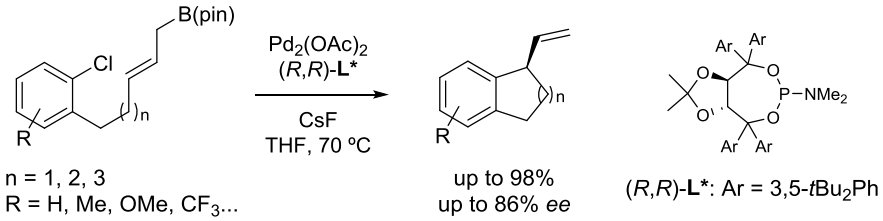
In his seminal work, Tietze[39] had demonstrated that a highly regio- and enantioselective intramolecular Heck reaction could be carried out on aryl halides with a tethered allylsilane moiety, whose elimination led to the construction of the tetralin framework of norsesquiterpenes with a tertiary stereocenter. This methodology was later applied to the enantioselective synthesis of tetrahydroisoquinolines and benzazepines using (+)-TMBTP and (*R*)-BITIANP as chiral ligands (Scheme 1.10).[40]

[37] For a review see: Pan, D.; Jiao, N. *Synlett*, **2010**, 1577.
[38] Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc*. **2005**, *127*, 72.
[39] 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.* **1996**, 1981.
[40] Tietze, L. F.; Thede, K.; Schimpf, R.; Sannicolò, F. *Chem. Commun*. **2000**, 583.



Scheme 1.10.

More recently, aryl chlorides with tethered allylboronate units, underwent intramolecular M-H reaction in an enantioselective fashion using phosphoramidites derived from TADDOL as chiral ligands. However, the procedure has only been applied to the construction of five-, six-, and seven-membered carbocycles (Scheme 1.11).[41]

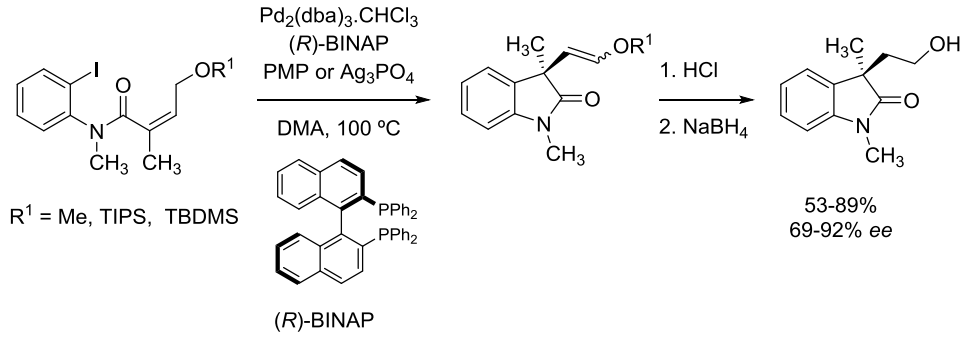


Scheme 1.11.

On the other hand, the work of Shibasaki on the synthesis of (–)-eptazocine[42] set the basis for the asymmetric generation of benzylic quaternary stereocenters using allyl silyl/alkyl ethers as coupling partners in the M-H cyclization of aryltriflates, being the formation of an

[41] Schuster, C. H.; Coombs, J. R.; Kasun, Z. A.; Morken, J. P. *Org. Lett.* **2014**, *16*, 4420.
[42] Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc*. **1993**, *115*, 8477; Correction: Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11207.

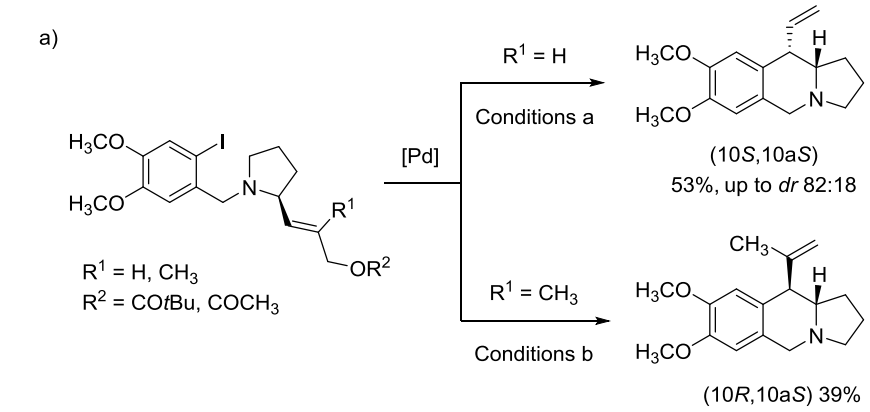
enol ether the driving force of the reaction. Later on, Overman[43] reported the intramolecular M-H reaction of substituted *N*-(*o*-iodophenyl)acrylamides using (*R*)-BINAP as chiral ligand (Scheme 1.12). The cyclization provided substituted oxindoles with high regio- and enantioselectivity, using $Pd_2(dba)_3.CHCl_3$ either in the presence of Ag_3PO_4 (cationic pathway) or a base as PMP (neutral pathway). In this case, silyloxy or alkoxy groups are retained in the coupling step, and β'-hydride elimination is favored obtaining enol ethers that could afterwards be cleaved by acidic hydrolysis and reduced to alcohols.

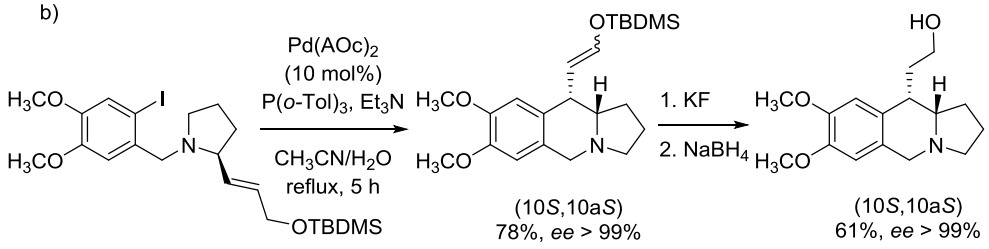


Scheme 1.12.

Our group has developed similar approaches for the generation of tertiary and quaternary stereocenters by Mizoroki-Heck reaction of *N*-(*o*-iodobenzyl)pyrrolidine derivatives with a protected allyl alcohol moiety.[36] A change in the protecting group of the alcohol allowed the selective β´-leaving group elimination (when pivalate or acetate were used, Scheme 1.13a) or β´-hydride elimination (when TBDMS was used, Scheme 1.13b) leading to the corresponding functionalized tetrahydropyrrolo[1,2-*b*]isoquinolines.

[43] a) Overman, L. E.; Poon D. J. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 518. b) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488. c) Dounay, B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261.

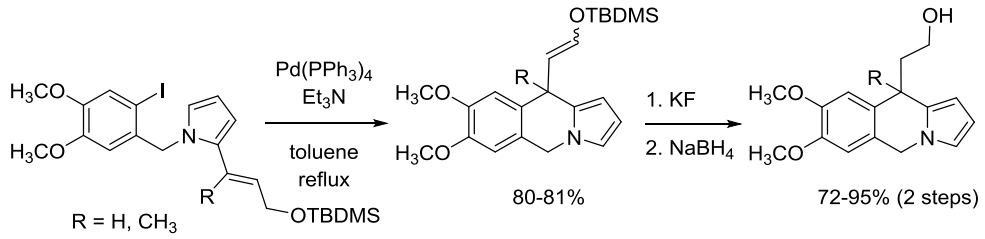




Scheme 1.13.

Thus, the intramolecular M-H reaction of enantiomerically pure *N*-(*o*-iodobenzyl)pyrrolidine derivatives took place with β´-alkoxy group elimination to afford 10-vinyl substituted pyrroloisoquinolines in moderate yields and diastereoselectivities (Scheme 1.13a, conditions a). Different catalytic systems and experimental conditions have been tried to control the stereoselectivity of these reactions, but only moderate diastereoselectivity (82:18) was obtained. When a substituted alkene is used ($R^1 = CH_3$), the diastereoselectivity is reversed, but only in low yield (Scheme 1.13a, conditions b). On the contrary, when an allyl silyl ether was used as coupling partner, β-hydride elimination took place leading to an enol ether, which could be derivatized to the corresponding

enantiomerically pure alcohol (Scheme 1.13b). This strategy could also be applied to the corresponding pyrrole derivatives generating both tertiary and quaternary stereocenters with excellent yields (Scheme 1.14). However, the enantioselective variant using $Pd(OAc)_2$ or $Pd_2(dba)_3$ and (*R*)-BINAP, or other chiral ligands, under different experimental conditions, only led to low enantiomeric excesses (up to 18% *ee*).

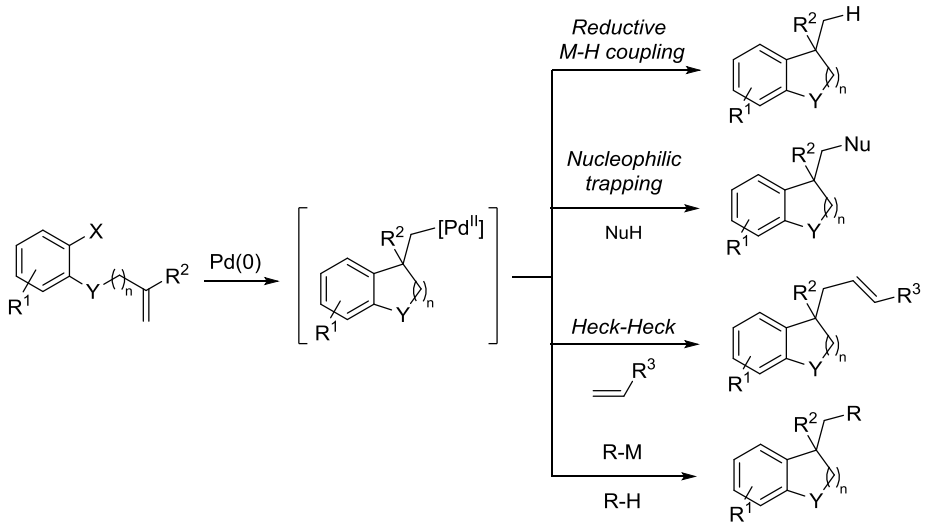


Scheme 1.14.

1.2. Cascade reactions initiated by intramolecular carbopalladation

Palladium-catalyzed cascade cyclizations are powerful tools for the synthesis of heterocycles with stereocenters.[44] The M-H reaction is an ideal starting point for a cascade reaction, as the intermediate $C(sp^3)$-Pd(II) species obtained after intramolecular carbopalladation could be further functionalized. In many occasions a 1,1-disubstituted alkene is used as coupling partner to prevent β-hydride elimination, generating a quaternary center, but tertiary centers can be formed as well. This intermediate α-alkylpalladium (II) species can be involved afterwards in different processes, as summarized in Scheme 1.15. Reductive Heck cyclizations can be developed in the presence of hydride donors, or alternatively, the intermediate can be trapped with different nucleophiles. Besides, functionalization can be introduced through further coupling reactions, such as M-H, Suzuki, Sonogashira, or direct arylation reactions, among others.

[44] For general reviews, see: a) Xu, P.-F.; Wang, W., Eds., *Catalytic Cascade Reactions*, John Wiley & Sons, Inc.: Hoboken, **2014**. b) Tietze, L. F., Ed., *Domino Reactions: Concepts for Efficient Organic Synthesis*, Wiley-VCH: Weinheim, **2014**. For recent reviews on Palladium-Catalyzed Cascade reactions, see reference 22.

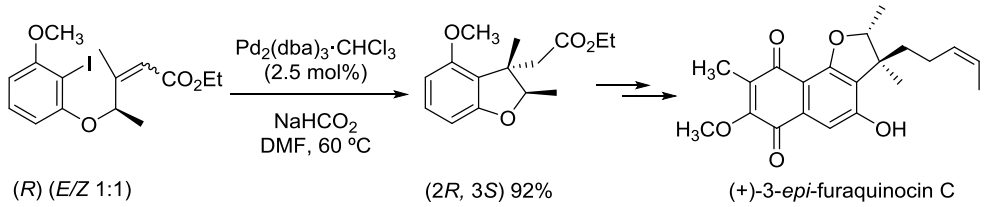


Scheme 1.15.

1.2.1. Reductive Mizoroki-Heck coupling

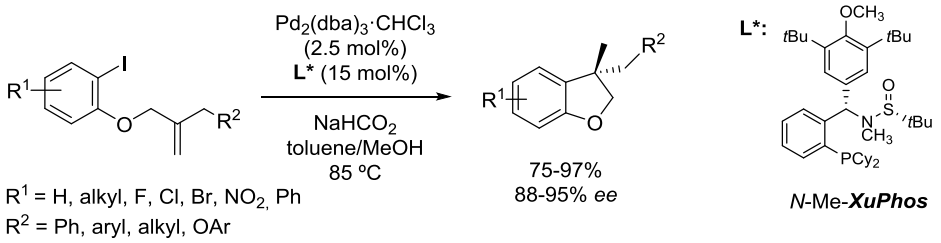
The reductive M-H coupling has been well-studied and applied in synthesis[45] since the seminal work on hydroarylation of alkenes reported by Cacchi,[46] being tertiary amines and sodium formate the most commonly used hydride sources. Thus, a quaternary stereocenter could be generated with complete diastereoselectivity by cyclization of an enantiomerically pure aryl ether (*E/Z* 1:1). This cyclization was the key to establish the 2,3-*cis*-dimethyldihydrobenzofuran moiety present in natural products such as (+)-3-*epi*-furaquinocin C (Scheme 1.16).[47] A related strategy had been previously applied by the same group for the diastereoselective generation of a quaternary stereocenter in the enantioselective synthesis of (–)-galanthamine.[48]

[45] For recent reviews: a) Oxtoby, L. J.; Gurak, J. A.; Wisniewski, S. R.; Eastgate, M. D.; Engle, K. M. *Trends in Chemistry* **2019**, *1*, 572. b) Gosh, T. *ChemistrySelect* **2019**, *4*, 4747.
[46] Cacchi, S.; Arcadi, A. *J. Org. Chem*. **1983**, *48*, 4236.
[47] Pu, L.-Y.; Chen, J.-Q.; Li, M.-L., Li, Y.; Xie, J.-H.; Zhou, Q.-L. *Adv. Synth. Catal*. **2016**, *358*, 1229.
[48] Chen, J.-Q.; Xie, J.-H.; Bao, D.-H.; Liu, S.; Zhou, Q.-L. *Org. Lett.* **2012**, *14*, 2714.



Scheme 1.16.

A highly enantioselective variant of this reaction has been developed recently carrying out the cyclization of allyl aryl ethers in the presence of chiral ligands for palladium (Scheme 1.17).[49] Modest conversions and enantioselectivities (28-78% *ee*) were obtained using commercially available ligands, such as (*R*)-BINAP and (*R*)-XylBINAP, or with PHOX ligands. However, the design of a new chiral sulfinamide phosphine ligand (*N*-Me-***XuPhos***) was crucial to obtain consistently good yields and excellent enantioselectivities (>90% *ee*) for the formation of the quaternary center in dihydrobenzofurans, with a wide variety of substitution patterns.

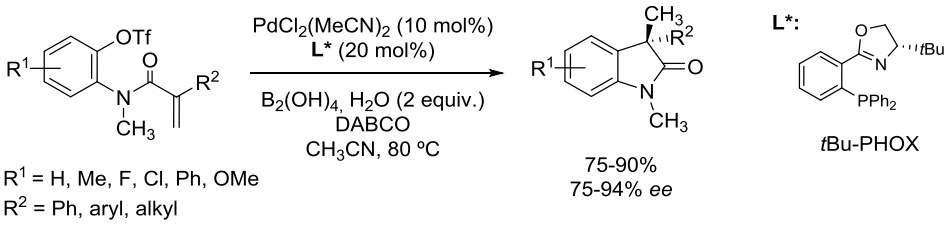


Scheme 1.17.

An enantioselective synthesis of 3,3-disubstituted oxindoles has also been reported using diboron-water as hydride source (Scheme 1.18).[50] In this case, when triflates were used as substrates, *t*Bu-PHOX ligand afforded the best enantioselectivity (75-94% *ee*) for the formation of quaternary centers. Again, ligands as (*R*)-BINAP or (*R*)-SEGPHOS gave

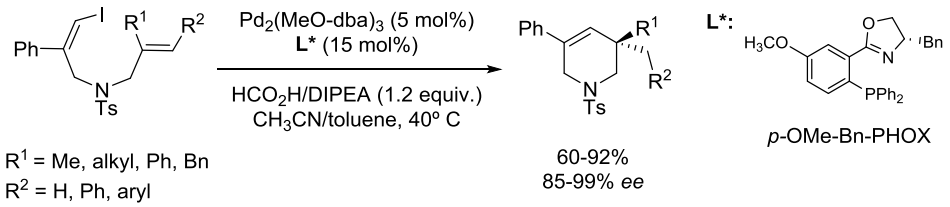
[49] Zhang, Z.-M.; Xu, B.; Qian, Y.; Wu, L.; Wu, Y.; Zhou, L.; Liu, Y.; Zhang, J. *Angew. Chem. Int. Ed*. **2018**, *57*, 10373.
[50] Kong, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed*. **2017**, *56*, 3987.

lower conversions and enantioselectivities. In addition, the structure of the base was important, as the use of DIPEA or DBU gave low conversions. Interestingly, the reaction took place using sodium formate as hydride source, but with a lower enantioselectivity (70% *ee*). Although the reduction step is not involved in the stereodeterminant step, the presence of a nucleophile ($NaHCO_2$) might modify the coordination sphere of the metal and, as a result, the enantioselectivity of the carbopalladation. This gives an idea of the difficulty in developing these enantioselective reactions, in which multiple variants have to be controlled.



Scheme 1.18.

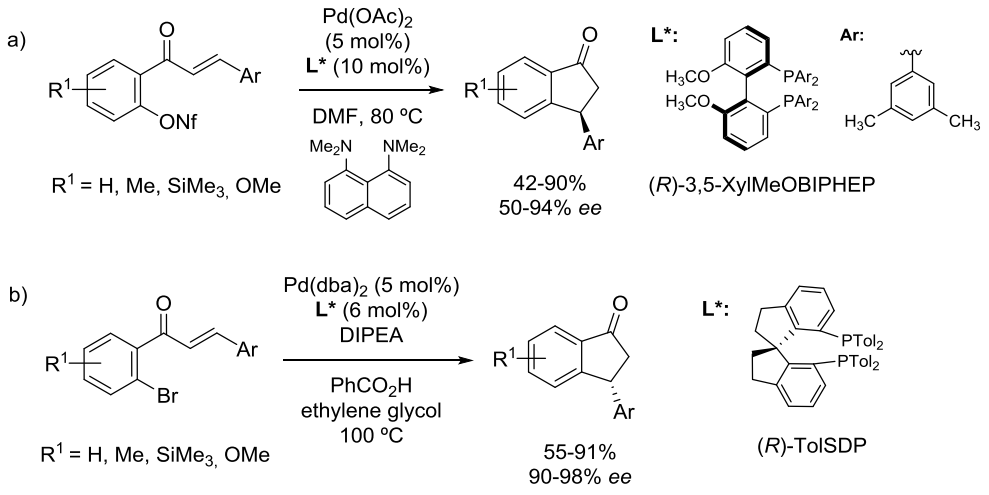
Most of the examples described involve 5-*exo* cyclizations, but the formation of a quaternary stereocenter through a 6-*exo* carbopalladation has also been accomplished (Scheme 1.19).[51] Thus, vinyl halides were cyclized to afford tetrahydropyridines with good to excellent enantioselectivities using a PHOX-derived ligand. As in the previous example, the hydride source had an important impact on enantioselectivity, as the employment of HCO_2H/DIPEA gave higher enantioselectivity than the use of HCO_2H/Et_3N.



Scheme 1.19.

[51] Hou, L.; Yuan, Y.; Tong, X. *Org. Biomol. Chem*. **2017**, *15*, 4803.

Tertiary centers can also be generated through reductive M-H reactions, but, in this case, it is necessary to avoid the undesirable β-hydride elimination. Two significant examples applied to the synthesis of carbocycles are shown on Scheme 1.20. Buchwald described the intramolecular insertion of aryl nonaflates onto an enone moiety. Thus, β-hydride elimination is precluded by the initially formed *cis*-configured palladium enolate intermediate, allowing hydride transfer. In this case, the proton sponge (Scheme 1.20a) is used as hydride donor in the presence of (*R*)-3,5-XylMeOBIPHEP as chiral ligand.[52] More recently, a related strategy has been described using aryl bromides, with a combination of benzoic acid and DIPEA in ethylene glycol to form an alkylamonium salt *in situ*, which acts as hydrogen bond donor to help halide dissociation, driving the reaction through a cationic mechanism. The best enantioselectivities were obtained with (*R*)-TolSDP, while BIHEP or SEGPHOS ligands afforded much lower enantioselectivities (Scheme 1.20b).[53]

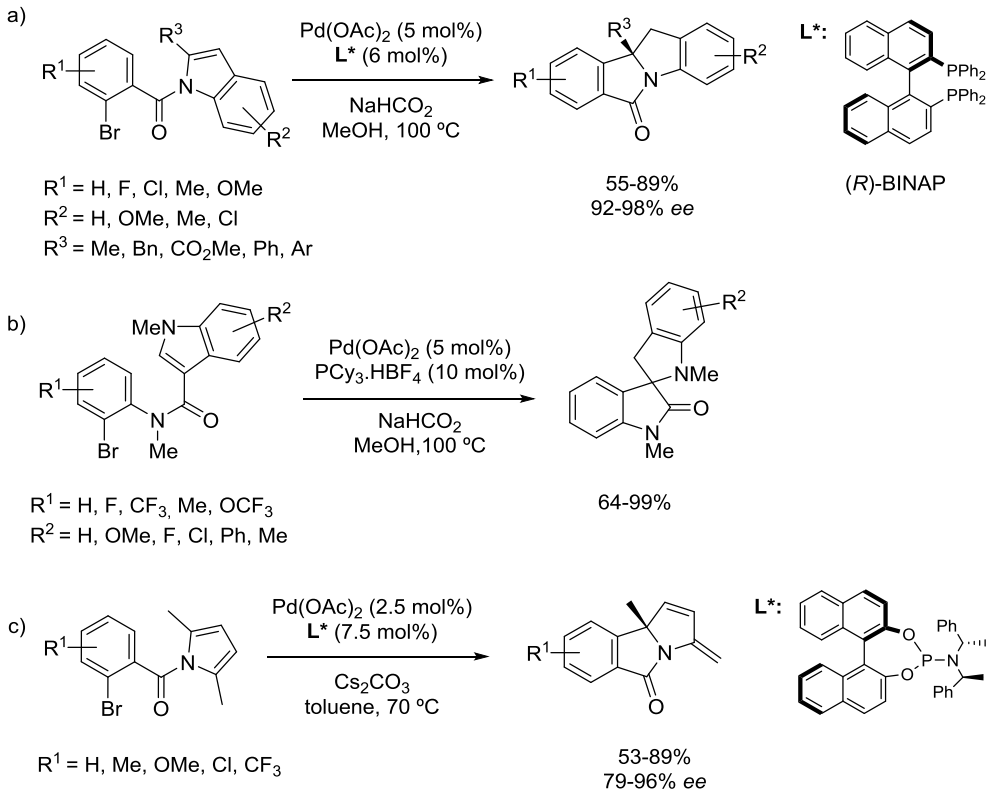


Scheme 1.20.

[52] Minatti, A.; Zheng, X.; Buchwald, S. L. *J. Org. Chem*., **2007**, *72*, 9253.
[53] Yue, G.; Lei, K.; Hirao, H.; Zhou, J. *Angew. Chem. Int. Ed*. **2015**, *54*, 6531.

A different strategy for the generation of a stereocenter is through a dearomatization reaction. In a seminal contribution to this area, Buchwald developed an intramolecular enantioselective dearomatization reaction of anilines, obtaining 3,3-disubstituted-3a*H*-indoles with excellent enantioselectivity in the presence of base,[54] although the reaction does not proceed through a Heck-type carbopalladation mechanism. However, an asymmetric arylative dearomatization of indoles *via* reductive M-H reaction has been developed for the generation of C-2 quaternary stereocenters with good yields and excellent enantioselectivities (Scheme 1.21a). The reaction could be carried out using a combination of formic acid with different bases (Et_3N, TMEDA, DIPEA), but sodium formate resulted the most efficient hydride donor. In addition, although ligand screening indicated that bidentate phosphines were efficient (SEGPHOS, SYNPHOS), the best results were obtained with (*R*)-BINAP.[55] Modifying the structure of the substrates, the same group has extended the reaction to the synthesis of spiropyrrolidine oxindoles, but only in the racemic version (Scheme 1.21b).[56] The asymmetric dearomatization of pyrroles has also been developed through a M-H reaction, although in this case there is no reduction of the alkylpalladium intermediate. Thus, pyrrolines bearing a quaternary stereocenter could be obtained from bromides in good yields and excellent enantioselectivities in the presence of Feringa's phosphoramidite. Notably, PHOX ligands or SEGPHOS led to high yields but very poor enantioselectivities (Scheme 1.21c).[57]

[54] García-Fortanet, J.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc*. **2009**, *131*, 6676.
[55] Shen, C.; Liu, R.-R.; Fan, R.-J.; Li, Y.L.; Xu, T.-F., Gao, J.-R.; Jia, Y.-X. *J. Am. Chem. Soc*. **2015**, *137*, 4936.
[56] Liu, R.-R.; Xu, Y.; Liang, R.-X.; Xiang, B.; Xie, H.-J.; Gao, J.-R.; Jia, Y.-X. *Org. Biomol. Chem*. **2017**, *15*, 2711.
[57] Yang, P.; You, S.-L. *Org. Lett*. **2018**, *20*, 7684.



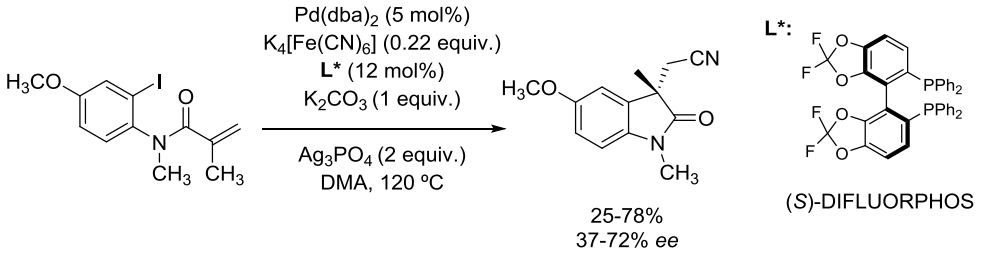
Scheme 1.21.

1.2.2. Carbopalladation followed by nucleophilic trapping

Different types of nucleophilic trapping reactions have also been described. In this context, a versatile approach is the trapping of the alkylpalladium intermediate formed after carbopalladation with cyanide. It was first developed by Grigg using KCN as the cyanide source,[58] but improved conditions were later reported employing $K_4[Fe(CN)_6]$.[59] In this

[58] Grigg, R.; Santhakumar, V.; Sridharan, V. *Tetrahedron Lett*. **1993**, *34*, 3163.
[59] a) Cheng, Y.; Duan, Z.; Yu, L.; Li. Z.; Zhu, Y.; Wu, Y.; *Org. Lett.* **2008**, *10*, 901. b) Jaegli, S.; Vors, J. P. Neuville, L. Zhu, J. *Synlett* **2009**, *2009*, 2997. c) Jaegli, S.; Vors, J. P.; Neuville, L.; Zhu, J.

context, Zhu and coworkers developed an efficient synthesis of 3-substituted-3-cyanomethyl-2-oxindoles from *ortho*-iodoanilide using $K_4[Fe(CN_6)]$ as trapping agent for the σ-alkylpalladium intermediate. In addition, an enantioselective variant of this domino process was also developed, obtaining enantioselectivities up to 72% *ee* by using (*S*)-DIFLUORPHOS as chiral ligand and slightly modifying reaction conditions (Scheme 1.22).[60]



Scheme 1.22.

More recently, a diastereoselective variant has been developed by Lautens, obtaining dihydroisoquinolinones in excellent yields and high diastereoselectivities from enantiomerically pure *N*-allylcarboxamides (Scheme 1.23a).[61] In this case, substoichiometric ammounts of $Zn(CN)_2$ are used as cyanide source, which highly covalent nature leads to decreased amounts of free cyanide, preventing catalyst deactivation usually associated to the formation of stable cyano complexes.[62] Following this work, the same group described a more complex bisfunctionalization reaction, initiated by dearomatization of indoles, leading to the formation of complex indolines bearing contiguous tertiary and quaternary carbons, with excellent yields and diastereoselectivities (Scheme 1.23b).[63] More

Tetrahedron **2010**, *66*, 8911. d) Lu, Z.; Hu. C.; Guo, J.; Li, J.; Cui, Y.; Jia, Y. *Org. Lett.* **2010**, *12*, 480.

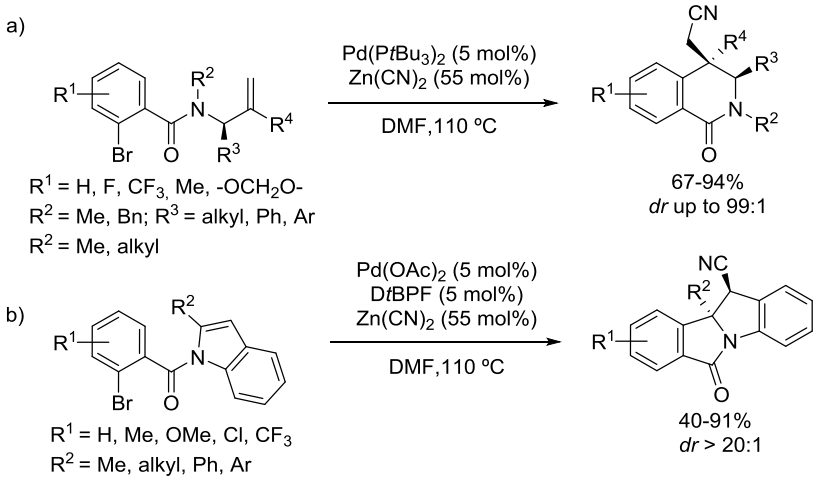
[60] Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem. Eur. J.* **2007**, *13*, 961.

[61] Yoon, H.; Petrone, D. A.; Lautens, M. *Org. Lett.* **2014**, *16*, 6420.

[62] Sundermeier, M.; Zapf, A.; Mutyala, S; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 1828.

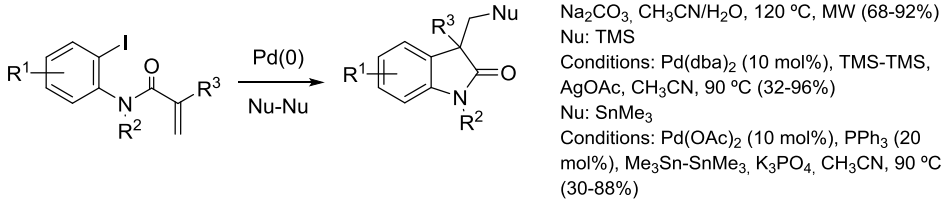
[63] Petrone, D. A.; Yen, A.; Zeidan, N.; Lautens, M. *Org. Lett.* **2015**, *17*, 4838.

recently, this type of intramolecular arylcyanation reaction has been described to proceed efficiently using nickel catalysis, instead of palladium.[64]



Scheme 1.23.

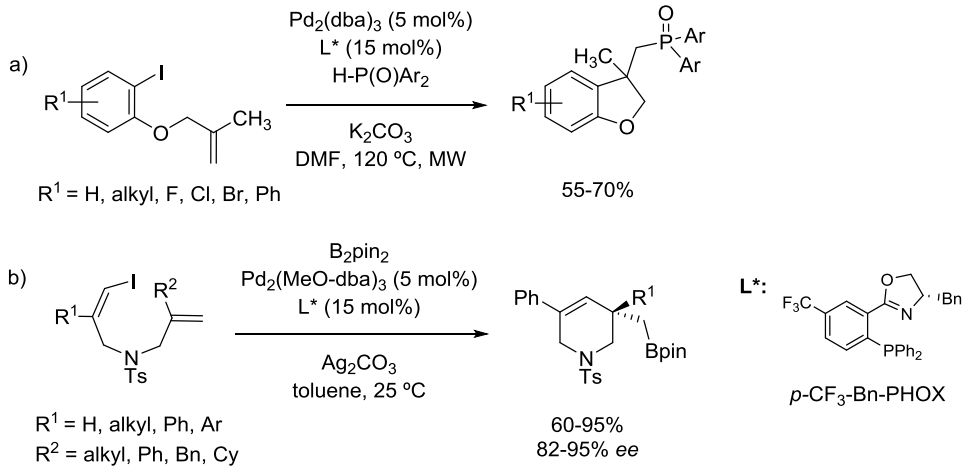
Different functionalization can be introduced varying the type of nucleophile used. Thus, borylation, silylation and stannilation reactions have been developed for the synthesis of functionalized oxoindolines, by trapping the alkyl palladium intermediate with *bis*(pinacolato)diborane,[65] hexamethyldisilane or hexamethyldistannane,[66] respectively (Scheme 1.24).



Scheme 1.24.

[64] Yen, A.; Lautens, M. *Org. Lett*. **2018**, *20*, 4323.
[65] Vachhani, D. D.; Butani, H. H.; Sharma, N.; Bhoya, U. C., Shan, A. K.; Van der Eycken, E. V. *Chem. Commun*. **2015**, *51*, 14862.
[66] Xiao, G.; Chen, L.; Zhou, B.; Deng, G.; Gong, J.; Liang, Y. *Adv. Synth. Catal*. **2018**, *360*, 3477.

Alternatively, phosphorylation reactions have also been accomplished using arylphosphine oxides under MW irradiation for the synthesis of dihydrofurans (Scheme 1.25a).[67] An enantioselective variant for vinylborylation reaction has also been developed for the synthesis of tetrahydropyridines in the presence of a PHOX-based ligand with high enantioselectivity and moderate to good yields (Scheme 1.25b). However, in this case, the authors proposed a mechanism in which the transmetalation would be prior to the carbopalladation.[68]

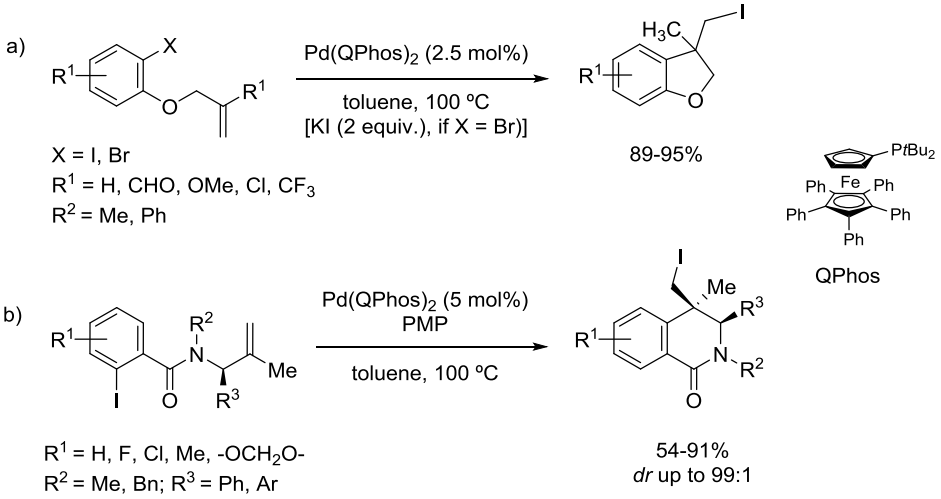


Scheme 1.25.

Carboiodination reactions have also been developed. In this case, instead of an external anion capture event, the C-I bond is formed through reductive elimination of the alkylpalladium iodide initially formed when extremely bulky phosphines (such as QPhos) are used (Scheme 1.26a). In this way, 3-iodomethylbenzofurans could be obtained in excellent yields, forming two new bonds and incorporating all substrate atoms (X = I) in the product.[69] The reaction could be extended to the formation of chromanes and

[67] Ramesh, K.; Satyanarayana, G. *Eur. J. Org. Chem*. **2019**, 3856.
[68] Jiang, Z.; Hou, L.; Ni, C.; Chen, J.; Wang, D.; Tong, X. *Chem. Commun*. **2017**, *53*, 4270.
[69] Newman, S. G.; Lautens, M. *J. Am. Chem. Soc*. **2011**, *133*, 1778.

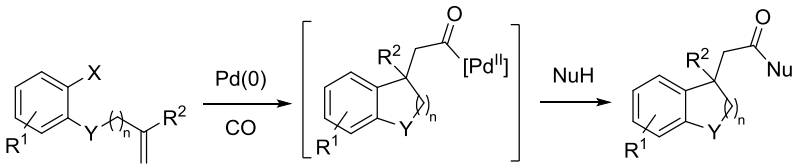
isochromanes,[70] and also to the use of aryl bromides (X = Br), simply adding an excess of potassium iodide as iodination agent. Computational studies showed that the use of bulky phosphines is crucial for the reactivity, as, after migratory insertion, a tricoordinate alkylpalladium species is formed, which undergoes reductive elimination to generate the alkyl iodide. On the contrary, when less bulky phosphines are used, tetracoordinated species which do not undergo reductive elimination are formed.[71] The procedure has been extended to the synthesis of enantioenriched dihydroisoquinolines by diastereoselective carboiodination of *N*-allylcarboxamides,[72] and it was found that the addition of PMP significantly increases the diastereoselectivity in the presence of QPhos (Scheme 1.26b). More recently, these carboiodination reactions have also been developed under nickel catalysis.[73]



Scheme 1.26.

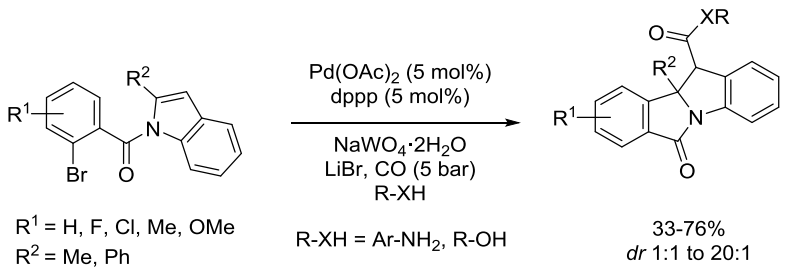
[70] Petrone, D. A.; Malik, H. A.; Clemenceau, A.; Lautens, M. *Org. Lett*. **2012**, *18*, 4806.
[71] Lan, Y.; Yoon, H.; Weinstabl, H.; Lautens, M. *Angew.Chem. Int. Ed.* **2014**, 5*3*, 7908.
[72] Petrone, D. A.; Malik, H. A.; Clemenceau, A.; Lautens, M. *Org. Lett*. **2012**, *18*, 4806.
[73] a) Yoo, H.; Marchese, A. D.; Lautens, M. *J. Am. Chem. Soc*. **2018**, *140*, 10950. b) Marchese, A. D.; Lind, F.; Mahon, A. E.; Yoon, H.; Lautens, M. *Angew. Chem. Int. Ed.* **2019**, 5*8*, 5095.

An interesting alternative, that increases the versatility of these reactions, is to carry out a CO insertion after carbopalladation, generating in this way an acylpalladium intermediate that can afterwards be trapped with different nucleophiles either in an inter- or intramolecular fashion (Scheme 1.27). The first applications of this methodology were reported by Grigg,[74] but the enantioselective variants have been described only in the recently.



Scheme 1.27.

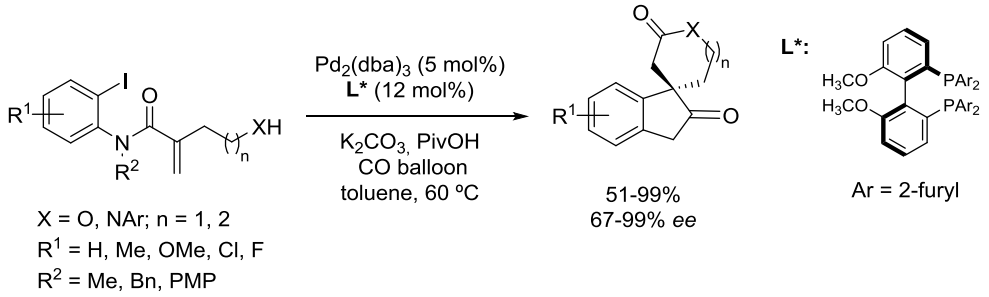
In this context, the first example of a dearomative carbonylation reaction of indoles has been recently reported using CO (5 bar) and anilines or alcohols as nucleophiles. In this way, after optimization of reaction conditions to avoid side reaction (for instance, direct carbonylation of the precursor), moderate to good yields of indolines were obtained in the presence of dppp, although with generally modest diastereoselectivities (Scheme 1.28).[75]



Scheme 1.28.

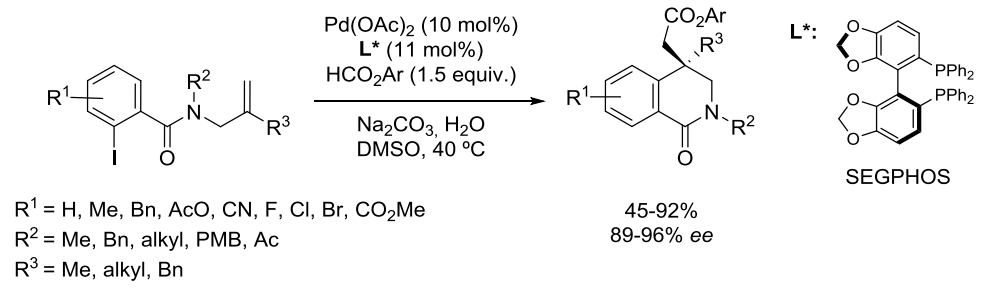
[74] Representative examples: a) Grigg, R.; Sridharan, V. *Tetrahedron Lett*. **1993**, *34*, 7471. b) Anwar, U.; Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 1361.
[75] Wang, H.; Wu, X.-F. *Org. Lett*. **2019**, *21*, 5264.

On the contrary, when an oxygen or nitrogen-based nucleophile is tethered to the alkene, a second cyclization reaction takes place. The ring size can be modulated changing the tether between the alkene and the nucleophilic atom. Thus, spirofused lactones and lactams were obtained in excellent yields and enantioselectivities when the reaction was carried out in the presence of chiral biphosphine ligands (Scheme 1.29).[76]



Scheme 1.29.

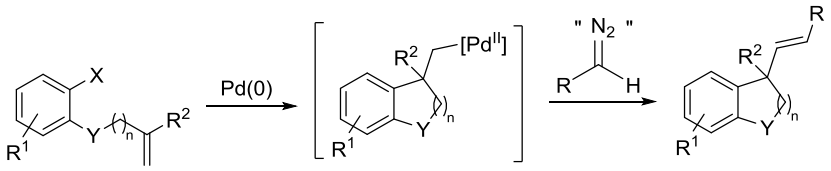
Formate esters have also been used as a source of CO. In fact, under the reaction conditions, aryl formates generate CO and phenols that, after CO insertion, act as nucleophiles. Thus, 3,4-dihydroisoquinolinones have been obtained in generally high yields and enantioselectivity using SEGPHOS as chiral ligand (Scheme 1.30).[77]



Scheme 1.30.

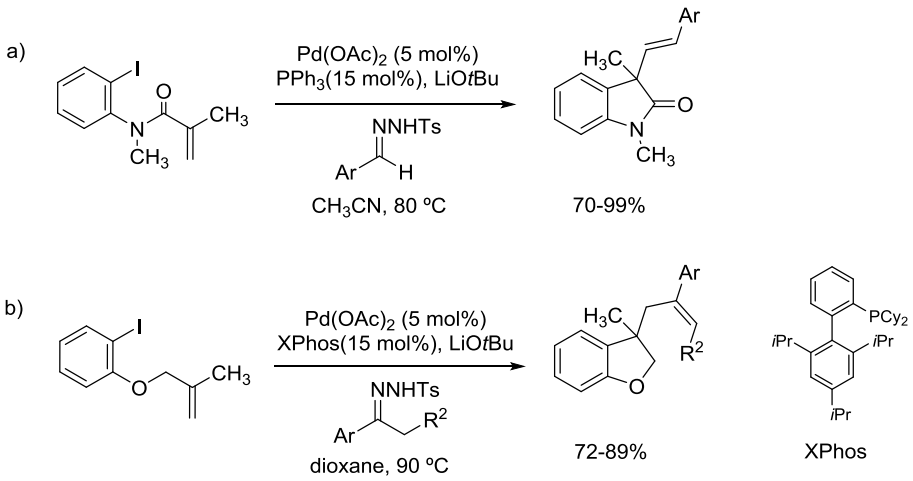
[76] Hu, H.; Teng, F.; Liu, J.; Hu, W.; Luo, S.; Zhu, Q. *Angew. Chem. Int. Ed.* **2019**, *58*, 9225.
[77] Cheng, C.; Wan, B.; Zhou, B.; Gu, Y.; Zhang, Y. *Chem. Sci*. **2019**, *10*, 9853.

In a different termination approach, reaction of the alkylpalladium intermediate formed after carbopalladation with a carbene precursor would give an alkene *via* carbene insertion and β-hydride elimination (Scheme 1.31). In this context, tosylhydrazones are efficient carbene precursors that are frequently used in metal catalyzed cross coupling reactions.[78]



Scheme 1.31.

Thus, oxoindolines that incorporate a new alkene functionality in their structure have been synthesized by reaction of an acrylamide with a variety of *N*-tosylhydrazones in good yields (Scheme 1.32a).[79]

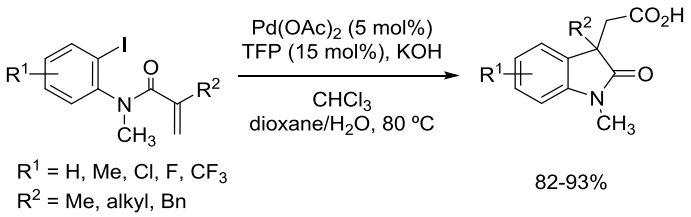


Scheme 1.32.

[78] Barluenga, J.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486.
[79] Liu, X.; Ma, X.; Huang, Y.; Gu, Z. *Org. Lett.* **2013**, *15*, 4814.

The reaction could also be extended to the use of enolizable ketone-derived tosylhydrazones (Scheme 1.32b). The regioselectivity of the final β-hydride elimination can be controlled using bulky ligands, such as XPhos and, in this way, the less substituted alkene is formed with complete regio- and stereoselectivity, obtaining a wide variety of functionalized dihydrobenzofurans.[80] The procedure cannot be applied to the formation of tertiary stereocenters because β-hydride elimination after carbopalladation is faster than carbene insertion. Therefore, a substituent is required in the alkene to avoid this elimination. Besides, when bromides are used as precursors, direct carbene coupling product is observed.

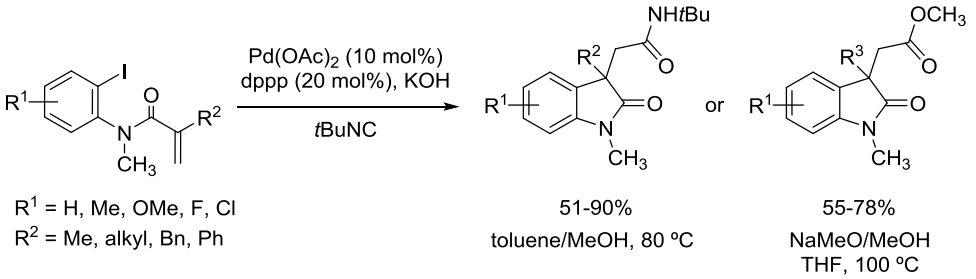
Alternatively, chloroform has been used as a dichlorocarbene precursor. Thus, coordination of the alkylpalladium intermediate formed after carbopalladation of acrylamides with dichlorocarbene, followed by hydrolysis under aqueous basic conditions, produced carboxylic acids. In consequence, $CHCl_3$ would be an alternative to carbonylation reactions (Scheme 1.33).[81]



Scheme 1.33.

In a related fashion, the alkylpalladium formed after carbopalladation can also undergo migratory insertion of isocyanide, and, depending on the reaction conditions, amides or esters could be selectively obtained (Scheme 1.34).[82]

[80] Gao, Y.; Xiong, W.; Chen, H.; Wu, W.; Peng, J.; Gao, Y.; Jiang, H. *J. Org. Chem*. **2015**, *80*, 7456.
[81] Liu, X.; Li, B.; Gu, Z. *J. Org. Chem*. **2015**, *80*, 7547.
[82] Kong, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed*. **2016**, *55*, 9714.



Scheme 1.34

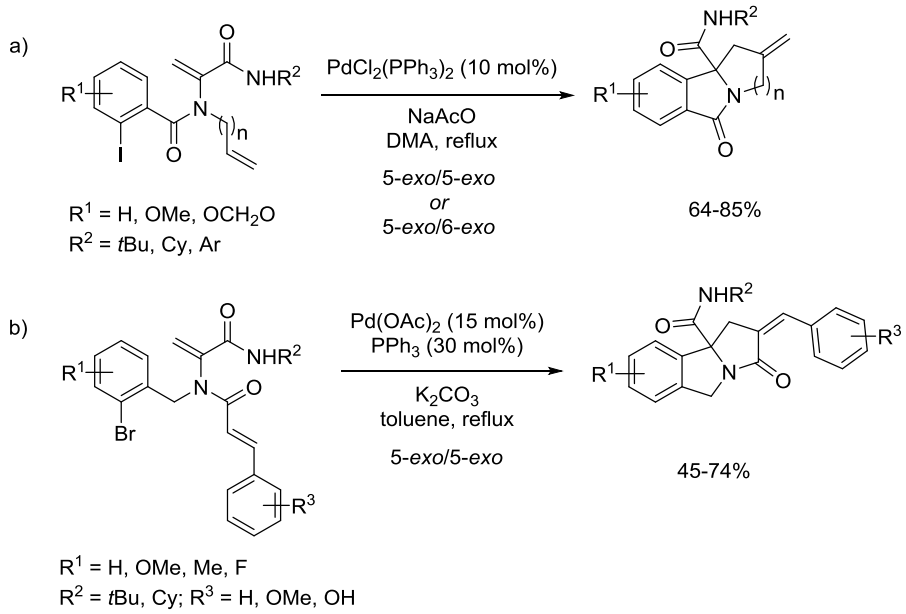
1.2.3. Carbopalladation followed by other couplings

As shown in Scheme 1.15, the σ-alkylpalladium(II) intermediate obtained after the starting carbopalladation can participate in a second inter- or intramolecular cross-coupling reaction. Different termination events have been developed, that imply Heck, Suzuki or Sonogashira couplings, and direct C-H arylation reactions. For these tandem reactions to efficiently proceed it is important to find the adequate catalyst and experimental conditions to suppress the direct coupling with the aryl halide precursor and, therefore, allow the carbopalladation to occur first. Consequently, the starting carbopalladation is generally a 5-*exo* process, so this method has been applied mainly for the construction of functionalized five-membered heterocycles.

The first example of an enantioselective palladium-catalyzed polyene cyclization was reported by Overman in the synthesis of spirocyclic trienones[83] and a nice application of this strategy is the total synthesis of the marine natural product (+)-Xestoquinone described by Keay.[84] Fused indolizidine and pyrrolizidine frameworks have been efficiently assembled in one step *via* a Heck-Heck reaction of structurally related amides shown on Scheme 1.35. It is noteworthy that, in both cases, the first 5-*exo* carbopalladation reaction

[83] Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.
[84] Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766.

with the enamide moiety to generate the quaternary center is favored over a possible 6-*exo* process with the other alkene (Scheme 1.35).[85]



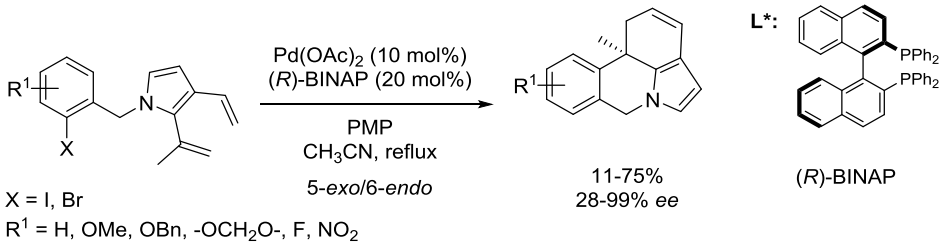
Scheme 1.35.

In this context, we have developed an asymmetric Heck-Heck 6-*exo*/6-*endo* reaction for the enantioselective synthesis of Lycorane-type alkaloids starting from *N*-benzyl-2,3-dialkenylpyrroles using different chiral ligands (Scheme 1.36).[86] Thus, a wide variety of enantiomerically enriched C-11b substituted Lycorane analogues, with different substitution patterns on the aromatic ring or even heteroaromatic rings, were efficiently

[85] a) García-González, M. C.; Hernández-Vázquez, E.; Gordillo-Cruz, R. E.; Miranda, L. D. *Chem. Commun*. **2015**, *51*, 11669. b) Miranda, L. D.; Hernández-Vázquez, E. *J. Org. Chem*. **2015**, *80*, 10611.

[86] a) Coya, E.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2015**, *357*, 3206. b) Blázquez-Barbadillo, C.; Aranzamendi, E.; Coya, E.; Lete, E.; Sotomayor, N.; González-Díaz, H. *RSC Adv.*, **2016**, *6*, 38602.

obtained by using (*R*)-BINAP as chiral ligand. This reaction will be further discussed in the following section.

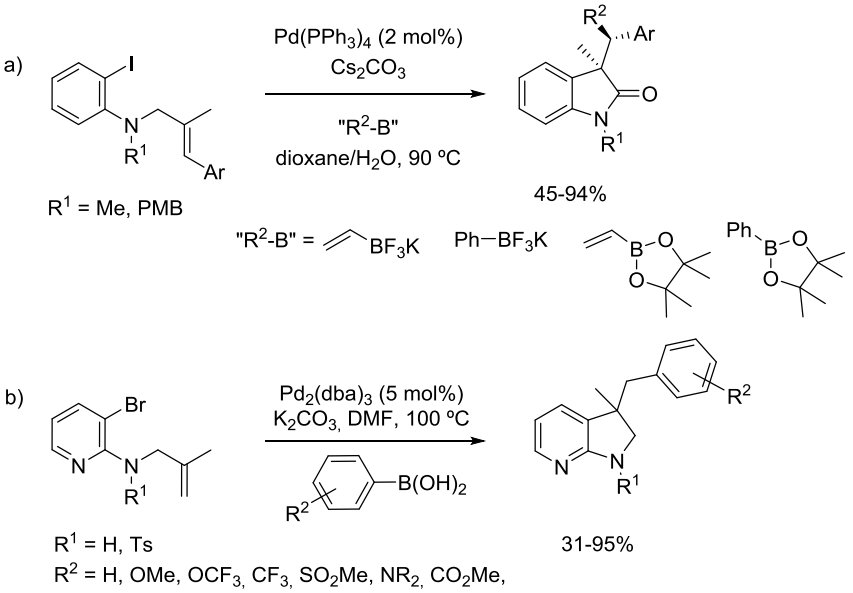


Scheme 1.36.

Another termination event is the coupling with boronic acids in a Suzuki reaction. In this context, the first examples of a Heck cyclization in tandem with a Suzuki reaction were reported by Grigg.[87] More recently, this type of domino carbopalladation/cross-coupling reaction has been employed for the diastereospecific construction of 3,3-disubstituted oxindoles starting form substituted *N*-(*o*-iodophenyl)acrylamides with different substitution patterns and different organoborane species (Scheme 1.37a).[88] The stereospecific initial *syn* palladation step allowed the generation of the two vicinal stereocenters with complete diastereoselectivity. The substituent on nitrogen atom (R^1) is essential for the rate of carbopalladation to compete with the direct Suzuki coupling, as unsubstituted amides (R^1 = H) led to direct cross-coupling products. Besides, a series of azaindolines with a quaternary stereocenters at C-3 were synthesized by applying this type of palladium-catalyzed domino reaction on pyridin-2-amines using arylboronic acids (Scheme 1.37b).[89] In this case, the reaction works with unprotected amines (R^1 = H) using $Pd(OAc)_2$ as catalyst with phosphines, such as JohnPhos or P(*o*-Tol)$_3$, although $Pd_2(dba)_3$ promoted the reaction in the absence of phosphines. The procedure is compatible with a wide range of functional groups

[87] a) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65. b) Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803.
[88] Seashore-Ludlow, B.; Somfai, P. *Org. Lett.* **2012**, *14*, 3858.
[89] Schempp, T. T.; Daniels, B. E.; Staben, S. T.; Stivala, C. E. *Org. Lett.* **2017**, *14*, 3616.

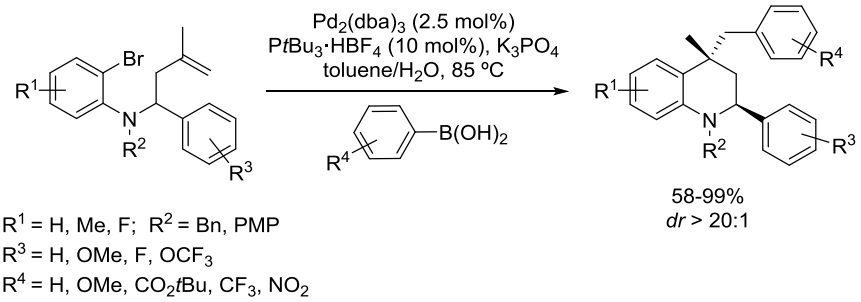
and can be extended to the preparation of all four azaindoline isomers. Finally, the enantioselective version was attempted using chiral phosphines as ligands, but racemic compounds were obtained. More recently, the preparation of 3,3-disubstituted oxindoles by similar Ni-catalyzed Heck/Suzuki cascade reaction has been reported.[90]



Scheme 1.37.

There are few examples of formation of six-membered heterocycles by carbopalladation/Suzuki coupling sequence. An illustrative example is the reaction of functionalized *o*-bromoanilines with boronic acids using a tetrafluoroborate phosphine as ligand for the diastereoselective synthesis of 2,4,4-trisubstituted tetrahydroquinolines (Scheme 1.38).[91] The reaction works in the presence of more common phosphines, such as XPhos, PCy_3 or PPh_3, but lower levels of diastereoselectivity were achieved. As discussed earlier, the use of secondary amines as substrates (R^2 = H) led only to direct cross-coupling products.

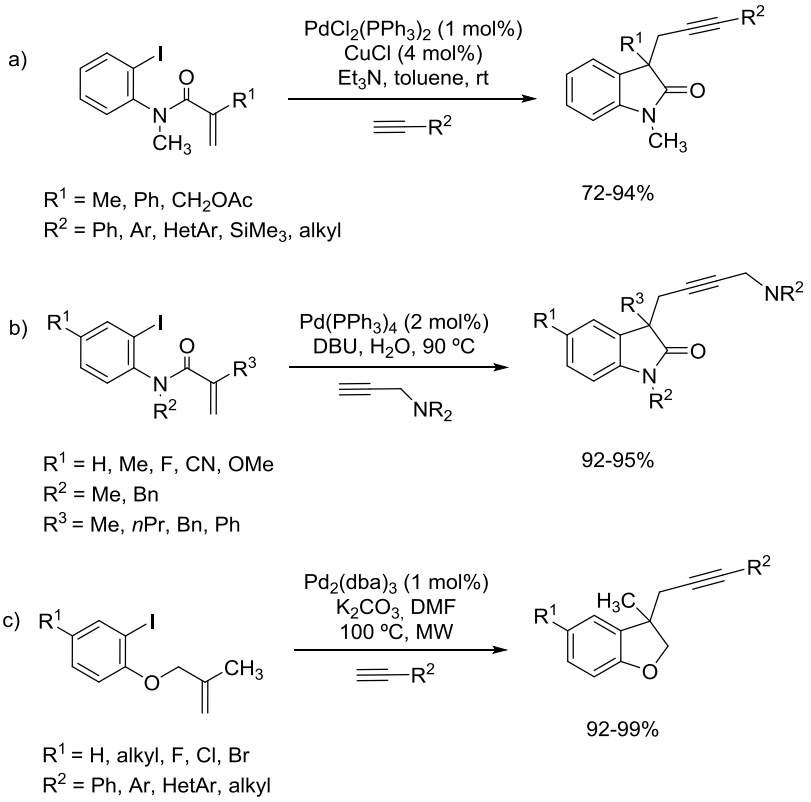
[90] Li, Y.; Wang, K.; Ping, Y.; Wang, Y.; Kong, W. *Org. Lett.* **2018**, *20*, 921.
[91] Wilson, J. E. *Tetrahedron Lett.* **2012**, *53*, 2308.



Scheme 1.38.

The σ-alkylpalladium intermediate formed after carbopalladation can be also coupled with alkynes in a Sonogashira reaction (Scheme 1.39). Thus, carbopalladation/Sonogashira cascade reaction has been developed on acrylamides or allyl ethers to access to 3,3-disubstituted oxindoles and dihydrobenzofurans, respectively. In the first case (Scheme 1.39a),[92] screening of reaction conditions showed that $PdCl_2(PPh_3)_2$ was the best catalyst using CuCl as co-catalyst. These conditions could be applied to a wide range of terminal alkynes obtaining excellent yields of oxindoles. However, when the corresponding esters or thioesters (O or S instead of N-Me) were submitted to the optimized reaction conditions, only the direct Sonogashira coupling products were obtained. These reactions have also been developed using water as solvent in the absence of copper co-catalyst using propargyl amines as coupling partners (Scheme 1.39b).[93] In addition, cyclization of allyl ethers could be accomplished under microwave assisted conditions using low catalyst loadings in the absence of copper (Scheme 1.39c).[94] Thus, dihydrobenzofurans were obtained in almost quantitative yields in very short reaction times (15 min MW *vs* 24 h thermal conditions).

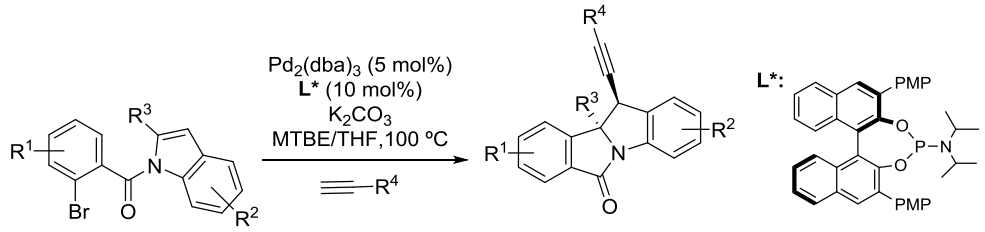
[92] Zhou, M.-B.; Huang, X.-C.; Lui, Y.-Y.; Song, R.-J.; Li, J.-H. *Chem. Eur. J.* **2014**, *20*, 1843.
[93] Wang, D.-C.; Wang, H.-X.; Hao, E.-J.; Jiang, X.-H.; Xie, M.-S.; Qu, G.-R.; Guo, H.-M. *Adv. Synth. Catal.* **2016**, *358*, 494.
[94] Karu, R.; Gedu, S. *Green Chem*. **2018**, *20*, 369.



Scheme 1.39.

An enantioselective variant of this cascade process has also been described which involved a dearomatization reaction of indoles (Scheme 1.40).[95] Interestingly, the addition of CuI completely suppressed the reactivity and it was found that the best results in terms of enantioselectivity were obtained when the reactions were carried out using $Pd_2(dba)_3$ in the presence of K_2CO_3 as base and BINOL-based phosphoramidite as chiral ligand. Thus, a wide variety of alkynes could be efficiently coupled to obtain indolines, bearing quaternary and tertiary vicinal stereocenters, with excellent enantiomeric purities.

[95] Liu, R.-R.; Wang, Y.-G-; Li, Y.-L.; Huang, B.-B.; Liang, R.-X.; Jia, Y.-X. *Angew. Chem. Int. Ed.* **2017**, *56*, 7475.



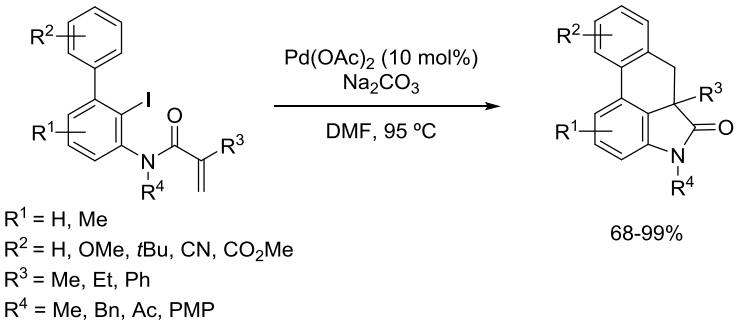
R^1 = H, Me, OMe, F
R^2 = H, F, Cl, Me, *i*Pr
R^3 = Me, Et, Ph, Ar, 2-furyl, CO_2Me
R^4 = Ph, Ar, HetAr, alkyl, CH_2NR_2, $SiMe_3$, etc

50-93%
88-97% *ee*

Scheme 1.40.

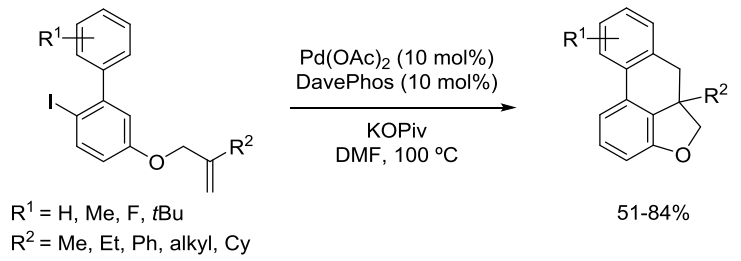
Cascade processes involving a C-H direct arylation event have been also described in both intra- and intermolecular fashion. In the intramolecular variant, the alkylpalladium intermediate formed after carbopalladation would be able to carry out a C-H activation in a conveniently tethered aromatic or heteroaromatic ring, generating in this way a palladacycle able to form a C-C bond *via* reductive elimination. The first examples of this type of reactions for the synthesis of heterocycles were reported by Grigg over twenty years ago,[96] but synthetic applications to more elaborated systems, as well as mechanistic studies, are currently being developed.[97] Recent example is depicted in Scheme 1.41. For instance, when biarylic acrylamides are treated with $Pd(OAc)_2$ and base in DMF, fused indolinones are obtained in good yields (Scheme 1.41)[98] in a process that implies the formation of two C-C bonds and a quaternary stereocenter.

[96] For the first examples of Heck cyclization/intramolecular direct C-H arylation for the synthesis of spiroheterocycles, see: a) Grigg, R.; Fretwell, P.; Meerholtz, C.; Sridharan, V. *Tetrahedron* **1994**, *50*, 359. b) Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V. *Tetrahedron Lett.* **1995**, *36*, 8137.
[97] Ye, J.; Shi, Z.; Sperger, T.; Yasukawa, Y.; Kingston, C.; Schoenebeck, F.; Lautens, M. *Nat. Chem.* **2017**, *9*, 361.
[98] Saha, N.; Wang, H.; Zhang, S.; Du, Y.; Zhu, D.; Hu, Y.; Huang, P.; Wen, S. *Org. Lett*. **2018**, *20*, 712.



Scheme 1.41.

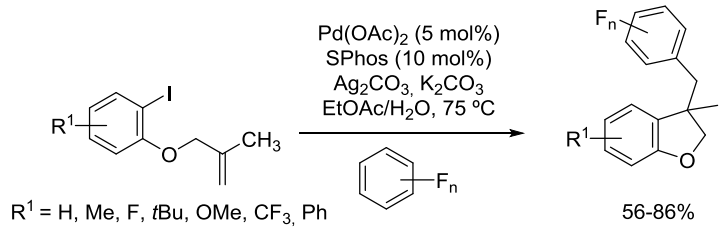
Around the same concept, more complex sequences have also been developed. Thus, it has been recently shown that iodide atom on the substrate does not need to be *ortho* to the tethered alkene to start the carbopalladation. As depicted in Scheme 1.42, a sequence involving oxidative addition on substrates with the iodide atom in *para* position to the tethered alkene, followed by two consecutive [1,4]-palladium migrations using the *ortho* aromatic ring as conveyor, allows the intramolecular carbopalladation of the alkene followed by a C-H activation to obtain fused dihydrofurans.[99]



Scheme 1.42.

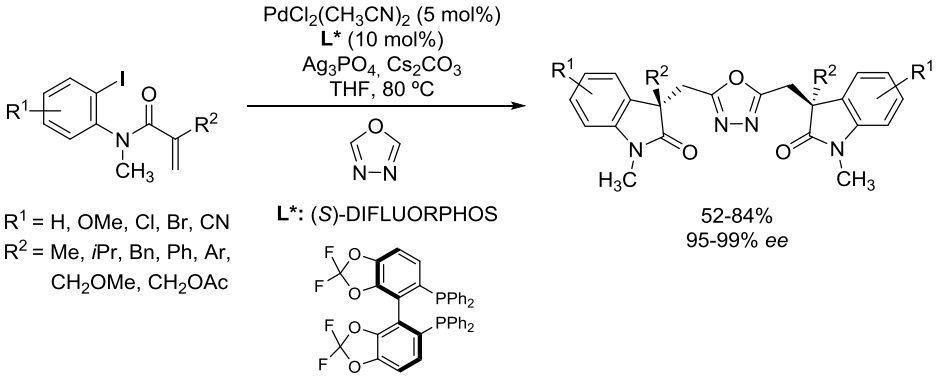
Electron-deficient polyfluoroarenes can be used for the intramolecular C-H arylation of the alkylpalladium intermediates obtained from allyl aryl ethers to form polyfluorinated dihydrobenzofurans (Scheme 1.43).[100]

[99] Li, P.; Li, Q.; Weng, H.; Diao, J.; Yao, H.; Lin, A. *Org. Lett*. **2019**, *21*, 6765.
[100] Wu, X.-X; Chen, W.-L; Shen, Y.; Chen, S.; Xu, P.-F; Liang, Y.-M. *Org. Lett*. **2016**, *18*, 1784.



Scheme 1.43.

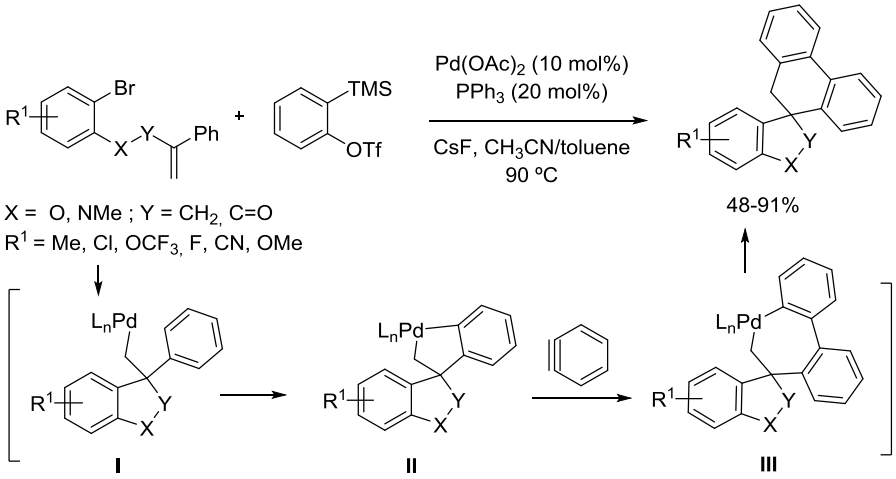
Heteroarenes have also been used as coupling partners for the formation of functionalized oxindolines.[101] Enantioselective variants have been developed starting from acrylamides and oxazoles using PHOX-based ligands leading to oxindoles that could be further elaborated to pyrroloindolines.[102] This reactivity has also been used for the double carbopalladation/C-H arylation of acrylamides to obtain bis(oxindoles) with consistently very high enantiomeric purities, in the presence of a chiral bidentate phosphine, such as (*S*)-DIFLUORPHOS (Scheme 1.44).[103]



Scheme 1.44.

[101] Sharma, U. K.; Sharma, N.; Kumar, Y.; Singh, B. K.; Van der Eycken, E. V. *Chem. Eur. J.* **2016**, *22*, 481.
[102] Kong, W.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc*. **2015**, *137*, 16028.
[103] Tong, S.; Limouni, A.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem. Int. Ed*. **2017**, *56*, 14192.

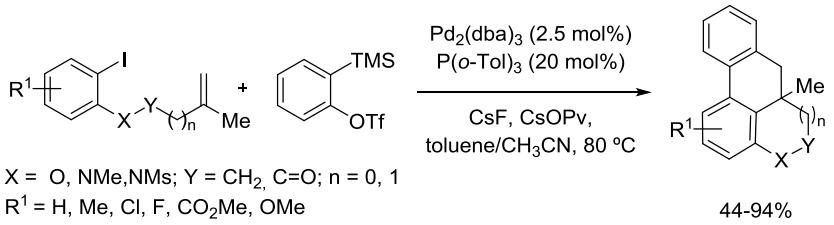
More complex cascade reactions have also been developed taking advantage of the versatility of the alkylpalladium(II) intermediate (**I**, Scheme 1.45).[104] Thus, the palladacycle **II** formed after C-H activation can be trapped with an aryne generated *in situ* to obtain **III**. In this case, both the substrate and the reaction conditions have to be designed to match the formation rates of the alkylpalladium and the aryne, avoiding [1,4]-palladium shift on **I**, which would lead to the formation of undesirable byproducts. Thus, ethers or amines or amides could afford [4,5]-spirocycles with complete regioselectivity in generally high yields. Interestingly, using substrates in which the initial carbopalladation occurs *via* a 6-*exo*-trig cyclization, mixtures of regioisomers were obtained due to competing C-H activation reactions. In a further extension of this methodology, palladacycles of structure **II** have also been trapped with carbenoid precursors, such as α-diazocarbonyl compounds, to obtain spirocycles.[105]



Scheme 1.45.

[104] a) Pérez-Gómez, M.; García-López, J. A. *Angew. Chem. Int. Ed*. **2016**, *55*, 14389. b) Yoon, H.; Lossouarn, A.; Landau, F.; Lautens, M. *Org. Lett*. **2016**, *18*, 6324. c) Pérez-Gómez, M.; Navarro, L.; Saura-Llamas, I.; Bautista, D.; Lautens, M.; García-López, J. A. *Organometallics*, **2017**, *36*, 4465.
[105] Pérez-Gómez, M.; Hernández-Ponte, S.; Bautista, D.; García-López, J. A. *Chem. Commun*. **2017**, *53*, 2842.

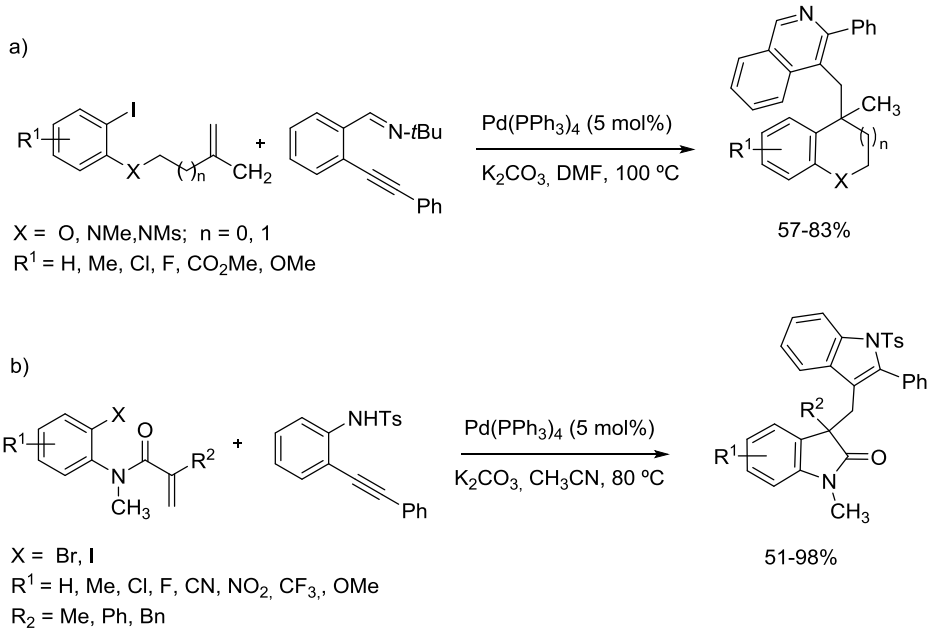
In a related strategy, the use of substrates in which the β-hydride elimination is blocked by an alkyl substituent, instead of an aromatic ring, leads to the formation of heterocycle fused 9,10-dihydrophenanthrenes (Scheme 1.46).[106] The use of CsOPiv as base was crucial as other organic or inorganic bases afforded only low yields of desired product. In general, electron withdrawing substituents in the aryl iodide resulted in higher yields, which is consistent with a base induced palladation in the C-H functionalization step. In this case, the formation of a six membered ring through a 6-*exo* initial carbopalladation is possible, obtaining fused quinoline systems in good yields (X = NMe, NMs; Y = CH_2, n = 1).



Scheme 1.46.

The alkylpalladium(II) species obtained after intramolecular carbopalladation can be involved in a wide variety of reactions. In a different approach, these intermediates have been used to promote cyclization of alkynes containing a proximate nucleophilic group (Scheme 1.47). Thus, functionalized isoquinolines[107] and indoles are obtained in good yields forming two cycles, two C-C and a C-N bond in a single step.[108]

[106] Yao, T.; He, D. *Org. Lett*. **2017**, *19*, 842.
[107] Yao, T.; Liu, T.; Zhang, C. *Chem. Commun*. **2017**, *53*, 2386.
[108] Yan, K.; Liu, L.; Chen, J.; Guo, J.; Yao, H.; Lin, A. *Org. Lett*, **2018**, *20*, 3477.


a)
R1
I
X
n
CH2
N-tBu
Ph
Pd(PPh3)4 (5 mol%)
K2CO3, DMF, 100 ºC
N
Ph
CH3
R1
n
X
X = O, NMe,NMs; n = 0, 1
R1 = H, Me, Cl, F, CO2Me, OMe
57-83%
b)
R1
X
O
N
CH3
R2
NHTs
Ph
Pd(PPh3)4 (5 mol%)
K2CO3, CH3CN, 80 ºC
NTs
Ph
R2
R1
O
N
CH3
X = Br, I
R1 = H, Me, Cl, F, CN, NO2, CF3,, OMe
R2 = Me, Ph, Bn
51-98%

Scheme 1.47.

2. OBJECTIVES

As has been shown in the previous section, the intramolecular Mizoroki-Heck reaction constitutes a powerful tool for the construction of medium-sized carbocycles and heterocycles. The rich reactivity of the alkylpalladium(II) species obtained after intramolecular carbopalladation of well-designed substrates makes them highly valuable intermediates to participate in further functionalization reactions, generating a tertiary or quaternary stereocenter and increasing molecular complexity in a single step. Thus, besides the great number of applications described, the discovery and utilization of cascade processes with high regio- and stereoselectivity is a greatly active area. In addition, the use of chiral ligands for palladium has allowed the development of enantioselective variants that are widely used in synthesis. However, the advances in asymmetric carbopalladation-initiated cascades is not straightforward, as the presence of other reagents, such as external nucleophiles, may alter the coordination sphere of palladium and have an impact in the enantioselectivity.

In this context, and in close connection to previous results from our group, the main objective of this part of the work was to study the application of Mizoroki-Heck reaction for the generation of quaternary centers through 6-*exo*-trig cyclization in the synthesis of pyrrolo[1,2-*b*]isoquinoline frameworks (or hetero-fused analogs and homologous larger rings).

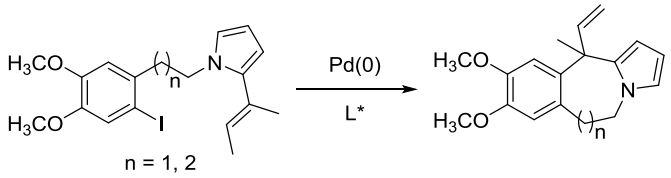
For this purpose, different strategies will be applied:

a) Blocking the β-hydride elimination using trisubstituted alkenes as coupling partners.

Our group has described the synthesis of pyrrolo[1,2-*b*]isoquinolines from 2-alkenyl substituted *o*-iodobenzylpyrroles, in which the β-elimination is blocked by a substituent on the alkene, through an intramolecular enantioselective Mizoroki-Heck reaction.[36] Thus, the cyclization reaction proceeded with moderate enantioselectivity (78% *ee*), but low yield

(5%) when using $Pd(OAc)_2$ as catalyst and (*R*)-BINAP as chiral phosphine ligand (Scheme 1.7, p. 12).

In this context, our first goal was to study the possibility of extending this process to the construction of analogous seven- and eight-membered rings both in a racemic and an enantioselective fashion (Scheme 1.48).



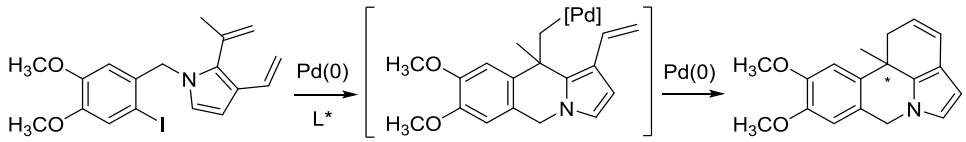
Scheme 1.48.

b) Cascade reactions

We also wanted to study in depth the generation of quaternary center through cascade processes. For that purpose, we selected different substrates which, after an initial 6-*exo* carbopalladation, would lead to an σ-alkylpalladium(II) intermediate that could be involved in an anion capture event or in another coupling reaction.

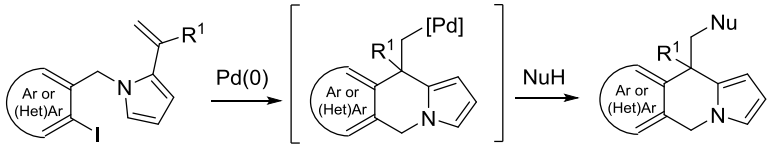
In this context, our group has been able to perform a 6-*exo*/6-*endo* Heck-Heck cascade process on *N*-benzyl 2,3-dialkenylpyrroles to access the tetracyclic Lycorane core present in the *Amaryllidaceae* alkaloids. This methodology allows the synthesis of a wide variety of enantiomerically enriched (11*bR*)-substituted pyrrolophenanthridines with different substitution patterns on the aromatic ring, and also heteroaromatic rings (Scheme 1.36).[86a] However, the enantioselectivities obtained were moderate to good in most cases, so we decided to develop a computational model capable of predicting the enantiomeric excess and the yield of Heck-Heck cascade reactions.[86b] In this way, we would have an useful tool that would help us to select the best catalyst, ligands and experimental conditions, without engaging in a long term empirical investigation.

Thus, our goal was to use the designed computational model with the aim of improving the enantioselectivity of the polyene cyclization reaction. For that purpose, reaction conditions and chiral ligands that predict better *ee* values for the construction of the tetracyclic product would be tested (Scheme 1.49).



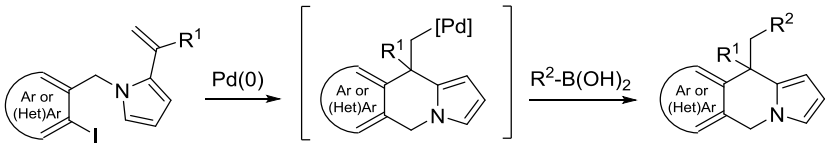
Scheme 1.49.

As mentioned before, the σ-alkylpalladium(II) intermediate formed after the starting carbopalladation can also be involved in a nucleophilic trapping reaction. Thus, our next task was to test a cyanation reaction with a nucleophile, such as $K_4[Fe(CN)_6]$, as termination approach for palladium-catalyzed cascade reaction of 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles as substrates (Scheme 1.50).



Scheme 1.50.

Finally, our last objective was to explore the possibility of involving the σ-alkylpalladium(II) intermediate obtained after the first cyclization of 2-alkenyl substituted *o*-benzylpyrroles in a different termination event, such a Suzuki coupling reaction (Scheme 1.51). The reaction would be tested first in a racemic fashion and, afterwards, the enantioselective version of this process would be attempted by using different types of chiral ligands.



Scheme 1.51.

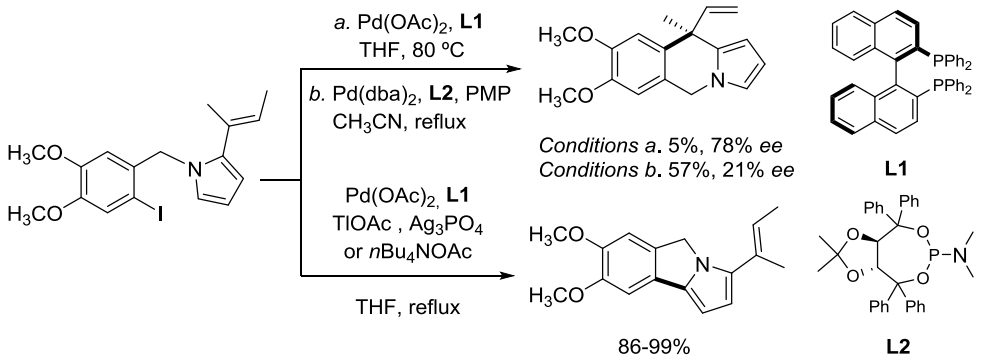
In this PhD project, we were expected to develop synthetic methodologies for the preparation of series of compounds with the pyrrolo[1,2-*b*]isoquinoline core, which is a common structural motif among many biologically active alkaloids and synthetic molecules with anticancer, antiviral, anti-inflammatory and antiparasitic properties. Therefore, as a complementary objective, the anti-leishmanicidal activity of some of the synthesized pyrrolo[1,2-*b*]isoquinolines would be evaluated to identify new lead compounds for the treatment of this neglected disease. For that purpose, biological assays against visceral (*L. donovani*) and cutaneous (*L. amazonensis*) leishmaniasis, as well as their cytotoxicity, would be carried out by Dr. M. A. Dea from University CEU Cardenal Herrera (Valencia).

3. RESULTS AND DISCUSSION

3.1. Mizoroki-Heck reaction for the formation of a quaternary center on C-11 of pyrrolo[1,2-*b*]benzazepines and C-12 of pyrrolo[1,2-*b*]benzazocines

As stated in the previous section, our group has studied the stereocontrolled generation of a quaternary stereocenter through the Mizoroki-Heck reaction of 2-alkenyl substituted benzylpyrroles, in which β-elimination is blocked by a substituent. Thus, a promising enantioselectivity (78% *ee*) was obtained when (*R*)-BINAP was employed as chiral ligand in combination with $Pd(OAc)_2$, although the corresponding pyrrolo[1,2-*b*]isoquinoline was achieved in very low yield. All attempts carried out to improve the outcome of the reaction resulted in loss of enantioselection and only when CH_3CN was used as solvent the yield improved to 57% (Scheme 1.52).[36]

The enantioselectivity of the reaction is attributed to the migratory insertion into the alkene. The reaction conditions that favor a cationic mechanism in which no dissociation of the ligands occurs (often bidentate phosphines) are usually critical to obtain good enantioselectivity. However, in our case, when the addition of additives as thallium or silver salts was tried to promote a cationic mechanism, a change in the chemoselectivity of the reaction in favor of the direct arylation on the pyrrole ring was observed, and the pyrrolo[2,1-*a*]isoindole was formed in excellent yield (Scheme 1.52).



Scheme 1.52.

Considering these precedents, our first goal was to study the extension of the described enantioselective intramolecular Mizoroki-Heck reaction in the synthesis of pyrrolo[1,2-*b*]isoquinolines to the construction of medium-sized rings (seven- and eight- membered rings) (Scheme 1.48). Thus, the possibility of generation of a quaternary center in a stereocontrolled way *via* asymmetric intramolecular Mizoroki-Heck reaction of 2-alkenyl substituted *N*-(*o*-iodoarylalkyl)pyrroles would be investigated.

*3.1.1. Synthesis of 2-alkenyl substituted (o-iodoarylalkyl)pyrroles **5a,b***

The synthetic route designed for the synthesis of the 2-alkenyl substituted *N*-(*o*-iodoarylalkyl)pyrroles **5a,b** precursor of the intramolecular Mizoroki-Heck reaction is described in Scheme 1.53.

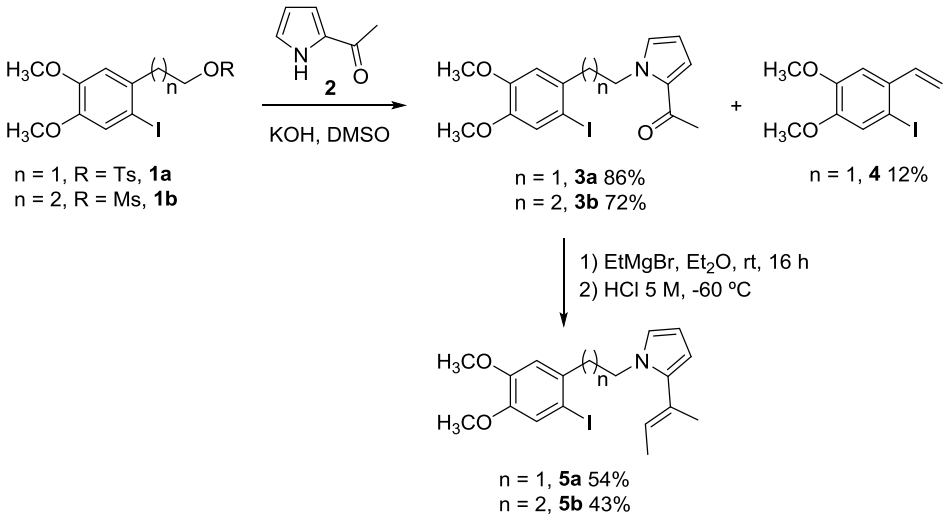
The synthetic route began with alkylation reaction of the previously synthesized sulfonates **1a,b**[109] with commercially available 2-acetylpyrrole (**2**) under the conditions previously employed in our research group for alkylation of similar substrates[109,110] which enabled the preparation of the *N*-phenethyl- and *N*-phenylpropylpyrroles **3a,b** in good yields. The alkylation reaction of tosylate **1a** with **2** led to a minor amount of the iodinated styrene **4** (12%) as a by-product, due to a β-elimination reaction of the tosylate **1a**. The formation of a conjugated system may be the reason for this process to occur (Scheme 1.53).

The last step in the synthesis of the 2-alkenyl substituted *N*-(*o*-iodoarylalkyl)pyrroles was the introduction of the olefin function. We tried to incorporate it through a Wittig reaction, but treatment of the ketones **3a,b** with ethyltriphenylphosphonium bromide and K*t*BuO did not lead to the desired **5a,b** products and unreacted starting materials **3a,b** were recovered.

---

[109] a) Ruiz, J.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311. b) Coya, E.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2014**, *356*, 1853.
[110] a) Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.* **2003**, *5*, 1115. b) Ruiz, J.; Lete, E.; Sotomayor, N. *Tetrahedron* **2006**, *62*, 6182. c) Lage, S.; Martínez-Estíbalez, U.; Sotomayor, N.; Lete, E. *Adv. Synth. Catal.* **2009**, *351*, 2460.

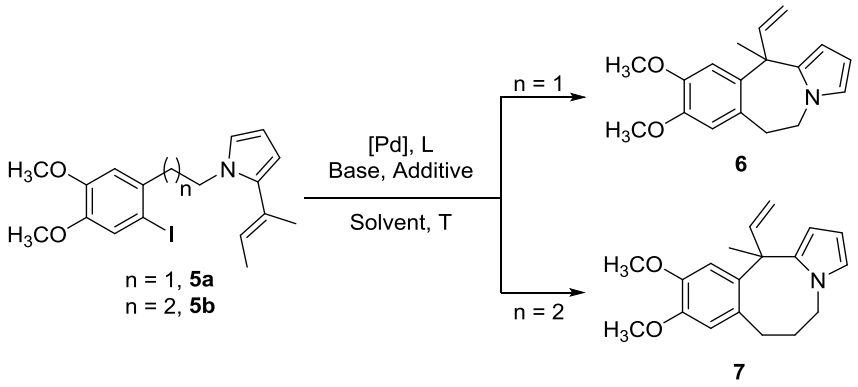
Alternatively, we carried out a 1,2-addition of a Grignard reagent to the carbonyl group of **3a,b**, with the subsequent elimination of water in acidic media. Thus, 2-alkenyl substituted *N*-(*o*-iodoarylalkyl)pyrroles **5a,b** were obtained in moderate yields as single *E* diastereomers (Scheme 1.53). The choice of the temperature was crucial to achieve the diastereocontrol of the reaction, as attempts carried out at -20 and -40 ºC led to mixtures of diastereomers in variable ratios.



Scheme 1.53.

*3.1.2. Intramolecular Mizoroki-Heck reaction of 2-alkenyl sustituted N-(o-iodoarylalkyl)pyrroles **5a,b***

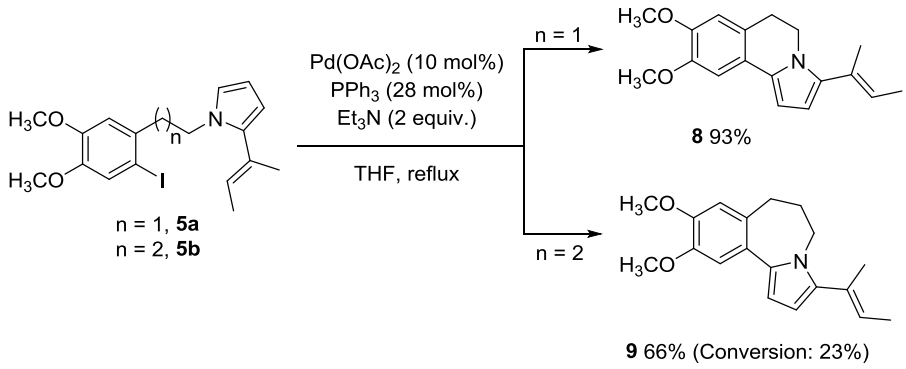
Once the 2-alkenyl *N*-(*o*-iodoarylalkyl)pyrroles **5a,b** were synthetized, we started the study of the intramolecular Mizoroki-Heck reaction to access to pyrrolo[1,2-*a*]benzazepine and pyrrolo[1,2-*a*]benzazocine skeletons (Scheme 1.54).



Scheme 1.54.

As stated before, our group has studied the synthesis of enantioenriched pyrrolo[1,2-*b*]isoquinoline analogous to **6** and **7** through an asymmetric Mizoroki-Heck reaction of a properly substituted 2-alkenyl *N*-(*o*-iodobenzyl)pyrrole.[36] Thus, we proceeded to investigate the possibility of formation of a quaternary center by 7-*exo* and 8-*exo* cyclization reactions, employing different reaction conditions based on that precedents. For that purpose, we began the study performing the Mizoroki-Heck reaction of substrates **5a,b** in a racemic fashion.

Firstly, pyrroles **5a,b** were treated with $Pd(OAc)_2$ (10 mol%), PPh_3 (28 mol%) and Et_3N in THF. The reaction mixture was heated for 6 h in the case of *N*-phenethylpyrrole **5a** and 48 h in the case of *N*-phenylpropylpyrrole **5b**. However, treatment of **5a** under former reaction conditions afforded direct arylation product **8** over the pyrrole ring, instead of the desired pyrrolo[1,2-*a*]benzazepine **6** (Scheme 1.55). Analogously, when **5b** was subjected to the Mizoroki-Heck conditions previously mentioned, expected pyrrolo[1,2-*a*]benzazocine **7** was not obtained. Instead, a inseparable mixture of substrate **5b** and corresponding direct arylation product **9** in a (5:1) ratio in favor of **5b** was isolated. As both compounds showed identical R_f in TLC, their separation was not possible by column chromatography regardless the mobile phase employed and, consequently, complete characterization of the pyrrolo[1,2-*a*]benzazepine **9** was not achieved (Scheme 1.55).



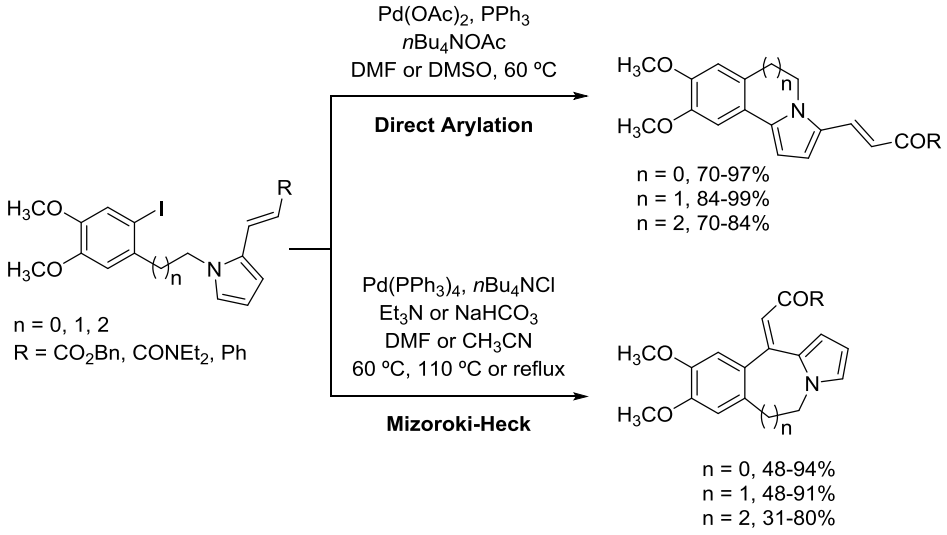
Scheme 1.55.

The formation of direct arylation products **8** and **9** instead of expected pyrrolo[1,2-*a*]benzazepine **6** and pyrrolo[1,2-*a*]benzazocine **7** derived from Mizoroki-Heck reaction is not unprecedented. In fact, Mizoroki-Heck and direct arylation reactions share the same type of reaction intermediates, so chemoselectivity problems may arise when functionalized substrates as 2-alkenyl substituted *N*-(*o*-iodoarylalkyl)pyrroles **5a,b** are used.

The electrophilic Pd(II) species formed after the oxidative addition step of the Mizoroki-Heck mechanism have also been considered as reactive intermediates in direct arylation reactions of (hetero)arenes with aryl halides, a related coupling reaction that has been widely studied.[111]

[111] 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*, 1173; c) Li, B. J.; Yang, S. D.; Shi, Z. J. *Synlett* **2008**, 949; d) Miura, M.; Satoh, T. *Modern Arylation Methods*, Ackermann, L. Ed.; Wiley-VCH: Weinheim, **2009**, p. 335; e) Catellani, M.; Motti, E.; Della Ca, N. *Acc. Chem. Res.* **2008**, *41*, 1512; f) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269; g) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447; h) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; i) Livendahl, M.; Echavarren, A. M. *Isr. J. Chem.* **2010**, *50*, 630; j) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem.* **2010**, *2*, 20; k) Su, Y. X.; Sun, L. P. *Mini-Rev. Org. Chem.* **2012**, *9*, 87; l) Kozkushlov, S. I.; Potukuchi, H. K.; Ackermann, L. *Cat. Sci. Tech.* **2013**, *3*, 562; m) Sharma, A.; Vacchani, D.; Van der Eycken, E. *Chem. Eur. J.* **2013**, *19*, 1158.

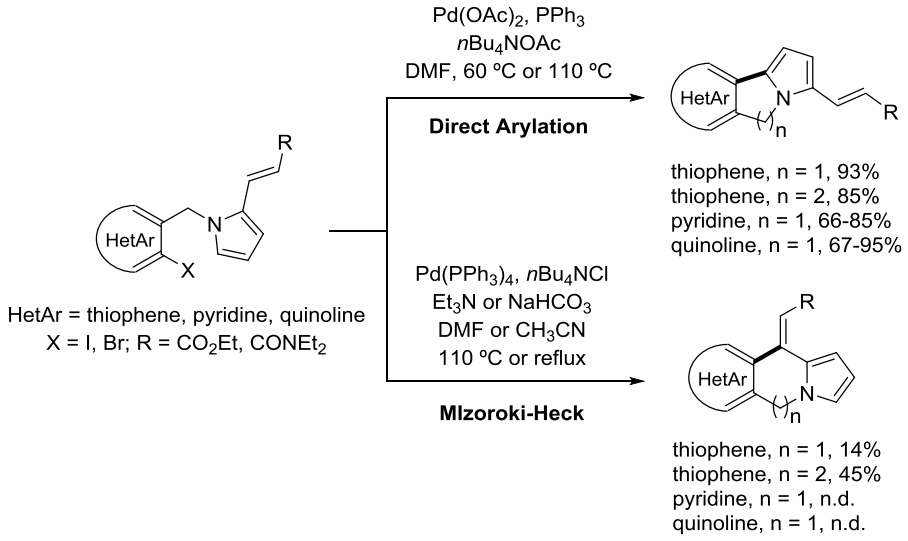
In this context, our group has studied the competition between intramolecular direct arylation and Mizoroki-Heck reactions. In fact, we have demonstrated that palladium-catalyzed intramolecular reaction of substrates, such as 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles (n = 0), can be switched from the alkene moiety (Mizoroki-Heck) to the pyrrole nucleus (direct arylation) by choosing the adequate catalytic system, regardless of the nature of the substituent on the alkene (Scheme 1.56).[110c] In this way, when the reaction was performed in presence of $Pd(OAc)_2$, PPh_3 and $n$$Bu_4NOAc$ in DMSO, direct arylation products were obtained with complete chemoselectivity. On the other hand, conditions based on the use of $Pd(PPh_3)_4$, $n$$Bu_4NCl$ and $NaHCO_3$ in acetonitrile led to the formation of Mizoroki-Heck products with complete chemo- and regioselectivity, obtaining the corresponding pyrrolo[1,2-*b*]isoquinolines in good yields. This protocol could also be applied for the selective synthesis of seven- and eight-membered rings (n = 1 and n = 2).[109b] Thus, pyrroloisoquinoline, pyrroloazepine and pyrroloazocine cores were selectively and efficiently achieved by adequately choosing reaction conditions (Scheme 1.56).



Scheme 1.56.

Moreover, our group 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 1.57).[109b] In this case, direct arylation reaction was selectively controlled under conditions which favored a cationic or a CMD mechanism. However, when using conditions to favor neutral mechanism, the formation of direct arylation products was competitive with the formation of Mizoroki-Heck products and, thus, desired thienoindolizine (n = 1) and thienoazepine (n = 2) derivatives were obtained in low yields.

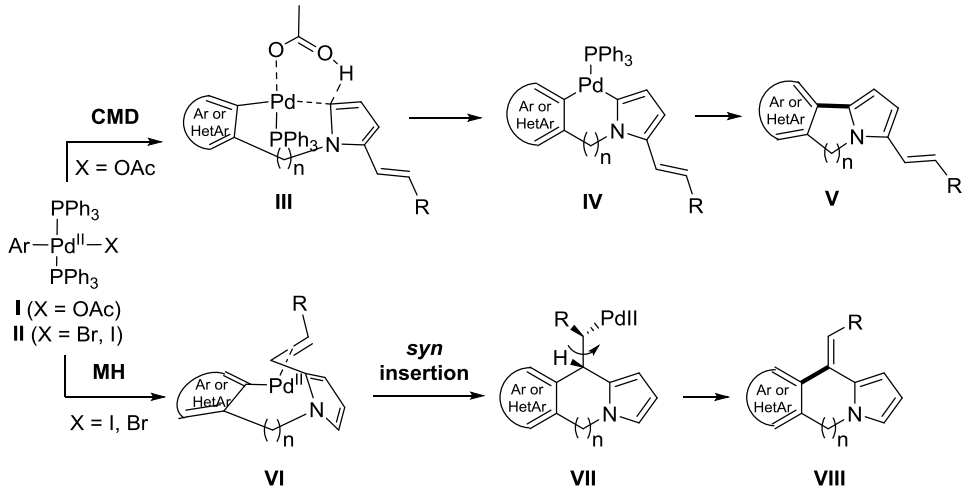
Finally, when electron-deficient heteroaryl halides, such as pyridinyl and quinolinyl halides, were evaluated as substrates, the direct arylation emerges as the predominant process under all conditions tested, even under conditions that should favor a neutral mechanism, and Mizoroki-Heck product formation was not observed (Scheme 1.57).[112]



Scheme 1.57.

[112] Rebolledo-Azcargorta, A. PhD Thesis, University of the Basque Country (UPV/EHU), **2016**.

The change in the chemoselectivity of the reaction from the alkene (Mizoroki-Heck) to the pyrrole nucleus (direct arylation) was explained through the formation of different intermediate palladium species in the catalytic system, as explained in detail by Jutand.[113]



Scheme 1.58.

Thus, when $Pd(OAc)_2/nPPh_3$ (n > 2) catalytic system is used, *trans* complex **I** (X = OAc) is formed after the oxidative addition to the heteroaryl halide, while, **II** (X = I) is the intermediate species in presence of $Pd(PPh_3)_4$ with an iodide ligand (Scheme 1.58). It has been reported that the acetate ion is easily dissociable, and an equilibrium could be established between [*trans*-(Het)ArPd(PPh_3)(OAc)] species **I** and cationic $[ArPd(PPh_3)]^+$ 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 palladium (II) species would react preferentially at the more electron-rich pyrrole nucleus, and a cationic mechanism could take place. Besides, acetate ion would be able to assist the abstraction of the proton in α

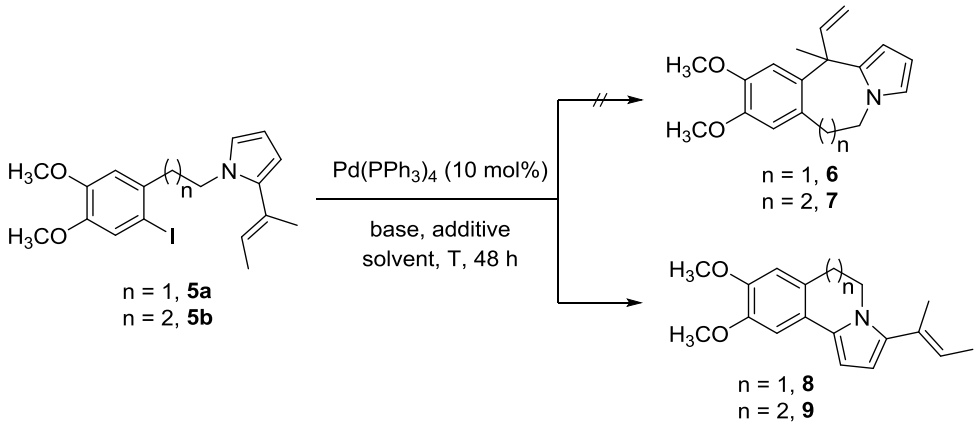
[113] a) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009; b) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818; c) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605; d) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

position to the nitrogen atom in the pyrrole nucleus (**III**) and finally result in arylation product **V**, through a CMD mechanism. On the contrary, in the presence of $Pd(PPh_3)_4$ as catalyst, the neutral pathway may take place providing Heck-type intermediate **VII**, which, after *syn* palladium hydride elimination, would give **VIII** as main product.

At this point, in view of the evident competition between intramolecular Mizoroki-Heck and direct arylation reactions, we decided to try different reaction conditions in order to evaluate if the change in the palladium source, base and the use of additives allowed the formation of Mizoroki-Heck products **6** and **7**. Thus, we tested different cyclization conditions using $Pd(PPh_3)_4$ as catalyst attending to precedents previously stated in our research group (Scheme 1.59 and Table 1.1).[109,110]

However, the use of $Pd(PPh_3)_4$, $NaHCO_3$ and nBu$_4$NCl in acetonitrile at reflux as catalytic system over **5a,b** yielded identical results to those obtained using $Pd(OAc)_2$ as catalyst (Table 1.1, Entries 1 and 5). In fact, reaction of **5a** under mentioned conditions led to pyrrolo[2,1-*a*]isoquinoline **8** as a single product in good yield (78%). The outcome of the cyclization reaction over *N*-phenylpropylpyrrole **5b** was again the inseparable mixture of unreacted starting material and arylation product **9**. Reaction time of 48 h was established in order to obtain comparable results with those reported in our research group in the study of Mizoroki-Heck reaction over analogous *N*-(*o*-iodobenzyl)pyrrole.[110]

In view of these results, different conditions were tested in order to achieve a change in the chemoselectivity of the process towards pyrrolo[1,2-*a*]benzazepine **6** and pyrrolo[1,2-*a*]benzazocine **7**. However, the change in the base and the solvent (Table 1.1, Entries 3 and 6) did not vary the outcome of the reaction. In fact, direct arylation product **8** was obtained in low yield (34%) when **5a** was used as substrate, whereas reaction over **5b** afforded the inseparable mixture of starting material and direct arylation product **9**, with no evidence of Mizoroki-Heck cyclization.



Scheme 1.59.

Table 1.1. Mizoroki-Heck reaction of **5a,b** in racemic version using $Pd(PPh_3)_4$ as catalyst.

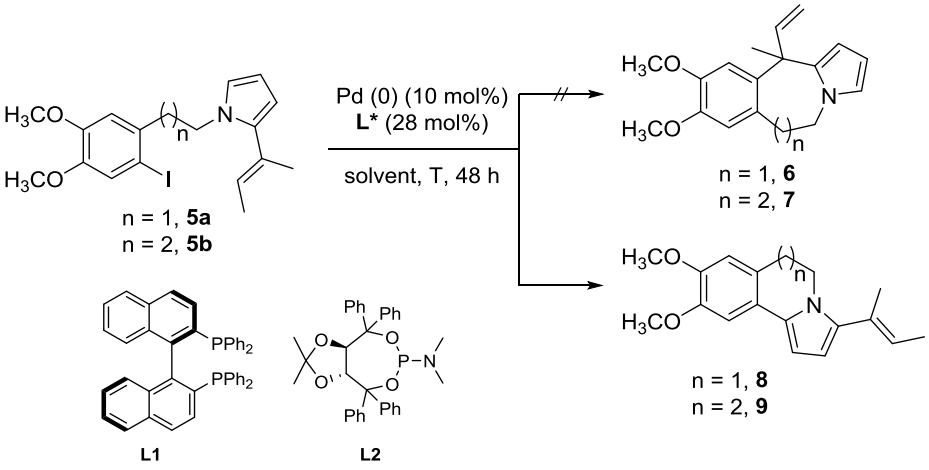
Entry	Subs.	Base (equiv.)	Additive (equiv.)	Solvent	T (°C)	Prod.	Conv. (%)	Yield (%)
1	**5a**	$NaHCO_3$ (2.5)	nBu$_4$NCl (1.5)	CH_3CN	Refl.	**8**	63	78[a]
2[b]	**5a**	Et_3N (12)	nBu$_4$NCl (2)	DMF	110	**8**	62	22[a]
3	**5a**	Et_3N (12)	nBu$_4$NCl (2)	DMF	110	**8**	79	34[a]
4	**5a**	Et_3N (2.5)	-	Toluene	Refl.	**8**	85	41[a]
5	**5b**	$NaHCO_3$ (2.5)	nBu$_4$NCl (1.5)	CH_3CN	Refl.	**9**	63[c]	74[c]
6	**5b**	Et_3N (12)	nBu$_4$NCl (2)	DMF	110	**9**	61[c]	43[c]
7	**5b**	Et_3N (2.5)	-	Toluene	Refl.	**9**	52[c]	87[c]

[a] Isolated yield. [b] 3 mol% of $Pd(PPh_3)_4$. [b] Determined by ^{1}H NMR spectroscopy.

Finally, the use of reaction conditions in absence of additives (Table 1.1, Entries 4 and 7) using Et_3N as base in toluene at reflux gave similar results.

At this point, despite the impossibility of formation of desired Mizoroki-Heck products, we decided to carry out the cyclization reaction of *N*-phenethylpyrrole **5a** and *N*-phenylpropylpyrrole **5b** in an enantioselective fashion in order to study the possible change in chemoselectivity of the Mizoroki-Heck reaction that could cause the variation of both the phosphane ligand and palladium source (Scheme 1.60 and Table 1.2).

Thus, pyrroles **5a,b** were treated with $Pd(OAc)_2$ and (*R*)-BINAP in THF, conditions that afforded the analogous 6-*exo* cyclization over analogous 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrrole with moderate enantiomeric excess (78% *ee*) and low yield (5%).[36] However, cyclization of **5a,b** under the mentioned enantioselective Mizoroki-Heck reaction conditions did not lead to the construction of the pyrrolo[1,2-*a*]benzazepine **6** and pyrrolo[1,2-*a*]benzazocine **7** (Table 1.2, Entries 1 and 4). Again, the reaction of the *N*-phenethylpyrrole **5a** gave the direct arylation product **8** with moderate yield and conversion, while the *N*-phenylpropylpyrrole **5b** provided the mixture of starting material and arylation product **9**.



Scheme 1.60.

Table 1.2. Mizoroki-Heck reaction of **5a,b** using chiral ligands.

Entry	Subs.	[Pd]	L*	Solvent	T (ºC)	Prod.	Conv. (%)	Yield (%)
1	**5a**	$Pd(OAc)_2$	**L1**	THF	Refl.	**8**	39	74[a]
2	**5a**	$Pd_2(dba)_3 \cdot CHCl_3$	**L1**	DMF	80	**8**	40	87[a]
3[b]	**5a**	$Pd(dba)_2$	**L2**	CH_3CN	Refl.	**8**	50	90[a]
4	**5b**	$Pd(OAc)_2$	**L1**	THF	Refl.	**9**	83[c]	17[c]
5	**5b**	$Pd_2(dba)_3 \cdot CHCl_3$	**L1**	DMF	80	**9**	55[c]	32[c]
6[b]	**5b**	$Pd(dba)_2$	**L2**	CH_3CN	Refl.	**9**	67[c]	19[c]

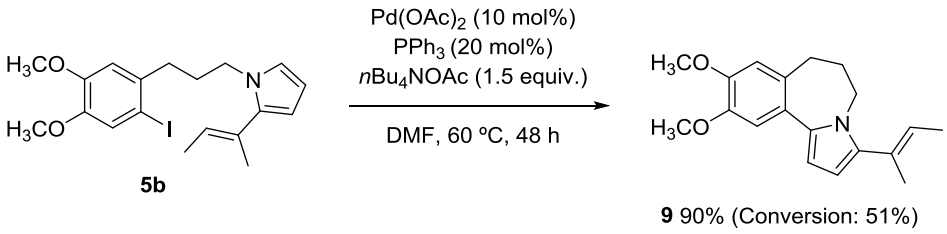
[a] Isolated yield. [b] PMP (1.1 equiv.) was used as base. [c] Determined by ^{1}H NMR spectroscopy.

Considering the obtained results, a change in the palladium source to $Pd_2(dba)_3 \cdot CHCl_3$ was attempted (Table 1.2, Entries 2 and 5), as it has been one of the most widely employed catalysts in intramolecular Mizoroki-Heck reactions together with $Pd(OAc)_2$. However, the products obtained under those reaction conditions were once again the direct arylation product **8** for **5a** and the previously mentioned inseparable mixture of **5b** and **9** in the case of **5b**.

Finally, we decided to change again the catalytic system to $Pd(dba)_2$ using the chiral phosphoramidite **L2** as ligand in the presence of PMP as base (Table 1.2, Entries 3 and 6),[114,115] conditions that gave good yields (57%), but poor enantioselectivities (21% *ee*) in the enantioselective Mizoroki-Heck reaction over analogous 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrrole.[36] However, the reaction outcome was identical and no formation of the cyclization Mizoroki-Heck product was observed in any case.

[114] Phosphoramidite ligand **L2** is one of the few examples of monodentate ligands that has led to good enantioselectivities in the intramolecular asymmetric Mizoroki-Heck of an cyclohexadienone: Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184.
[115] PMP base (1,2,2,6,6-pentamethyl piperidine) is a highly basic, more sterically hindered and stable tertiary amine that has demonstrated to increase selectivity and reactivity *via* neutral pathway, see: McCartney, D.; Guiry, P. *J. Chem. Soc. Rev.* **2011**, *40*, 5122.

As stated before, ^{1}H NMR spectra of reaction mixtures of *N*-phenylpropylpyrrole **5b** revealed the formation of the arylation product **9**, which could not be completely purified and characterized. For this reason and to unambiguously confirm the structure of the arylation product, we decided to apply over substrate **5b** the reaction conditions established by our group for direct arylation reactions (Scheme 1.61)[109b,110c] in order to obtain pyrrolo[1,2-*a*]benzaepine **9** regioselectively and, thus, to achieve its characterization and the confirmation of the structure.



Scheme 1.61.

Optimized conditions by our group for the direct arylation reaction are those in which $Pd(OAc)_2$ is used as catalyst, PPh_3 as ligand and nBu$_4$NOAc as additive in DMSO or DMF at 60 ºC.[109b,110c] In this way, the use of 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3 and 1.5 equivalents of nBu$_4$NOAc led to a inseparable mixture of **5b** and the arylation product **9** in a 3.3:1 ratio in favor to **9** after 48 h using DMF as solvent. Thus, the conversion of the reaction was not complete, reason why the ^{1}H NMR spectra shows predominantely the characteristic signals of the pyrrolo[1,2-*a*]benzazepine **9**, together with the peaks of starting material **5b**. Even so, the presence of the arylation product **9** in the mixture of two products was confirmed by detection of pyrrolo[1,2-*a*]benzazepine **9** mass in the High Resolution Mass Spectroscopy (HRMS) spectra.

In conclusion, diverse reactions conditions employed over the starting materials **5a,b** were inneficient to afford the Mizoroki-Heck products **6** y **7**, obtaining mainly direct arylation cyclization on the pyrrole ring, which demostrated the high preference of the direct

arylation process, being impossible to control the selectivity of the reaction. In addition, in the case of **5b**, the conversion was not complete, showing the difficulty of construction of eight-membered rings with quaternary centers through intramolecular Mizoroki-Heck reaction.

3.2. Heck-Heck cascade reactions. Access to tetracyclic core of the Lycorane alkaloids

As stated in previous section, our group has applied the asymmetric palladium-catalyzed polyene cyclization over 2,3-dialkenylpyrroles to the construction of a wide variety of enantiomerically enriched C-11b substituted pyrrolophenanthridines or Lycorane analogues (Scheme 1.36). For that purpose, different bidentate and monodentate phosphines (such as DIOP, SEGPHOS, Xyl-BINAP, CHIRAPHOS or TADDOL-based phosphoramidites) were tested and, although all of them were able to promote the cyclization in generally good yields, (*R*)-BINAP provided the best results in terms of enantioselectivity (up to 99% *ee*), using $Pd(OAc)_2$ as catalyst and PMP as base in acetonitrile. Besides, a wide range of substrates was subjected to optimized reaction conditions and we demonstrated that the reaction tolerated different substitution patterns on the aromatic ring, and also heteroaromatic rings.[86a]

It is noteworthy that the reaction was completely selective towards Heck-Heck process, and no other cyclization pathways were observed even when using conditions that favor a cationic type mechanism. Thus, it was established that a 6-*exo* carbopalladation generates the quaternary stereocenter, giving rise to the σ-alkylpalladium intermediate that undergoes a 6-*endo* insertion to give the tetracyclic structural core of Lycorane alkaloids. Previous DFT studies on related 6-*exo*/6-*endo* cascades had shown that the main factor controlling the exo/endo selectivity at thermodynamic and kinetic levels is the relative stability of the cyclic system resulting from migratory insertion.[116]

[116] Balcells, D.; Maseras, F.; Keay, B. A.; Ziegler, T. *Organometallics* **2004**, *23*, 2748.

At this point, despite the interesting results obtained in our study of the asymmetric palladium-catalyzed Heck-Heck cascade reaction, we considered that the enantiomeric excess values achieved were susceptible of improvement. However, the yield and stereochemical outcome of the Mizoroki-Heck reaction depends on numerous factors and, hence, it is particularly difficult to rationalize how the different parameters affect the reaction outcome. Hence, one of the main challenges in the field of asymmetric Mizoroki-Heck reactions is the selection or the design of the adequate catalyst or experimental conditions for a given reaction without engaging in a long term empirical investigation.

In this context, Machine Learning (ML) approaches can help to develop computational models to predict reactivity or even selectivity. In fact, methodologies based on Quantitative Structure-Reactivity Relationship (QSRR) modeling have been applied to predict enantioselectivity and chemical reactivity of different types of reactions.[117] Additionally, our group has combined both Perturbation Theory (PT) and ML ideas to create a qualitatively new class of chemoinformatic model to correlate and predict the enantioselectivity and/or yield of intramolecular carbolithiation, α-amidoalkylation reactions and Parham cyclizations.[118] Attending to these precedents, our group has also developed a general chemoinformatic model for the prediction of the enantioselectivity and the yield of polyene cyclization reactions, in collaboration with Prof. Humberto González-Díaz (Ikerbasque Research Professor, UPV/EHU).[86b]

The general workflow used to seek the computational model is shown in Figure 1.1. The first step was the compilation of a large dataset of enantioselective Heck–Heck cascade reactions, including polyene cyclization reactions developed in our group[86a] and related

[117] a) Aguado-Ullate, S.; Urbano-Cuadrado, M.; Villalba, I.; Pires, E.; García, J. I.; Bo, C.; Carbó, J. J. *Chem. Eur. J.* **2012**, *18*, 14026. b) Huang, H.; Zong, H.; Biang, G.; Yue, H.; Song, L. *J. Org. Chem.* **2014**, *79*, 9455. c) Milo, A.; Neel, A. J.; Toste, F. D.; Sigman, M. S. *Science* **2015**, *347*, 737. d) Zahrt, A. F.; Athavale, S. V.; Denmark, S. E. *Chem. Rev.* **2019**, DOI: 10.1021/acs.chemrev.9b00425.

[118] a) González-Díaz, H.; Arrasate, S.; Gomez-SanJuan, A.; Sotomayor, N.; Lete, E.; Besada-Porto, L.; Ruso, J. M. *Curr. Top. Med. Chem.* **2013**, *13*, 1713. b) Aranzamendi, E.; Arrasate, S.; Sotomayor, N.; González-Díaz, H.; Lete, E. *ChemOpen* **2016**, *5*, 540. c) Simón-Vidal, L.; García-Calvo, O.; Oteo, U.; Arrasate, S.; Lete, E.; Sotomayor, N.; González-Díaz, H. *J. Chem. Inf. Model.* **2018**, *58*, 1384.

reactions reported previously in the literature.[84,119] Once the dataset of enantioselective palladium-catalyzed Heck-Heck cascade reactions was collected, all data were organized in a rectangular array, in which the columns were the different variables for the reaction and the rows are different reactions.

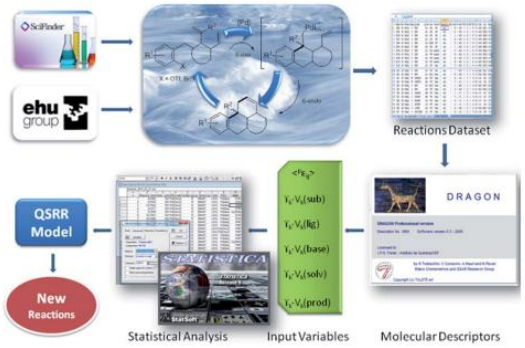
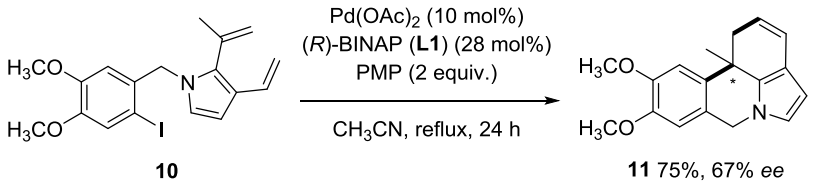


Figure 1.1. General workflow used to develop the computational model, obtained from reference 86b.

Next step consisted of the calculation by Dragon software of the molecular descriptors used to quantify the chemical structure of all the molecules involved in the reaction and, then, the variables related to the structural properties of each molecule involved in the reaction and the factors which quantify non-structural parameters were calculated. Finally, the data was processed to find the computational model using statistical analysis software.

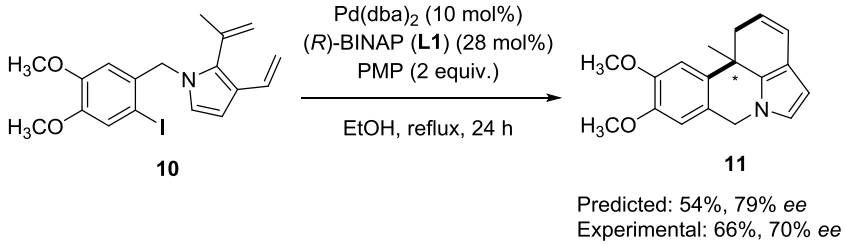
Once the theoretical model was designed, which included the expected value of reaction efficiency as starting point and added successive corrections, we proceeded to illustrate the pratical use of the model, choosing for that purpose the Heck-Heck reaction over 2,3-dialkenyl *N*-(*o*-iodobenzyl)pyrrole **10** previously studied by our research group (Scheme 1.62).

[119] a) Lau, S. Y. W.; Keay, B. A. *Synlett* **1999**, 605. b) Lau, S. Y. W.; Andersen, N. G.; Keay, B. A. *Org. Lett.* **2001**, *3*, 605. c) Gorobets, E.; Sun, G.-R.; Wheatley, B. M. M.; Parvez, M.; Keay, B. A. *Tetrahedron Lett.* **2004**, *45*, 3597. d) Rankic, D.; Lucciola, D.; Keay, B. A. *Tetrahedron Lett.* **2010**, *51*, 5724. e) Lucciola, D.; Keay, B. A. *Synlett* **2011**, 1618.



Scheme 1.62.

We first synthesized the precursor for the polyene reaction, that is, the 2,3-dialkenyl *N*-(*o*-iodobenzyl)pyrrole **10** following the procedure described by our group.[86a] Then, we tested the reaction conditions that predicted best value of enantioselectivity for the Heck-Heck cascade reaction, which implied the change of the catalyst from $Pd(OAc)_2$ to $Pd(dba)_2$ and the use of ethanol as solvent instead of acetonitrile. This way, tetracyclic compound **11** was obtained in 66% yield and 70% *ee* (Scheme 1.63), values that were in concordance with the prediction made by the computational model for the polyene cyclization (yield of 54% and 79% *ee*) taking into account the complexity of the problem and the error of the experimental method.



Scheme 1.63.

At this point, we considered that, although the obtained *ee* values were interesting, they could be improved by either tunning the experimental conditions (palladium source, solvent, etc.) or by changing the chiral ligand in the Heck-Heck cascade reaction. Therefore, we decided to study the effect of the concentration of the catalyst, ligand and base on the reactivity and enantioselectivity of the polyene cyclization reaction with the aim

of obtaining better values of *ee*. Thus, we took advantage of the developed computational model to create a computational simulation that took into account the effect of concentration of the catalyst, ligand and base on the reaction outcome. For that purpose, different theoretical entries were substituted in the model and the resulting values of enantiomeric excesses were plotted in a ternary phase diagram (Figure 1.2),[86b] which permitted to visualize the results more clearly. In fact, it allows to determine rapidly the reaction conditions that would lead to higher (green) or lower (red) enantiomeric excess only with a visual inspection of the diagram. In addition, the ternary diagram showed that the enantioselectivity phase encircles certain lower-upper limits, which are the following: 2.5–7.5 mol% of $Pd(dba)_2$ as catalyst, 2.5–7.5 equiv. of PMP as base and 7.5–20 mol% (*R*)-BINAP as ligand.

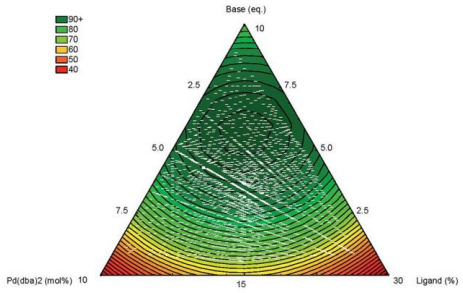
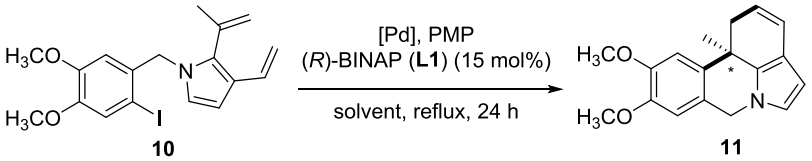


Figure 1.2. Ternary diagram of phases for the enantioselectivity of the Heck–Heck cascade reaction, obtained from reference 86b.

At this point, according to the objectives of this PhD work, our next goal was to test the ability of the developed model and, consequently, of the ternary phase diagram to predict the effect of the concentration of the catalyst, ligand and base over the enantioselectivity of the palladium-catalyzed asymmetric polyene cyclization reaction previously studies in our group.

Thus, we started our study using the catalyst, ligand and base loadings stated at the center-top-area of the tertiary diagram of phases, which predicted the best results in terms of enantioselectivity (coloured green in the diagram). In this way, when the reaction was performed using 5 mol% of $Pd(dba)_2$ as catalyst, 15 mol% of (*R*)-BINAP as chiral ligand and 5 equiv. of PMP as base in EtOH at reflux, no improvement in the cascade reaction outcome was observed and **11** was obtained in very low yield (13%) and moderate *ee* (62%) (Table 1.3, Entry 1). Then, we moved to one of the corners of the tertiary diagram of phases and we carried out the reaction employing less catalyst loading (2.5 mol%) and more equivalents of base (7.5 equiv.), obtaining better yield and enantioselectivity in contrast to previous conditions (Entry 3). When the reaction was carried out using 7.5 mol% of $Pd(dba)_2$ and 2.5 equiv. of PMP, mantaining the ligand loading of 15 mol%, the cyclized product **11** was obtained in better yield, but similar *ee* (Entry 3).



Scheme 1.64.

Table 1.3. Effect of the concentration of the catalyst and base on enantioselectivity of the Heck-Heck cascade reaction.

Entry	[Pd] (mol%)	PMP (equiv.)	Solvent	Yield (%)[a]	*ee* (%)[a]
1	$Pd(dba)_2$ (5)	5	EtOH	13	62
2	$Pd(dba)_2$ (2.5)	7.5	EtOH	22	68
3	$Pd(dba)_2$ (7.5)	2.5	EtOH	48	69
4	$Pd(OAc)_2$ (2.5)	7.5	CH_3CN	71	64
5	$Pd(OAc)_2$ (7.5)	2.5	CH_3CN	88	64

[a] Isolated yield. [b] % *ee* determined by using Chiral Stationary Phase HPLC using a Chiralcel OZ3 column and hexano/*i*PrOH 1% as eluent. tr (major): 21.4 min. tr (minor): 23.4 min.

Using $Pd(OAc)_2$ and acetonitrile, the tetracyclic compound **11** could be obtained in a yield up to 88%, but slight decrease in enantioselectivity was observed (Table 1.3, Entries 4-5).

In conclusion, although all the reaction conditions tested did not improve the enantiomeric excess with respect to those previously achieved with experimentally optimized reaction conditions (70% *ee*), it is remarkable that comparable results in terms of enantioselectivity could be obtained reducing the amount of palladium precatalyst to 2.5 mol%, increasing the yield up to 88% from 66%.

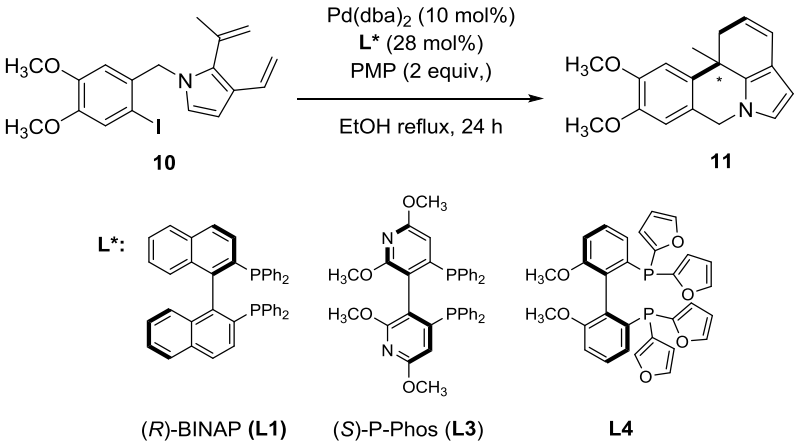
On the other hand, the designed chemoinformatic model included a study of the effect of different ligands structures and the nature of the substrates (halides *vs.* triflates) over the enantioselectivity in Heck-Heck cascade reaction of different 2,3-dialkenylpyrroles using $Pd(dba)_2$ in ethanol.

According to the model, halides would afford better *ee* values than the corresponding triflates, so, considering this prediction together with the difficulties associated to the synthesis of the triflates, we decided not to study the Heck-Heck reaction over these substrates.

On the contrary, we decided to focus on the effect of the ligand structure over the *ee* (%). The screening of the computational model revealed that the higher enantioinduction would be afforded employing chiral ligands as (*R*)-BINAP (**L1**), as well as commercially available bipyridine (*S*)-P-Phos **L3**. Therefore, we carried out the Heck-Heck cascade reaction under experimentally optimized reaction conditions [$Pd(dba)_2$ (10 mol%) and PMP (2 equiv.) at refluxing EtOH] using **L3** (28 mol%) as ligand, and, to our delight, slight improvement in enantioselectivity (-73% *ee*) was observed (Table 1.4, Entry 2). It is noteworthy that, in this case, we isolated the *S*-enantiomer of **11**, the opposite to the one achieved using (*R*)-BINAP (**L1**) as chiral ligand.

Then, we selected the commercially available ligand **L4**, which, although is not collected in the chemoinformatic model, it is recognized as privileged ligand for enantioselective Heck-

type reactions. Unfortunately, the *S*-enantiomer of tetracyclic compound **11** was obtained in lower yield and enantioselectivity (Table 1.4, Entry 3).



Scheme 1.65.

Table 1.4. Study of the effect of different chiral ligands over the enantioselectivity

Entry	L* (mol%)	Yield (%)[a]	*ee* (%)[b]
1	(*R*)-BINAP (**L1**)	66	70 (*R*)
2	(*S*)-P-Phos (**L3**)	52	-73 (*S*)
3	**L4**	20	-57 (*S*)

[a] Isolated yield. [b] % *ee* determined by using Chiral Stationary Phase HPLC using a Chiralcel OZ3 column and hexano/*i*PrOH 1% as eluent. tr (major): 21.4 min. tr (minor): 23.4 min.

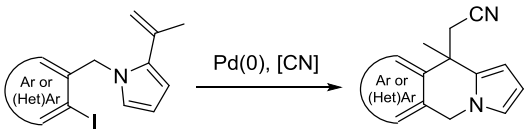
With this brief analysis of chiral ligands, we demonstrated that the prediction of the designed model was correct, as **L3** was found to be an adequate ligand for enhancing the enantioselectivity of the polyene cyclization reaction. However, only a slight increase in enantiomeric excess was observed (-73% *ee vs.* 70% *ee*) under the experimental conditions employed. As a consequence, different essays should be performed to improve this

outcome, which could include the use of (*S*)-P-Phos ligand (**L3**) under different reaction conditions or the use of other promising non commercially available chiral ligands (DIFLUORPHOS, for instance).

In conclusion, although it has been shown that the designed computational model is useful to choose the adequate experimental conditions and optimal chiral ligands, further work should be carried out to improve the enantiomeric excess of the palladium-catalyzed enantioselective polyene cyclization reaction.

3.3. Intramolecular carbopalladation/cyanation cascade

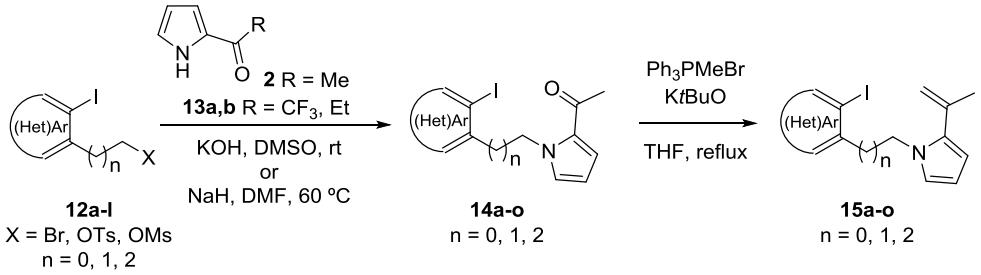
A termination approach for a palladium catalyzed cascade reaction is involving the alkylpalladium intermediate formed after carbopalladation in a nucleophilic capture event. Thus, as indicated in Objectives (Scheme 1.50), our next task was to study the possibility of trapping the σ-alkylpalladium intermediate formed after cyclization of 2-alkenyl substituted *N*-(*o*-iodoarylalkyl)pyrroles with a nucleophile. For that purpose, we chose a cyanide ion as nucleophile that would allow the sequential formation of C-C and C-CN bonds and the generation of a quaternary stereocenter.



Scheme 1.66.

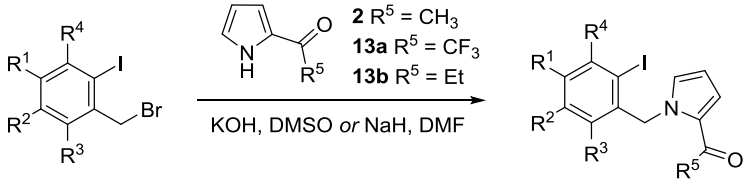
*3.3.1. Synthesis of 2-alkenyl N-(o-iodoarylalkyl)pyrroles **15a-o***

In this section, the preparation of the precursors for the carbopalladation/cyanation sequence is presented. Thus, the synthesis of required *N-(o*-iodobenzyl)pyrroles **15a-k**, *o*-iodothiophenylpyrrole **15l**, *o*-iodopyridine **15m** and *N-(o*-iodoarylalkyl)pyrroles **15n,o** was carried out following the general procedure described in Scheme 1.67.



Scheme 1.67.

As shown in Scheme 1.68, the synthesis of *N-(o*-iodophenyl)pyrroles **15a-k** started by alkylation of commercially available 2-acylpyrroles **2** and **13a,b** with the bromides **12a-k** previously prepared.[120] In this way, 2-acylpyrroles **14a-k** were obtained in good to excellent yields (66-99%).



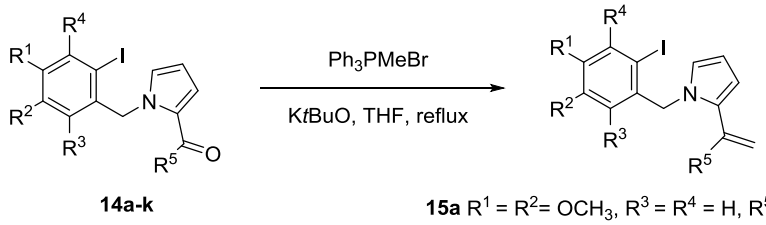
12a $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$
12d $R^1 = R^2 = R^3 = R^4 = H$
12e $R^1 - R^2 = OCH_2O$, $R^3 = R^4 = H$
12f $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$
12g $R^1 = R^3 = H$, $R^2 = R^4 = OCH_3$
12h $R^1 = R^3 = R^4 = H$, $R^2 = F$
12i $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$
12j $R^1 = R^3 = R^4 = H$, $R^2 = OBn$
12k $R^1 = OCH_3$, $R^2 = OBn$, $R^3 = R^4 = H$

14a $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$, $R^5 = CH_3$ (81%)
14b $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$, $R^5 = CF_3$ (86%)
14c $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$, $R^5 = Et$ (76%)
14d $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = CH_3$, (83%)
14e $R^1 - R^2 = OCH_2O$, $R^3 = R^4 = H$, $R^5 = CH_3$ (84%)
14f $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$, $R^5 = CH_3$ (69%)
14g $R^1 = R^3 = H$, $R^2 = R^4 = OCH_3$, $R^5 = CH_3$ (75%)
14h $R^1 = R^3 = R^4 = H$, $R^2 = F$, $R^5 = CH_3$ (99%)
14i $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$, $R^5 = CH_3$ (93%)
14j $R^1 = R^3 = R^4 = H$, $R^2 = OBn$, $R^5 = CH_3$ (83%)
14k $R^1 = OCH_3$, $R^2 = OBn$, $R^3 = R^4 = H$, $R^5 = CH_3$ (66%)

Scheme 1.68.

[120] Bromides **12a-k** were prepared from commercially available benzylic alcohols by selective iodination with $I_2/AgCOOCF_3$ followed by treatment with PBr_3. See: Ref. 109a and Ref. 110a.

Finally, 2-alkenyl *N*-(*o*-iodobenzyl)pyrroles **15a-k** were obtained by introduction of the olefin moiety through Wittig reaction of **14a-k** with ethylenetriphenylphosphorane bromide (previously obtained by deprotonation of methyltriphenylphosphonium bromide with K*t*BuO at rt for 30 min), obtaining the desired products **15a-k** in good to excellent yields (55-93%) (Scheme 1.69).

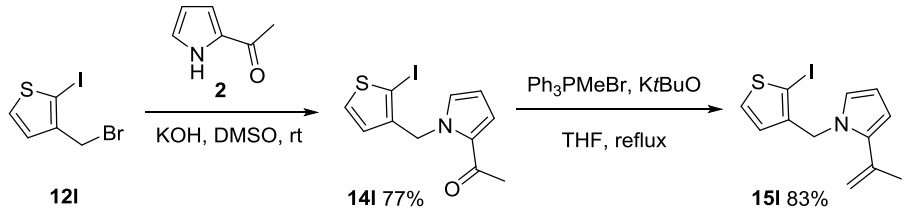


14a-k

15a $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$, $R^5 = CH_3$ (86%)
15b $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$, $R^5 = CF_3$ (60%)
15c $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$, $R^5 = Et$ (72%)
15d $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = CH_3$ (93%)
15e R^1 - $R^2 = OCH_2O$, $R^3 = R^4 = H$, $R^5 = CH_3$ (65%)
15f $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$, $R^5 = CH_3$ (85%)
15g $R^1 = R^3 = H$, $R^2 = R^4 = OCH_3$, $R^5 = CH_3$ (66%)
15h $R^1 = R^3 = R^4 = H$, $R^2 = F$, $R^5 = CH_3$ (93%)
15i $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$, $R^5 = CH_3$ (81%)
15j $R^1 = R^3 = R^4 = H$, $R^2 = OBn$, $R^5 = CH_3$ (77%)
15k $R^1 = OCH_3$, $R^2 = OBn$, $R^3 = R^4 = H$, $R^5 = CH_3$ (55%)

Scheme 1.69.

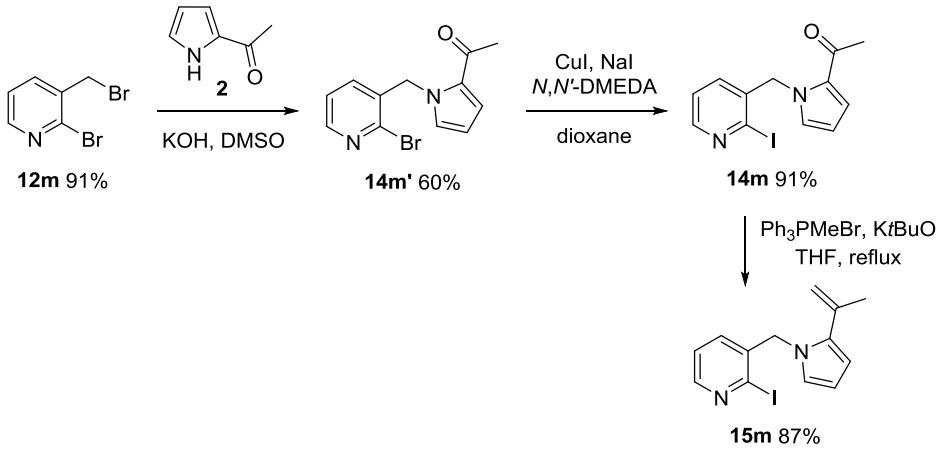
Analogously, *o*-iodothiophenylpyrrole **15l** was efficiently prepared following an identical synthetic pathway (Scheme 1.70).



12l **14l** 77% **15l** 83%

Scheme 1.70.

On the other hand, the synthetic route designed for *o*-iodopyridine **15m**, illustrated in Scheme 1.71, is slightly different, as it includes an additional reaction step. The synthesis started with the alkylation reaction of previously synthesized 2-bromo-3-bromomethylpyridine (**12m**)[121] with commercially available 2-acetylpyrrole (**2**) under standard reaction conditions, which enabled the preparation of **14m'** in moderate yield. Then, the desired iodinated derivative **14m** was prepared from the corresponding bromo derivative **14m'** by treatment with NaI/CuI in dioxane.[122] Finally, olefination step was performed under Wittig reaction conditions (methyltriphenylphosphonium bromide and *t*BuOK in THF at reflux), obtaining *o*-iodopyridine **15m** in good yield (87%).



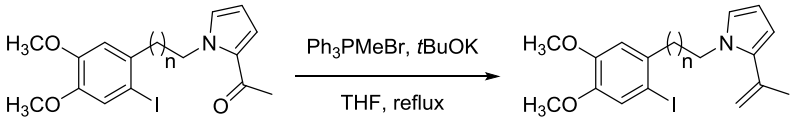
Scheme 1.71.

Finally, *N-(o*-iodoarylalkyl)pyrroles **15n,o** homologous to *N-(o*-iodobenzyl)pyrrole **15a** were synthesized. In previous work on intramolecular Mizoroki-Heck reaction (see Section 3.1.1, Scheme 1.53), we have synthesized ketones **3a,b** (Scheme 1.52), which are also suitable for the synthesis of the precursors for the intramolecular domino Heck/cyanation reaction. In fact, *N-(o*-iodoarylalkyl)pyrroles **15n,o** could be easily obtained by introducing

[121] Bromide **12m** was obtained by bromination of previously synthesized 2-bromo-3-hydroxymethylpyridine from commercially available 2-bromopyridine-3-carboxaldehyde. See: Ref. 110a and Ref. 110b.

[122] Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844.

the olefin function through a Wittig reaction in the last step of the synthetic route. Thus, the ketones **3a,b** were obtained in moderate to good yields (Scheme 1.72).



3a n = 1
3b n = 2

15n n = 1, 78%
15o n = 2, 46%

Scheme 1.72.

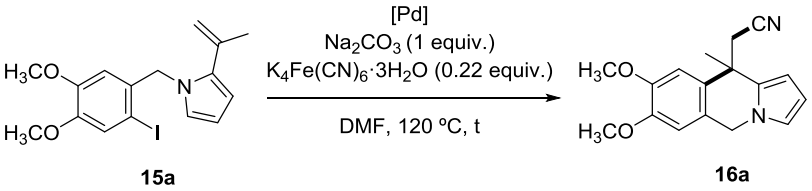
*3.3.2. Intramolecular carbopalladation/cyanation cascade on **15a-o***

Once the precursors had been obtained, we decided to investigate the carbopalladation/cyanation cascade reaction over model substrate **15a** in order to access pyrroloisoquinoline structural core. For that purpose, we chose $K_4Fe(CN)_6 \cdot 3H_2O$ as cyanation agent, as it has been demonstrated that is non-toxic compared with traditional cyanation reagents [KCN, NaCN, $Zn(CN)_2$, TMSCN] and it can easily be handled without special precautions.[123] In addition, it allows the use of substoichiometric amounts of reagent, as all cyanide ions bound to the iron (II) center can be released in the cyanation reaction. Finally, we also thought that phosphane free catalytic systems could be appropiate for economical and environmental reasons, so we focused on the use of catalytic systems in the absence of phosphane ligands.

Thus, we started treating **15a** with $K_4Fe(CN)_6 \cdot 3H_2O$ as cyanide source, $Pd(OAc)_2$ as catalyst and Na_2CO_3 as base in DMF at 120 ºC in preliminary studies of the domino Heck/cyanation reaction.[59d] However, under these conditions, only small amounts of pyrroloisoquinoline **16a** were obtained from a complex mixture of products after 3 h, even when catalyst loading was increased to 10 mol% (Table 1.5, Entries 1-3). Longer reaction times (48 h) did not improve significantly the results (Entry 4). The change in the base to

[123] Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1338.

Et_3N (Entry 5) and the increase of the cyanide agent (Entry 6) did not afford better results. The use of other palladium sources was completely unsuccessful and starting material **1a** was recovered (Entries 8-9). Finally, the use of a phosphane ligand, as PPh_3, gave similar results (Entry 10).



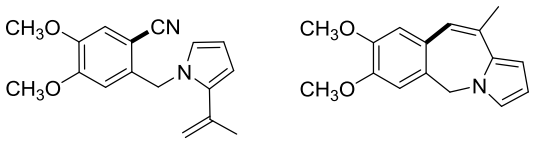
Scheme 1.73.

Table 1.5. Preliminary studies of the carbopalladation/cyanation cascade reaction.

Entry	[Pd] (mol %)	Time (h)	Yield 16a (%)[a]
1	$Pd(OAc)_2$ (1.5)	3	12
2	$Pd(OAc)_2$ (5)	3	11
3	$Pd(OAc)_2$ (10)	3	8
4	$Pd(OAc)_2$ (10)	48	11
5[b]	$Pd(OAc)_2$ (10)	48	14
6[c]	$Pd(OAc)_2$ (10)	48	14
7	$Pd(PPh_3)_4$	48	16
8	$Pd(dba)_2$	48	n.r.
9	$Pd_2(dba)_3 \cdot CHCl_3$	48	n.r.
10[d]	$Pd(OAc)_2$	48	11

[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] Et_3N (6 equiv.) was used as base. [c] 0.44 equiv. of $K_4Fe(CN)_6 \cdot 3H_2O$. [d] PPh_3 (28 mol%) was used as ligand.

In view of these poor results, we devoted special attention to ^{1}H NMR spectra of the crude reaction mixtures in order to better understand the reaction and determine possible side-products. Thus, after exhaustive analysis of NMR spectra, we were able to identify two by-product in the reaction mixtures: direct aryl halide cyanation product **17a** and small amounts of 7-*endo* palladation/β-elimination product **18** (Figure 1.3).



17a **18**

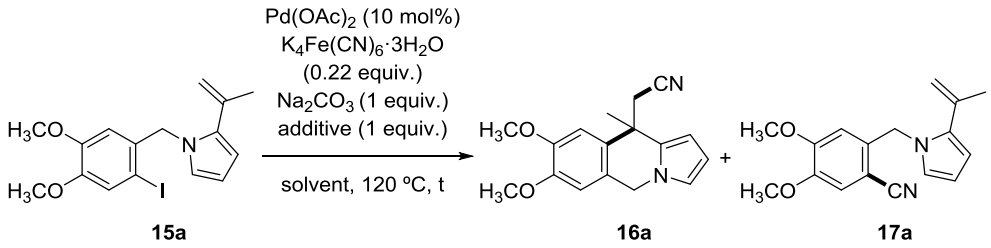
Figure 1.3.

Therefore, we next focused our attention on optimization of the reaction conditions to control the chemoselectivity of the process favouring the 6-*exo* carbopalladation over the early coupling with cyanide ion.

It is well-known that the presence of a phase transfer agent may shorten the reaction time and minimize side reactions in Heck-type processes. Therefore, we reasoned that the use of *n*Bu_4NCl may increase the rate of the carbopalladation/cyanation sequence.[124] When the reaction was carried out adding *n*Bu_4NCl to previous reaction conditions, we observed that the yield slightly improved (19%), although it was still low and competitive direct cyanation coupling was not supressed (Table 1.6, Entry 2). Then, we decided to perform the reaction changing the solvent to a mixture DMF/H_2O (95:5) in absence of additive, as it is reported that the regioselectivity can be controlled in the presence of water.[59d] In this case, the use of DMF/H_2O was benefitial to the carbopalladation/cyanation cascade rate and it was completed in just 1 h, but, again, the pyrroloisoquinoline **16a** was isolated in low yield (16%). Finally, the treatment of *N*-(*o*-iodobenzyl)pyrrole **15a** with $K_4Fe(CN)_6{\cdot}3H_2O$ as cyanide source, $Pd(OAc)_2$ as catalyst and Na_2CO_3 as base in the presence of *n*Bu_4NCl as

[124] For the effect of the addition of tetrabutylamonium halides in the reaction rate of the Heck reaction, see, for instance: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009, and references cited therein.

additive in a mixture DMF/H_2O (95:5) at 120 ºC, provided the cyclization product **16a** in moderate yield (43%) in just 1 h, together with byproduct **17a** (36%), derived from direct cyanation coupling (Table 1.6, Entry 4).



Scheme 1.74.

Table 1.6. Screening of solvents and effect of additives.

Entry	Additive	Solvent	Time (h)	Conv. (%)[a]	Yield 16a (%)[b]	Yield 17a (%)[b]
1[c]	-	DMF	3	62	8	24
2	*n*Bu_4NCl	DMF	48	84	19	19
3	-	DMF/H_2O (95:5)	1	>99	16	12
4	*n*Bu_4NCl	DMF/H_2O (95:5)	1	>99	43	36
5	*n*Bu_4NCl	DMF/H_2O (9:1)	1	>99	50	35
6	*n*Bu_4NCl	DMF/H_2O (8:2)	1	>99	54	32
7	*n*Bu_4NCl	DMF/H_2O (7:3)	24	>99	31	46
8	*n*Bu_4NCl	DMF/H_2O (5:5)	48	n.r.	-	-
9	18-*crown*-6	DMF/H_2O (8:2)	48	n.r.	-	-
10	TlOAc	DMF/H_2O (8:2)	48	88	16	10
11	Ag_3PO_4	DMF/H_2O (8:2)	48	n.r.	-	-

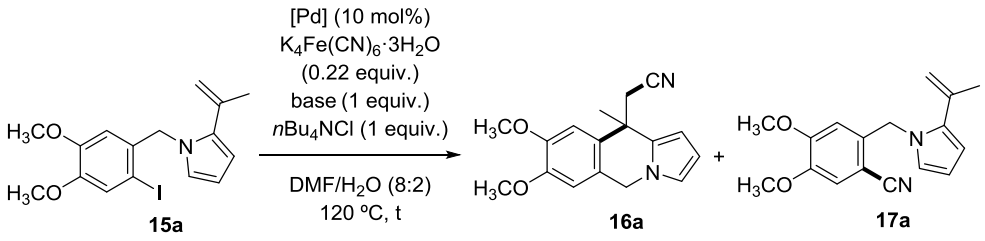
[a] Determined considering the amount of substrate **15a** recovered. [b] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [c] Included in Table 1.5 (Entry 3).

Encouraged by this promising result, we tested different ratios of the mixture DMF/H_2O as solvent. Increasing water proportion to 20% yielded the desired 6-*exo* Heck product **16a** in an improved yield (54%). However, it was not possible to avoid the formation of direct cyanation coupling product **17a**, which was isolated in 32% yield. An attempt to make the protocol greener by increasing the amount of water to 30% resulted in a poorer yield of **16a** (31%) and direct cyanation coupling became the major pathway (Table 1.6, Entry 7). Unfortunately, when a mixture DMF/H_2O (1:1) was used as solvent, the carbopalladation/cyanation sequence did not proceed and unreacted starting material **15a** was recovered quantitatively.

Then, we evaluated the effect of different additives in the domino Heck/cyanation reaction. For that purpose, we selected first the transfer-phase agent 18-*crown*-6, as it has been demonstrated that macrocylic polyethers or *crown* ethers possess the ability to solubilize a variety of inorganic salts in aprotic solvents.[125] This way, in the case of $K_4Fe(CN)_6 \cdot 3H_2O$, the potassium ion would coordinate to the crown ether forming a complex and, consequently, "naked" cyanide would be obtained to act as nucleophile. However, Heck/cyanation reaction did not proceed in the presence of 18-*crown*-6 and only substrate **15a** was recovered (Table 1.6, Entry 9). Additionally, we evaluate the use of silver[16,126] and thallium[17,127] salts, such as TlOAc or Ag_3PO_4, as they have been found to be efficient halide scavengers that facilitate the formation of cationic palladium intermediate enhancing the reaction performance. However, decomposition of the starting material **15a** occurred when TlOAc was used as additive and, consequently, pyrroloisoquinoline **16a** could be isolated only in a 16% yield (Table 1.6, Entry 10). Moreover, the use of Ag_3PO_4 as halide scavenger was completely unsuccessful, recovering unreacted starting material **15a**. Thus, it has been

[125] Cook, F. L.; Bowers, C. W.; Liotta, C. L. *J. Org. Chem.* **1974**, *39*, 3416.
[126] For examples of silver salts as halide scavengers, see: a) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986**, *51*, 5286. b) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. c) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919.
[127] For representative examples of thallium salts as halide scavengers, see: a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Tetrahedron Lett.* **1991**, *32*, 1753. b) Carfagna, C.; Musco, A.; Sallese, G.; Santi, R.; Fiorani, T. *J. Org. Chem.* **1991**, *56*, 261.

demonstrated that *n*Bu_4NCl resulted essential to shorten the reaction time and to enhance the formation of cyclized product **16a**.



Scheme 1.75.

Table 1.7. Effect of palladium catalyst and base in the Heck/cyanation reaction of **15a**.

Entry	[Pd]	Base	Time (h)	Conv. (%)[a]	Yield 16a (%)[b]	Yield 17a (%)[b]
1[c]	$Pd(OAc)_2$	Na_2CO_3	1	>99	54	32
2	$Pd(TFA)_2$	Na_2CO_3	4	>99	46	30
3	$PdCl_2$	Na_2CO_3	48	84	26	29
4	$Pd(PPh_3)_4$	Na_2CO_3	48	91	33	22
5	$Pd(PPh_3)_2Cl_2$	Na_2CO_3	48	70	30	28
6	$Pd(CH_3CN)_2Cl_2$	Na_2CO_3	4	>99	30	35
7	$Pd(dba)_2$	Na_2CO_3	48	88	37	48
8	$Pd_2(dba)_3·CHCl_3$	Na_2CO_3	48	86	53	27
9[d]	$Pd(OAc)_2$	K_2CO_3	6	>99	13	-
10	$Pd(OAc)_2$	Cs_2CO_3	48	84	33	36
11	$Pd(OAc)_2$	$NaHCO_3$	48	91	32	25
12	$Pd(OAc)_2$	Et_3N	48	70	31	50
13	$Pd(OAc)_2$	PMP	24	>99	6	23

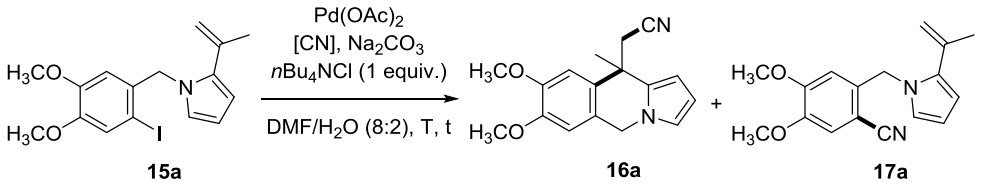
[a] Determined considering the amount of substrate **15a** recovered. [b] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [c] Included in Table 1.6 (Entry 6). [d] 7-*endo* product **18** (26%) was isolated as by-product.

Next, several attempts were tried to improved the efficiency of the cyclization reaction by varying the palladium sources (Table 1.7). Unfortunately, lower yields of the corresponding pyrroloisoquinoline **16a** were obtained in most cases. Only similar result (53%) was achieved when $Pd_2(dba)_3 \cdot CHCl_3$ was used as catalyst, but with lower conversion (86%) (Entry 8). Therefore, among the tested palladium catalysts, previously used $Pd(OAc)_2$ was proved to be the most suitable and, consequently, it was selected as best catalyst for further optimization of the reaction conditions.

Essays with different bases are also collected in Table 1.7 (Entries 9-13). Screening of different carbonates as base, including K_2CO_3, Cs_2CO_3 and $NaHCO_3$, always failed to give better results. Besides, no improvements in yield or chemoselectivity were achieved when organic bases were used. In fact, when Et_3N was employed as base direct cyanation coupling product **17a** was obtained as major product (Entry 12) and the yield of the target pyrroloisoquinoline **16a** decreased dramatically by using PMP as base (Entry 13).

We continued the optimization of the reaction conditions by using different cyanide agents (Table 1.8, Entries 2 and 3) . However, the formation of the Heck/cyanation product **16a** was not detected when traditional cyanation reagents, such as $Zn(CN)_2$ or TMSCN, were employed and starting material **15a** remained intact in the reaction.

Furthermore, different temperatures were tried, but neither the increase nor the decrease led to improved results (Table 1.8, Entries 4 and 5). However, we realized that, when the reaction was carried out at 80 ºC, we obtained similar yield (49%) with only partial conversion of **15a** (74%), so it is likely that the increase in temperature led to decomposition of the substrate **15a**. However, $K_4Fe(CN)_6 \cdot 3H_2O$ as cyanation agent and n-Bu_4NCl as additive in a mixture DMF/H_2O (8:2) at 120 ºC were selected as the best conditions for futher optimization (Entry 6).



Scheme 1.76.

Table 1.8. Screening of cyanation reagent and temperature. Effect of different reagent loadings in the carbopalladation/cyanation reaction of **15a**.

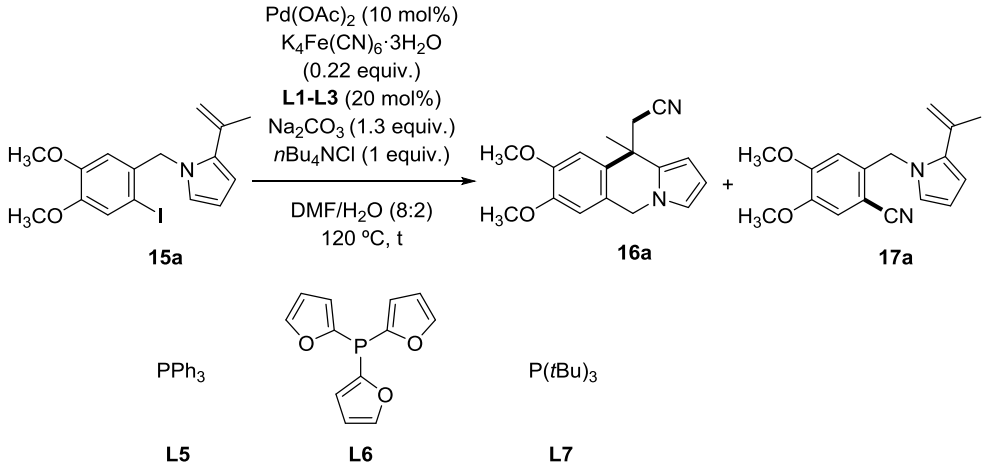
Ent.	$Pd(OAc)_2$ (mol%)	[CN] (equiv.)	Na_2CO_3 (equiv.)	T (ºC)	Time (h)	Conv (%)[a]	Yield 16a (%)[b]	Yield 17a (%)[b]
1[c]	10	$K_4Fe(CN)_6{\cdot}3H_2O$ (0.22)	1	120	1	>99	54	32
2	10	$Zn(CN)_2$ (0.55)	1	120	48	n.r.	-	-
3	10	TMSCN (1.3)	1	120	48	n.r.	-	-
4	10	$K_4Fe(CN)_6{\cdot}3H_2O$ (0.22)	1	80	48	74	49	15
5	10	$K_4Fe(CN)_6{\cdot}3H_2O$ (0.22)	1	refl.	1	>99	50	18
6	10	$K_4Fe(CN)_6{\cdot}3H_2O$ (0.44)	1	120	24	>99	51	37
7	5	$K_4Fe(CN)_6{\cdot}3H_2O$ (0.22)	1	120	5	>99	34	51
8	10	$K_4Fe(CN)_6{\cdot}3H_2O$ (0.22)	1.3	120	1	>99	65	26

[a] Determined considering the amount of substrate **15a** recovered. [b] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [c] Included in Table 1.6 (Entry 6).

Then, some final attempts, which included different cyanide agent, catalyst and base loadings, were tried. In this way, it was found that the amount of cyanating agent had an influence on the conversion rate, as the use of 0.44 equivalents of cyanide source (Table 1.8, Entry 6) instead 0.22 equivalents required longer reaction times (24 h *vs.* 1 h) to give

similar results. The decreased catalytic activity in the presence of excess of cyanating agent is likely due to higher concentration of free cyanide ions in the reaction mixture, which leads to partial catalyst deactivation owing to the formation of catalytically inactive palladium(II)-cyano complexes.[128] On the other hand, decreasing the catalyst loading to 5 mol% provided direct cyanation coupling compound **17a** as major product (51%) (Table 1.8, Entry 7) and caused a marked decrease in overall yield of the cyclized pyrroloisoquinoline **16a** (34%). Finally, to our delight, the yield of **16a** was significantly improved to 65% by increasing the quantity of Na_2CO_3 (Table 1.8, Entry 8).

At this point, we have shown that is it possible to carry out the 6-*exo*-*trig* carbopalladation/cyanation cascade using a phosphane-free catalytic system. However, the overall yield obtained is moderate, as the competitive direct cyanation coupling reaction and decomposition of the substrate could not be completely suppressed under optimized reaction conditions. Thus, a series of phosphane ligands were screened to improve the efficiency of the cascade cyclization of **15a** (Scheme 1.77, Table 1.9).



Scheme 1.77.

[128] Gerber, R.; Oberholzer, M.; Frech, C. M. *Chem. Eur. J.* **2012**, *18*, 2978.

Table 1.9. Optimization of reaction of **15a** in the presence of phosphanes

Entry	[Pd]	Ligand	Time (h)	Yield 16a (%)[a]	Yield 17a (%)[a]
1[b]	$Pd(OAc)_2$	-	1	65	26
2	$Pd(OAc)_2$	**L5**	6	44	40
3	$Pd(OAc)_2$	**L6**	1	52	35
4	$Pd(OAc)_2$	**L7**	24	24	56
5	$Pd(TFA)_2$	**L6**	24	33	31
6	$Pd(dba)_2$	**L6**	6	42	33
7	$Pd_2(dba)_3 \cdot CHCl_3$	**L6**	1	36	39

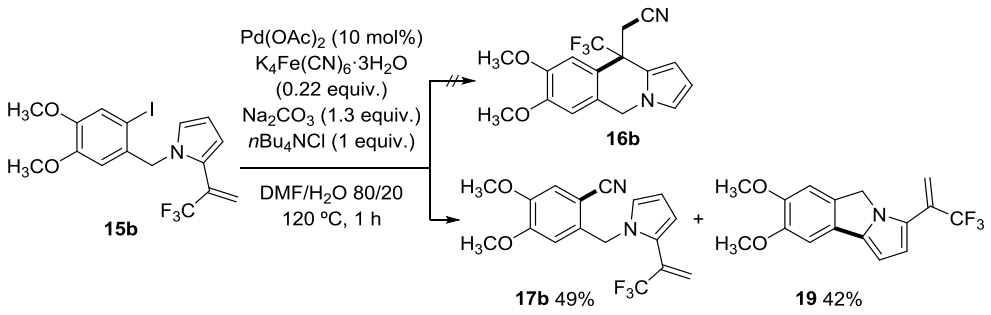
[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] Included in Table 1.8 (Entry 8).

Unfortunately, we found that the reaction resulted less efficient under same reaction conditions in the presence of various phosphanes (20 mol%), such as triphenylphosphane (**L5**) (Table 1.9, Entry 2), tri(furan-2-yl)phosphane (**L6**) (Table 1.9, Entry 3) or tri-*tert*-butylphosphane (**L7**) (Table 1.9, Entry 4). In fact, when **L5** and **L6** were used as ligands, lower yields of **16a** were achieved (44 and 52%, respectively) (Entries 2 and 3). The reaction using P(*t*Bu)$_3$ (**L7**) was even less efficient, and required 24 h to obtain **16a** in low yield (24%) with an increased yield of direct coupling by-product **17a** (56%) (Entry 4). Besides, the results could not be improved even changing the palladium source when **L6** was used as ligand (Entries 5-7).

In view of these results, we can conclude that the ligand is not necessary for the efficient formation of pyrroloisoquinoline **16a** and we decided not to carry out further optimization of the conditions for the carbopalladation/cyanation cascade on substrate **15a**. Thus, after extensive experimentation, the optimal conditions were established as $Pd(OAc)_2$ (10 mol%), $K_4Fe(CN)_6 \cdot 3H_2O$ (0.22 equiv.), Na_2CO_3 (1.3 equiv.) and *n*Bu_4NCl (1 equiv.) in a mixture DMF/H_2O (8:2) at 120 ºC.

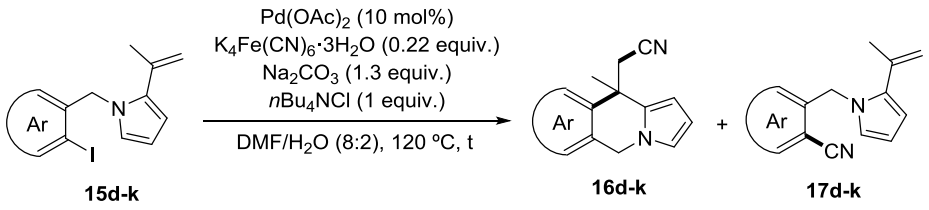
At this point, we decided to test the applicability of the studied domino Heck/cyanation reaction, scaling up the reaction of **15a** to 0.5 gram quantities (1.3 mmol). As a result, pyrroloisoquinoline **16a** was obtained in disminished yield (51% *vs.* 65%) and product of direct aryl halide cyanation **17a** was isolated in an increased yield (40% *vs.* 26%), compared with the results obtained when reaction was carried out in a 0.3 mmol scale.

Moreover, with the optimal conditions in hand, the generality of the carbopalladation/cyanation reaction was subsequently investigated. For that purpose, we studied the extension of the procedure to 2-alkenyl *N*-(*o*-iodobenzyl)pyrroles **15b-k**, with different substitution patterns in the alkene and on the aromatic ring. Thus, when an electron-withdrawing group, such as CF_3, was incorporated in the alkene (**15b**, $R^2 = CF_3$), the carbopalladation/cyanation sequence did not take place and pyrroloisoquinoline **16b** was not observed. Instead, direct cyanation coupling (**17b**) and intramolecular direct arylation (**19**) products were isolated in moderate yields (49% *vs.* 42%, respectively) (Scheme 1.78).



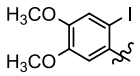
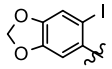
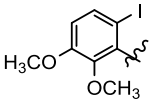
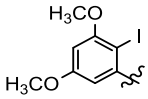
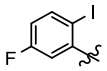
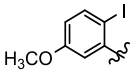
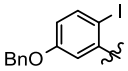
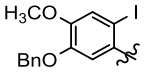
Scheme 1.78.

Then, we evaluated the effect of different substitution patterns on the aromatic ring (**15d-k**) in the construction of the corresponding pyrroloisoquinolines **16** (Table 1.10). Thus, it was proved that the procedure was compatible with a wide variety of mono- and dioxygenated substrates, obtaining the corresponding cyclized products in low to moderate yields (Table 1.10, Entries 3-4 and 7-9). In addition, the reaction could also be applied to the non-substituted benzene ring (Entry 2) or to a fluoro-substituted derivative (Entry 6).



Scheme 1.79.

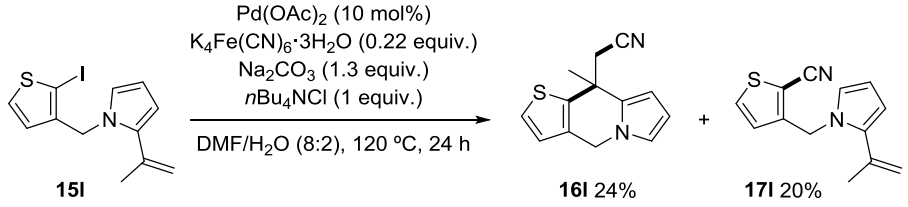
Table 1.10. Carbopalladation/cyanation reaction of substrates **15a-k**

Entry	Ar	Time (h)	Product	Yield 16 (%)[a]	Product	Yield 17 (%)[a]
1		1	**16a**	65	**17a**	26
2		4	**16d**	25	**17d**	41
3		1	**16e**	37	**17e**	38
4		2	**16f**	39	**17f**	29
5		48	**16g**	21[b]	**17g**	-[c]
6		48	**16h**	16	**17h**	18
7		6	**16i**	23[d]	**17i**	28
8		1	**16j**	23	**17j**	15
9		24	**16k**	16	**17k**	30

[a] Isolated yield. [b] Conversion: 63%. [c] 1**7g** was detected by ^{1}H NMR in reaction crude, but it could not be isolated. [d] Conversion: 94%.

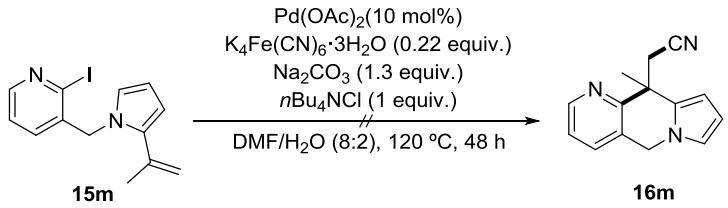
Then, we decided to explore the use of heteroaromatic halides as coupling partners in the carbopalladation/cyanation cascade reaction. For that purpose, we chose an electron-rich, such as thiophenylpyrrole **15l**, and a electron-deficient, like iodopyridine **15m**, heteroaryl halides as substrates in order to extend the utility of the process to the synthesis of thienoindolizine **16l** and pyrrolonaphthyridine **16m** systems, respectively.

Thus, treatment of **15l** with $Pd(OAc)_2$ with $K_4Fe(CN)_6{\cdot}3H_2O$ in the presence of Na_2CO_3 and nBu$_4$NCl in a mixture DMF/H_2O (8:2) at 120 ºC gave thienoindolizine **16l** in low yield (24%) after 24 h, together with direct cyanation coupling product **17l** (20%) (Scheme 1.80).



Scheme 1.80.

Unfortunately, iodopyridine **15m** did not undergo the desired transformation under previously optimized reaction conditions, providing only recovered starting material (Scheme 1.81).

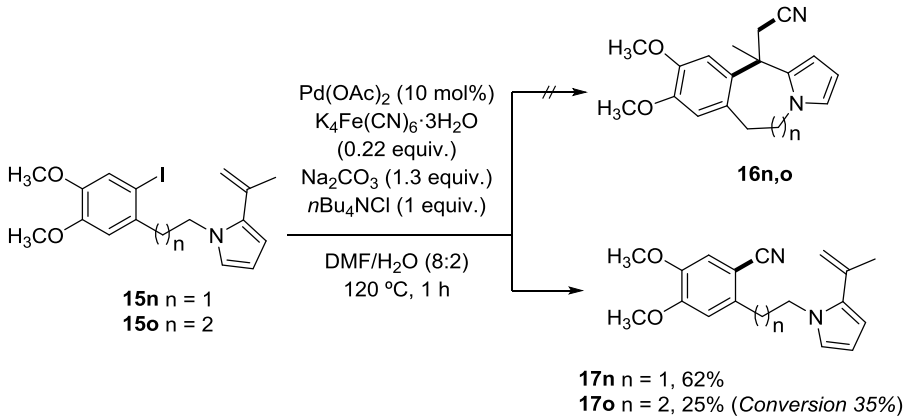


Scheme 1.81.

In view of the poor results obtained in the scope of the domino carbopalladation/cyanation sequence and having demonstrated that the use of non chiral phosphane ligands has not a beneficial influence in the construction of pyrroloisoquinoline **16a** (Table 1.9), no efforts were made to carry out the enantioselective version of the reaction.

Finally, to further highlight the applicability of Heck/cyanation cascade, we studied the possibility of extending this methodology to the construction of analogous seven- and eight-membered rings, whose synthesis is not so general and usually requires higher catalyst loadings and higher temperatures, as medium-sized rings are generally more difficult to synthesize than their lower counterparts.

For that purpose, we applied the reaction conditions which proved successful for the synthesis of pyrroloisoquinoline **16a** to *N*-phenethylpyrrole **15n** and *N*-phenylpropylpyrrole **15o** in order to access to pyrrolo[1,2-*a*]benzazepine and pyrrolo[1,2-*a*]benzazocine skeletons through 7-*exo* and 8-*exo* cyclizations, respectively. However, when substrate **15n** was subjected to carbopalladation/cyanation conditions, no cyclization took place and, consequently, no visible evidence for the desired pyrrolobenzepine **16n** was observed. Instead, direct cyanation product **17n** was isolated in good yield (62%). Similarly, treatment of **15o** under the same reaction conditions led to low conversions (35%) and only product of direct cyanation coupling **17o** was obtained in poor yield (25%). These latest results reveal the difficulty that implies the construction of medium-sized rings, which is even more emphasized when the process involves the generation of a quaternary center.



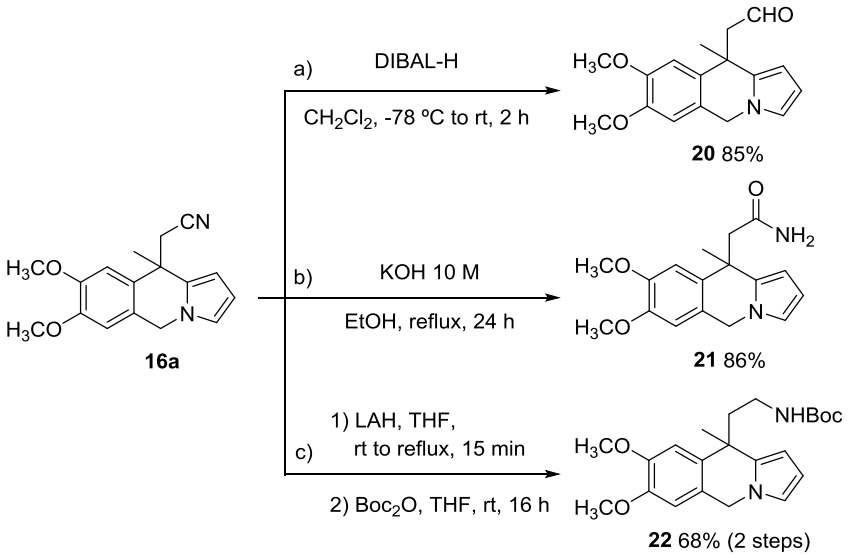
Scheme 1.82.

In conclusion, it has been shown that 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles **15** are suitable substrates for the generation of C-10 disubstituted pyrrolo[1,2-*b*]isoquinolines **16** with a quaternary center. In fact, they can undergo cyclization through a 6-*exo* carbopalladation process forming a σ-alkylpalladium intermediate that can be trapped with a cyanide source as nucleophile. The domino process can be carried out by using a phosphane-free precatalytic system and, besides, it has been demonstrated that the presence of a phosphane ligand has not a benefitial effect over the reaction outcome. In fact, 6-*exo* carbopalladation pathway is not favored when phosphane ligands are used. However, nBu$_4$NCl and water were found to be crucial to allow the 6-*exo* carbopalladation to occur at a competitive rate, although direct cyanation coupling process can not be suppressed. The Heck/cyanation sequence tolerates a wide variety of substitution patterns on the aromatic ring. Thus, different mono-, dioxygenated, non substituted or even fluoro-derivative substrates can be used, but overall yields of corresponding pyrroloisoquinolines **16** are low in most cases and direct cyanation coupling pathway is always competitive. Finally, initial basis for application of carbopalladation/cyanation cascade to electron-rich heteroaromatic halides has been established, but the extension to electron-deficient heteroaromatic halides and to the construction of seven- and eight-membered rings has not been successful and needs further experimentation.

*3.3.3. Derivatization of pyrroloisoquinoline **16a***

Finally, a series of derivatization experiments were undertaken to examine the synthetic utility of the pyrrolo[1,2-*b*]isoquinoline **16a**. Specifically, we focused our attention on derivatization of the nitrile moiety present in pyrroloisoquinoline **16a**, as it is a versatile functional group that can be efficiently used for various organic transformations. Hence, we attempted the conversion of the cyano moiety of the carbapalladation/cyanation product **16a** to the corresponding aldehyde, amide and amine (Scheme 1.83).

Thus, pyrroloisoquinoline **16a** was selectively reduced with diisobutylaluminium hydride (DIBAL-H) in CH_2Cl_2 to the corresponding aldehyde, giving pyrroloisoquinoline **20** in very good yield (85%) (Scheme 1.83a).[129]



Scheme 1.83

On the other hand, when nitrile group of **16a** was submitted to a basic hydrolysis by treatment with KOH 10 M at reflux,[130] the corresponding amide **21** was achieved in excellent yield (86%) (Scheme 1.83b).

In addition, we tried the reduction of the cyano group of the pyrroloisoquinoline **16a** to a primary amine by reaction with LAH.[131] However, although the formation of the amine was verified by ^{1}H NMR analysis, it resulted difficult to isolate by column chromatography probably due to high polarity of the formed product. Thus, to facilitate further purifications, we decided to functionalize the corresponding amine group by protection with Boc_2O. In

[129] Shiba, T.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.*, **2013**, *135*, 13636.
[130] Yoon, H.; Petrone, D. A.; Lautens, M. *Org. Lett.* **2014**, *16*, 6420.
[131] Yen, A.; Lautens, M. *Org. Lett.* **2018**, *20*, 4323.

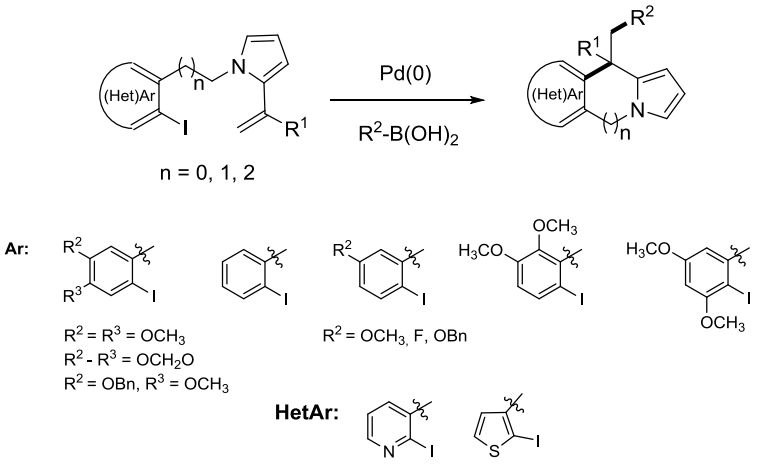
this way, *N*-Boc protected amine **22** could be easily isolated in a 68% overall yield over two reaction steps from pyrroloisoquinoline **16a** (Scheme 1.83c).

With these few organic transformations, we have shown the versatility of nitrile functional group, as the cyano moiety present in pyrroloisoquinoline **16a** has been found to be a key precursor for the efficient synthesis of aldehydes, amide or amines.

3.4. Intramolecular carbopalladation/Suzuki coupling cascade

According to our objectives, our next task was to explore the possibility of involving the σ-alkylpalladium(II) intermediate obtained after the starting carbopalladation in a second intermolecular cross coupling reaction. For that purpose, we chose a Suzuki coupling as termination approach that would allow the sequential formation of two C-C bonds and the generation of a quaternary stereocenter (Scheme 1.84).

In our previous work on Heck/cyanation cascade reaction (see Section 3.3), we had synthesized a series of substrates with the general structure shown in Scheme 1.84, which are also suitable for the Heck-Suzuki reaction.



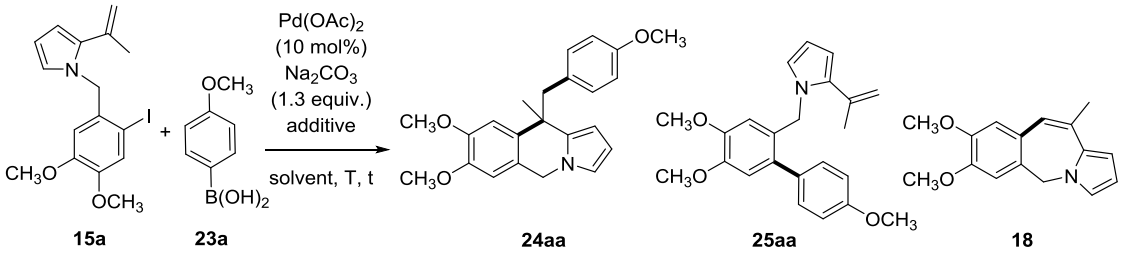
Scheme 1.84.

We started our study using 2-iodobenzylpyrrole **15a** as substrate in the presence of (*p*-methoxyphenyl)boronic acid (**23a**) (Table 1.11), focusing on the use of catalytic systems in the absence of phosphane ligands. In fact, as mentioned in section 3.3.2, besides the economical and environmental reasons for the development and application of phosphane-free catalytic systems, we reasoned that these conditions could be, in principle, suitable for the sterically more demanding generation of a quaternary stereocenter.

Thus, treatment of **15a** with **23a** using $Pd(OAc)_2$ as catalyst and sodium carbonate as the base in DMF at 120 ºC in the absence of any phosphane ligand led to a sluggish reaction, recovering unreacted **15a** (24%) after 48 hours. In addition, under these preliminary conditions, the reaction was not selective and the desired pyrroloisoquinoline **24aa** was obtained as major product, together with two main by-products (**25a** and **18**) derived from direct Suzuki coupling of **15a** with the aryl iodide and 7-*endo* palladation/β-elimination pathway, respectively (Table 1.11, Entry 1). This result shows the feasibility of the cascade reaction using a phosphane-free catalytic system, but also shows the difficulty of performing the 6-*exo* carbopalladation process for the generation of a quaternary center, as both the direct Suzuki coupling to form **25a** and the 7-*endo* Heck pathway leading to **18** compete effectively.

Consequently, our first challenge was to control the chemoselectivity of the process by the adequate choice of the catalytic system and/or experimental conditions. For that purpose, we focused on the optimization of reaction conditions to favor the 6-*exo* carbopalladation reaction *vs.* the 7-*endo* process and the early direct Suzuki coupling (Table 1.11).

We firstly tried to carry out the reaction in the presence of water, as a mixture DMF/H_2O (8:2) was found to be the best solvent for the Heck/cyanation reaction studied in section 3.3.2. Although full conversion was achieved in 48 h, similar yields of pyrroloisoquinoline **24aa** and benzazepine **18** were obtained and only the amount of undesired **25aa** increased (Table 1.11, Entry 2).



Scheme 1.85.

Table 1.11. Carbopalladation/Suzuki sequence on **15a** with **23a**. Optimization of reaction conditions with phosphane-free catalytic systems.

Entry	Additive (equiv.)	Solvent	Time (h)	Yield 24aa (%)[a]	Yield 25aa (%)[a]	Yield 18 (%)[a]
1	-	DMF	48[b]	34	4	23
2	-	DMF/H_2O (8:2)	48	30	12	21
3	*n*Bu_4NCl (1)	DMF/H_2O (8:2)	2	22	33	26
4	*n*Bu_4NCl (1)	DMF/H_2O (8:2)[c]	48[d]	27	27	29
5	*n*Bu_4NCl (1)	DMF	1	47	7	19
6	*n*Bu_4NCl (2)	DMF	1	56	-	13
7	*n*Bu_4NCl (3)	DMF	1	52	-	7
8	*n*Bu_4NI (1)	DMF	1	51	-	16
9	*n*Bu_4NOAc (2)	DMF	1	10	-	14

[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] Conversion: 76%. [c] 90 ºC. [d] Conversion: 84%.

The addition of *n*Bu_4NCl (1 equiv.) dramatically increased the reaction rate,[124] which was completed in 2 h, but the reaction was not selective once again. In this case, direct Suzuki coupling was the major pathway (**25aa**), with also a significant amount of the 7-*endo* Heck

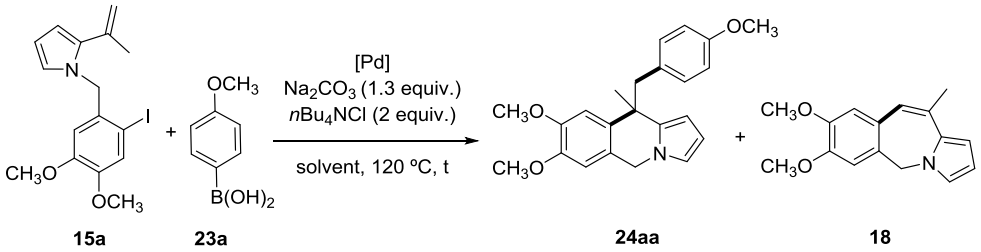
pathway (Entry 3). Lowering the temperature to 90 ºC resulted in a much slower reaction, with almost no selectivity, isolating the three reaction products in comparable yields (Entry 4). Fortunately, when the reaction was performed in the absence of water, using DMF as solvent, pyrroloisoquinoline **24aa** was isolated as the major compound with a remarkable increased yield (Entry 5). Finally, the addition of 2 equivalents of nBu$_4$NCl completely suppressed the direct Suzuki pathway and cyclization product **24aa** was isolated as the major compound in 56% yield (Entry 6). In fact, as stated in section 3.3.2, the presence of halide anions can favor the formation of the domino Heck/Suzuki product due to an increase in the rate of some of the steps of the catalytic cycle of the Heck reaction.[124] On the contrary, increasing concentration of halide anions has the opposite effect on the trasmetalation step of the Suzuki reaction. [132] Therefore, we reasoned that the use of a higher concentration of additive may slow down the direct Suzuki coupling allowing the 6-*exo* carbopalladation to occur at a competive rate. However, neither the use of 3 equivalents of nBu$_4$NCl nor the change to nBu$_4$NI or nBu$_4$NOAc improved the isolated yield of cyclized product **24aa** (Entries 7-9).

Furthermore, we evaluated the modification of the palladium precatalyst and the solvent (Table 1.12), but no significant improvement was observed in carbopalladation/Suzuki coupling reaction efficiency, obtaining moderate yields of **24aa** in all essays. Interestingly, in the presence of PPh$_3$, the Suzuki coupling was the major pathway (28% of **25aa**), despite the use of nBu$_4$NCl, and only a low yield of **24aa** (25%) was isolated (Table 1.12, Entry 3).

At this point, the optimal conditions were defined as: Pd(OAc)$_2$ (10 mol%), Na$_2$CO$_3$ (1.3 equiv.) and nBu$_4$NCl (2 equiv.) in DMF at 120 ºC. However, it is noteworthy that, as shown in Tables 1.11 and 1.12, the 7-*endo* Heck pathway which led to **18** could not be completely suppressed under any of the reaction conditions tested.

[132] Amatore, C.; Le Duc, G.; Jutand, A. *Chem. Eur. J.* **2013**, *19*, 10082.

Moreover, the overall isolated yield is rather low due to the difficulties associated with the separation and purification of compounds by flash chromatography, but no formation of other products was detected by ^{1}H NMR of the crude reaction mixtures.



Scheme 1.86.

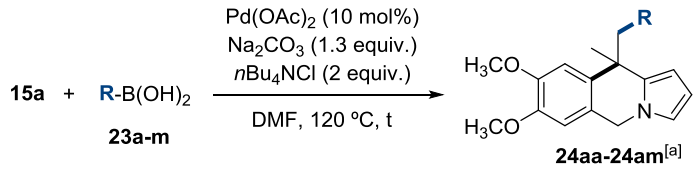
Table 1.12. Effect of the palladium catalyst and solvent in the carbopalladation/Suzuki sequence on **15a** with **23a**.

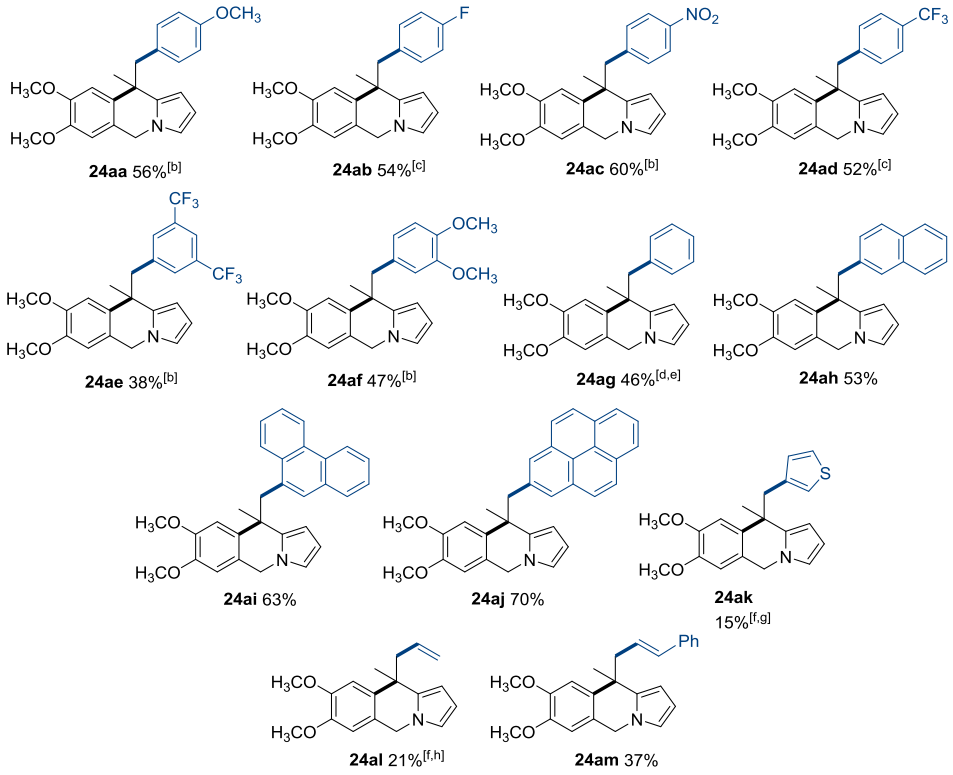
Entry	[Pd]	Solvent	Time (h)	Yield 24aa (%)[a]	Yield 18 (%)[a]
1[b]	$Pd(OAc)_2$	DMF	1	56	13
2[c]	$Pd(TFA)_2$	DMF	2	46	11
3[d]	$Pd(PPh_3)_4$	DMF	9	25	15
4	$Pd_2(dba)_3{\cdot}CHCl_3$	DMF	4	42	10
5	$Pd(OAc)_2$	Toluene[d]	2	34	21
6	$Pd(OAc)_2$	THF[d]	5	52	17
7	$Pd(OAc)_2$	Dioxane[d]	1	56	25
8	$Pd(OAc)_2$	CH_3CN[d]	2	40	29

[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] Included in Table 1.11 (Entry 6). [c] 9% of **25aa** also isolated. [d] 28% of **25aa** was also isolated. [e] Reflux.

Having established the optimal reaction conditions (Table 1.11, Entry 6), we then turned our attention to the scope of different boronic acids **23a-m**. The obtained results are summarized in Table 1.13.

Table 1.13. Extension of phosphane-free reaction to boronic acids **23a-m**





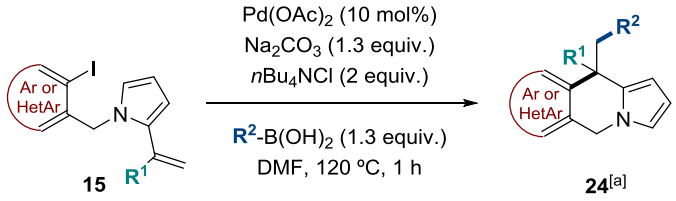
[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] 11-17 % of **18** was also isolated. [c] Reaction time: 2 h. [d] Reaction time: 4 h. [e] 19% of **24ag** was obtained when phenylboronic acid pinacol ester was used instead of **23g**. [f] Reaction time: 48 h. [g] Conversion: 76%. [h] Potasium trifluorovinyl borate was used. Conversion: 89%.

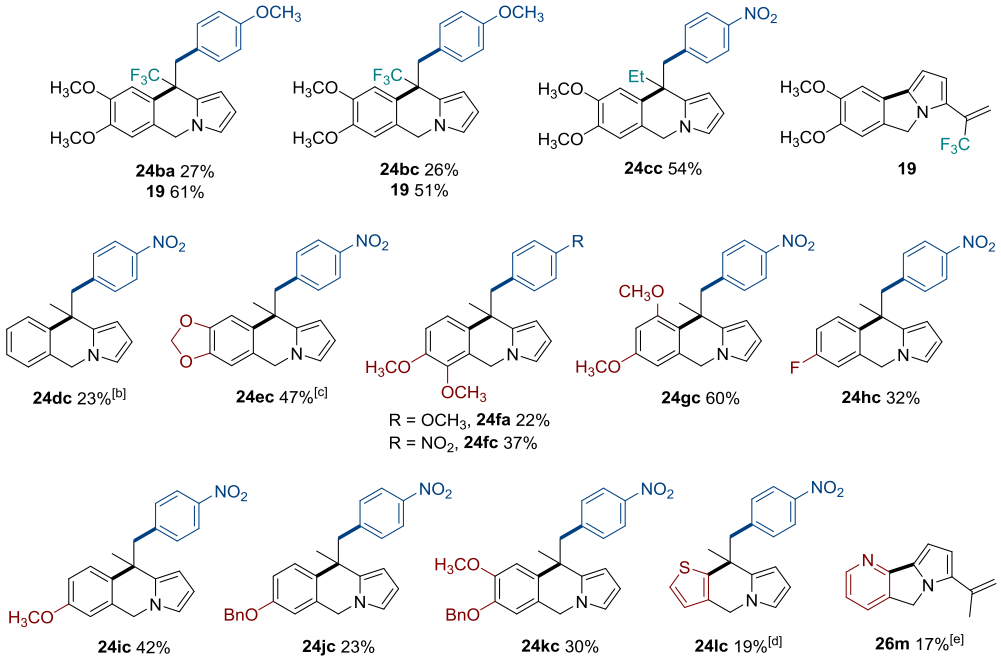
As shown in Table 1.13, moderate to good yields of pyrrolosiquinolines **24aa-24aj** were obtained when electron rich, electron deficient or even polycyclic aryl boronic acids were used. Moreover, minor amounts of the pyrroloazepine **18** were detected by ^{1}H NMR and in some of the experiments it was isolated and quantified. However, no formation of the direct Suzuki coupling was detected in any case. Besides, when phenylboronic acid pinacol ester was used instead of **23g**, lower yield of **24ag** (19% *vs.* 46%) was obtained**.** The reaction with thiophen-3-ylboronic acid **23k** was much slower (48 h), recovering 24% of starting material and giving only a low yield of **24ak**. Finally, alkenes could also be coupled through carbopalladation/Suzuki cascade procedure, although with a lower yield.

To further extend the reaction scope, we elected to pursue the use of different 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles **15b-k**, with different substitution patterns on the aromatic ring and the alkene (Table 1.14). It is interesting that when an electron-withdrawing group, such as CF_3, is incorporated in the alkene (**15b**, $R^2 = CF_3$), the intramolecular direct arylation of the aryl iodide with pyrrole C-5 position becomes the preferred pathway leading to **19** as the major compound. Hence, **24ba** and **24bc** were obtained only in low yields. This type of reactivity has been shown to be competitive in Heck reactions with related substrates, using Pd/phosphane catalytic systems, especially when a cationic mechanism is favored and has also been observed in the Heck/cyanation cascade (Scheme 1.81).[36,109b] Fortunately, formation of corresponding pyrrolo[2,1-*a*]isoindoles was not observed when the alkene was substituted with an alkyl group, and **24cc** was obtained from **15c** (R^2 = Et) in moderate yield (54%).

The reaction could also be extended to benzylpyrroles with different substitution patterns on the aromatic ring (**15d-k**) or even heteroaromatic rings (**15l,m**), obtaining, in most cases, the corresponding pyrroloisoquinolines **24** with moderate to good yields (Table 1.14). Thus, the carbopalladation/Suzuki cascade reaction was applied to a wide variety of mono- and dioxigenated compounds. Moreover, the cyclization reaction of non-substituted benzene ring and fluoro-subtituted derivative substrates was also possible leading to the corresponding pyrroloisoquinolines **24dc** and **24hc**.

Table 1.14. Carbopalladation/Suzuki reaction of substrates **15b-m.**





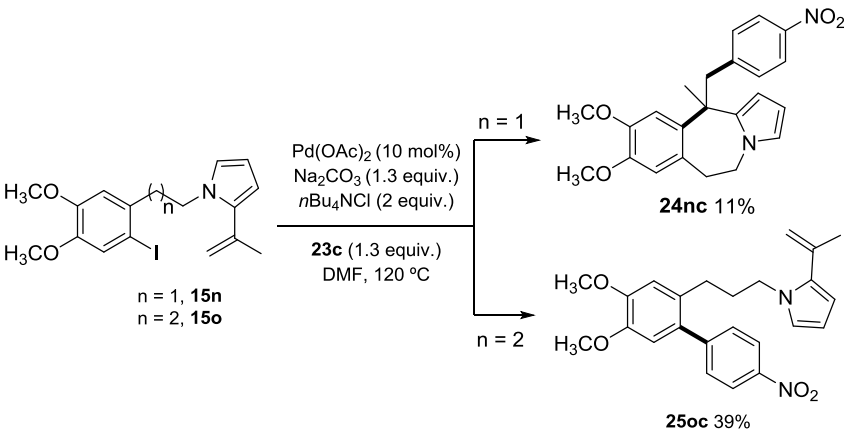
[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] Reaction time: 4h. [c] Reaction time: 3 h. [d] Reaction time: 24 h. [e] Reaction time: 48 h.

Additionally, as we performed in section 3.3.2 for the Heck/cyanation cascade reaction, we decided to test the applicability of the domino carbopalladation/Suzuki reaction, studying the extension of the developed procedure to electron-rich and electron-deficient heteroaromatic halides as coupling partners. For this purpose, thiophenylpyrrole **15l** and iodopyridine **15m** were subjected to previously optimized reaction conditions. To our

delight, carbopalladation/Suzuki sequence took place when electron-rich heteroaromatic halide **15l** was used as substrate, but only small amounts (19%) of thienoindolizine **24lc** could be isolated from a messy mixture of products.

We also explored the carbopalladation/Suzuki reaction with an electron-deficient heteroaryl halide. In this case, 6-*exo* carbopalladation reaction of iodopyridine **15m** under previously optimized reaction conditions was not favoured and, hence, no evidence of the expected pyrroloisoquinoline was observed. Instead, the reaction afforded a complex mixture of products from which only direct arylation product **26m** could be isolated in a low yield (17%). Noteworthy that, although direct Suzuki coupling product was also observed in ^{1}H NMR spectra of the reaction crude, it was no possible to isolate and quantify it due to degradation of the compound during purification step.

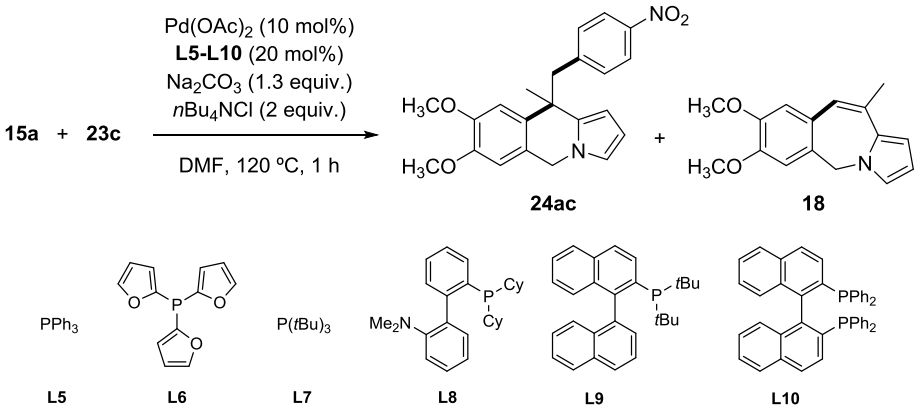
Then, we studied the extension of the methodology to the generation of medium-sized rings, such as benzazepine and benzazocine through 7-*exo* and 8-*exo* cyclizations. For that purpose, we applied the optimized reaction conditions for the synthesis of pyrroloisoquinolines **24aa** to *N*-iodophenethylpyrrole **15n** and *N*-iodophenylpropylpyrrole **15o**. In this way, **15n** led to a mixture of products from which pyrrolobenzazepine **24nc** could be isolated only in low yield (11%) (Scheme 1.87). It is worth noting that direct Suzuki coupling product could be distinguished in the ^{1}H NMR analysis of the reaction crude, but it could not be isolated due to difficulties during purification by flash chromatography and, therefore, its complete characterization was not possible. Unfortunately, the cyclization of *N*-phenylpropylpyrrole **15o** did not take place and direct Suzuki coupling product **25oc** was isolated as unique product in moderate yield (39%). In this case, the low efficiency of the coupling could be associated to decomposition of starting material **15o**, which was observed in the ^{1}H NMR spectra of the reaction crude.



Scheme 1.87.

In view of these results, we have established the basis for the generation of seven-membered ring through a Heck/Suzuki cascade, but additional experimentation is needed to obtain pyrrolobenzazepine **24nc** efficiently. In addition, further investigations should be carried out to set the optimal conditions for the construction of the eight-membered ring.

At this point, we have shown that it is possible to carry out the 6-*exo*-*trig* carbopalladation/Suzuki cascade using a phosphane-free catalytic system. However, the overall yields obtained are moderate in many cases, as the competitive 7-*endo* cyclization/elimination leading to **18** could not be completely suppresed under the best cyclization reaction conditions. Although we had previously shown that the formation of quaternary stereocenters *via* Heck reaction was possible on related substrates in the presence of phosphane ligands,[86] the use of $Pd(PPh_3)_4$ on the coupling of **15a** with **23a** led to a non selective reaction (Table 1.12, Entry 3). With these precedents, we decided to carry out a further optimization of the reaction conditions, studying the effect that a phosphane ligand could have in the carbopalladation/Suzuki process. For that purpose, we chose different phosphanes to employ in the reaction of **15a** with boronic acid **23c** (Scheme 1.88), which had given a moderate yield of **24ac** under the phosphane-free reaction conditions (60%, Table 1.13, Entry 3).



Scheme 1.88.

Table 1.15. Optimization of reaction of **15a** with **23c** in the presence of phosphanes.

Entry	[Pd]	L	Yield 24ac (%)[a]	Yield 18 (%)[a]
1	$Pd(OAc)_2$	**L5**	70	4
2	$Pd(OAc)_2$	**L6**	74	9
3	$Pd(OAc)_2$	**L6**[b,c]	67	8
4	$Pd(OAc)_2$	**L7**	70	6
5	$Pd(OAc)_2$	**L8**	65	4
6	$Pd(OAc)_2$	**L9**	66	9
7	$Pd(OAc)_2$	**L10**[d]	53	12
8	$Pd(dba)_2$	**L6**[e]	79	-
9	$Pd_2(dba)_3 \cdot CHCl_3$	**L6**	86 (94)[i]	-
10	$Pd_2(dba)_3 \cdot CHCl_3$	**L2**[f,g]	30	33
11	$Pd_2(dba)_3 \cdot CHCl_3$	**L2**[h]	29	18

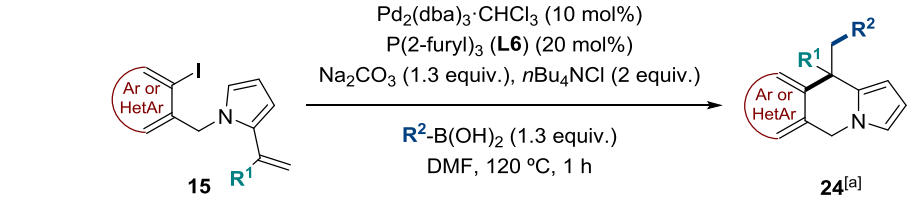
[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] 28 % of **L6** was used. [c] Reaction time: 3 h. [d] Reaction time: 24 h. [e] Reaction time: 4 h. [f] Reaction time: 48 h. [g] nBu$_4$NCl was not used. [h] Ag_3PO_4 was used as base instead of Na_2CO_3. [i] Isolated yield when the reaction was carried out on 1.3 mmol (500 mg) scale.

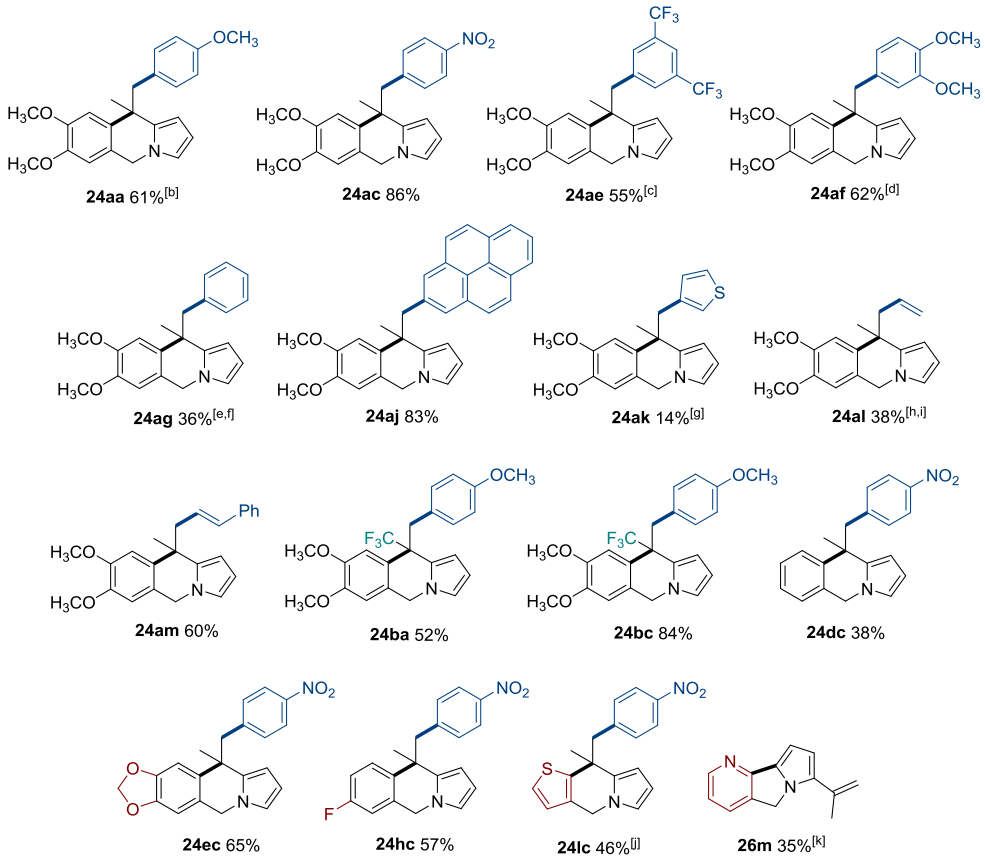
We were pleased to find that the carbopalladation/Suzuki cascade reaction took place efficiently using previously optimized reaction conditions in the presence of various phosphanes (20 mol%), such as triphenylphosphane (**L5**) (Table 1.15, Entry 1), tri(furan-2-yl)phosphane (**L6**) (Table 1.15, Entry 2) or tri-*tert*-butylphosphane (**L7**) (Table 1.15, Entry 4). In fact, although the formation of the 7-*endo* Heck product (**18**) could not be completely avoided (4-9 % of **18** was isolated as by-product), the use of phosphane ligands led to the formation of **24ac** with an increased yield (70-74%). The use of a higher amount of the phosphane led to a slower reaction with a lower isolated yield of pyrroloisoquinoline **24ac** (Entry 3). The choice of the phosphane ligand has been shown to have a determinant effect on the *endo*/*exo* selectivity in related Heck cyclizations.[133] However, minor amounts of **18** (Entries 5 and 6) were also isolated when the reaction was carried out in the presence of DavePhos (**L8**) and TrixiePhos (**L9**). The reaction using *rac*-BINAP (**L10**) was less efficient, and required longer reaction time to obtain a moderate yield of **24ac** (Entry 7). To our delight, the formation of the *endo* adduct **18** could be completely avoided changing the palladium source. Thus, the use of bis(dibenzylidene)palladium(0) with tri(furan-2-yl)phosphane (**L6**) gave **24ac** in good yield and with complete selectivity (Entry 8). Finally, the change of the palladium source to tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct was found to be more efficient, obtaining pyrroloisoquinoline **24ac** in a 86% yield (Entry 9). Moreover, it has been demonstrated that the use of nBu$_4$NCl is still neccesary, as a much slower and non selective reaction took place in its absence (Entry 10). In fact, under these conditions, **18** was obtained as the major product after 48 h, although no direct Suzuki coupling product was detected. Finally, the change of the base for a silver salt (Ag_3PO_4) also resulted in a selectivity loss (Entry 11).

Additionally, to showcase the scalability of this method, we decided to conduct the reaction of **15a** with **23c**, which afforded the best cyclization performance, on a 0.5 gram scale (1.3 mmol) under the optimized conditions, obtaining the pyrroloisoquinoline **24ac** in excellent yield (94%).

[133] Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc*. **2010**, *132*, 14048; Correction: Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc*. **2012**, *134*, 16917.

Table 1.16. Synthesis of pyrroloisquinolines **24** using **15** as substrate and **L6** as ligand.





[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] 12% of **18** was isolated. [c] 16% of **18** was isolated. [d] Reaction time: 4 h. [e] Reaction time: 6 h. [f] 22% of **18** was isolated. [g] 11% of **18** and 50% of **25k** were isolated. [h] Reaction time: 24 h. [i] 24% of **18** was isolated. [j] Reaction time: 2h. [k] Reaction time: 48 h.

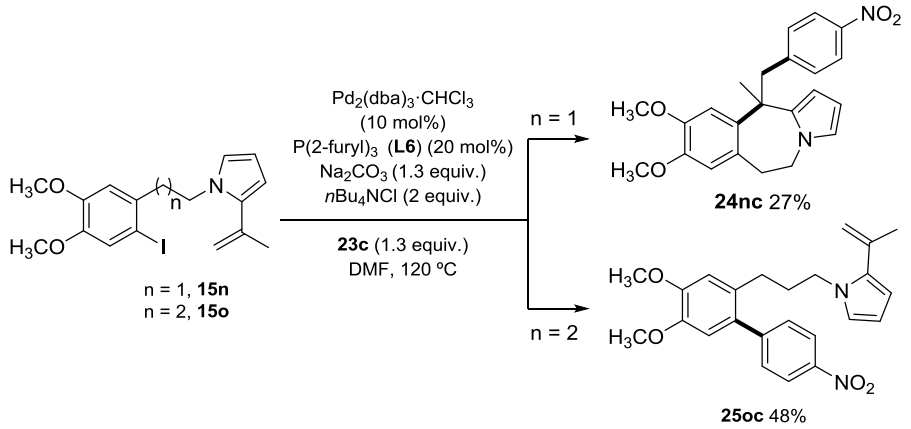
Once the reaction conditions were newly optimized, we tested the use of selected boronic acids **23**. As shown in Table 1.16, in most of the cases (**24aa**, **24ac**, **24ae**, **24af**, **24aj**, **24al**, **24am**), the results could be significantly improved with respect to the yield obtained with the phosphane-free catalytic system (see Table 1.13). However, in some of the cases, minor amounts of **18** were also isolated (Table 1.16, 11-24%). In the case of **24ag**, a slightly lower yield (36%) was obtained, probably due to difficulties during purification by flash chromatography, and the *endo*-Heck cyclization product **18** was also isolated (22%). The reaction with thiophen-3-ylboronic acid **23k** gave again a low yield of **24ak** (15% Table 1.13 *vs*. 14% Table 1.16), although, under conditions in the presence of phosphane **L6**, the main reaction pathway was the direct Suzuki coupling, obtaining **25kc** in a 50% yield. Finally, the coupling with alkenes could be also significantly improved by using phosphane **L6** as ligand (Table 1.16, **24al** and **24am**).

Moreover, we evaluated the effect of the use of phosphane **L6** over substrates with different substituents on the alkene and benzene ring (**15b**, **15d**, **15e** and **15h**), obtaining, in all cases, improved yields of the expected pyrroloisoquinolines (Table 1.16). Significantly, the use of the phosphane ligand completely changed the chemoselectivity when **15b** ($R^2 = CF_3$) was reacted with **23a** and **23c**. Thus, the direct arylation pathway leading to **19** was completely suppressed and 10b-trifluoromethylsubstituted pyrroloisoquinolines **24ba** and **24bc** were obtained in good yields. This result probably reflects the change from a cationic (phosphane-free) to a neutral pathway for the initial carbopalladation step.

Additionally, we decided to apply the new best reaction conditions with **L6** to the electron-rich and electron-deficient heteroaromatic substrates **15l** and **15 n** in order to study the effect of the phosphane ligand in the efficiency of carbopalladation/Suzuki cascade. To our delight, cyclization reaction of **15l** took place, obtaining the corresponding thienoindolizine **24lc** in an improved yield (46%) with respect to the achieved in absence of phosphane **L6** as ligand (19%). Unfortunately, iodopyridine **15m** was unfavourable to cyclization reaction under previously optimized reaction conditions in the presence of **L6**, and a complex mixture of products was obtained from which only direct arylation product **26m** was

isolated in a moderate yield (35%). In this case, as happened when phosphane-free catalytic system was used, although detected in the crude reaction by ^{1}H NMR, direct Suzuki coupling product could not be isolated and quantified due to difficulties during its separation by column chromatography.

Finally, we decided to investigate the effect of the phosphane ligand **L6** in the synthesis of analogous medium-sized rings. For this purpose, *N*-(*o*-iodoarylalkyl)pyrroles **15n,o** were subjected to newly optimized reaction conditions for the synthesis of pyrroloisoquinolines **24** through carbopalladation/Suzuki reaction. In this way, **15n** provided again a mixture of products under cyclization conditions from which pyrrolobenzazepine **24nc** could be isolated in an increased yield (27%) regarding the obtained with phosphane-free catalytic system (11%). On the other hand, treatment of **15o** under former conditions in the presence of phosphane **L6** led to the formation of direct Suzuki coupling product **25oc** in moderate yield (48%), instead of expected 8-*exo* cyclization product (Scheme 1.89).



Scheme 1.89.

In view of these preliminary results, we concluded that, although the formation of pyrrolobenzazepine **24nc** is possible, further investigation for the efficient 7-*exo* cyclization process is necessary. In addition, optimization of reaction conditions, including different catalysts, bases, solvents, etc., should be carried out for the synthesis of the analogous pyrrolobenzazocine.

Having established the formation of the quaternary stereocenter in racemic fashion, we decided to explore the possibility of an enantioselective version of the carbopalladation/Suzuki cascade reaction. For this purpose, we selected once again the reaction of **15a** with **23c** as a model for optimization of the reaction conditions and, firstly, a screening of different type of privileged chiral ligands, represented in Figure 1.4, was carried out.

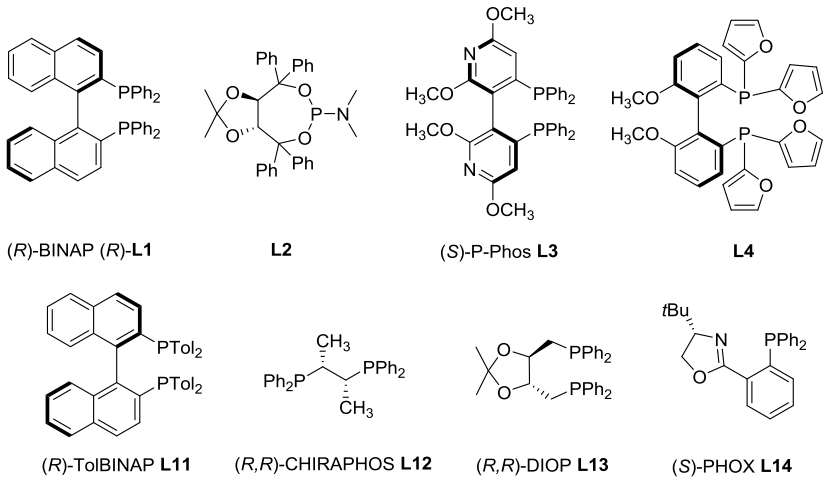
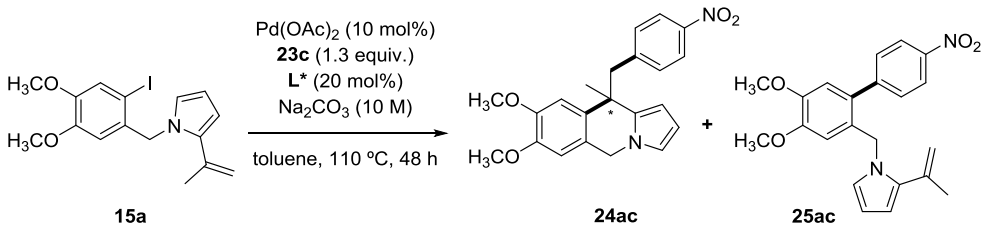


Figure 1.4.

We started the study using (*R*)-BINAP as chiral ligand, because, as shown in previous sections, it is an appropriate ligand to control the enantioselectivity of the carbopalladation step in enantioselective Heck-Heck cascade of related substrates.[86a] Unfortunately, in this case, the use of (*R*)-BINAP, using palladium acetate in toluene, led to low conversions and only low yield of **24ac** was obtained with poor enantioinduction (18%, -25% *ee*). Besides, direct Suzuki coupling product **25ac** was isolated in 16% yield (Table 1.17, Entry 1). Even lower results were achieved when BINAP derivate **L11** was employed in cyclization reaction (Entry 5). The use of TADDOL-derived phosphoramidite **L2** led to the best results in terms of enantioselectivity (44% *ee*) and only small amounts of direct Suzuki coupling product **25ac** were isolated (7%) (Entry 2). Phos-type ligand **L3** provided racemic

pyrroloisoquinoline **24ac** in very poor yield (14%) (Entry 3). Biphosphine **L4** gave the best yield of **24ac** with a 24% *ee*, but direct Suzuki coupling could not be suppressed, obtaining **25ac** in 19% yield (Entry 4). **L12** was found to be almost catalitically inactive, leading to only traces of cyclized product **24ac** with poor enantioinduction (Entry 6). When (*R*,*R*)-DIOP (**L13**) was used as chiral ligand, **24ac** was obtained in moderate yield, although with minimal enantioselectivity (38%, -9% *ee*). Finally, PHOX-type ligand **L14** shut the reaction down completely and **15a** was recovered quantitatively (Entry 8). Thus, in view of these results, we selected chiral ligand **L2** for further optimization of the reaction conditions.



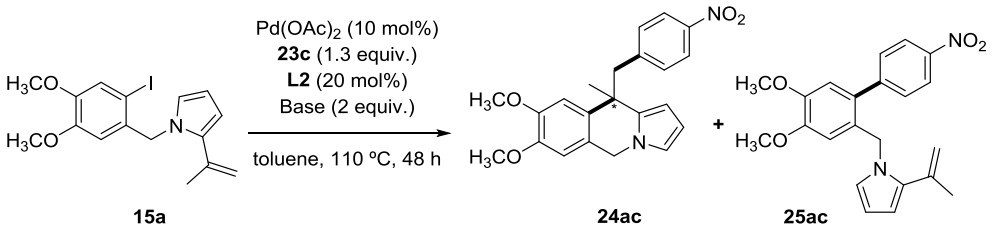
Scheme 1.90.

Table 1.17. Reaction of **15a** with **23c** using chiral phosphanes.

Entry	L*	Conversion (%)	Yield 24ac (%)[a]	*ee* (%)[b]	Yield 25ac (%)[a]
1	(*R*)-**L1**	50	18	-25	16
2	**L2**	52	28	44	7
3	**L3**	26	14	<2	5
4	**L4**	62	39	24	19
5	**L11**	38	13	-16	18
6	**L12**	13	3	-10	7
7	**L13**	72	38	-9	21
8	**L14**	n.r.	-	-	-

[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] Determined by chiral stationary phase HPLC (Chiralcel ADH, 90% hexane/*i*-propanol, 1 mL/min).

At this point, we evaluated the effect of the base concentration and the use of additives using **L2** as chiral ligand. Then, different bases were screened to improve the efficiency of the enantioselective carbopalladation/Suzuki cascade reaction.



Scheme 1.91.

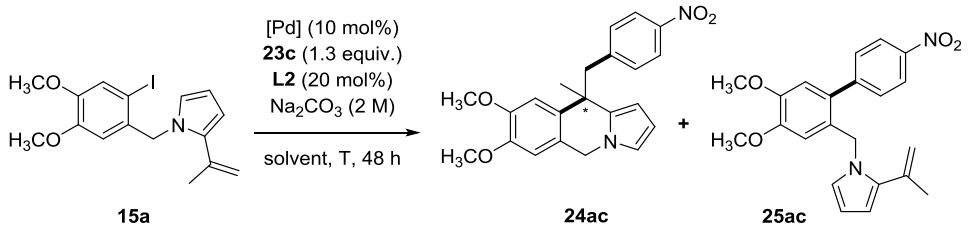
Table 1.18. Base screening of the reaction of **15a** with **23c** using **L2** as ligand

Entry	Base	Conversion (%)	Yield 24ac (%)[a]	*ee* (%)[b]	Yield 25ac (%)[a]
1[c]	Na_2CO_3	n.r.	-	-	-
2[d]	Na_2CO_3	>99	61	4	-
3[e]	Na_2CO_3 (10 M)	52	28	44	7
4	Na_2CO_3 (5M)	65	41	34	9
5	Na_2CO_3 (2 M)	>99	63	34	23
6[c]	Na_2CO_3 (1 M)	>99	57	27	24
7	K_2CO_3	87	60	29	19
8	Cs_2CO_3	84	54	30	26
9	$NaHCO_3$	n.r.	-	-	-
10	Et_3N[e]	83	46	2	32

[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] Determined by chiral stationary phase HPLC (Chiralcel ADH, 90% hexane/*i*-propanol, 1 mL/min). [c] Reaction time: 48 h. [d] *n*Bu_4NCl (2 equiv.) was used as additive. [e] 6 equiv. [e] Included in Table 1.18 (Entry 2).

Thus, we showed that the reaction did not proceed at all after 48 h in the absence of *n*Bu_4NCl using solid Na_2CO_3 (Table 1.18, Entry 1). The use of *n*Bu_4NCl accelerated the reaction (Entry 2), but led to an almost racemic compound (4% *ee*). The reactivity could be recovered using an aqueous solution of base (Entries 3-6). As shown in Table 1.18, best *ee* results were obtained with the use of a 10 M aqueous solution of Na_2CO_3, providing cyclized product **24ac** in low yield (Entry 3). Decreasing the concentration of the base solution was found to be more efficient in terms of yield, but lower enantioselectivities were obtained. It is remarkable that, in these cases, the reaction was non-selective and direct Suzuki coupling product **25ac** was isolated as a by-product. At this point, conditions in Entry 5 (2 M base) were selected for further optimization. Then, we tried different bases, both inorganic and organic bases, but no improvement in yield or enantioselectivity was observed (Table 1.18, Entries 7-10). Besides, it is worth noting that the desired reaction was completely shut down when $NaHCO_3$ was used as base.

Further attempts were conducted to increase both the yield and enantioselectivity of domino carbopalladation/Suzuki reaction using different solvents and palladium sources. Thus, solvent examination revealed that CH_3CN and dioxane provided almost racemic **24ac** in a slightly decreased yield (46% and 43%, respectively). DMF afforded desired cyclized product in good yield (64%), but with no enantioinduction. A poor yield of **24ac** was achieved in EtOH and the reaction was fully supressed in water. The use of other non-polar solvents, such as *p*-xylene and mesitylene, gave comparable results of yield and *ee* values to those obtained carrying out the reaction in toluene (Table 1.19, Entries 7-8). Finally, no better results in terms of enantioselectivity were obtained by using different palladium catalysts (Entries 10-12). However, replacing the palladium precursor with $Pd(dba)_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$ the yield of the cyclization reaction remarkably improved.



Scheme 1.92.

Table 1.19. Effect of palladium precatalyst and solvent in the reaction of **15a** with **23c** using **L2** as ligand and Na_2CO_3 (2 M) as base.

Entry	[Pd]	Solvent	T (ºC)	Conv. (%)	Yield 24ac (%)[a]	*ee* (%)[b]	Yield 25ac (%)[a]
1[c]	$Pd(OAc)_2$	Toluene	110	> 99	63	34	23
2	$Pd(OAc)_2$	CH_3CN	Reflux	> 99	46	-5	43
3	$Pd(OAc)_2$	EtOH	Reflux	91	26	-10	49
4[d]	$Pd(OAc)_2$	Dioxane	Reflux	> 99	43	10	30
5[e]	$Pd(OAc)_2$	DMF	Reflux	> 99	64	< 2	7
6	$Pd(OAc)_2$	H_2O	Reflux	n.r.	-	-	-
7[d]	$Pd(OAc)_2$	p-xylene	Reflux	> 99	59	27	17
8	$Pd(OAc)_2$	Mesitylene	Reflux	83	51	30	21
10	$Pd(TFA)_2$	Toluene	110	92	53	26	29
11	$Pd(dba)_2$	Toluene	110	> 99	68	25	25
12[d]	$Pd_2(dba)_3 \cdot CHCl_3$	Toluene	110	> 99	72	22	-

[a] Isolated yield. Reactions were carried out in a 0.3 mmol scale. [b] Determined by chiral stationary phase HPLC (Chiralcel ADH, 90% hexane/*i*-propanol, 1 mL/min). [e] Included in Table 1.19 (Entry 5). [d] Reaction time: 24 h. [e] Reaction time: 3 h.

After extensive experimentation, we found that only modest enantioselectivities (up to 44% *ee*) could be obtained in the carbopalladation/Suzuki cascade of **15a** with **23c** by using chiral non racemic phosphanes, such as phosphoramidite **L2**. Thus, we decided not to study the scope of the asymmetric version of the palladium-catalyzed intramolecular Heck/Suzuki cascade reaction. In addition, due to the low enantiomeric excess achieved, the absolute configuration could not be determined.

In conclusion, it has been shown that 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles **15** can undergo cyclization through a 6-*exo* carbopalladation process forming σ-alkylpalladium that can be trapped with different boronic acids, generating C-10 disubstituted pyrrolo[1,2-*b*]isoquinolines **24** with a quaternary center. The domino process can be carried out by using a phosphane free precatalytic system. In fact, under these reaction conditions, 6-*exo* carbopalladation reaction is favoured *vs*. the direct Suzuki coupling, although the 7-*endo* process is competitive. Nevertheless, it has been demonstrated that the use of phosphane ligands, such as tri(furan-2-yl)phosphane (**L6**), suppresses the 7-*endo* Heck pathway. Besides, combination of **L6** ligand with $Pd_2(dba)_3.CHCl_3$ leads in most cases to a significant increase in the yield of the pyrroloisoquinolines **24**. On the other hand, the presence of $n Bu_4NCl$ is found to be crucial to allow the 6-*exo* carbopalladation to occur at a competitive rate, avoiding in this way the direct Suzuki coupling. Electron rich and electron deficient arylboronic acids can be used for the domino Heck/Suzuki reaction, although coupling with alkenyl or heteroaryl (thiophenyl) boronic acids provide lower yields. In addition, initial basis for application of carbopalladation/Suzuki cascade to heteroaromatic halides has been established, and also to the construction of seven- and eight-membered rings. Finally, the use of chiral non racemic phosphanes, such as phosphoramidite **L2**, gave only modest enantioselectivities.

4. ANTI-LEISHMANICIDAL ASSAYS OF PYRROLOISOQUINOLINE DERIVATIVES

Nitrogen heterocycles are privileged scaffolds present in innumerable bioactive natural products and pharmaceuticals. For example, 59% of the small-molecule drugs approved by the U.S. FDA contain a nitrogen heterocycle, either saturated (piperidine and pyrrolidine) or aromatic/partially hydrogenated derivatives (quinoline, isoquinoline and their dihydro counterparts).[134] The high percentages of these privileged frameworks far surpass the impact numbers for sulfur (26%) and fluorine (13%).[135] In this PhD thesis, we have developed synthetic methodologies for the preparation of different benzo(hetero)fused six-membered heterocycles. Particularly, we have synthesized several compounds with the pyrrolo[1,2-*b*]isoquinoline core, which is a common structural motif among many biologically active alkaloids[136] and in many molecules exhibiting useful therapeutic (anticancer, antiplasmodial, neuroprotective, antiviral, etc.) properties.[137] Moreover, isoquinoline alkaloids may present biological activity against tropical diseases caused by protozoan parasites, such as leishmaniasis.[138]

Leishmaniasis is a neglected parasitic disease, endemic in about 100 countries, with morbidity and mortality increasing daily. The disease in caused by protozoan pathogens of the *Leishmania* genus that are transmitted by sanflies. *Leishmania* parasites cause many

[134] Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.
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[136] For selected reviews on alkaloids, see: a) Hoshino, O. *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, **1998**, Vol. 51, p. 323. b) He, M.; Qu, C.; Gao, O.; Hu, X.; Hong, X. *RSC Adv.* **2015**, *5*, 16562. c) Nair, J. J.; van Staden, J.; Bastida, J. *Curr. Med. Chem.* **2016**, *23*, 161−185. d) Chemler, S. R. *Curr. Bioact. Compd.* **2009**, *5*, 2. e) Burtoloso, A. C. B.; Bertonha, A. F.; Rosset, I. G. *Curr. Top. Med. Chem.* **2013**, *14*, 191. f) Pereira, M. de F.; Rochais, C.; Dallemagne, P. *Anti-Cancer Agents Med. Chem.* **2015**, *15*, 1080.
[137] a) Evidente, A.; Kornienko, A. *Phytochem. Rev.* **2009**, *8*, 449. b) Su, B.; Cai, C.; Deng, M.; Liang, D.; Wang, L.; Wang, Q. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2881. c) Cortes, N.; Posada-Duque, R. A.; Álvarez, R.; Alzate, F.; Berkov, S.; Cardona-Gomez, G. P.; Osorio, E. *Life Sci.* **2015**, *122*, 42. d) Zhan, G.; Zhou, J.; Liu, J.; Huang, J.; Zhang, H.; Liu, R.; Yao, G. *J. Nat. Prod.* **2017**, 80, 2462. e) Nair, J. J.; van Staden, J. *Planta Med.* **2019**, 637.
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human infections ranging from visceral disease to cutaneous and mucocutaneous forms. Visceral leishamaniasis (VL) is the most severe form of human leishmaniasis caused by *Leishmania donovani*, while the cutaneous (CL) and monocutaneous leishmaniasis (MCL) results from infection with *Leishmania amazonensis*.[139] Immunosuppresed patients related to HIV co-infection or solid organ transplantation are prone to infection by *Leishmania*, which can also promote cancer development.[140]

Leishmaniasis treatment is always systemic with antiparasitic drugs. Current anti-leishmanial therapeutics are hampered by drug toxicity, high cost, need for parenteral administration, increasing treatment failure rates, and emergence of drug resistance. Treatment depends not only on the etiological species and the infection type, but also on the place where the disease was acquired. There are few well-validated molecular drug targets in *Leishmania*, and the molecular targets of the current clinical molecules are unknown.[141] For example, VL is treated with a combination of pentavalent antimonials and paromomycin (PM) in Africa (Figure 1.5). However, liposomal amphotericin B (L-AmB) and multidrug therapy (L-AmB + miltefosine, L-AmB + PM or miltefosine + PM) are the most recommended treatments for VL in India, as almost all infections are resistant to pentavalent antimonials in this country. These facts may reflect different drug susceptibility of Leishmania species in Brazil (*L. amazonensis*) and in India (*L. donivane*). L-AmB is also recommended for VL in the Mediterranean area and South America. However, these drugs can have significant side effects, as miltefosine can cause birth defects if taken within three months of getting pregnant.[142] On the other hand, proven treatments of CL are scarce, being

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paromomycin, pentamidine and the triazol derivative fluconazole the most effective drugs (Figure 1.5).[143]

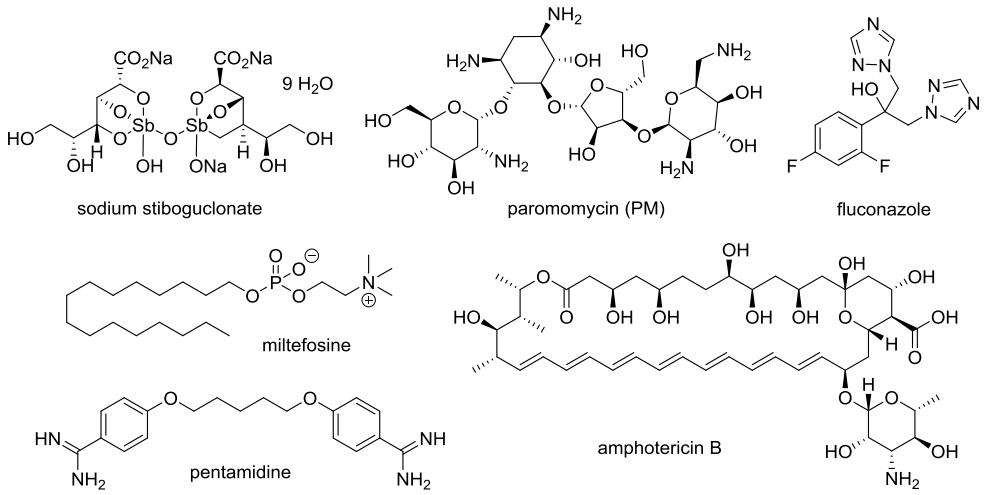

Figure 1.5.

Among the latest advances in this field stand out a novel anti-leishmanial drug-like chemical series based on a pyrazolopyrimidine scaffold has recently been developed targeting to Cyclin-dependent kinase 12,[144] and identified as selective inhibitor of the kinetoplastid proteasome, such as GNF6702 and GSK3186899, with unprecedented *in vivo* efficacy (Figure 1.6).[145] Besides, the development of Nanoparticle Drug Delivery Systems (NDDS) to achieve better drug delivery profiles, controlled release, *etc*. could also be crucial. Consequently, the discovery of new anti-leishmanial drugs, the validation of new drug targets, and the development of new NDDS for anti-leishmanial drugs is an active field of research of great interest for medicinal chemistry and pharmaceutical industry.[146]

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[146] Vaghela, R.; Kulkarni, P. K.; Osmani, R. A. M.; Bhosale, R. R.; Naga Sravan Kumar Varma, V. *Curr. Drug Targets* **2017**, *18*, 1598.

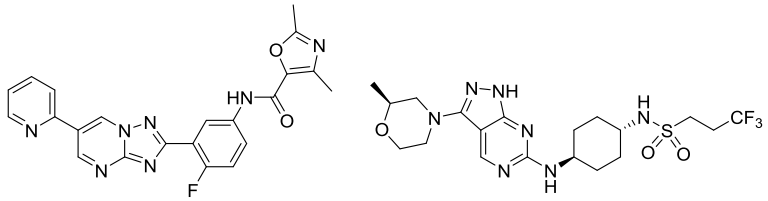


Figure 1.6.

Currently, identification of new effective and safe drugs for some infectious diseases, as Leishmaniasis, is crucial to advance in obtaining new lead compounds and disease control.[147] Therefore, we decided to investigate the anti-leishmanial activity of the obtained pyrrolo[1,2-*b*]isoquinolines. The assays against visceral (*L. donovani*) and cutaneous (*L. amazonensis*) leishmaniasis, as well as their cytotoxicity have been carried out by Dr. M. A. Dea from University CEU Cardenal Herrera (Valencia).

Thus, the newly synthesized C-10 substituted 5,10-dihydropyrrolo[1,2-*b*]isoquinoline derivatives **16** and **24** (Figure 1.7) were screened against two species of Leishmania, *L. amazonensis* and *L. donovani*, which cause VL and CL/MCL respectively. *In vitro* promastigote susceptibility assays and *in vitro* intracellular amastigote susceptibility assays have been carried out, as well as cytotoxicity assay on J774 cell line of macrophages. The J774 cell line is a line of macrophagues used to test cytotoxicity of drugs *in vitro* prior to animals tests (see Experimental Section). Miltefosine was the drug of reference, as it can be used for the treatment of the three forms of the disease.

The initial screening on the *in-vitro* promastigote assays revealed that some 5,10-dihydropyrrolo[1,2-*b*]isoquinolines favorably could be compared to Miltefosine in terms of activity against *L. amazonensis.*In general, best activity was found for the 10-arylmethyl substituted derivatives **24aa**, **24ac**, **24ae**, **24af**, **24ag**, **24aj**, **24bc**, **24dc** and **24ec**, whereas

[147] Hendrickx, S.; Caljon, G.; Maes, L. *Parasitol. Res.* **2019**, *118*, 2743.

the presence of a cyanomethyl group at C-10b resulted in compounds with weaker activity (Table 1.20, Entries 12-19).

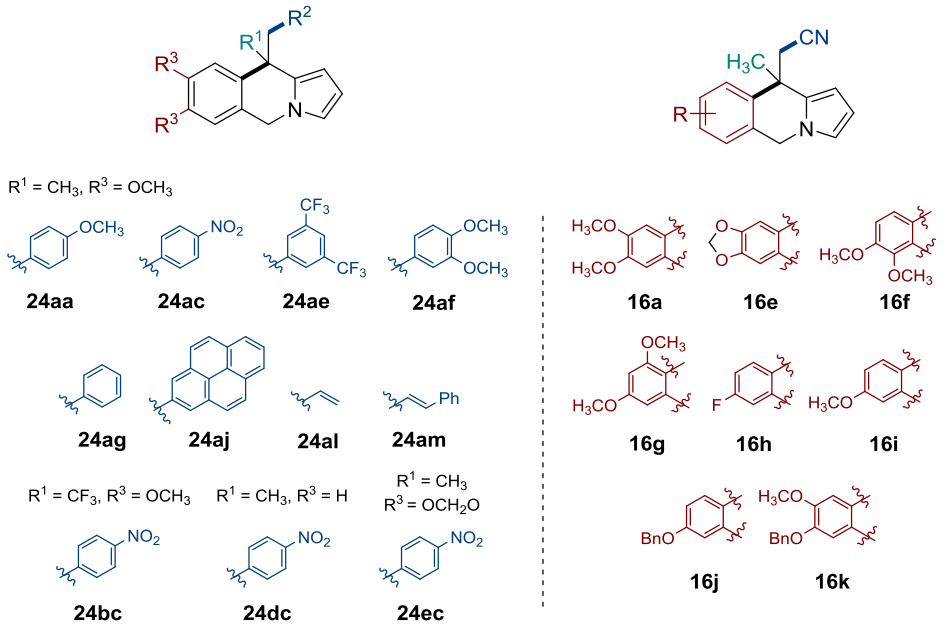


Figure 1.7

The more active compounds **24af** and **24bc** have an IC_{50} = 1.3 ± 1.1 and IC_{50} = 1.7 ± 0.1, respectively *vs. L. amazonensis* promastigotes, being above 10 times more active than Miltefosine with IC_{50} = 12.5 ± 0.41. In addition, and very notably, almost all pyrroloisoquinolines are less toxic than the drug of reference with values of concentration of the compound that produces 50% reduction of cell viability, Cytotoxic Concentration CC_{50} >100 or in the range 70-100 in J774 cells. In consonance with this, the Selectivity Index SI = CC_{50}/IC_{50} is higher for almost all pyrroloisoquinolines than for Miltefosine whose SI is only 4.43. The aromatic substitution pattern of the pyrroloisoquinoline core also plays an important role. Thus, the presence of electron-donating substituents has been found to have a positive impact on anti-leishmanial activity. In fact, the IC_{50} values of

compounds **24aa** and **24af** were considerably lower than the one for the unsubstituted derivative **24ag** (Table 1.20, Entries 1 and 4 *vs.* 5).

Table 1.20. IC_{50} Leishmanicidal and cytotoxic effects from pyrroloisoquinoline derivatives (expressed as μg/mL) on *in vitro* promastigote assay.

Entry	Comp.	*L. amazonensis*		*L. donovani*		Macrophages J774
		IC_{50} ± SD	**SI**	**IC_{50} ± SD**	**SI**	**CC_{50} ± SD**
1	**24aa**	9.6±0.8	>10.4	17.23±0.65	>5.80	100
2	**24ac**	6.8±0.3	>14.8	30.25±1.65	>3,31	100
3	**24ae**	18.6±1.0	>1.2	52.27±5.09	0.42	21.98±1.88
4	**24af**	1.3±1.1	>9.7	15.09±1.32	>6.63	100
5	**24ag**	5.7±0.2	>17.5	10.10±0.67	>9.90	100
6	**24aj**	16.8±0.2	>6.0	39.36±0.73	>2.54	100
7	**24al**	6.6±0.4	>15.1	35.26±4.16	>2.84	100
8	**24am**	4.4±0.2	>23.0	12.10±0.74	>8.27	100
9	**24bc**	1.7±0.1	>60.2	7.10±2.12	>14.09	100
10	**24dc**	50.1±2.0	>2.0	50.75±8.35	>1.97	100
11	**24ec**	2.9±0.1	>34.3	11.00±1.42	>9.09	100
12	**16a**	87.3±11.6	>1.1	63.87±3.27	>1.57	100
13	**16e**	20.6±0.3	>4.9	31.99±3.20	>3.13	100
14	**16f**	48.3±1.8	>2.1	N/A	N/A	100
15	**16g**	26.5±1.7	>3.8	N/A	N/A	100
16	**16h**	23.2±0.4	>4.3	46.18±1.84	>2.17	100
17	**16i**	31.1±2.7	>3.2	90.83±8.69	>1.10	100
18	**16j**	5.2±0.02	>13.9	19.79±0.11	3.69	73.00±14.01
19	**16k**	8.9±0.1	>7.8	12.32±1.90	5.68	70.00±9.80
20	**Miltefosine**	12.5±0.4	4.43	0.06±0.01	923.33	55.40±4.19

Therefore, in general, the analyzed pyrroloisoquinolines could be more active and safer to use as anti-leishmanicidal drug than Miltefosine for the treatment of *L. amazonensis* according to the tests carried out. This represents a very interesting result, considering that many anti-Leishmanial drugs, including Miltefosine, are relatively toxic and present important side effects, such as, vomiting, abdominal pain, fever, headaches, and decreased kidney function, or even Stevens-Johnson syndrome or low blood platelets. Conversely, all pyrroloisoquinolines tested are notably less active than Miltefosine for the treatment of *L. donovani*. Thus, only compound **24bc** appears again as one of the more active compounds of both series with IC_{50} = 7.10 ± 2.12.

Interestingly, we could observe a certain tendency in the behavior of the pyrroloisoquinolines against the promastigotes of the two different species of Leishmania studied. In fact, we found a regression coefficient of R = 0.67 for the IC_{50} of pyrroloisoquinoline derivatives in *L. amazonensis* vs. *L. donovani*, as graphically illustrated in Figure 1.8. It may indicate a similar mechanism of action of these pyrroloisoquinolines in the two different species. In any case, the confirmation of this particular finding is beyond the present study.

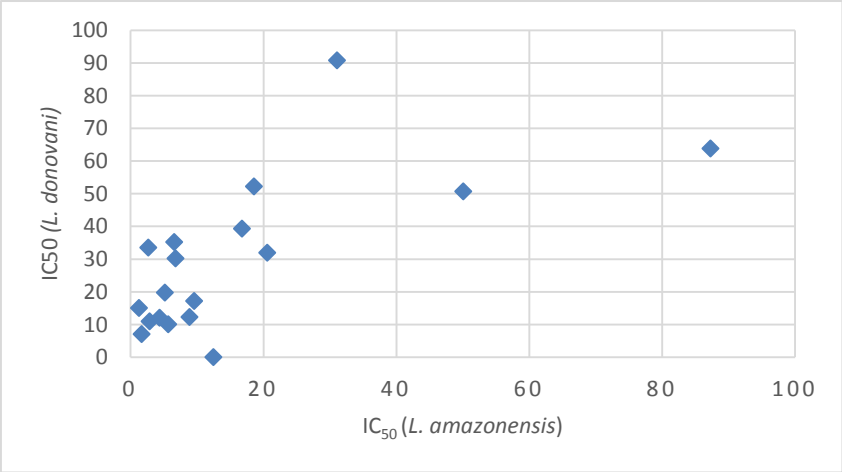


Figure 1.8. IC_{50} of pyrroloisoquinoline derivatives in *L. amazonenzis* vs. *L. donovani*

Then, the most active compounds of the promastigote assays were screened against amastigotes of *L. amazonensis* and *L. donovani*. In this case, all pyrroloisoquinolines tested were notably less active than Miltefosine for the treatment of *L. donovani* amastigotes. However, we found again that these compounds have IC_{50} values in the range 11-24, which are similar or even better than Miltefosine IC_{50} = 19.38 ± 2.87. All of them have also a notably high SI (between 3-8), which is 2- to 4-fold higher than Miltefosine (SI = 2). In this case, pyrroloisoquinoline **24ag** showed the best activity with IC_{50} = 11.20 ± 0.88 and higher selectivity with SI > 8.93.

Table 1.21. IC_{50} Leishmanicidal and cytotoxic effects from pyrroloisoquinoline derivatives (expressed as μg/mL) on *in vitro* amastigote assay.

Entry	Comp.	*L. amazonensis*		*L. donovani*		Macrophages J774
		IC_{50} ± SD	**SI**	**IC_{50} ± SD**	**SI**	**CC_{50} ± SD**
1	**24aa**	18.74±4.35	>5.34	16.34±2.73	>6.12	100
2	**24ac**	21.24±5.12	>5.34	11.21±2.60	>8.92	100
3	**24af**	23.92±2.26	>4.18	18.22±0.13	>5.49	100
4	**24ag**	11.20±0.88	>8.93	18.35±1.32	>5.45	100
5	**24al**	12.34±2.70	>8.10	72.51±11.92	>1.38	100
6	**24am**	24.90±2.50	>4.02	6.02±0,05	>16.61	100
7	**24bc**	24.53±1.98	>4.08	9.59±1.80	>10.43	100
8	**24ec**	27.95±6.93	>3.58	24.88±3.49	>4.02	100
9	**16j**	ND	-	14.70±2.80	4.97	73±14
10	**Miltefosine**	19.38±2.87	2.85	0.15±0.02	369.33	55.40±4.19

We can conclude that C10-arylmethyl substituted dihydropyrroloisoquinoline series seems to be safer than the drug of reference for the treatment of *L. amazonensis* amastigotes, presenting similar or even better activity. These results are promising, as the amastigotes

are inside the human macrophage cells in the present model of experimental assay. Therefore, we have found clear clues that these pyrroloisoquinolines are able to cross/attached host and parasite barriers to exert their activity without damaging the host membrane, that is, macrophage membrane. Thus, they first need to cross the membrane of the J774 rodent macrophage cells (host) and, next, they have to cross Parasitophorous Vacuole Membrane (PVM). Last, if the activity is not directly over PVM, the compounds should cross the parasite membrane to reach their molecular target in the membrane or inside the parasite. Thus, the PVM prevents the acidification of the media by lysosomes of the host cell to destroy an invading parasite. PVM is shapped by the parasite using parts of the membrane of the host cell. The PVM surrounds the intracellular parasite, creating a separate bubble of cytoplasm-filled plasma membrane within the host cell.[148] Futher studies are needed to determine the exact mechanism of action of this series of compounds.

[148] Kemp, L.E.; Yamamoto, M.; Soldati-Favre, D. *FEMS Microbiol. Rev*. **2013**, *37*, 607.

II

Synthesis of Chiral Hybrid Guanidine/Amine Ligands

1. INTRODUCTION

The design of ideal catalysts able to efficiently promote a desired transformation is one of the primary goals in synthetic chemistry. Thus, the suitability of different organic compounds in the development of highly homogeneous metal-based catalysts has been widely studied.

In this context, guanidines have attracted much attention as, in addition to their well-known applicability as organocatalysts,[1] they have shown remarkable applications as ligands in transition metal coordination chemistry and as superbasic proton sponge. In fact, guanidines have been found to be excellent N-donor ligands due to the ability to delocalize a positive charge over the guanidine moiety, behavior that leads to strongly basic and highly nucleophilic compounds with an enhanced capability to coordinate to metal ions. Consequently, guanidine-type ligands have been employed for the preparation of highly active homogeneous catalysts in combination with transition metals, which is of interest for a variety of applications.[2]

Modular synthesis of bis(guanidines) allows a flexible ligand synthesis derived from the combination of different spacers and guanidine groups. As a consequence, bis(guanidine) ligand libraries have been developed, including peralkylguanidines.

In this context, Harmjanz and coworkers[3] reported the preparation of 1,3-bis(*N,N,N',N'*-tetramethylguanidino)propane (**btmgp**), which represented the first bidentate peralkylated guanidine ligand that consisted of two tetramethylguanidine units bridged with an alkyl

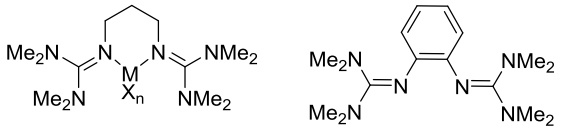
[1] For selected reviews on the use of guanidines as organocatalysts, see: a) Selig, P., Ed., *Guanidines as Reagents and Catalysts I. Topics in Heterocyclic Chemistry*, Vol. 50, Springer: Cham (Switzerland), **2017**. b) Selig, P., Ed., *Guanidines as Reagents and Catalysts II. Topics in Heterocyclic Chemistry*, Vol. 51, Springer: Cham (Switzerland), **2017**. c) Dong, S.; Feng, X.; Liu, X. *Chem. Soc. Rev.* **2018**, *47*, 8525.

[2] For recent reviews, see: a) Stanek, J.; Rösener, T.; Metz, A.; Mannsperger, J.; Hoffmann, A.; Herres-Pawlis, S. *Top Heterocycl Chem* **2017**, *51*, 95. b) Cui, X.-Y.; Tan, C.-H.; Leow, D. *Org. Biomol. Chem.* **2019**, *17*, 4689.

[3] Polh, S.; Harmjanz, M.; Schneider, J.; Saak, W.; Henkel, G. *J. Chem. Soc., Dalton Trans.* **2000**, 3473.

linker. It was thought that the steric demands of the two tetramethylguanidine residues, the flexible trimethylene bridge backbone and the strong basicity of guanidine moieties could make **btmgp** ligand a versatile tool in metal complex chemistry. Therefore, the complexation chemistry of the ligand was examined towards the preparation of $[MX_n(btmgp)]$ type coordination compounds with copper and iron salts in different oxidation states through the diimine nitrogens of **btmgp** (Figure 2.1).

Among the wide variety of peralkylguanidine ligands with a different bridging moieties, the coordination chemistry of 1,2-bis(tetramethylguanidino)benzene (**btmgb**) (Figure 2.1) has been widely studied. Thus, several reports based on the use of this chelating bis(guanidine) ligand for the synthesis of late- and post-transition-metal complexes, such as platinum, zinc, magnesium or aluminium, have been published.[4,5]



[(btmgp)MX$_n$]
M = Cu(I), Cu(II), Fe(II)
X = Cl, I

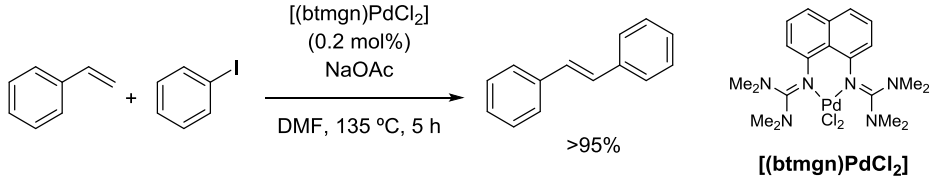
btmgb

Figure 2.1.

On the other hand, Sundermeyer and coworkers[6] reported on the synthesis of 1,8-bis(tetramethylguanidino)naphthalene (**btmgn**), an extremely basic guanidine derivative and kinetically active proton sponge. In fact, it presents two basic nitrogen centers in the molecule with the adequate orientation to uptake a proton, which constitutes the general backbone of all proton sponges. Besides, 1,8-bis(tetramethylguanidino)naphthalene exhibits a rich coordination chemistry through the lone pairs at the imine-nitrogen atoms. Thus, the first transition metal complexes of the proton sponge 1,8-bis(tetramethylguanidino)naphthalene with palladium and platinum salts were prepared in

[4] Peters, A.; Wild, U.; Hübner, O.; Kaifer, E.; Himmel, H.-J. *Chem. Eur. J.* **2008**, *14*, 7813.
[5] Reinmuth, M.; Wild, U.; Rudolf, D.; Kaifer, E.; Enders, M.; Wadepohl, H.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2009**, 4795.
[6] Raab, V.; Kipke, J.; Gschwind, R. M.; Sundermeyer, J. *Chem. Eur. J.* **2002**, *8*, 1682.

2008 by Himmel.[7] Additionally, preliminary catalytic studies revealed that Heck reaction between styrene and phenyl iodide could be efficiently catalyzed by [(btmgn)$PdCl_2$] complex, yielding almost quantitatively *trans*-stilbene using very low catalytic loading (0.2 mol%) (Scheme 2.1). Furthermore, platinum complexes with **btmgn** were found to be a highly active catalyst for hydrosilylation reaction between Et_3SiH and trimethyl(vinyl)silane.



Scheme 2.1.

A related class of widely studied guanidine-type ligands is represented by bis(imidazolin-2-imine) ligands, which exhibit pronounced electron-donating capacity due to the particularly effectiveness of the imidazolium ring to stabilize a positive charge. This way, the contribution of the mesomeric structure **B** of imidazole-based ligands (Figure 2.2) becomes more pronounced upon metal complexation.[8] As a consequence, bis(imizadolidin-2-imine) ligands show great tendency to stabilize catalytically active complexes. The coordination chemistry of the poly(imidazolin-2-imine) ligands depends on the steric and electronic properties of the ligands, which can be easily changed by introducing different 2-iminoimidazolines or by using different bridging moieties.

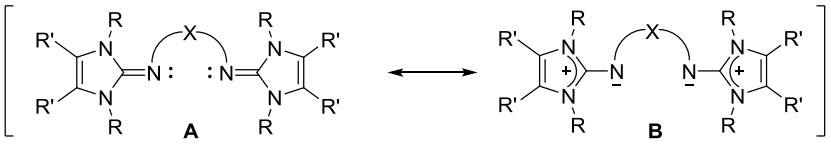


Figure 2.2.

[7] Wild, U.; Hübner, O.; Maronna, A.; Enders, M.; Kaifer, E.; Wadepohl, H.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2008**, 4440.
[8] Petrovic, D.; Hill, L. M. R.; Jones, P. G.; Tolman, W. B.; Tamm, M. *Dalton Trans.* **2008**, 887.

An example of bis(imidazolin-2-imine) ligand is 1,2-bis(*N,N'*-dimethyl-*N,N'*-ethyleneguanidino)benzene (**bdmegb**), which was found to be a powerful hydrogen acceptor. In fact, the bidentate type hydrogen bonding interaction between two guanidinyl functions in **bdmegb** ligand and the OH group of a variety of hydrogen donor aromatics led to successful complexation (Figure 2.3a).[9] Furthermore, the coordination to different metal ions has also been studied. Thus, the preparation of mononuclear Zn(II), Co(II) and Ni(II) complexes has been achieved (Figure 2.3b) from which $CoCl_2$-guanidine complex resulted suitable for paramagnetic NMR spectroscopic studies, such as $^1J_{C,H}$ correlation experiments.[10,11]

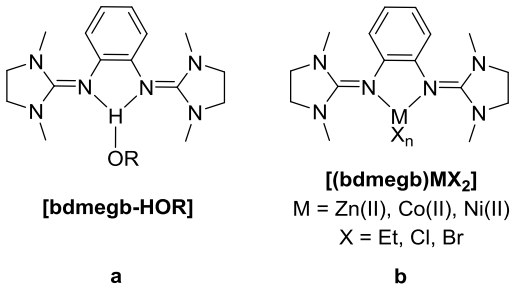


Figure 2.3.

On the other hand, 1,2-bis(imidazolin-2-imino)ethane ligands $\mathbf{BL^{Me}}$ and $\mathbf{BL^{iPr}}$ derived from 1*H*-imidazole heterocycle have found widespread use in organometallic and coordination chemistry (Figure 2.4a). Thus, it was possible the isolation of very stable half-sandwich 16-electron pentamethylcyclopentadienyl-ruthenium(II) complexes with an unusual stability derived from the strong basic nature of the novel bis(imidazolin-2-imine) ligands. In constrast, $\mathbf{BL^{Me}}$ and $\mathbf{BL^{iPr}}$ complexes displayed strong binding towards σ-donor/π-acceptor ligands such as CO or isocyanides. Consequently, complexes formed between $\mathbf{BL^{Me}}$ and $\mathbf{BL^{iPr}}$ and ruthenium(II) salts resulted highly reactive in the activation of small molecules

[9] Kawahata, M.; Yamaguchi, K.; Ishikawa, T. *Cryst. Growth Des.* **2005**, *5*, 373.
[10] Roquette, P.; König, C.; Hübner, O.; Wagner, A.; Kaifer, E.; Ender, M.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2010**, 4770.
[11] Reinmuth, M.; Neuhaüser, C.; Walter, P.; Enders, M.; Kaifer, E.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2011**, 83.

such as N_2 and H_2 and also promising candidates for catalytic applications.[12] Similar donor properties were found in analogous molybdenum(0) half-sandwich complexes of ethylene-bridged bis(imidazolin-2-imine) ligands **BL^{Me}** and **BL^{iPr}**.[13]

Finally, Tamm and coworkers[14] described a pyridine-bridged bis(imidazolin-2-imine) pincer ligand **TL^{tBu}** capable of forming highly reactive copper(I) complexes that allowed effective aerobic CO_2 fixation, C-Cl bond activation and Cu(I) disproportionation. The same group extended the study of the coordination chemistry of **TL^{tBu}** pincer ligand to "earlier" first row transition metals (manganese, iron, cobalt and nickel)[15] and to different lanthanide metals (yttrium, erbium and lutetium), in which the bulky bis(imidazolin-2-imine)pyridine ligand was coordinated to the metal center in a tridentate fashion (Figure 2.4b).[16]

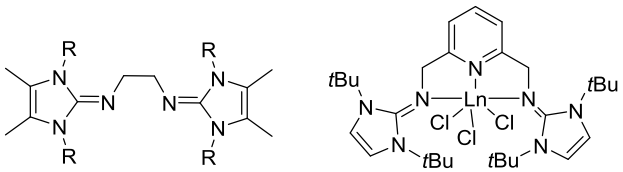
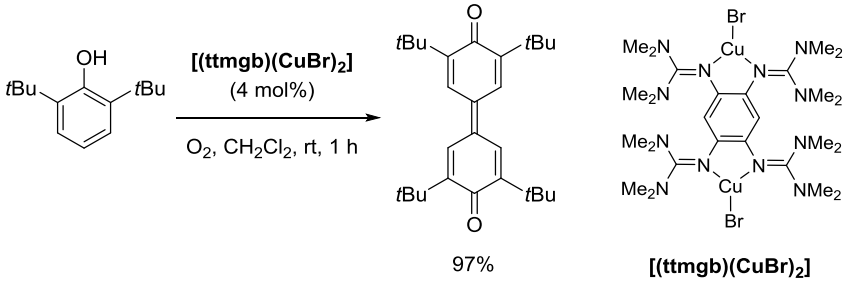


Figure 2.4

The wide variety of mononuclear metal complexes of guanidine-type ligands that have been synthesized demonstrate the important role that these ligands play in coordination chemistry. However, Himmel and coworkers considered the development of a structurally

[12] Petrovic, D.; Glöge, T.; Bannenberg, T.; Hrib, C. G.; Randoll, S.; Jones, P. G.; Tamm, M. *Eur. J. Inorg. Chem.* **2007**, 3472.
[13] Petrovic, D.; Hrib, C. G.; Randoll, S.; Jones, P. G.; Tamm, M. *Organometallics* **2008**, *27*, 778.
[14] Petrovic, D.; Bannenberg, T.; Randoll, S.; Jones, P. G.; Tamm, M. *Dalton Trans.* **2007**, 2812.
[15] Filimon, S.-A.; Petrovic, D.; Volbeda, J.; Bannenberg, T.; Jones, P. G.; Freiherr von Richthofen, C.-G.; Glaser, T.; Tamm, M. *Eur. J. Inorg. Chem.* **2014**, 5997.
[16] Panda, T. K.; Petrovic, D.; Bannenberg, T.; Hrib, C. G.; Jones, P. G.; Tamm, M. *Inorg. Chim. Acta* **2008**, *361*, 2236.

related class of potentially strong electron donors and N-bases by introduction of at least four guanidine groups on aromatic systems. This way, binuclear metal complexes would be formed through the coordination of the tetraguanidine ligand to two metal centers. For instance, 1,2,4,5-tetrakis(tetramethylguanidino)benzene (**ttmgb**) (Scheme 2.2)[17] was found to be a good chelating ligand for the construction of binuclear late transition-metal complexes with zinc, copper and platinum.[18,19] More recently, it was demonstrated that copper(I) catalysts bearing the redox-active guanidine ligand **ttmgb**, [$(CuBr)_2$(ttmgb)], could also efficiently promote the oxidative C-C homo- and cross-coupling reactions of phenols.[20]



Scheme 2.2.

Structurally related ligands containing a tetraguanidine unit have also been described to form complexes with Co(II), Ni(II), Au(I) and mainly Cu(I).[21,22,23,24]

[17] Peters, A.; Kaifer, E.; Himmel, H.-J. *Eur. J. Org. Chem.* **2008**, 5907.
[18] Peters, A.; Trumm, C.; Reinmuth, M.; Emeljanenko, D.; Kaifer, E.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2009**, 3791.
[19] Emeljanenko, D.; Peters, A.; Wagner, N.; Beck, J.; Kaifer, E.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2010**, 1839.
[20] Schön, F.; Kaifer, E.; Himmel, H.-J. *Chem. Eur. J.* **2019**, *25*, 8279.
[21] Vitske, V.; König, C.; Hübner, O.; Kaifer, E.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2010**, 115.
[22] Vitske, V.; Roquette, P.; Leingang, S.; Adam, C.; Kaifer, E.; Wadepohl, H.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2011**, 1593.
[23] Ziesak, A.; Wesp, T.; Hübner, O.; Kaifer, E.; Wadepohl, H.; Himmel, H.-J. *Dalton Trans.* **2015**, *44*, 19111.
[24] Emeljanenko, D.; Peters, A.; Vitske, V.; Kaifer, E.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2010**, 4783.

So far, the selected examples of guanidine-type ligands show identical donor strengths and substituents with exactly the same steric demand. However, the construction of hybrid guanidine ligands by combination of a very strong N-donor guanidine moiety with a different weak donor function is also possible. This way, the ligand enables the creation of a catalytic system with a strong complexation of the transition metal and a flexible coordination sphere.

In this context, Herres-Pawlis and coworkers considered that the combination of the excellent donor properties of guanidines with additional coordination space for precoordination of substrates could improve the catalytic activity of the existing guanidine-based zinc complexes in lactide polymerization reaction.[25] Thus, they modified the symmetric bis(*N*,*N*,*N'*,*N'*-tetramethylguanidino)ethane ligand system analogous to **btmgp** ligand (Figure 2.1) by substituting one bulky guanidine moiety by a pyridine or quinoline unit, leading to guanidine-pyridine and guanidine-quinoline ligands shown in Figure 2.5. These hybrid ligands were then employed for the synthesis of the first zinc complexes of guanidine-pyridine and guanidine-quinoline hybrid ligands, which were proved to be active initiators in the ring-opening polymerization of D,L-lactide, allowing the formation of polylactides with high molecular weight values.[26]

Several applications have been found for this type of hybrid ligands. For instance, the guanidine-based cobalt complexes showed a potential application in detector or sensor technology, as the inherent fluorescence of the hybrid ligands was totally quenched when cobalt atom was coordinated.[27] Furthermore, copper complexes of the guanidine-pyridine hybrid ligands, **TMGpy** and **DMEGpy** (Figure 2.5), were shown to mediate in the solvent-free atom transfer radical polymerization of styrene.[28]

[25] Börner, J.; Herres-Pawlis, S.; Flörke, U.; Huber, K. *Eur. J. Inorg. Chem.* **2007**, 5645.
[26] Börner, J.; Flörke, U.; Huber, K.; Döring, A.; Kuckling, D.; Herres-Pawlis, S. *Chem. Eur. J.* **2009**, *15*, 2362.
[27] Hoffmann, A.; Börner, J.; Flörke, U.; Herres-Pawlis, S. *Inorg. Chim. Acta* **2009**, *362*, 1185.
[28] Hoffmann, A.; Bienemann, O.; dos Santos-Vieira, I.; Herres-Pawlis, S. *Polymers* **2014**, *6*, 995.

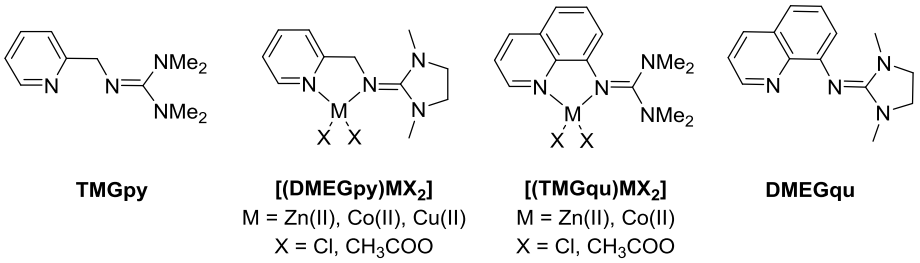
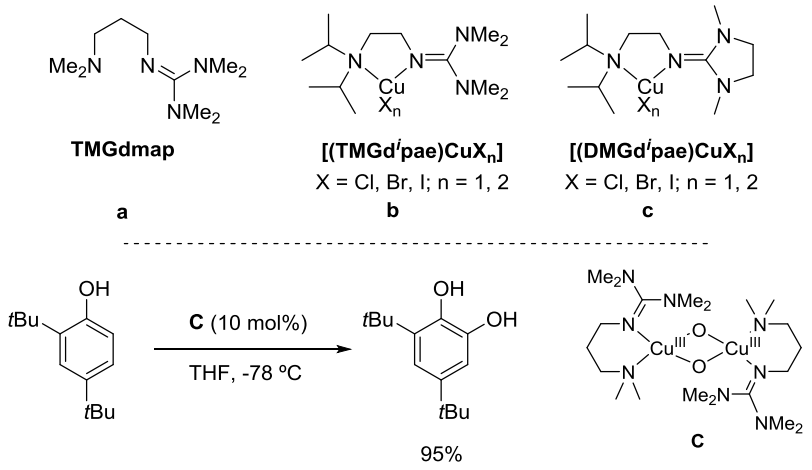


Figure 2.5.

Additionally, various hybrid ligands that combine a guanidine moiety and an amine group have also been developed (Scheme 2.3). In this context, the permethylated-amine-guanidine bidentate ligand **TMGdmap**, based on a 1,3-propanediamine backbone, readily reacted with O_2 forming a bis(μ-oxo)dicopper(III) complex (**C**) capable of promoting an oxidative transformation, such as the hydroxylation of phenolates to catecholates in similar manner to tyrosinase. (Scheme 2.3a)[29]

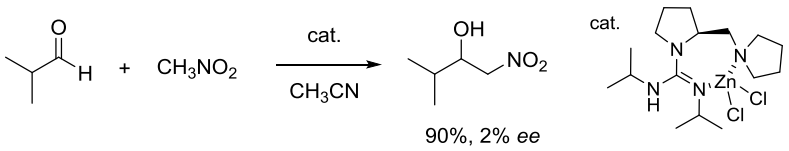


Scheme 2.3.

[29] Herres-Pawlis, S.; Verma, P.; Haase, R.; Kang, P.; Lyons, C. T.; Wasinger, E. C.; Flörke, U.; Henkel, G.; Stack, T. D. P. *J. Am. Chem. Soc.* **2009**, *131*, 1154.

Later, the same group reported the synthesis of the heterobidentate nitrogen donor ligands **TMGd^{i}pae** and **DMEGd^{i}pae** depicted in Scheme 2.3b and 2.3c,[30] whose catalytic complexes with copper halides were evaluated in atom transfer radical polymerization, showing a high potential activity due to the high polymerization rate, good solubility and an adequate control of radical polymerization.

As shown, guanidines are well-known and studied versatile ligands. However, little is known about the suitability of chiral metal complexes of guanidine as asymmetric catalysts. In this context, Anders group[31] reported the synthesis of chiral zinc(II) and molybdenum(0) guanidine complexes and investigated the applicability of a neutral Zn(II) complex as chiral catalyst in asymmetric Henry reaction between 2-methylpropanol and nitromethane. Thus, the corresponding β-nitroalcohol was obtained in excellent yield, although with unsatisfactory outcome in terms of enantioselectivity (Scheme 2.4).

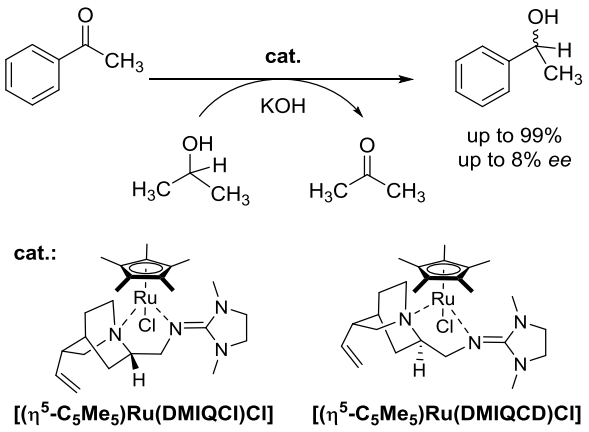


Scheme 2.4.

Later, Tamm and coworkers synthesized two quinine-derived guanidine chiral ligands by connecting a quinuclidine core and an imidazolidin-2-imine moiety. This way, the first *N*,*N*-bidentate ligands bearing a configurationally stable N*-stereogenic center in their uncoordinated form were reported.[32] These ligands were able to form stable chelate complexes with Ru(II), Pd(II) and Ni(II), which could show potential utility in asymmetric transition metal catalysis. However, when Ru(II) complexes were tested as catalyst in the enantioselective transfer hydrogenation of acetophenone, using 2-propanol as organic

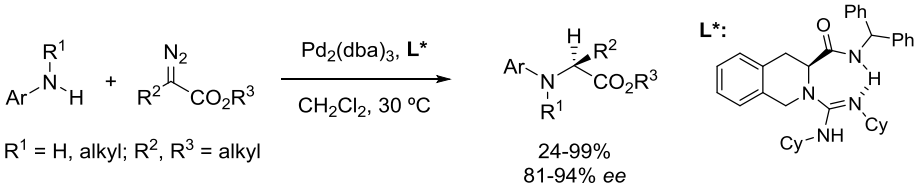
[30] Bienemann, O.; Haase, R.; Jesser, A.; Beschnitt, T.; Döring, A.; Kuckling, D.; dos Santos-Vieira, I.; Flörke, U.; Herres-Pawlis, S. *Eur. J. Inorg. Chem.* **2011**, 2367.
[31] Köhn, U.; Schulz, M.; Görls, H.; Anders, E. *Tetrahedron: Asymmetry* **2005**, *16*, 2125.
[32] Filimon, S.-A.; Hrib, C. G.; Randoll, S.; Neda, I.; Jones, P. G.; Tamm, M. *Z. Anorg. Allg. Chem.* **2010**, *636*, 691.

hydrogen donor, only low enantiomeric excesses were obtained, which indicated that the chiral induction of the quinuclidine moiety is not effective (Scheme 2.5).



Scheme 2.5.

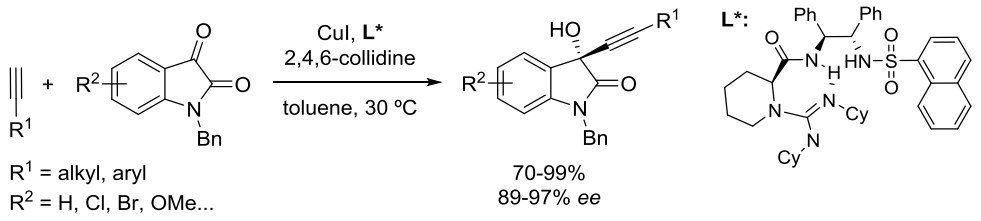
More recently, it has been shown that the complex formed by a chiral guanidine ligand in combination with Pd(0) constitute an efficient catalyst for the asymmetric N-H insertion reaction of α-diazoesters with secondary and primary anilines. Thus, various enantioenriched α-amino acid derivatives were readily achieved in good yields (24-99%) and excellent *ee* values (81-94% *ee*), although the structure of the active species is unknown (Scheme 2.6).[33]



Scheme 2.6.

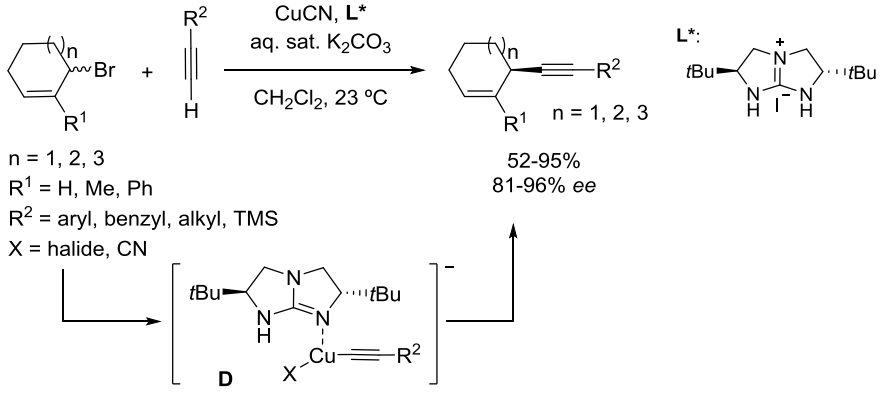
[33] Zhu, Y.; Liu, X.; Dong, S.; Zhou, Y.; Li, W.; Lin, L. L.; Feng, X. *Angew. Chem. Int. Ed.* **2014**, *53*, 1636.

A related bifunctional chiral guanidine ligand bearing a sulfonamide unit was found to efficiently catalyze the enantioselective alkynylation of isatins with terminal alkynes in the presence of CuI and 2,4,6-collidine (Scheme 2.7).[34]



Scheme 2.7.

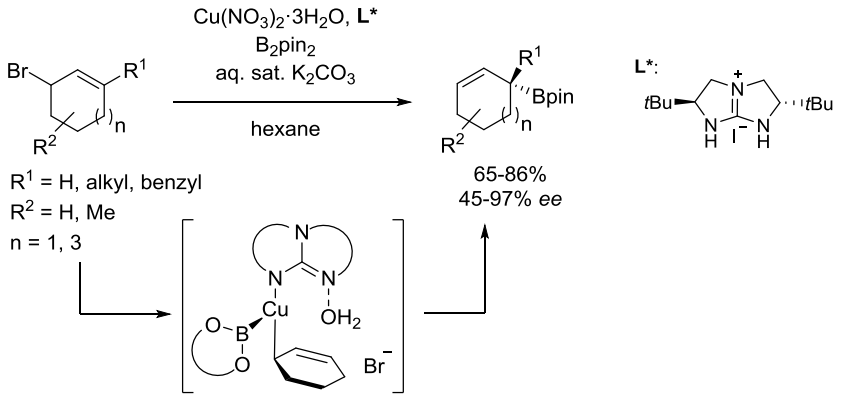
Recently, a monodentate chiral guanidine-copper complex was shown to catalyze asymmetric allylic alkynylation of racemic cyclic allylic bromides with terminal alkynes under biphasic conditions. A linear correlation between the enantiopurity of the catalyst and reaction product indicates that the nucleophilic anionic guanidine-copper complex **D** might be the active catalytic species (Scheme 2.8).[35]



Scheme 2.8.

[34] Chen, Q.; Tang, Y.; Huang, T.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2016**, *55*, 5286.
[35] Cui, X.-Y.; Ge, Y.; Tan, S. M.; Jiang, H.; Tan, D.; Lu, Y.; Lee, R.; Tan, C.-H. *J. Am. Chem. Soc.* **2018**, *140*, 8448.

Additionally, the same chiral guanidine-Cu(I) complex was efficiently employed as catalyst in a S_N2' borylation process, which afforded enantiopure secondary and tertiary cyclic allylboronates from racemic allylic bromides (Scheme 2.9).[36]



Scheme 2.9.

[36] Ge, Y.; Cui, X.-Y.; Tan, S. M.; Jiang, H.; Ren, J.; Lee, N.; Lee, R.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2019**, *58*, 2382.

2. OBJECTIVES

As stated in previous section, guanidines represent a class of N-donor ligands with a rich coordination chemistry and, in particular, the practical applicability of their copper complexes has been demonstrated. However, few reports based on the development of chiral hybrid guanidine-type ligands capable of forming transition metal complexes have been published.

Therefore, we decided to synthesize a new family of chiral hybrid guanidine ligands that include an amine group and a (protected) hydroxyl group in their structure (Figure 2.6), which show a suitable coordination sphere for the formation of catalytically active complexes with transition metals. Different substituents would be used to modulate the basicity of guanidine and amine, which could regulate the catalytic activity of metal complexes in different enantioselective reactions.

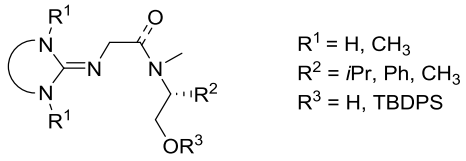
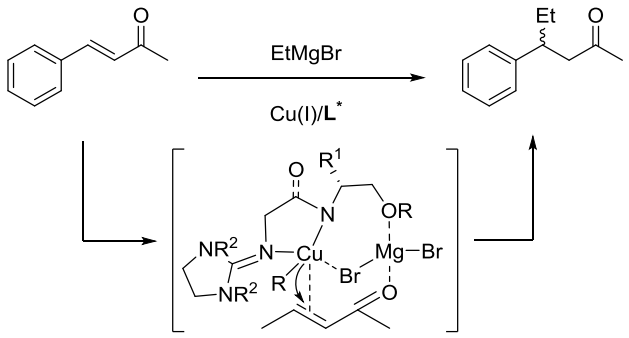


Figure 2.6.

Then, catalytic capacity of the synthesized enantiopure hybrid guanidine/amine ligands would be evaluated in two widely studied copper(I)-catalyzed reactions, such as conjugate addition of a Grignard reagent to an acyclic α,β-unsaturated ketone and Henry reaction.

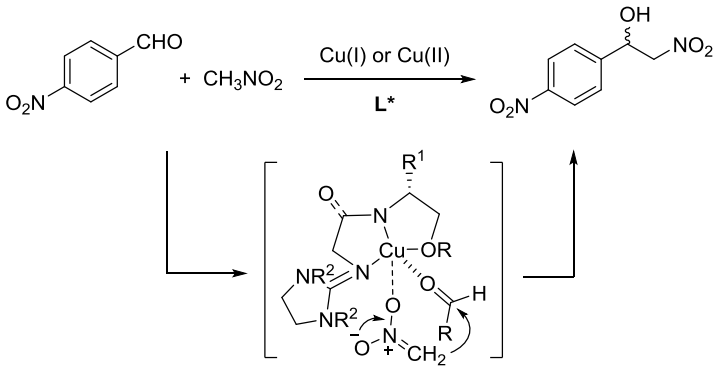
Thus, we chose first the asymmetric conjugate addition reaction between a highly reactive Grignard reagent, such as EtMgBr, and the acyclic α,β-unsaturated ketone *trans*-4-phenyl-3-buten-2-one (Scheme 2.10)**.** In fact, it was thought that the structure of designed hybrid ligands could favor the generation of monoorganocuprates [RCuX(L*)] and could be appropriate for avoiding the formation of homocuprates that would lead to non-catalyzed reactions. Moreover, this way, bimetallic assistance between copper and magnesium could

take place in the intermediate reactive species that would be essential for the substrate activation and stereochemical control of the reaction (Scheme 2.10).



Scheme 2.10.

Finally, the efficiency of the hybrid guanidine/amine ligands would also be tested in the copper-catalyzed asymmetric Henry reaction between 4-nitrobenzaldehyde and nitromethane (Scheme 2.11), where the nitronate and the aldehyde would coordinate to copper to produce the addition product.

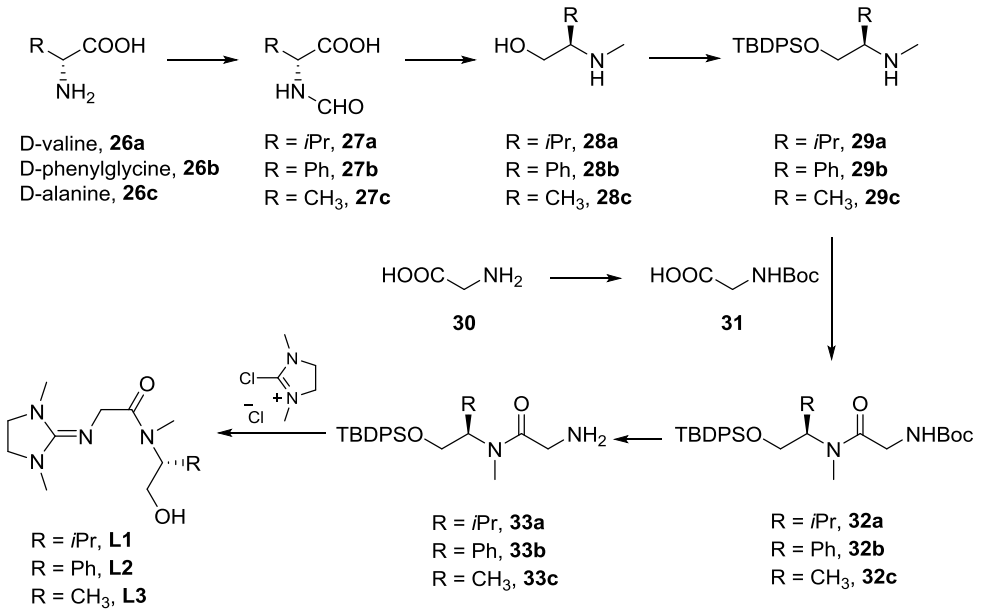


Scheme 2.11.

3. RESULTS AND DISCUSSION

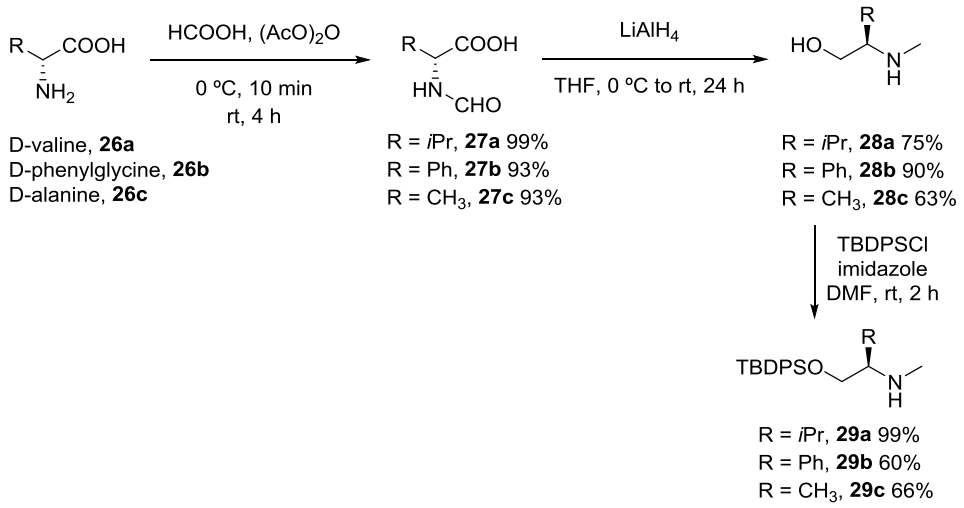
3.1. Synthesis of new chiral hybrid guanidine/amine ligands L1-L12

The synthetic route designed for the formation of enantioenriched hybrid guanidine/amine ligands **L1-L3** is described in Scheme 2.12, which were synthesized by alkylation of an enantiomerically pure diamine **33a-c** with an adequate imidazolinium salt. The enantiopure amines **33a-c** were previously synthesized through condensation of *O*-protected aminoalcohols **29a-c** with *N*-Boc protected glycine **31**, followed by deprotection of hydroxyl group of **32a-c**. The *O*-protected alcohols **29a-c** were obtained from the corresponding alcohols **28a-c**, which were synthesized through reduction of formamides **27a-c**, derived from *N*-formylation of commercially available amino acids **26a-c**.



Scheme 2.12.

The synthetic route began with *N*-formylation reaction of commercially available amino acids [D-valine (**26a**), D-(-)-α-phenylglycine (**26b**) and D-alanine (**26c**)] with formic acid and acetic anhydride,[37] which provided the corresponding formamides **27a-c** in excellent yields (93-99%). Then, simultaneous reduction of amide to amine and carboxylic acid to alcohol using $LiAlH_4$[37] afforded alcohols **28a-c**. A subsequent treatment of alcohols **28a-c** with *tert*-butyldiphenylsilyl chloride in presence of imidazole led to the corresponding protected alcohols **29a-c** (Scheme 2.13).

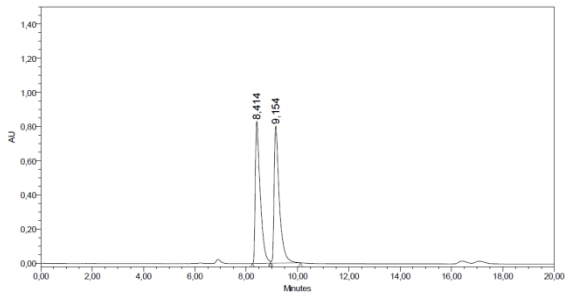


Scheme 2.13.

At this point, we checked that no racemization had taken place. For that purpose, we determined the *ee* value of **29a** and we found that the isopropyl-substituted *O*-protected alcohol had a high enantiomerical purity (92% *ee*), although it was slightly lower than the optical purity of commercially available D-valine (99% *ee*). The enantiomeric excess (%) measurement of protected alcohol **29a** was determined by chiral stationary phase HPLC, in comparison with the racemic mixture (Figure 2.7A). By analogy, we assumed that no racemization took place in the synthesis of protected alcohols **29b,c**.

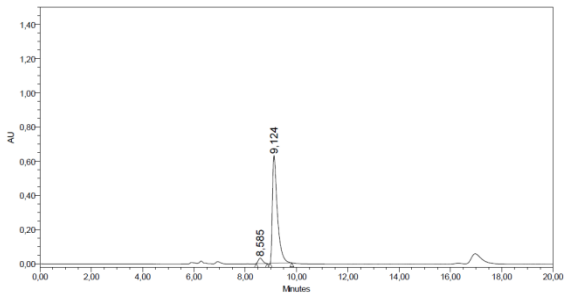
[37] Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang, T.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem.* **1992**, *57*, 5383.

A.



	RT	Area	% Area	Height
1	8,414	11104500	49,51	831549
2	9,154	11322298	50,49	801619

B.

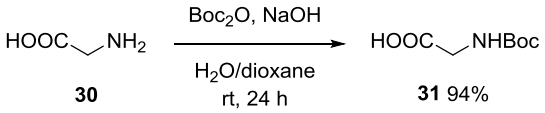


	RT	Area	% Area	Height
1	8,585	366163	4,14	31437
2	9,124	8486164	95,86	629724

Figure 2.7. HPLC chromatograms of **29a**. Chiralcel ADH, hexane/*i*PrOH 1%, 0.5 mL/min: **A.** racemic mixture. **B.** 92% *ee.*

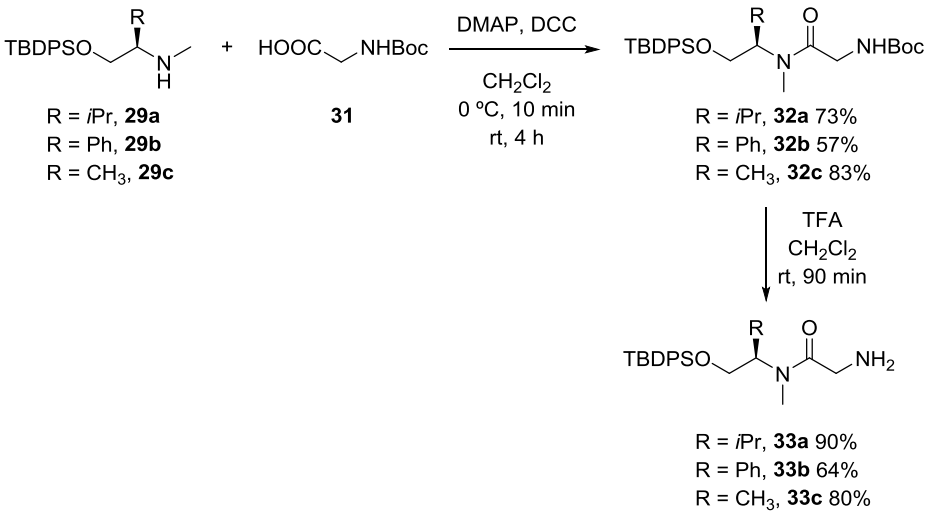
The synthetic route continued with the *N*-alkylation reaction between amino alcohols **29a-c** and Boc-protected glycine **31** previously prepared by reaction of commercially available glycine with anhydride Boc_2O and NaOH in a mixture H_2O/dioxane at room temperature (Scheme 2.14).[38]

[38] Brough, P.; Klumpp, C.; Bianco, A.; Campidelli, S.; Prato, M. *J. Org. Chem.* **2006**, *71*, 2014.



Scheme 2.14.

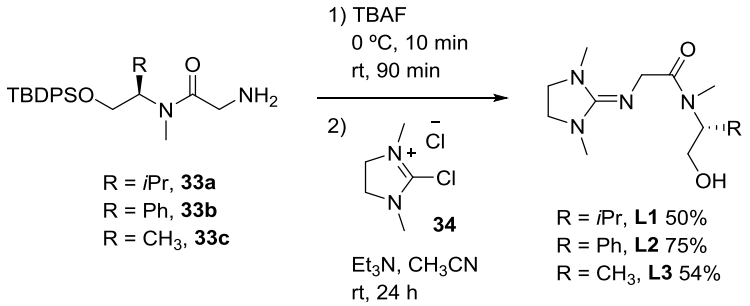
Next, direct amide formation between carboxylic acid group of **31** and amine moiety of **29a-c** in the presence of DMAP and DCC afforded amides **32a-c** in good yields (57-83%). Then, amino group was selectively deprotected, obtaining the corresponding free amines **33a-c** in good to excellent yields (64-90%) (Scheme 2.15).



Scheme 2.15.

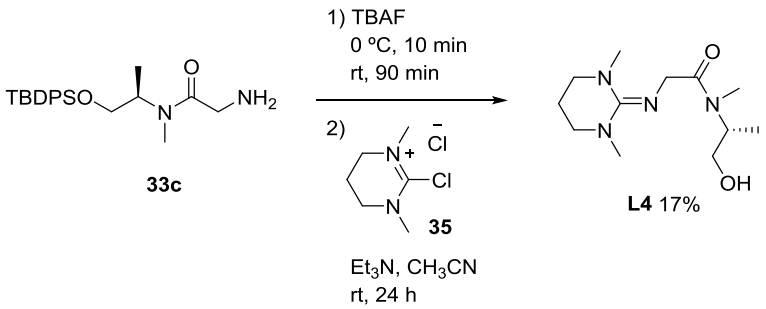
The last step of the synthesis consisted of deprotection of hydroxyl group followed by condensation reaction of commercially available 2-chloro-1,3-dimethylimidazolinium chloride (**34**) under the presence of triethylamine,[39] which led to desired hybrid guanidine/amine ligands **L1-L3** in moderate to good yields (50-75%) (Scheme 2.16).

[39] Kantlehner, W.; Haug, E.; Mergen, W. W.; Speh, P.; Maier, T.; Kapassakalidis, J. J.; Bräuner, H.-J.; Hagen, H. *Liebigs Ann. Chem.* **1984**, *1*, 108.



Scheme 2.16.

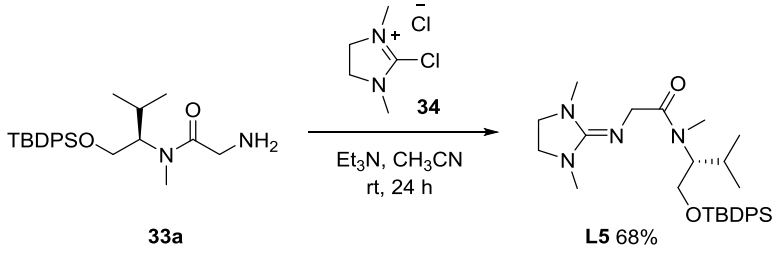
At this point, we designed another guanidine/amine ligand analogous to methyl-substituted **L3**, in which the guanidine moiety would be introduced by using a tetrahydropyridinium salt instead of imidazolinium salt (Scheme 2.17). Thus, a new ligand **L4** was synthesized from compound **33c** by deprotection of hydroxyl group, and subsequent alkylation with tetrahydropyridinium salt **35**, previously obtained by treatment of commercially available 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone with oxalyl chloride.[40] However, **L4** could be isolated in low yield, presumably due to difficulties associated to the practical manipulation of **35**, as it is a very hygroscopic salt.



Scheme 2.17.

[40] Kremzow, D.; Seidel, G.; Lehmann, C. W.; Fünstner, A. *Chem. Eur. J.* **2005**, *11*, 1833.

In addition, we decided to synthesize another ligand (**L5**) which retained the protecting group of the alcohol, so as to evaluate later the effect of that group in copper catalyzed reactions. Thus, the synthesis of new ligand **L5** was successfully achieved by direct alkylation of isopropyl-substituted **33a** with 2-chloro-1,3-dimethylimidazolium chloride (**34**) (Scheme 2.18).



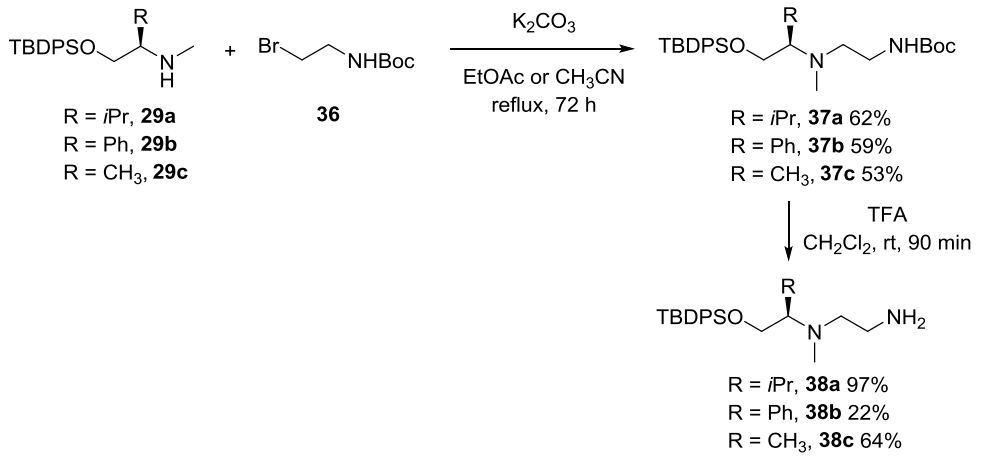
Scheme 2.18.

All the synthesized guanidine/amine ligands (**L1-L5**) have an amide moiety in their structure, which leads to the presence of rotamers due to slow rotation around the C-N bond, as it was shown in the corresponding ^{1}H and ^{13}C NMR experiments. The presence of rotamers could hinder the coordination to the metal and, consequently, the formation of Cu(I)/**L1-L5** complexes. Therefore, we decided to synthesize analogous amine ligands **L6-L8**, which have a more basic nitrogen atom.

The synthetic route designed for ligands **L6-L8**, illustrated in Schemes 2.19 and 2.20, is analogous to the one described for ligands **L1-L3**. Thus, the previously synthesized protected amino alcohols **29a-c** were subjected to different alkylation conditions with *tert*-butyl (2-bromoethyl)carbamate (**36**).[41] After some experimentation, we found that the best conditions for *N*-alkylation reaction between bromide **36** and amine group of β-substituted protected alcohols **29a-c** afforded the desired tertiary amines **37a-c** in acceptable yields (53-62%) (Scheme 2.19). The efficiency of the amine alkylation could not be improved using different reaction conditions (base, solvent, etc.). Next, deprotection of the amino

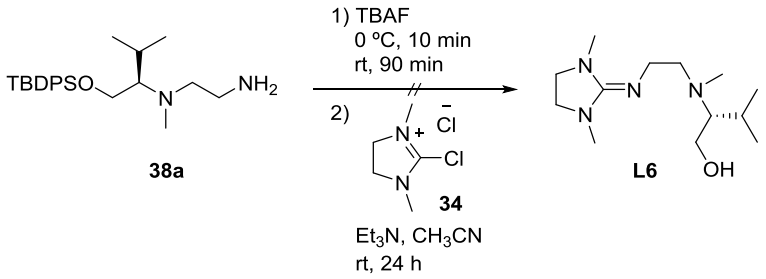
[41] Carbamate **36** was prepared by *N*-Boc protection of 2-bromoethylamine hydrobromide. See: Pandey, M. D.; Mishra, A. K.; Chandrasekhar, V.; Verma, S. *Inorg. Chem.*, **2010**, *49*, 2020.

group of **37a,c** with trifluoroacetic acid led to **38a** and **38c** in good to excellent yields, whereas deprotection of **37b** was not very efficient and free amine **38b** was obtained only in low yield (22%) (Scheme 2.19).



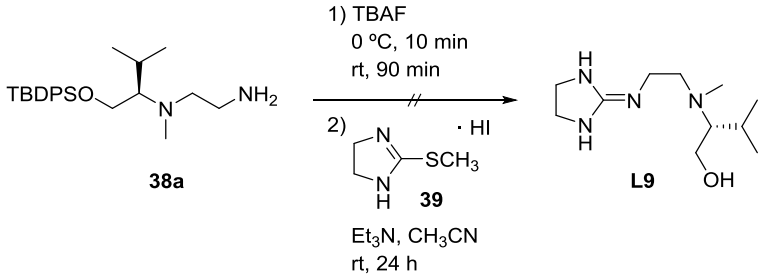
Scheme 2.19.

The last step of the synthesis consisted of deprotection of the alcohol and introduction of imidazolidium salt to afford guanidine moiety of ligands **L6**-**L8**. At this point, we chose **38a**, which was treated with tetrabutylammonium fluoride and, after 90 min, with 2-chloro-1,3-dimethylimidazolinium chloride (**9**). Unfortunately, only a complex mixture of products was obtained and ligand **L6** was not detected (Scheme 2.20). In view of the impossibility to synthesize ligand **L6**, no efforts were made for the construction of ligands **L7**-**L8**.



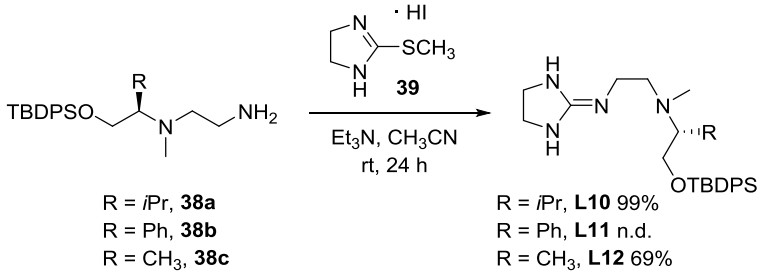
Scheme 2.20.

At this point, we considered to introduce the guanidine moiety using a different procedure (Scheme 2.21). For that purpose, we chose 2-methylthiodihydroimidazole hydroiodide **39** previously synthesized,[42] which would lead to a new ligand **L9**. Unfortunately, formation of **L9** was not observed after treatment of **38a** under classical alkylation reaction conditions.



Scheme 2.21.

Finally, we attempted the synthesis of another isopropyl-substituted ligand **L10**, analogous to **L9**, in which the alcohol remained protected (Scheme 2.22). Thus, **L10** was obtained in quantitative yield (99%) by direct alkylation of **38a** with **39**, avoiding the deprotection of hydroxyl group. Methyl-substituted **L12** ligand was also successfully synthesized in the same way, but phenyl-substituted ligand **L11** was not formed and unreacted starting material **38b** was isolated.



Scheme 2.22.

[42] Imidazole **39** was obtained from commercially available 2-imidazolethione by treatment with methyl iodide. See: Aspinall, S. R.; Bianco, E. J. *J. Am. Chem. Soc*. **1951**, *73*, 602.

In conclusion, it has been possible the synthesis of a new family of chiral hybrid guanidine/amine ligands with a suitable structure for the formation of mononuclear complexes in Cu(I) catalyzed reactions.

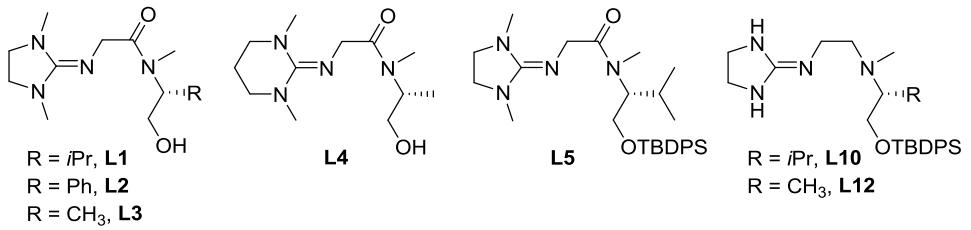


Figure 2.8.

Thus, our next goal was to evaluate the capability of the complexes of synthesized ligands and Cu(I) salts for achieving induction in conjugate addition of organomagnesium reagents to acyclic enones and Henry reaction.

3.2. Screening of the new catalytic systems in Cu(I)-catalyzed asymmetric conjugate addition reactions.

The copper-catalyzed asymmetric conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is one of the most relevant and versatile methods for the construction of C–C bonds. Controlling the regio- (1,4-addition *vs.* 1,2-addition) and the stereoselectivity of the copper-catalyzed conjugate addition is one of the main challenges of the reaction, which can be enabled by the use of adequately designed chiral ligands. Thus, enantioselective copper-catalyzed versions of conjugate addition have been extensively and successfully studied with different α,β-unsaturated carbonyl compounds and a variety of organometallic reagents, such as dialkylzinc,[43] organoboron[44] and silicon reagents.[45]

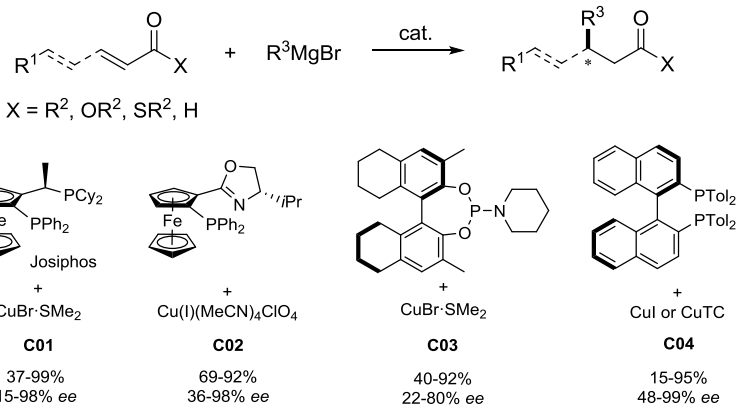
[43] a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. b) Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699; c) Wan, H.; Hu, Y.; Liang, Y.; Gao, S.; Wang, J.; Zheng, Z.; Hu, X. *J. Org. Chem.* **2003**, *68*, 8277.

However, the application of intrinsically very reactive Grignard reagents in asymmetric 1,4-addition to α,β-unsaturated carbonyl compounds has received less attention, due to difficulties associated to control the regioselectivity and avoid the preferential 1,2-attack. In addition, reaction outcome has shown a strong dependence on the structure of the substrate and ligand. Thus, the enantioselective copper-catalyzed conjugate addition of Grignard reagents to cyclic enones could be achieved using ferrocenyl-based diphosphine ligands.[46] However, the development of efficient catalytic systems for more challenging acyclic α,β-unsaturated enones has been limited, and only few notable examples of highly enantioselective copper-catalyzed conjugate addition reactions have been reported.

Thus, the first example of highly regio- and enantioselective copper-catalyzed conjugate addition of Grignard reagents to a range of both acyclic aliphatic and aromatic enones was reported by Feringa using Josiphos ligand in combination with $CuBr \cdot SMe_2$ as efficient catalytic system **C01** (Scheme 2.23).[47] Besides, the applicability of Josiphos based complex **C01** was further demonstrated, as it resulted also suitable for the copper-catalyzed asymmetric conjugate addition of several organomagnesium compounds to a large variety of acyclic α,β-unsaturated carbonyl derivatives, such as esters[48] and thioesther.[49] Additionally, a different chiral ferrocene-based phosphinooxazoline ligand in conjuction with $Cu(I)(MeCN)_4ClO_4$ formed the catalytic system **C02**, which efficiently catalyzed the

[44] a) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052. b) Ma, Y.; Song, C.; Ma, C.; Sun, Z.; Chai, Q.; Andrus, M. B. *Angew. Chem. Int. Ed.* **2003**, *42*, 5871.
[45] Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. b) Oi, S.; Taira, A.; Honna, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97.
[46] Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5834.
[47] López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, *126*, 12784.
[48] López, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 2752.
[49] Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966.

first 1,4-selective and enantioselective copper-catalyzed 1,4-addition of organomagnesium compounds to linear α,β,γ,δ-unsaturated ketones (Scheme 2.23).[50]



Scheme 2.23.

The use of phosphoramidites in the asymmetric Cu(I)-catalyzed conjugate addition of Grignard reagents to acyclic aliphatic and aromatic α,β-unsaturated enones has also been described. For instance, complex **C03** was used an active catalyst for the completely regioselective 1,4-addition of Grignard reagents to acyclic enones (Scheme 2.23).[51]

On the other hand, the chiral catalytic system **C04** prepared from (*R*)-Tol-BINAP and CuI has been successfully employed for the conjugate addition to α,β-unsaturated esters[52] and thioesters,[53] and, in combination with CuTC, to α,β-unsaturated aldehydes (Scheme 2.23).[54] It is noteworthy that competitive undesired direct carbonyl attack could not be completely

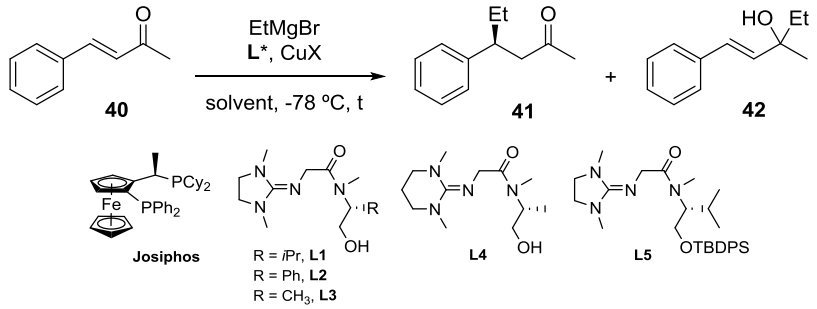
[50] Ma, Z.; Xie, F.; Yu, H.; Zhang, Y.; Wu, X.; Zhang, W. *Chem. Commun.* **2013**, *49*, 5292.
[51] Maciá, B.; Fernández-Ibáñez, M. A.; Mršić, N.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron Lett.* **2008**, *49*, 1877.
[52] Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 276.
[53] Maciá, B.; Geurts, K.; Fernández-Ibáñez, M. A.; ter Horst, B.; Minnaard, A.; Feringa, B. L. *Org. Lett.* **2007**, *9*, 5123.
[54] Palais, L.; Babel, L.; Quintard, A.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1988.

avoided, probably due to the high reactivity of the α,β-unsaturated aldehydes, and, therefore, 1,2-adducts were formed in the reaction together with the 1,4-products. However, moderate to good 1,4-regioselectivity was obtained by using TMSCl, as it is well-known to increase the rate of the conjugate addition of cuprates[55] and to favor the 1,4-addition on enals.[56]

As it has been shown, the most efficient catalytic systems used in the asymmetric copper-catalyzed conjugate addition of Grignard reagents to acyclic α,β-unsaturated carbonyl compounds are based on chiral ferrocene-based diphosphine or phosphinooxazoline, bidentate phosphine and phosphoramidite ligands. However, only few examples have been described for a highly regio- and enantioselective reaction and, consequently, it still remained challenging to design chiral catalysts able to catalyze the conjugate addition reaction of Grignard reagents to acyclic Michael acceptor with high yields and enantiomeric excesses.

Therefore, we decided to examine if the chiral hybrid guanidine/amine ligands synthesized in Section 3.1. could be suitable to control both the regio- and enantioselectivity of the conjugate addition of organomagnesium reagents to acyclic enones. Specifically, we would explore the ability of Cu(I)/**L1-L5** complexes to shift completely the reaction towards 1,4-selectivity, avoiding the inherent 1,2-addition, and to induce enantiocontrol in formation of 1,4-adduct. For that purpose, we selected the reaction between a highly reactive Grignard reagent, such as EtMgBr, and the acyclic α,β-unsaturated ketone *trans*-4-phenyl-3-buten-2-one (**40**), using different Cu(I) salts in the presence of **L1-L5** ligands (Scheme 2.24, Table 2.1)**.**

[55] a) Corey, E. J.; Boaz, N .W. *Tetrahedron Lett.* **1985**, *26*, 6015. b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. c) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.
[56] Chuit, C.; Foulon, J. P.; Normant, J. F. *Tetrahedron* **1980**, *36*, 2305.



Scheme 2.24.

Table 2.1. Screening of reaction conditions in the conjugate addition of EtMgBr over **40**.

Entry	CuX (5 mol%)	L* (6 mol%)	Solvent	t (min)	Yield 41 (%)[a]	Yield 42 (%)[a]	*ee* 41 (%)[b]
1	-	-	CH_2Cl_2	30	61	20	-
2	CuBr·SMe_2[c]	-	CH_2Cl_2	30	49	19	-
3[d]	CuBr·SMe_2	**Josiphos**	*t*BuOMe	120	73	-	97[e]
4	CuBr·SMe_2	**L1**	*t*BuOMe	60	45	17	<2
5	CuBr·SMe_2	**L1**	CH_2Cl_2	60	44	16	<2
6	CuBr·SMe_2	**L2**	CH_2Cl_2	60	42	19	<2
7	CuBr·SMe_2	**L3**	CH_2Cl_2	60	49	28	<2
8	CuBr·SMe_2	**L4**	CH_2Cl_2	45	49	19	<2
9	CuBr·SMe_2	**L5**	CH_2Cl_2	90	51	18	<2
10[f]	CuBr·SMe_2	**L4**	THF	60	13	25	<2
11[f]	CuBr·SMe_2	**L4**	Toluene	60	43	18	<2
12	CuBr	**L4**	CH_2Cl_2	45	53	12	<2
13	CuI	**L4**	CH_2Cl_2	45	46	37	<2
14[g]	CuBr·SMe_2	**L4**	CH_2Cl_2	145	36	7	<2
15[h]	CuBr·SMe_2	**L4**	CH_2Cl_2	45	47	18	<2

[a] Isolated yield. [b] Determined by chiral stationary phase HPLC (Chiralcel OJ-H, 99% hexane/*i*-propanol, 0.5 mL/min). [c] 1 equiv. of CuBr·SMe_2. [d] MeMgBr was used as Grignard reagent. [e] Performed according to Ref. 46. [f] Performed at -30 ºC. [g] 1.2 equiv. of BF_3·OEt_2 were added. [h] EtMgBr was slowly added to the reaction mixture over 30 min.

An initial screening of the reaction conditions was first carried out, performing the conjugate addition reaction of EtMgBr over the enone **40** in absence of Cu(I) salt and chiral ligand. Although both 1,2- and 1,4-adducts were formed, a clear preference towards 1,4-selectivity was observed (Table 2.1, Entry 1). When stoichiometric amount of $CuBr \cdot SMe_2$ was employed in the reaction without a chiral ligand, lower yield of 1,4-product **41** was obtained (Entry 2).

As a control reaction, we confirmed the efficiency of the conjugate addition of MeMgBr to **40** in *t*BuOMe using Josiphos as ligand. Thus, the reaction resulted highly regioselective towards 1,4-addition, isolating β-sustituted ketone **41** in good yield (73%) and excellent enantioselectivity (97% *ee*), completely consistent with the reported results.[46]

Once the preferential formation of 1,4-adduct **41** in the presence of Cu(I) salts was demonstrated, we decided to explore the combination of ligands **L1-L5** with $CuBr \cdot SMe_2$ (Table 2.1, Entries 5-9). All the ligands afforded 1,4-adduct as major product, but none of them was able to induce enantioselectivity in the process and, consequently, **41** was obtained as a racemic compound. In addition, 1,2-addition product **42** could never be completely suppressed. At this point, we chose **L4** as chiral ligand for further screening of the reaction conditions, as it was found to be superior in terms of regioselectivity.

Then, different solvents and commonly used Cu(I) salts, such as CuBr and CuI, were tested, but no significant improvement was observed on the selectivity of the reaction.

In parallel, we studied the effect of $BF_3 \cdot OEt_2$ on the regioselectivity of the process and we observed that the formation of undesired 1,2-adduct was reduced to 7% yield, although product **41** was obtained again as a racemate (Table 2.1, Entry 14). Finally, we realized that reagent addition rate did not affect the reaction outcome, as almost identical results in both regio- and enantioselectivity were obtained by switching from direct to slow addition of EtMgBr (Table 2.1, Entry 15).

In view of these results, the use of guanidine/amine ligands **L1-L5** in combination with Cu(I) salts was found not to be suitable for neither completely controlling the regioselectivity nor for achieving enantioinduction in the 1,4-addition reaction of reactive EtMgBr over enone **40**. We thought that a possible explanation for the lack of regio- and mostly enantiocontrol could be that Cu(I)/**L1-L5** complexes were not forming during the conjugated addition reaction. Therefore, we tried to crystallize the complexes between ligands **L1-L5** and Cu(I) salts in order to determine their structure by single crystal X-ray diffraction analysis. Unfortunately, all crystallization essays failed to afford the monocrystal that would allow to unambiguously confirm the structure of Cu(I)/**L1-L5** complexes by X-ray diffraction.

3.3. Screening of chiral hybrid guanidine/amine ligands in copper-catalyzed asymmetric Henry reaction.

Henry or nitroaldol reaction is also a valuable C-C bond forming reaction in organic synthesis.[57] The resulting product is a β-nitroalcohol, which, especially in an optically pure form, is a versatile intermediate for a diverse range of chemical transformations. In fact, the newly formed β-nitroalkanols functionality can be conveniently converted into β-hydroxycarbonyl compounds through Nef reaction,[58] amino alcohols by reduction[59] and other complex target molecules, which are then useful building blocks for the synthesis of biologically active compounds and pharmaceutical agents.

Owing to the usefulness of enantiomerically pure β-hydroxynitroalkanes in organic synthesis, remarkable efforts have been devoted toward the design and development of efficient catalytic systems for asymmetric variant of Henry reaction.[60] Thus, metal complexes with chiral ligands have been extensively studied and used as catalyst in

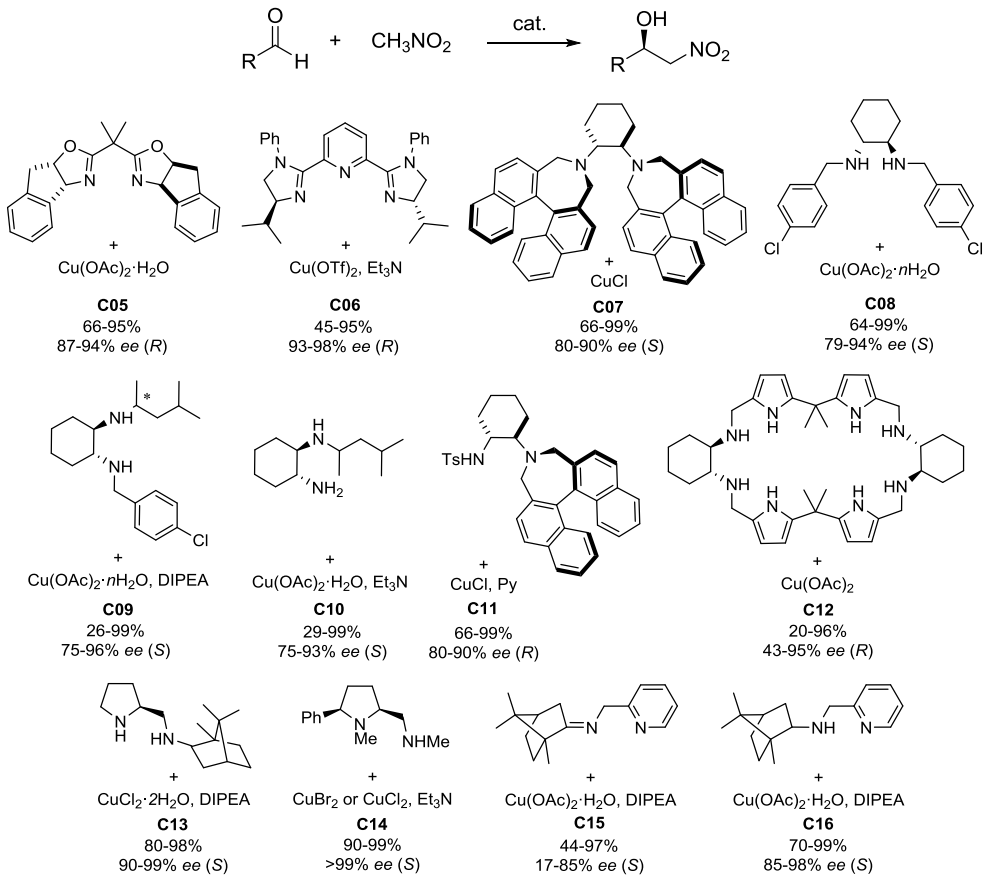
[57] Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.
[58] For a review on the Nef reaction, see: Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.
[59] Poupart, M.-A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356.
[60] For a review on asymmetric Henry reactions, see: Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561.

enantioselective nitroaldol reaction. Among metal catalysts, copper complexes have received special attention due to the low cost and toxicity of copper, together with its excellent chelating properties to coordinate with both bidentate and polydentate ligands. Consequently, many catalytic systems based on copper complexes of chiral ligands have been developed. Next, a brief summary including some representative examples of chiral ligands developed to promote the copper-catalyzed asymmetric Henry reaction of aromatic and aliphatic aldehydes with nitromethane will be presented.

N,N-donor ligands play an important role in asymmetric catalysis and, therefore, different types of these ligands have been used in the nitroaldol reaction. Among them, chiral bis(oxazolines), such as **C05** (Scheme 2.25),[61] have proven to be one of the most efficient chiral ligands to efficiently promote the asymmetric Henry reaction between a wide variety of aldehydes and nitromethane.[62]

The replacement of the oxygen atom of the oxazoline ring by a substituted nitrogen atom leads to new class of imidazoline ligands, like **C06** (Scheme 2.25),[63] which highly modular steric and electronic nature allows an adequate matching of chiral ligand, metal ion and substrate. Therefore, the achievement of excellent catalytic performance (activity and enantioselectivity) in the asymmetric nitroaldol reaction is facilitated.

[61] Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692.
[62] a) Christensen, C.; Juhl, K.; Jorgensen, K. A. *Chem. Commun.* **2001**, 2222. b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875. c) Risgaard, T.; Gothelf, K. V.; Jorgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153. d) Lu, S. F.; Du, D. M.; Zhang, S. W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433. e) Du, D. M.; Lu, S. F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712. f) Ginotra, S. K.; Singh, V. K. *Org. Biomol. Chem.* **2007**, *5*, 3932. g) Toussaint, A.; Pfaltz, A. *Eur. J. Org. Chem.* **2008**, 4591. g) Didier, D.; Magnier-Bouvier, C.; Schulz, E. *Adv. Synth. Catal.* **2011**, *353*, 1087.
[63] Ma, K. Y.; You, J. S. *Chem. Eur. J.* **2007**, *13*, 1863.



Scheme 2.25.

Chiral diamines constitute an extensive group of effective N,N-ligands that form stable metal complexes with wide application in different metal-catalyzed asymmetric transformations. Thus, several chiral secondary diamines derived from 1,2-diaminocyclohexane, both C_2-symmetric (e.g. **C07**[64] and **C08**[65]) and non-symmetric (e.g.

[64] Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5978.
[65] Kowalczyk, R.; Sidorowicz, L.; Skarzewski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 2310.

C09[66] and **C10**[67]), have been tested and efficiently used in asymmetric Henry reaction (Scheme 2.25). Moreover, sulfonylation of one of the nitrogen atoms of the 1,2-diamine group leads to asymmetric sulfonyldiamine ligands, including **C11** (Scheme 2.25).[68] More complex chiral macrocycles, such as **C12**,[69] have also been successfully utilized in enantioselective nitroaldol reaction (Scheme 2.25). Finally, different types of N,N-ligands with nitrogen-containing ring have also been developed. Some representative examples (**C13**,[70] **C14**,[71] **C15**[72] and **C16**[73]) are shown on Scheme 2.25.

In addition to N,N-donor ligands, different types of chiral ligands have also been employed in the copper-catalyzed asymmetric Henry reaction. Particularly, catalytic systems formed by *Cinchona* derived Schiff base ligands and copper salts have been efficiently employed in the asymmetric addition of nitromethane to a variety of aldehydes,[74] being **C17** a representative example (Scheme 2.26).[75] The use of chiral β-amino alcohols in copper-catalyzed enantioselective Henry reaction is more limited. In fact, only few examples have been published (e.g. **C18**,[76] **C19**[77] and **C20**[78]) and, in most cases, only moderate enantioselectivities have been obtained.

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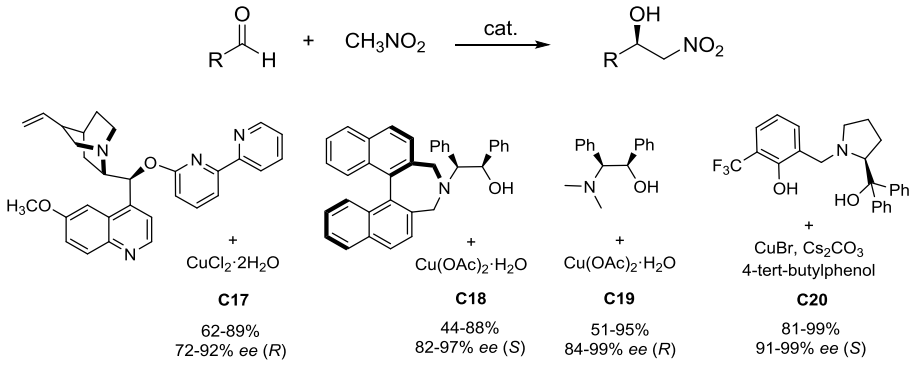
[66] Liu, F.; Gou, S.; Li, L.; Yan, P.; Zhao, C. *J. Mol. Catal. A: Chem.* **2013**, *379*, 163.
[67] Liu, F.; Gou, S.; Li, L. *Appl. Organometal. Chem.* **2014**, *28*, 186.
[68] Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903.
[69] Gualandi, A.; Cerisoli, L.; Stoeckli-Evans, H.; Savoia, D. *J. Org. Chem.* **2011**, *76*, 3399.
[70] Zhou, Y.; Dong, J.; Zhang, F.; Gong, Y. *J. Org. Chem.* **2011**, *76*, 588.
[71] Scharnagel, D.; Prause, F.; Kaldun, J.; Haase, R. G.; Breuning, M. *Chem. Commun.* **2014**, *50*, 6623.
[72] Blay, G.; Climent, E.; Fernandez, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2007**, *18*, 1603.
[73] Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Chem. Eur. J.* **2008**, *14*, 4725.
[74] a) Wie, Y.; Yao, L.; Zhang, B.; He, W.; Zhang, S. *Tetrahedron* **2011**, *67*, 8552. b) Yao, L.; Wei, Y.; Wang, P.; He, W.; Zhang, S. *Tetrahedron* **2012**, *68*, 9119. c) Zhang, L.; Wu, H.; Yang, Z.; Xu, X.; Zhao, H.; Huang, Y.; Wang, Y. *Tetrahedron* **2013**, *69*, 10644.
[75] Liu, M.; Ma, S.; Tian, Z.; Wu, H.; Wu, L.; Xu, X.; Huang, Y.; Wang, Y. *Tetrahedron: Asymmetry* **2013**, *24*, 736.
[76] Guo, Z.-L.; Zhong, S.; Li, Y.-B.; Lu, G. *Tetrahedron: Asymmetry*, **2011**, *22*, 238.
[77] Qin, D.-D.; Lai, W.-H.; Hu, D.; Chen, Z.; Wu, A.-A.; Ruan, Y.-P.; Zhou, Z.-H.; Chen, H.-B. *Chem. Eur. J.* **2012**, *18*, 10515.
[78] Lai, G.; Guo, F.; Zheng, Y.; Fang, Y.; Song, H.; Xu, K.; Wang, S.; Zha, Z.; Wang, Z. *Chem. Eur. J.* **2011**, *17*, 1114.

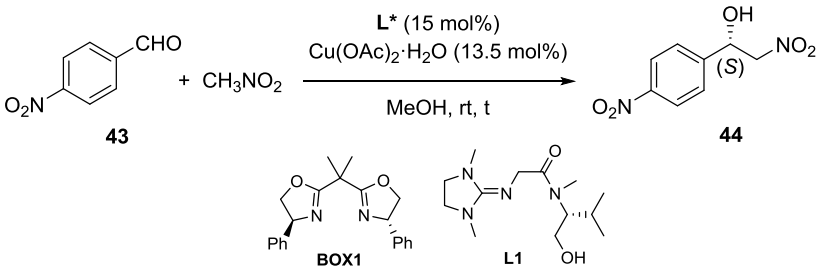


Scheme 2.26.

As shown in the previous brief introduction, successful results in terms of chemical yield and enantioselectivity have been obtained in copper-catalyzed asymmetric Henry reaction of a variety of aldehydes and nitromethane by using a wide range of structurally different chiral ligands. Therefore, we decided to explore if the synthesized ligands **L1-L5** were able to efficiently and stereoselectively promote the copper-catalyzed asymmetric nitroaldol reaction between 4-nitrobenzaldehyde (**43**) and nitromethane (Scheme 2.27).

Firstly, the reaction was carried out using $Cu(OAc)_2 \cdot H_2O$ in absence of any chiral ligand, obtaining the racemic β-nitroalcohol **44** in moderate yield (Table 2.2, Entry 1). Then, as a control reaction, we utilized a chiral bis(oxazoline) ligand **BOX1**, whose efficiency has been proved in copper-catalyzed enantioselective Henry reaction.[79] Thus, Henry adduct **44** was obtained in quantitative yield (99%) and moderate enantioselectivity (47% *ee*) after 24 h, which is in accordance with the reported results (43% *ee*).[79] When Henry reaction was carried out in the presence of previously synthesized chiral ligand **L1**, β-nitroalcohol **44** was obtained in moderate yield of 50%, although the product was almost racemic (Table 2.2, Entry 3).

[79] Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, W. *J. Am. Chem. Soc.* **2003**, *125*, 12692.



Scheme 2.27.

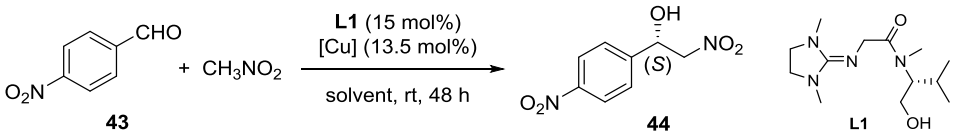
Table 2.2. Preliminary studies of Henry reaction of **43** with nitromethane.

Entry	L*	t (h)	Yield (%)[a]	*ee* (%)[b]
1	-	48	40	-
2	**BOX1**	24	99	47
3	**L1**	48	56	8

[a] Isolated yield. [b] Determined by chiral stationary phase HPLC (Chiralcel OD, 90% hexane/*i*-propanol, 1 mL/min).

Several attempts were then carried out using different solvents (Table 2.3, Entries 2-5), yielding **44** in moderate to excellent yields and promising enantioselectivities (up to 33% *ee*). Encouraged by these results, we decided to continue the study of the catalytic activity of complexes formed between **L1** and different copper(II) salts (Table 2.3). Unfortunately, Henry reaction did not take place when $CuCl_2$ and $Cu(OTf)_2$ were used and starting material **43** was quantitatively recovered (Table 2.3, Entries 3 and 4). The use of anhydrous copper(II) acetate led to desired product **44** in good yield (66%), but with no control of enantioselectivity (Entry 2). Finally, we tested a bulky copper(II) salt, such as $Cu(BARF)_2$, which was formed *in situ* in the reaction mixture by treatment of $CuCl_2$ (13.5 mol%) and NaBARF (15 mol%).[80] However, racemic product **44** was obtained in very low yield (11%).

[80] Wang, D.; Cao, P.; Wang, B.; Jia, T.; Lou, Y.; Wang, M.; Liao, J.*Org. Lett.* **2015**, *17*, 2420.



Scheme 2.28.

Table 2.3. Screening of copper sources and solvents in the Henry reaction of **43** with nitromethane using **L1** as chiral ligand.

Entry	[Cu]	Solvent	Yield (%)[a]	*ee* (%)[b]
1	$Cu(OAc)_2 \cdot H_2O$	MeOH	56	8
2	$Cu(OAc)_2 \cdot H_2O$	EtOH	92	7
3	$Cu(OAc)_2 \cdot H_2O$	Et_2O	91	12
4	$Cu(OAc)_2 \cdot H_2O$	CH_2Cl_2	53	33
5	$Cu(OAc)_2 \cdot H_2O$	THF	97	26
6	$Cu(OAc)_2$	MeOH	66	<2
7	$CuCl_2$	MeOH	n.r.	-
8	$Cu(OTf)_2$	MeOH	n.r.	-
9	$Cu(BARF)_2$	MeOH	11	<2
10	CuCl	MeOH	48	39
11	CuBr	MeOH	47	47
12	CuI	MeOH	8	<2
13	CuOAc	MeOH	95	<2
14	CuBARF	MeOH	57	<2
15	CuBr	EtOH	22	<2
16	CuBr	Et_2O	30	<2
17	CuBr	CH_2Cl_2	n.r.	-
18	CuBr	THF	n.r.	-

[a] Isolated yield. [b] Determined by chiral stationary phase HPLC (Chiralcel OD, 90% hexane/*i*-propanol, 1 mL/min).

Then, we evaluated different copper(I) salts for the formation of Cu(I)/**L1** complexes. Thus, when CuCl was used as Cu(I) source, β-nitroalcohol **44** was obtained in moderate yield and promising enantiomeric excess (48%, 39% *ee*) (Entry 10). The change of copper(I) salt to CuBr afforded **44** in similar yield to CuCl (47%) with an increased *ee* value (47% *ee*) (Entry 11). Unfortunately, when copper(I) acetate and bulky copper(I) salt CuBARF were employed, no enantiocontrol was obtained (Entries 13 and 14).

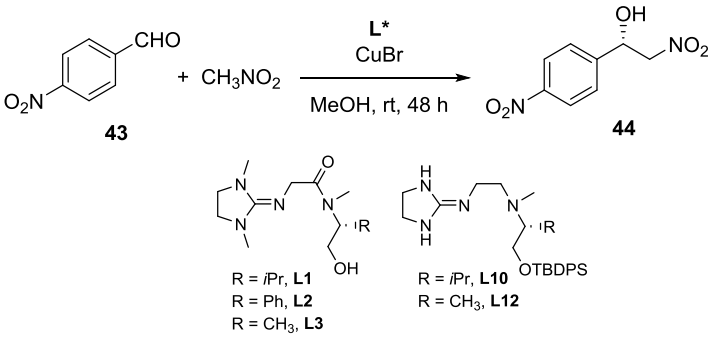
Next, we tested different solvents using CuBr/**L1** catalyst (Table 2.3, Entries 11-14), but the results obtained using MeOH could not be improved. Thus, we selected CuBr as copper source and methanol as solvent for later optimization of reaction conditions.

Subsequently, different CuBr and **L1** loadings were tested and we observed that both the increase and the decrease of copper(I) salt and ligand **L1** afforded product **44** with no enantioinduction (Table 2.4, Entries 2 and 3).

In view of this result, we thought that a problem in reproducibility of the reaction could be taking place. Therefore, reactions in Table 2.3 (Entries 6 and 7) were repeated several times using identical reaction conditions and employing freshly synthesized **L1**. Thus, although comparable yields were obtained, all attempts gave racemic β-nitroalcohol **44**. Moreover, an essay was carried out using freshly prepared CuBr[81] (instead of commercially available). Thus, **44** was obtained in 70% yield, but again as a racemate (Table 2.4, Entry 4), which confirmed our assumption about reproducibility difficulties during the process.

In view of those disappointed results, we tested **L2** and **L3** as chiral ligands. Unfortunately, no enantioinduction was observed and racemic β-nitroalcohol **44** was obtained (Table 2.4, Entries 5 and 6). Furthermore, we decided to check also ligands **L10** and **L12** which have a more basic amine nitrogen. However, Henry reaction of 4-nitrobenzaldehyde (**43**) with nitromethane using **L10** and **L12** as chiral ligands gave again unsatisfactory results in terms of enantioselectivity (Table 2.4, Entries 7 and 8).

[81] Lozano-Lavilla, O. Master Thesis, Universidad de Valladolid, **2016**.



Scheme 2.29.

Table 2.4. Screening of CuBr and **L1** loadings in Henry reaction of **43** with nitromethane.

Entry	CuBr (mol%)	L* (mol%)	Yield (%)[a]	*ee* (%)[b]
1[c]	15	**L1** (13.5)	47	47
2	20	**L1** (18)	93	<2
3	10	**L1** (9)	30	<2
4[d]	15	**L1** (13.5)	70	<2
5	15	**L2** (13.5)	45	<2
6	15	**L3** (13.5)	48	<2
7	15	**L10** (13.5)	56	<2
8	15	**L12** (13.5)	40	<2

[a] Isolated yield. [b] Determined by chiral stationary phase HPLC (Chiralcel OD, 90% hexane/*i*-propanol, 1 mL/min). [c] Included in Table 2.3 (Entry 7). [d] Performed using freshly prepared CuBr (see Ref. 81).

In summary, the synthesized chiral hybrid guanidine/amine ligands are not effective ligands for asymmetric Henry reaction between 4-nitrobenzaldehyde and nitromethane. However, no clear conclusions can be obtained about the reasons of this lack of activity, and future work would be required.

III

Use of *N*-alkenylnitrones in Inverse-Electron Demand Diels-Alder (IEDDA) Reaction

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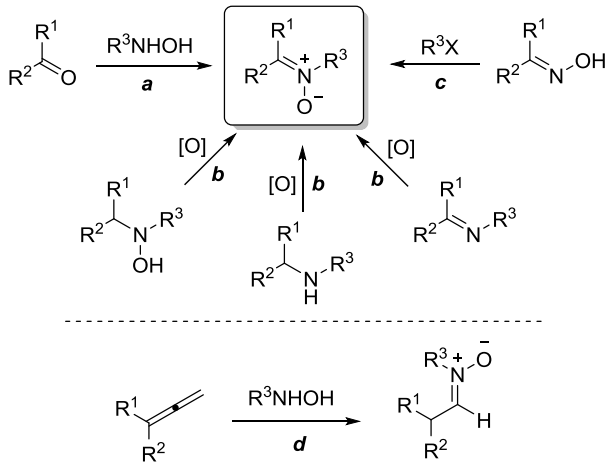
1. INTRODUCTION

In this chapter, the work carried out during a predoctoral stay in the laboratories of Prof. Laura L. Anderson in the Department of Chemistry at the University of Illinois at Chicago is described, which was focused on the use of *N*-alkenylnitrones as reactive intermediates in both inter- and intramolecular inverse-electron demand Diels-Alder (IEDDA) reactions.

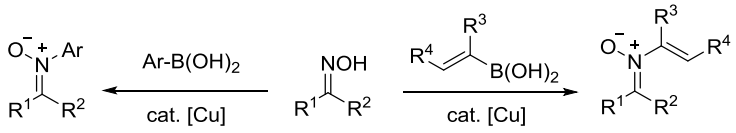
Nitrones are easily accessible and versatile reagents that can undergo a variety of organic transformations for the synthesis of a diverse array of heterocyclic compounds.[1] Nitrones are readily obtained by different methods which include: a) condensation reactions of *N*-substituted hydroxylamines with carbonyl compounds; b) oxidations of secondary amines, *N*-substituted hydroxylamines, and imines; c) *N*-alkylation of oximes; d) and Cope-type hydroamination reactions of alkynes and allenes with *N*-substituted hydroxylamines (Scheme 3.1).[1]



Scheme 3.1.

[1] For a review, see: Anderson, L. L. *Asian J. Org. Chem.* **2016**, *5*, 9.

In this context, the group of Prof. Anderson showed that copper-mediated Chan-Lam coupling reaction of oximes with alkenylboronic acids could be used for the preparation of various types of nitrones, such as *N*-vinyl, *N*-alkenyl and *N*-aryl nitrones (Scheme 3.2).[2,3] The simplicity of this method for the synthesis of nitrones provided a general platform for the use of these reactive reagents as precursors to a variety of challenging organic fragments and heterocyclic compounds.

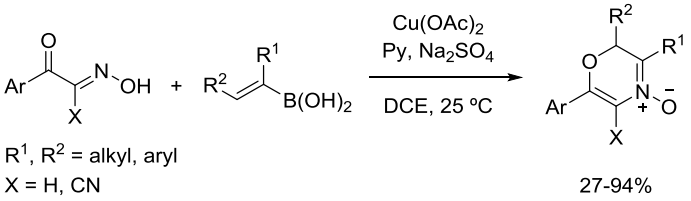


Scheme 3.2.

Examples developed by Anderson's group based on the use of *N*-vinyl, *N*-aryl and *N*-alkenyl nitrones obtained through copper-mediated cross-coupling reaction of oximes with boronic acids for the synthesis of heterocycles will be discussed.

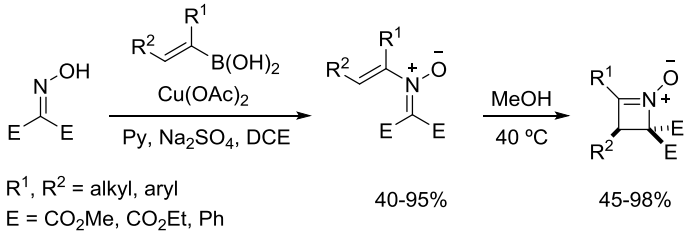
It has been demonstrated that remarkable electrocyclization reactions are accessible for *N*-alkenylnitrones, which have further diversified the use of nitrones in heterocycle synthesis. In fact, the first synthesis of 2*H*-1,4-oxazine *N*-oxides was achieved through a Chan-Lam coupling of α-keto-*N*-alkenylnitrones and subsequent spontaneous 6π electrocyclization (Scheme 3.3). Besides, initial functionalization studies showed that the unsaturated morpholine derivatives could be used as densely functionalized intermediates for their conversion into more complicated heterocyclic structures, such as fused oxazine-benzoxazolidines, phenol-substituted morpholines or furan-fused morpholines.[4]

[2] Mo, D.-L.; Wink, D. A.; Anderson, L. L. *Org. Lett.* **2012**, *14*, 5180.
[3] Mo, D.-L.; Anderson, L. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 6722.
[4] Son, J.; Kim, K. H.; Mo, D.-L.; Wink, D. J.; Anderson, L. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 3059.



Scheme 3.3.

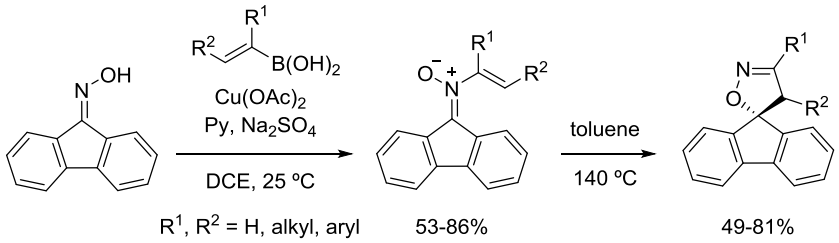
The optimization and scope of the facile synthesis of azetidine nitrones through the 4π-electrocyclization of *N*-alkenylnitrones has been also reported (Scheme 3.4). Moreover, the unsaturated and strained azetidine nitrones could be functionalized to highly substituted azetidines by diastereoselective cycloaddition, reduction, and alkylation reactions.[5]



Scheme 3.4.

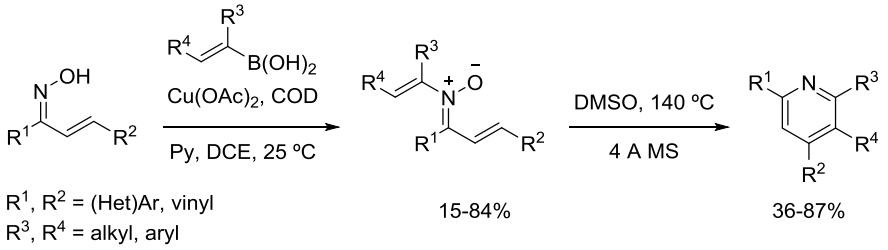
In addition, nitrones have been shown to undergo a variety of novel rearrangements reactions to provide different heterocycles. In this context, fluorenone-based *N*-vinylnitrones were obtained by copper-mediated cross-coupling of fluorenone oxime and vinylboronic acids. Then, these *N*-vinylnitrones underwent unprecedented thermal rearrangement to give spiroisoxazolines in moderate to high yields (Scheme 3.5).[2]

[5] Reidl, T. W.; Son, J.; Wink, D. J.; Anderson, L. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 11579.



Scheme 3.5.

N-Alkenyl-α,β-unsaturated nitrones could also be prepared through a Chan-Lam coupling of the corresponding α,β-unsaturated oximes and alkenylboronic acids. Then, a thermal rearrangement allowed the preparation of tri- and tetrasubstituted pyridines by a cyclization process that is thought to occur through an oxygen transfer from nitrone functionality to the β-position of the conjugated olefin, followed by nucleophilic attack of the enamine (Scheme 3.6).[6]

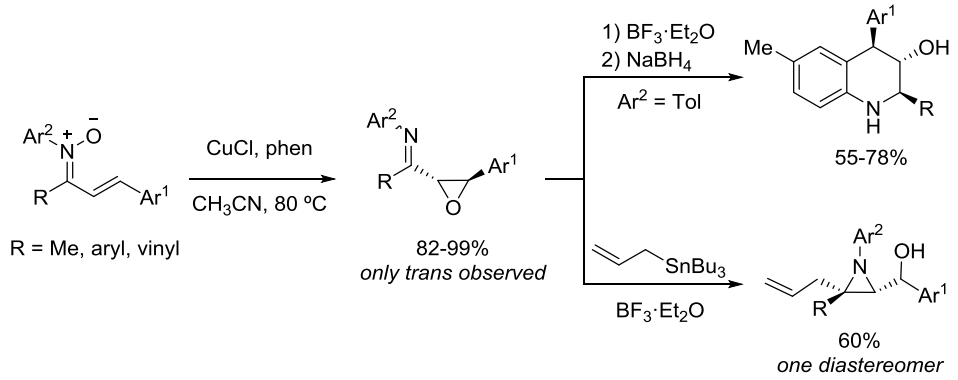


Scheme 3.6.

α,β-Unsaturated *N*-aryl nitrones could be transformed into α,β-epoxyketimines in high yield and excellent diastereoselectivity through a copper-catalyzed intramolecular oxygen-atom transfer reaction from a nitrone to an alkene. Further investigations of the synthetic utility of α,β-epoxyketimines afforded tetrahydroquinolines in the presence of a Lewis acid by a

[6] Kontokosta, D.; Mueller, D. S.; Mo, D.-L.; Pace, W. H.; Simpson, R. A.; Anderson, L. L. *Beilstein J. Org. Chem.* **2015**, *11*, 2097.

Friedel-Crafts-type epoxide opening, followed by imine reduction, as well as *N*-aryl trisubstituted aziridines with high diastereoselectivity (Scheme 3.7).[3]

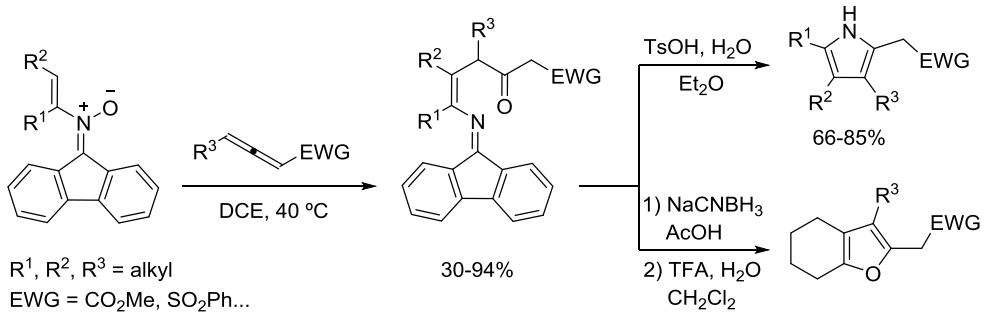


Scheme 3.7.

On the other hand, the addition and rearrangement reactivity of nitrones with allenes has been studied for the synthesis of a variety of different heterocycles.[7] Thus, cascade reactions involving nitrones and allenes are known to facilitate the rapid synthesis of several indole derivatives.[8]

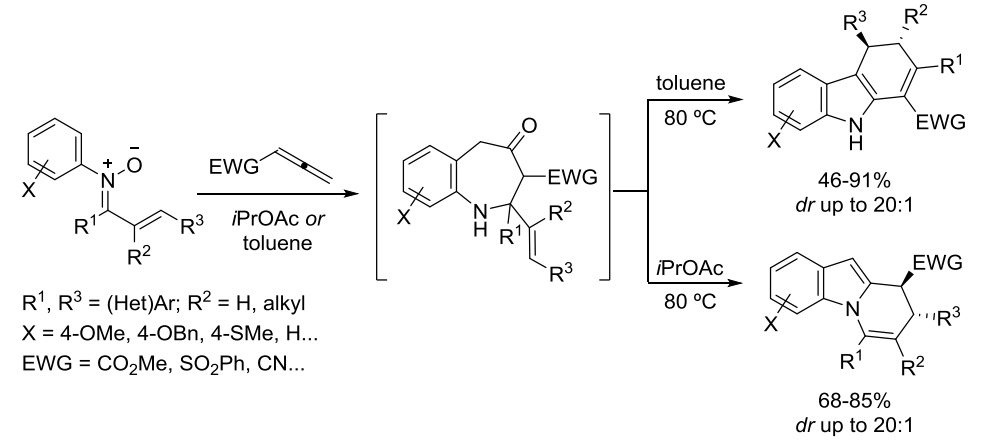
In this context, fluorenone-derived *N*-alkenylnitrones have also been reacted with electron-deficient allenes generating dialkenylhydroxylamines that underwent a subsequent spontaneous [3,3]-rearrangement to give 1,4-enamino ketones. The stability of the fluorenone imine-protecting group facilitated the isolation of the unusual 1,4-enamino ketones, which were shown to be effective synthetic intermediates for the preparation of highly substituted pyrroles and 1,4-diones that could be subsequently transformed into tetrasubstituted furans (Scheme 3.8).[9]

[7] a) Wilkens, J.; Kühling, A.; Blechert, S. *Tetrahedron* **1987**, *43*, 3237. b) Padwa, A.; Bullock, W. H.; Kline, D. N.; Perumattam, J. *J. Org. Chem.* **1989**, *54*, 2862.
[8] Anderson, L. L.; Kroc, M. A.; Reidl, T. W.; Son, J. *J. Org. Chem.* **2016**, *81*, 9521.
[9] Pecak, W. H.; Son, J.; Burnstine, A. J.; Anderson, L. L. *Org. Lett.* **2014**, *16*, 3440.



Scheme 3.8.

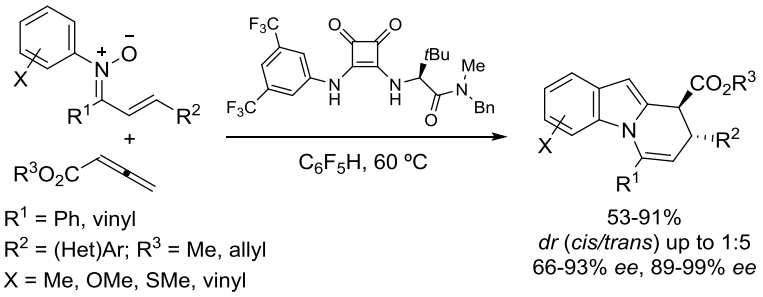
Additionally, a new cascade process allowed the preparation of two structurally distinct indole-based heterocycles in high yield and diastereoselectivity from identical non-heterocyclic starting materials. Specifically, the addition of *N*-aryl-α,β-unsaturated nitrones to electron-deficient allenes and the subsequent rearrangement process afforded a benzazepine intermediate whose ring-opening event could be directed toward the generation of dihydrocarbazole moiety or the formation of dihydropyridoindole scaffold depending on the choice of solvent (Scheme 3.9).[10]



Scheme 3 .9.

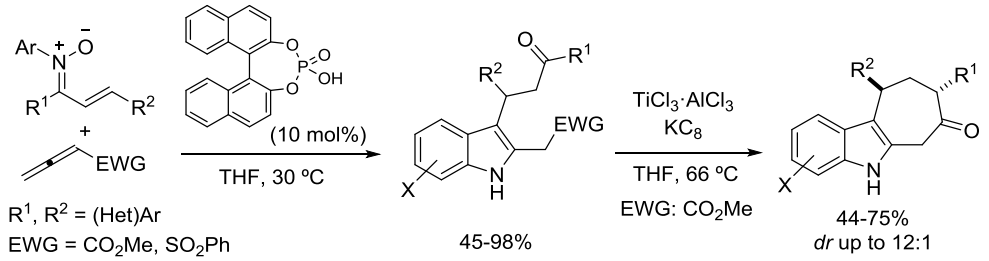
[10] Mo, D.-L.; Wink, D. J.; Anderson, L. L. *Chem. Eur. J.* **2014**, *20*, 13217.

The asymmetric variant of this cascade process has also been developed using a squaramide as catalyst. Thus, enantiomerically enriched dihydropyrido[1,2-*a*]indoles were efficiently obtained in good yield and high diastereoselection from *N*-aryl α,β-unsaturated nitrones and allenoates (Scheme 3.10).[11]



Scheme 3.10.

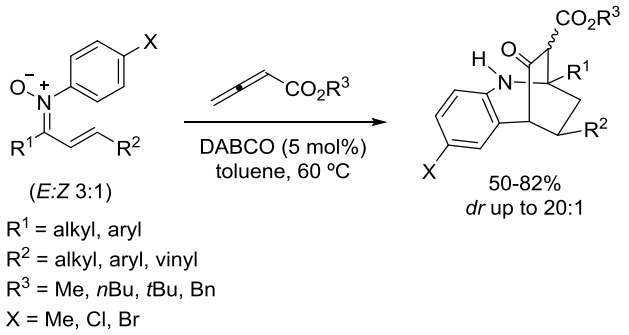
Additionally, *N*-aryl-α,β-unsaturated ketonitrones could participate in a hydrogen bond donor catalyzed cascade reaction with electron-deficient allenes in the presence of phosphoric acid catalyst. Thus, 3-functionalized indoles were obtained, which rapidly cyclized to synthetically challenging cycloheptanone-fused indoles through a McMurry coupling (Scheme 3.11). Moreover, initial attempts of catalytic asymmetric conditions to generate a carbon stereocenter in the 3-functionalized indoles provided the desired product with enantioselectivities up to 67% *ee*.[12]



Scheme 3.11.

[11] Pace, W. H.; Mo, D.-L.; Reidl, T. W.; Wink, D. J.; Anderson, L. L. A*ngew. Chem. Int. Ed.* **2016**, *55*, 9183.
[12] Kroc, M. A.; Prajapati, A.; Wink, D. J.; Anderson, L. L. *J. Org. Chem.* **2018**, *83*, 1085.

Recently, it has been demonstrated that medium-sized heterocyclic compounds could also be selectively synthesized through a catalyst-controlled cascade reaction system, obtaining synthetically challenging bridged bicyclictetrahydrobenz[*b*]azepin-4-ones from *N*-arylnitrones and allenes using a simple Lewis base catalyst, such as 1,3-diazabicyclo[2.2.2]octane (DABCO) (Scheme 3.12).[13]



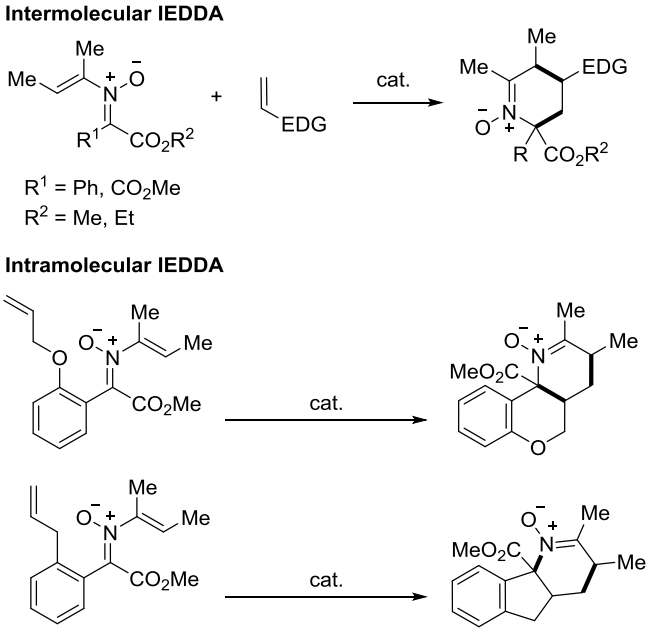
Scheme 3.12.

[13] Kroc, M. A.; Markiewicz, M.; Pace, W. H.; Wink, D. J.; Anderson, L. L. *Chem. Commun.* **2019**, *55*, 2309.

2. OBJECTIVES

As stated in previous section, the Anderson group demonstrated that oximes can participate in a copper-mediated C-N bond coupling to access *N*-aryl and *N*-alkenylnitrones that are inaccessible using traditional synthetic technology. Additionally, it has been found that *N*-alkenylnitrones represent versatile synthons for heterocycle synthesis, as they can undergo a variety of novel transformations. Thus, spirocyclic isoxazolines and α,β-epoxyimines have been obtained by rearrangement processes, cascade reactions have afforded tetrasubstituted pyrroles, and 6π-electrocyclizations have been used to obtain oxazine *N*-oxide heterocyclic structures.

In view of these precedents, the aim of this work was to further extend the use of *N*-alkenylnitrones. For that purpose, we chose to evaluate the nitrones depicted in Scheme 3.13 in both the inter- and intramolecular Inverse Electron Demand Diels-Alder (IEDDA) reactions.



Scheme 3.13.

Thus, the work will be divided into two parts:

a) Synthesis of *N*-alkenylnitrones, substrates for the inter- and intramolecular IEDDA reactions.

As stated in Introduction, the Anderson group discovered that *N*-alkenylnitrones can be obtained from oximes by a copper-mediated reaction with alkenylboronic acids. Therefore, our first objective would be the application of this methodology to the synthesis of *N*-alkenylnitrones with the adequate structure to act as electron-deficient azadienes in the intermolecular IEDDA reaction with different electron-rich dienophiles. Moreover, *N*-alkenylnitrones suitable for the intramolecular version of the reaction would also be prepared (Scheme 3.13).

b) Essays of intermolecular IEDDA reaction.

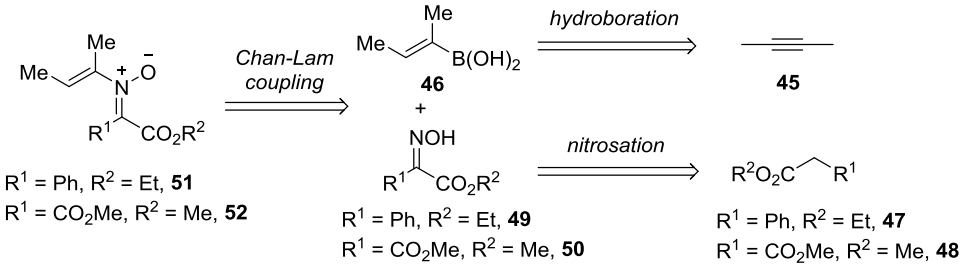
Once *N*-alkenylnitrones were synthesized, we would evaluate them as electron-deficient azadienes in the intermolecular IEDDA reaction with different electron-rich dienophiles for the synthesis of tetrahydropyridine *N*-oxides, using either organocatalysts or metal catalysts (Scheme 3.13).

3. RESULTS AND DISCUSSION

As stated in Objectives, the first task was the synthesis of the *N*-alkenylnitrones through a copper-mediated Chan-Lam coupling between *N*-alkenylboronic acids and oximes.

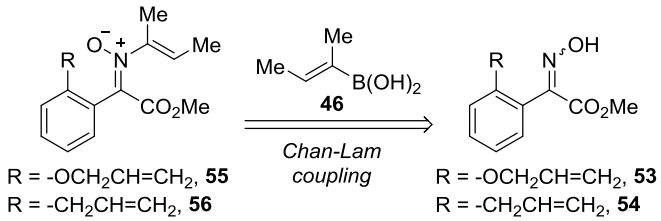
3.1. Synthesis of *N*-alkenylnitrones, substrates for the inter- and intramolecular IEDDA reactions.

N-Alkenylnitrones **51** and **52** could be obtained by copper-mediated Chan-Lam coupling between the corresponding ketoximes **49** and **50** prepared from commercially available reagents and alkenylboronic acid **46** readily obtained by the hydroboration reaction of 2-butyne with dibromoborane dimethyl sulfide complex (Scheme 3.14).



Scheme 3.14.

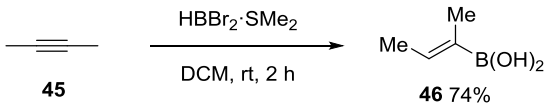
Analogously, *N*-alkenylnitrones **55** and **56**, which contain a tethered dienophile, could also be obtained through a copper-mediated coupling from the corresponding ketoximes. However, in this case, some synthetic steps were required to obtain the precursor of the ketoximes from commercially available sources (Scheme 3.15).



Scheme 3.15.

*3.1.1. Synthesis of the N-alkenylboronic acid **46***

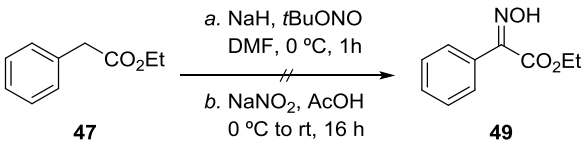
We first synthesized the *N*-alkenylboronic acid **46** required for the preparation of *N*-alkenylnitrones **51**-**52** and **55**-**56** in good yield (74%) through hydroboration of 2-butyne (**45**) with $HBBr_2 \cdot SMe_2$ followed by hydrolysis (Scheme 3.16).[2,4,14]



Scheme 3.16.

*3.1.2. Synthesis of the oximes **49**, **50**, **53** and **54***

Firstly, the formation of ketoxime **49** from ethyl phenylacetate (**47**) was attempted by treatment of **47** with NaH and *tert*-butyl nitrite[15] or $NaNO_2$.[16] Unfortunately, nitrosation reaction of **47** was totally unsuccessful regardless the utilized reaction conditions and always starting material was recovered (Scheme 3.17).



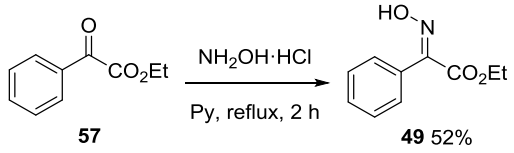
Scheme 3.17.

[14] a) Brown, H. C.; Campbell, J. B. *J. Org. Chem.* **1980**, *45*, 389. b) Patil, A. S.; Mo, D.-L.; Wang, H.-Y.; Mueller, D. S.; Anderson L. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 7799.

[15] a) Zhu, J.; Kong, Y.; Lin, F.; Wang, B.; Chen, Z.; Liu L. *Eur. J. Org. Chem.* **2015**, 1507. b) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.

[16] a) Mo, K.; Kang, S. B.; Kim, Y.; Lee, Y. S.; Lee, J. W.; Keum G. *Eur. J. Org. Chem.* **2015**, 1137. b) Owen, T.; Grandjean, F.; Long, G. J.; Domasevitch, K. V.; Gerasimchuk N. *Inorg. Chem.* **2008**, *47*, 8704. c) Gerasimchuk, N.; Gamian, A.; Glover, G.; Szponar B. *Inorg. Chem.* **2010**, *49*, 9863. d) Domasevitch, K. V.; Gerasimchuk, N. N.; Mokhir A. *Inorg. Chem.* **2000**, *39*, 1227.

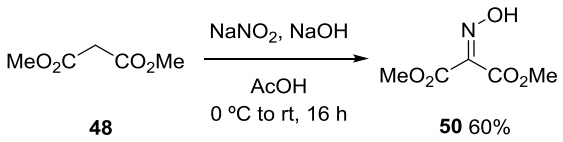
In view of the impossibility of direct formation of ketoxime **49**, we decided to begin the synthetic route using commercially available ethyl benzoylformate (**57**) as starting material. This way, *E* diastereomer of ketoxime **49** was easily accessed by condensation between the ketone and hydroxylamine hydrochloride (Scheme 3.18).[17]



57 **49** 52%

Scheme 3.18.

Next, we focused on our attention in the preparation of the analogous oxime **50** that was required for synthesizing malonate-derived *N*-alkenylnitrone **52**. In this case, nitrosation of dimethyl malonate (**48**) with sodium nitrite[16] afforded the corresponding ketoxime **50** in good yield (Scheme 3.19).



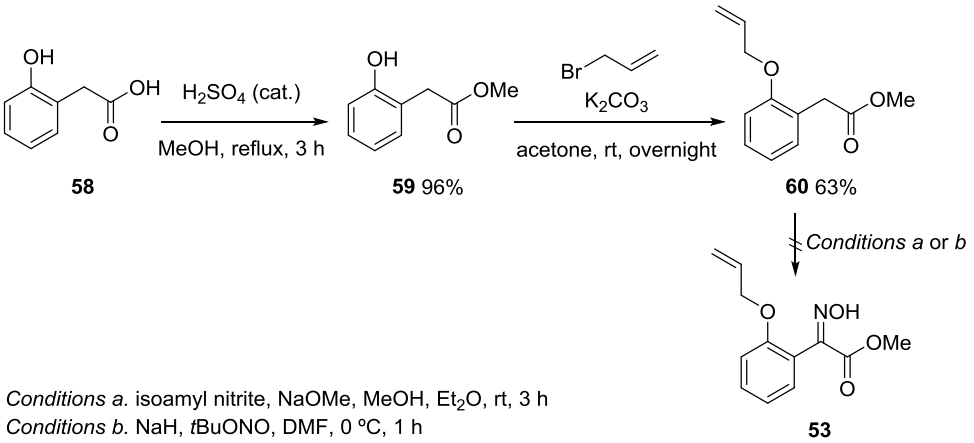
48 **50** 60%

Scheme 3.19.

At this point, we moved on the synthesis of oximes **53** and **54**. The synthetic route for the preparation of oxime **53** began with a quantitative esterification of the carboxylic acid **58** with methanol using acidic catalysis,[18] followed by an allylation of the phenol to obtain **60** (Scheme 3.20).[19] However, all attempts for the formation of the oxime **53** were unsuccessful. In fact, neither nitrosation of **60** with isoamyl nitrite in the presence of

[17] Hata, S.; Maeda, T.; Shimizu, M. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 1203.
[18] Aitken, H. R. M.; Furkert, D. P.; Hubert, J. G.; Wood, J. M.; Brimble, M. A. *Org. Biomolec. Chem.* **2013**, *11*, 5147.
[19] Lin, J.; Gerstenberger, B. S.; Stessman, N. Y. T.; Konopelski, J. P. *Org. Lett.* **2008**, *10*, 3969.

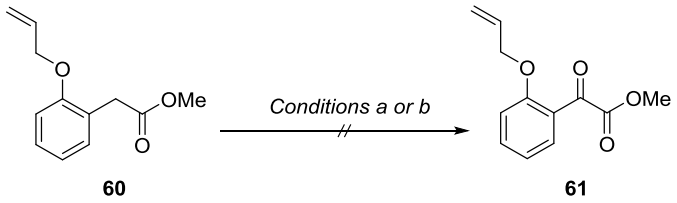
sodium methoxide[20] nor treatment of **60** with sodium hydride and *tert*-butyl nitrite[15] yielded ketoxime **53** and only starting material was recovered (Scheme 3.20).



Scheme 3.20.

In view of the impossibility of the direct formation of the α-ketoxime **53**, we considered the oxidation of the methylene group in α position to the carboxyl group, followed by condensation with hydroxylamine. However, when **60** was treated with an oxidizing agent as selenium dioxide in anisole,[21] decomposition of substrate **60** took place and the expected α-ketoester **61** was not obtained (Scheme 3.21). Additionally, we attempted the synthesis of α-ketoester **61** by using a diazo-tranfer reaction of **60** with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) in the presence of DBU and the subsequently conversion into the corresponding ketone by treatment with dry DMSO.[22] Thus, we were able to isolate the desired α-ketoester **61** in low yield (11%) from a complex mixture of products (Scheme 3.21).

[20] Stilz, H. U.; Guba, W.; Jablonka, B.; Just, M.; Klingler, O.; König, W.; Wehner, V.; Zoller, G. *J. Med. Chem.* **2001**, *44*, 1158.
[21] Koza, G.; Keskin, S.; Özer, M. S.; Cengiz, B.; Sahin, E.; Balci, M. *Tetrahedron* **2013**, *69*, 395.
[22] O'Connor, N. R.; Bolgar, P.; Stoltz, B. M. *Tetrahedron Lett.* **2016**, *57*, 849.

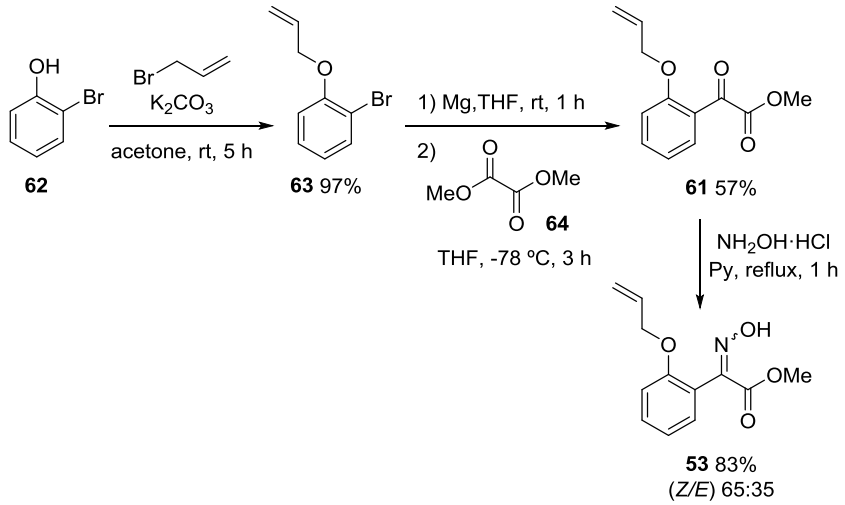


60 **61**

Conditions a. SeO_2, anisole, reflux 24 h (n.r.)
Conditions b. 1) *p*-ABSA, DBU, CH_3CN, 0 ºC to rt, 24 h. 2) dry DMSO, 75 ºC, 16 h (11%)

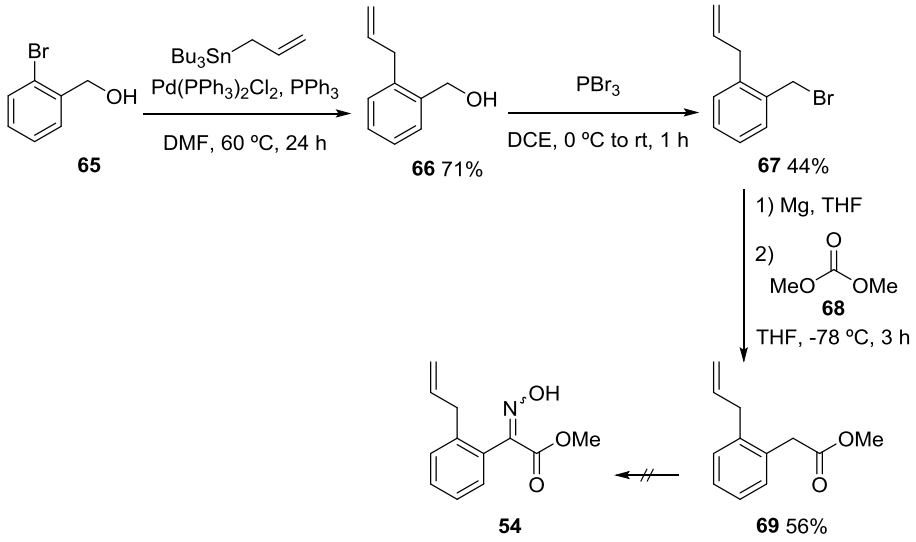
Scheme 3.21.

At this point, due to the low efficiency of the synthesis of ketoester **61**, we decided to change the strategy for the preparation of ketoxime **53**. For that purpose, we started with a nucleophilic allylic substitution of 2-bromophenol (**62**) with allyl bromide, which gave **63** in quantitative yield. Then, formation of the aryl magnesium bromide, followed by the addition to commercially available dimethyl oxalate (**64**) afforded the α-ketoester **61** in moderate yield (57%). Finally, condensation of the ketone moiety with hydroxylamine led to the ketoxime **53** in very good yield as a mixture of diastereomers (*Z*/*E* 65:35) (Scheme 3.22).



Scheme 3.22.

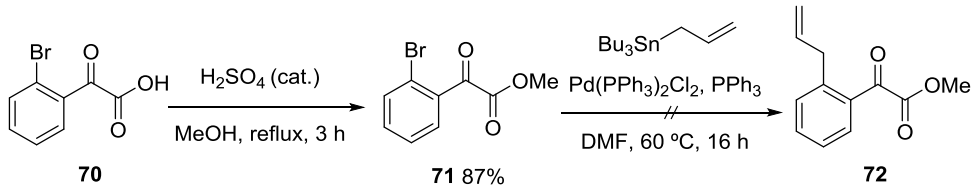
Next, we attempted the preparation of oxime **54** as illustrated in Scheme 3.23. Stille coupling reaction of commercially available 2-bromobenzyl alcohol (**65**) with tributyl(vinyl)tin gave **66**, which was then subjected to bromination with PBr_3, obtaining the corresponding benzyl bromide derivative **67** in moderate yield (44%). Next, reaction of a Grignard reagent from **67** with commercially available dimethyl carbonate (**68**) led to **25** in moderate yield (Scheme 3.23). At this point, as we did during the synthesis of **53**, we tried to incorporate either an oxime or ketone function in α position to carbonyl group of the ester functionality of **69** by treatment with isoamyl nitrite, selenium dioxide or *p*-ABSA. However, neither nitrosation nor oxidation were successful and, therefore, ketoxime **54** could not be obtained (Scheme 3.23).



Scheme 3.23.

Further attempts to access ketoxime **54** included a different synthetic route, which started with the efficient esterification of commercially available bromophenyloxoacetic acid (**70**). This way, **71**, which incorporated the α-ketoester moiety needed for the formation of the corresponding oxime, was obtained in very good yield (87%). Next, by analogy with the

synthetic route followed for the synthesis of **53**, we decided to incorporate the vinyl group prior to the formation of the ketoxime **54**. However, Stille reaction between **71** and tributyl(vinyl)tin did not take place and, therefore, **72** could not obtained (Scheme 3.24).



70 **71** 87% **72**

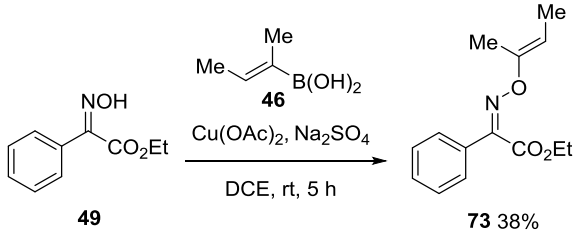
Scheme 3.24.

Due to the difficulties for the synthesis of oxime **54**, we focused on substrates **51**, **52** and **55** to continue with the preparation of the corresponding nitrones.

*3.1.2. Synthesis of the N-alkenylnitrones **51**, **52** and **55***

With the ketoximes **49**, **50** and **53** in hand, we proceeded to prepare the corresponding *N*-alkenylnitrones **51**, **52** and **55** *via* Chan-Lam coupling conditions, previously developed by Anderson group.

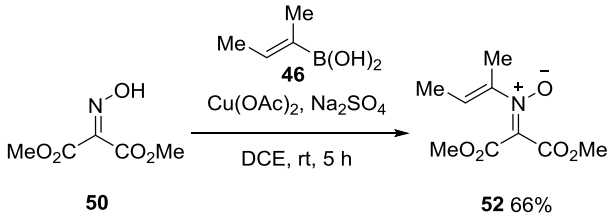
Firstly, we treated ketoxime **49** with *N*-alkenylboronic acid **46** previously prepared (Scheme 3.16) in the presence of $Cu(OAc)_2$. Unfortunately, *N*-vinylation of the oxime did not take place and, instead, *O*-alkenylated compound **73** (Scheme 3.25) could be identified in the ^1H NMR spectra of the reaction crude. However, isolation and complete characterization of **73** was not possible due to practical problems during purification step.



49 **46** **73** 38%

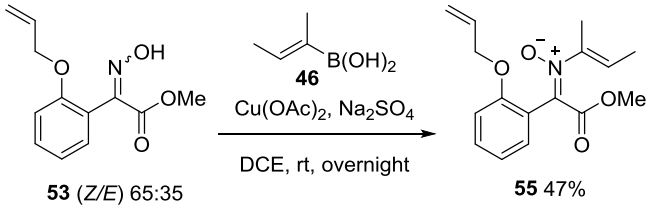
Scheme 3.25.

In view of this disappointing result, we did not make additional efforts for synthesizing *N*-alkenylnitrone **51** and we focused on our attention in the preparation of analogous malonate-derived *N*-alkenylnitrone **52**. In this case, ketoxime **50** was efficiently converted into the desired *N*-alkenylnitrone **52** through $Cu(OAc)_2$-catalyzed cross-coupling reaction with **46** (Scheme 3.26).[5]



Scheme 3.26.

Finally, treatment of the diastereomeric mixture of ketoxime **53** with *N*-alkenylboronic acid **46** under copper-mediated conditions afforded the *N*-alkenylnitrone **55** in moderate yield (Scheme 3.27).



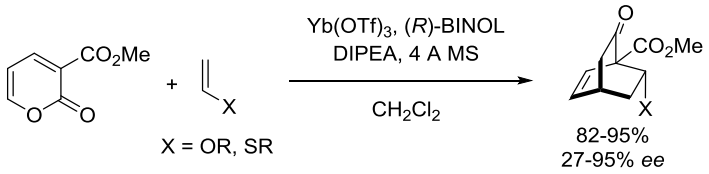
Scheme 3.27.

In conclusion, it has been possible the synthesis of the *N*-alkenylnitrone **52** suitable for the intermolecular version of the IEDDA reaction with different electron-rich dienophiles, as well as the *N*-alkenylnitrone **55** with a tethered dienophile adequate for the intramolecular variant of the reaction.

3.4. Intermolecular IEDDA essays on *N*-alkenylnitrone 52

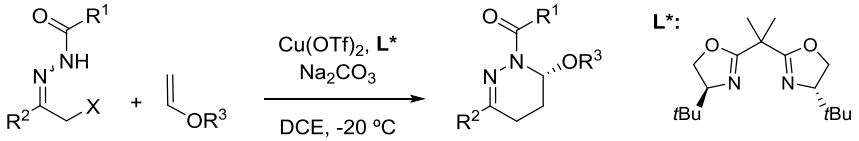
The IEDDA reaction has been recognized as a powerful method to efficiently construct various biologically important and synthetically valuable heterocycles. Different metal

catalysts have been successfully applied in both racemic and enantioselective IEDDA reactions. For instance, Markó and coworkers[23] reported the first asymmetric lanthanide-catalyzed IEDDA reaction of 3-carbomethoxy-2-pyrone derivatives with a series of electron-rich dienophiles, such as vinyl ethers and sulphides. Thus, optically active bicyclic lactones were obtained with modest to good enantioselectivities by using a chiral ytterbium complex, prepared from ytterbium triflate, BINOL and a tertiary amine, as catalyst (Scheme 3.28).



Scheme 3.28

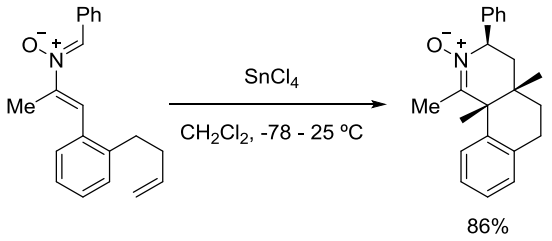
Additionally, bis(oxazoline)-type ligands in combination with copper salts have also been widely used in enantioselective Diels-Alder, as well as IEDDA reactions for the enantioselective synthesis of nitrogen-containing heterocycles.[24] Thus, for example, Chen and Xiao[24b] used a chiral copper/bis(oxazoline) complex as catalyst for a highly efficient and enantioselective IEDDA reaction of *in situ* generated 1,2-diaza-1,3-dienes with enol ethers, which allowed the access to pyridazine derivatives (Scheme 3.29).



Scheme 3.29.

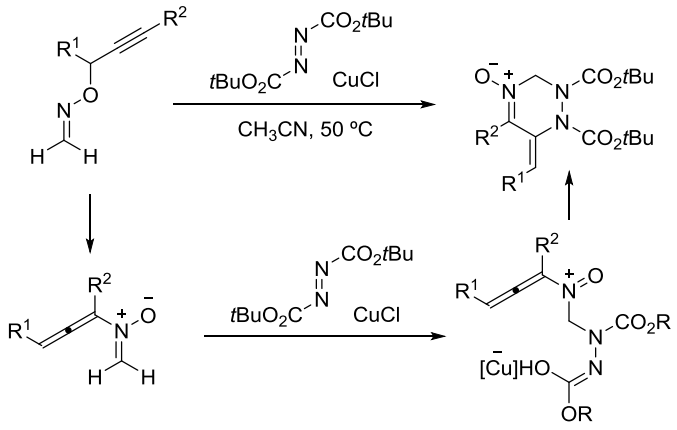
[23] Markó, I. E.; Evans, G. R.; Seres, P.; Chellé, I.; Janousek, Z. *Pure Appl. Chem.* **1996**, *68*, 113.
[24] a) Evans, D. A.; Barners, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582. b) Gao, S.; Chen, J.-R.; Hu, X.-Q.; Cheng, H.-G.; Lu, L.-Q.; Xiao, W.-J. *Adv. Synth. Catal.* **2013**, *355*, 3539.

On the other hand, nitrones have also been employed as electron-deficient azadienes in inverse-demand cycloaddition reactions for the synthesis of six-membered ring nitrones.[1] In this context, Denmark and Montgomery reported the first Lewis acid-promoted intramolecular [4+2] cycloaddition of *N*-vinylnitrones to access tetrahydropyridine *N*-oxide framework (Scheme 3.30).[25]



Scheme 3.30.

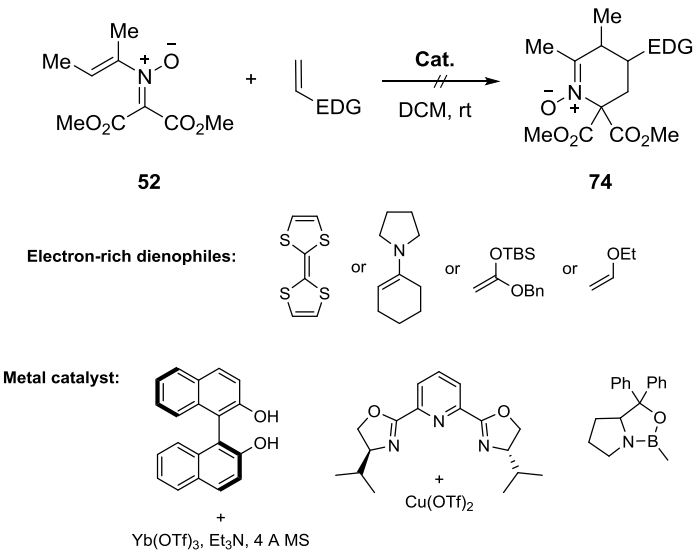
More recently, Nakamura and coworkers[26] described a similar inverse-demand [4+2] cycloaddition reaction of *N*-allenylnitrones, generated *in situ* through a copper-catalyzed 2,3-rearrangement of *O*-propargylic oximes, with azodicarboxylates to give 1,2,4-triazine oxides in good to high yields (Scheme 3.31).



Scheme 3.31.

[25] Denmark, S. E.; Montgomery, J. I. *J. Org. Chem.* **2006**, *71*, 6211.
[26] Nakamura, I.; Jo, T.; Zhang, D.; Terada, M. *Org. Chem. Front.* **2014**, *1*, 914.

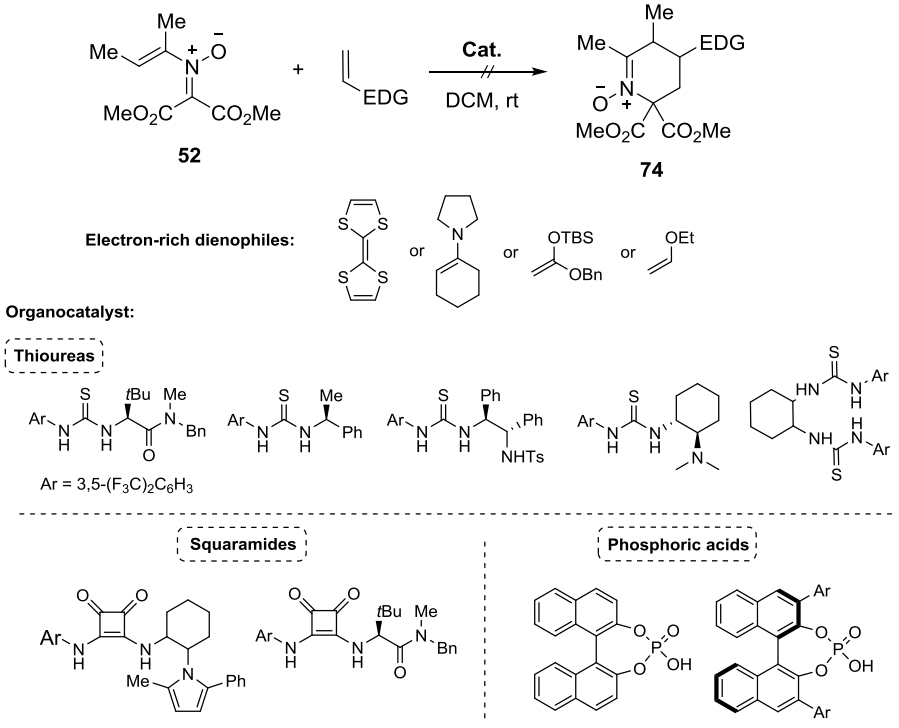
In view of these precedents and with *N*-alkenylnitrone **52** in hand, we evaluated it as electron-deficient diene in the IEDDA reaction with the different electron-rich dienophiles depicted in Scheme 3.32. Firstly, the reaction was carried out in the absence of any catalyst, but we observed that it did not take place and unreacted starting material was recovered. Therefore, we considered the use of metal catalysis. For that purpose, we tested different catalysts successfully employed in related reactions, such as previously mentioned chiral ytterbium triflate catalyst generated *in situ* from $Yb(OTf)_3$, (*S*)-BINOL and DBU,[23,27] a bis(oxazolinyl)pyridine-copper complex[24] and an oxazaborolidine.[28] Unfortunately, no reactivity of the *N*-alkenylnitrone was observed regardless the employed catalyst and starting material was recovered in all cases (Scheme 3.32).



Scheme 3.32.

[27] Markó, I. E.; Chellé-Regnaut, F. I.; Leroy, B.; Warriner, S. L. *Tetrahedron* **1997**, *38*, 4269.
[28] a) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. b) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388. d) Futatsugi, K.; Yamamoto, H. *Angew. Chem. Int. Ed*. **2005**, *44*, 1484.

Then, we decided to investigate the effect of different organocatalysts (Scheme 3.33). Hence, we tested different commercially available and synthesized thiourea and squaramides, which were evaluated as catalysts during the optimization of different reactions studied by Anderson and coworkers (e.g. asymmetric synthesis of dihydropyrido[1,2-*a*]indoles from nitrones and allenoates).[11] Additionally, we tried out a racemic and a chiral phosphoric acid, as they were efficiently employed as catalysts in the cascade synthesis of 3-functionalized indoles from *N*-aryl-α,β-unsaturated ketonitrones and electron-deficient allenes developed by Anderson's group.[12] However, as happened with the metal catalysis attempts, none of the organocatalysts was able to promote the IEDDA reaction of **52** and any of the electron-rich dienophiles, isolating starting material in all cases (Scheme 3.33).



Scheme 3.33.

In conclusion, the intermolecular IEDDA reaction of previously synthesized *N*-alkenylnitrone **52** with different electron-rich dienophiles was not successful under the reaction conditions tested neither using metal catalysis nor organocatalysis.

At this point my research stay at the University of Illinois at Chicago came to an end, so we could not evaluate previously synthesized *N*-alkenylnitrone **55** as precursor in the intramolecular IEDDA reaction. Therefore, the work is still open for further study.

IV

Final Conclusions

1. CONCLUSIONS

1. CONCLUSIONS

- Intramolecular palladium(0)-catalyzed reaction of 2-alkenyl substituted *N*-(*o*-iodoarylalkyl)pyrroles always led to direct arylation reaction on the pyrrole nucleus, regardless the catalytic system employed. No competition with the Mizoroki-Heck reaction for the formation of seven- and eight- membered rings was observed. Thus, the synthesis of pyrrolo[2,1-*a*]isoquinolines and pyrrolo[2,1-*a*]benzazepines has been achieved in high yields with complete chemoselectivity.

- The enantioselective palladium-catalyzed Heck-Heck reaction of 2,3-dialkenyl *N*-(*o*-iodobenzyl)pyrroles for the construction of the tetracyclic core of Lycorane alkaloids can be improved using experimental conditions predicted by a chemoinformatic model developed in our group. Thus, we have demonstrated that the reaction can be carried out employing more environmentally friendly conditions (e.g. the use of ethanol as solvent), achieving better yields and similar levels of enantioselection. More interestingly, the catalyst/base/ligand loadings can be reduced to 2.5 mol%, 2 equivalents and 15 mol%, respectively. On the other hand, the computational model has also been used to predict the effect of ligand structure over the enantioselectivity of the process. Experimental results confirm the ligand performance trends predicted by the model, but the enantioselectivity could only be slightly improved.

- 2-Alkenyl *N*-(*o*-iodobenzyl)pyrroles are suitable substrates for the generation of C-10 substituted pyrrolo[1,2-*b*]isoquinolines with a quaternary center through an initial carbopalladation followed by a cyanide trapping sequence. This intramolecular Heck/cyanation cascade is compatible with different substitution patterns on the aromatic ring, using a catalytic system in absence of phosphane ligands, although pyrrolo[1,2-*b*]isoquinoline yields are low to good, due to the competitive direct cyanation process.

- Intramolecular Heck/Suzuki cascade reaction can also take place to generate C-10 disubstituted pyrrolo[1,2-b]-isoquinolines through a palladium-catalyzed 6-*exo* carbopalladation of 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles followed by a cross-coupling reaction with boronic acids. A phosphane-free precatalytic system in the presence of nBu$_4$NCl can be used to favor the 6-*exo* carbopalladation reaction versus the direct Suzuki coupling, although the 7-*endo* process is competitive in some cases. Nevertheless, the use of phosphane ligands has been found to suppress the 7-*endo* pathway. Thus, the combination of tri(furan-2-yl)phosphane with $Pd_2(dba)_3 \cdot CHCl_3$ leads in most cases to a significant increase in the yields of the pyrroloisoquinolines. The carbopalladation/Suzuki sequence can be efficiently applied to a wide variety of electron-rich and electron-deficient arylboronic acids, but coupling with alkenyl or heteroaryl (thiophenyl) boronic acids provides lower yields. Besides, the domino reaction can also be extended to 2-iodobenzylpyrroles with different substitution patterns on the aromatic ring and the alkene. Finally, only modest enantioselection (up to 44% *ee*) could be obtained using chiral non-racemic phosphanes.

- Anti-leishmanicidal activity and citotoxicity of some of the synthesized pyrrolo[1,2-*b*]isoquinolines have been evaluated through biological assays against visceral (*L. donovani*) and cutaneous (*L. amazonensis*) leishmaniasis carried out by Dr. M. A. Dea from University CEU Cardenal Herrera (Valencia). Thus, pyrroloisoquinolines have been found to be more active and safer than the drug of reference Miltefosine for the treatment of cutaneous leishmaniasis. Particularly, 10-benzyl substituted derivatives present better activity than the compounds with a cyanomethyl group at C-10. Besides, the presence of electron-donating substituents seems to have a positive impact on anti-leishmanicidal activity. On the other hand, tested pyrroloisoquinolines are less active than Miltefosine for the treatment of visceral leishmaniasis, as well as *L. donovani* amastigotes.

- A new family of enantiopure hybrid guanidine/amine ligands designed to form catalytically active complexes with transition-metals has been efficiently prepared. However, their screening in conjugate addition reaction of organomagnesium reagents to acyclic enones and enantioselective Henry reaction catalyzed by copper has led to low levels of enantioinduction. Future work would be required in order to establish conclusions about the lack of activity.

- Copper-catalyzed Chan-Lam coupling reaction between oximes and alkenylboronic acids has allowed the efficient synthesis of *N*-alkenylnitrones with the adequate structure for their use in both inter- and intramolecular inverse electron demand Diels-Alder reaction. However, the evaluation of the *N*-alkenylnitrones as electron-deficient azadienes in the intermolecular IEDDA reaction with different electron-rich dienophiles has not been successful under the reaction conditions attempted neither using metal catalysis nor organocatalysis.

V

Experimental Section

1. GENERAL METHODS AND MATERIALS

2. MIZOROKI-HECK REACTION FOR THE GENERATION OF QUARTERNARY CENTERS

2.1. Mizoroki-Heck reaction for the formation of a quaternary center on C-11 of pyrrolo[1,2-*b*]benzazepines and C-12 of pyrrolo[1,2-*b*]benzazocines

2.1.1. Synthesis of 2-alkenyl substituted (o-iodoarylalkyl)pyrroles ***5a,b***

2.1.2. Intramolecular Mizoroki-Heck reaction of 2-alkenyl substituted N-(o-iodoarylalkyl)pyrroles ***5a,b***

2.2. Heck-Heck cascade reactions. Access to tetracyclic core of the Lycorane alkaloids

2.3. Intramolecular carbopalladation/cyanation cascade

1. GENERAL METHODS AND MATERIALS

NMR

Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H NMR and ^{13}C NMR) were acquired at 25 ^{o}C on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) and on a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR; $(CD_3)_2CO$, 2.05 ppm for ^{1}H NMR and 28.8 ppm for ^{13}C NMR; D_2O, 4.79 ppm for ^{1}H), 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; m, multiplet; br s, broad singlet. Assignments of individual ^{13}C and 1H resonances are supported by DEPT experiments and 2D correlation experiments (COSY, HSQCed or HMBC). Selective nOe or NOESY experiments were performed when necessary.[1]

IR

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

MS

GC-MS analyses were performed on an Agilent 7890A, using a column HP-1 (100% methylpolysiloxane, 30 m x 0.25 mm x 0.25 µm). Mass spectra were recorded using electron impact conditions (EI) at 70 eV on an Agilent MSD 5975 C spectrometer. High resolution mass spectra (HRMS) were performed by the Mass Spectrometry General Service at the University of Basque Country using a Ultra Performance Liquid Chromatography (Acquity UPLC, Waters Cromatografía S.A.) in tandem with a QTOF mass spectrometer (SYNAPT G2 HDMS, Waters Cromatografía S.A.) with an electrospray ionization source (ESI) in a positive mode.

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

m.p.

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

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 ADH and OD columns (0.46 x 25 cm) were used in isocratic elution mode. Specific conditions are indicated for each case.

Polarimetry

Optical rotations were measured at 20 ^{o}C on a Jasco P-2000 polarimeter with sodium lamp at 589 nm and a path length of 1 dm. Solvent and concentrations are specified in each case.

Reagents and Solvents

Anhydrous solvents were dried under activated molecular sieves prior to their use.[2]

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 account when the reaction batches were calculated, including: *n*Bu_4NCl 97% purity, *n*Bu_4NOAc 97% purity, 4-methoxyphenylboronic acid 95% purity, 4-nitrophenylboronic acid 95% purity and (*S*)-P-Phos 97% purity.

Palladium catalyst were purchased from Sigma-Aldrich and were used without further purification: $Pd(OAc)_2$ 98% purity, $Pd(TFA)_2$ 97% purity, $Pd(PPh_3)_4$ 99% purity, $Pd(dba)_2$ 99.9% purity, $Pd_2(dba)_3{\cdot}CHCl_3$ 97% purity, $PdCl_2(CH_3CN)_2$ 99% purity, $Pd(PPh_3)_2Cl_2$ 98% purity and $PdCl_2$ 99% purity.

[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.

Miscellaneous

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

For anhydrous conditions, all the glassware was previously dried for 12 h prior to utilizing in an over at 130 ^{o}C and allowed to cool down under a dehumidified atmosphere and purged with argon. The addition of solutions and liquids were carried out by over-dried syringe or cannula.[4]

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.

Anti-leishmanicidal assays

The following species of *Leishmania* were used: *L. donovani* (MHOM/IN/80/DD8) was purchased (ATCC, USA) and *L. amazonensis* (MHOM/Br/79/Maria) were kindly provided by Prof. Alfredo Toraño (Instituto de Salud Carlos III, Madrid).

The *in vitro* promastigote susceptibility assay,[5] *in vitro* intracellular amastigote susceptibility assay[6] and cytotoxicity assay[7] were carried out following the procedures previously described.

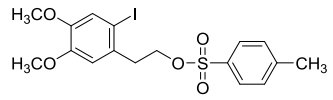
[3] Stahl, E. *Thin Layer Chromatography.* Springler-Verlag: Berlin, **1969**.
[4] Harwood, L. M.; Moody, C. J.; Percy, J. M. *Experimental Organic Chemistry: Standard and Microscale*, 2nd Ed., Blackwell Science: Oxford, **1999**.
[5] Bilbao-Ramos, P.; Galiana-Roselló, C.; Dea-Ayuela, M. A.; González-Alvarez, M.; Vega, C.; Rolón, M.; Pérez-Serrano, J.; Bolás-Fernández, F.; González-Rosende, M. E. *Parasitol. Int.* **2012**, *61*, 604.

2. MIZOROKI-HECK REACTION FOR THE GENERATION OF QUARTERNARY CENTERS

2.1. Mizoroki-Heck reaction for the formation of a quaternary center on C-11 of pyrrolo[1,2-*b*]benzazepines and C-12 of pyrrolo[1,2-*b*]benzazocines

2.1.1. Synthesis of 2-alkenyl substituted (o-iodoarylalkyl)pyrroles ***5a,b***

2-iodo-4,5-dimethoxyphenethyl 4-methylbenzenesulfonate (1a).[8] Tosyl chloride (2.77 g, 14.54 mmol) and Et_3N (2.0 mL, 14.54 mmol) were added over a solution of 2-(2-iodo-4,5-dimethoxyphenyl)ethanol (3.73 g, 12.12 mmol) in dry CH_2Cl_2 (30 mL) at 0 ºC. The reaction was stirred at rt for 30 min and then washed with HCl 5 M (10 mL). The resulting aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, petroleum ether/EtOAc 6/4) afforded **1a** as a white solid (5.50 g, 98%): **m.p.** (petroleum ether/EtOAc): 109-110 °C; **IR** (ATR): 1360 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH_3), 2.98 (t, J = 6.8 Hz, 2H, ArCH_2), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.18 (t, J = 6.8 Hz, 2H, CH_2OTs), 6.65 (s, 1H, H_{6Ar}), 7.09 (s, 1H, H_{3Ar}), 7.24 (d, J = 8.1 Hz, 2H, H_{2tol}, H_{6tol}), 7.66 (d, J = 8.3 Hz, 2H, $H_{3tol,}$ H_{5tol}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 21.6 (CH_3), 39.6 (ArCH_2), 55.9 (OCH_3), 56.1 (OCH_3), 69.3 (CH_2OTs), 87.9 (C_{2Ar}), 113.2 (C_{6Ar}), 121.6 (C_{3Ar}), 127.48 (C_{2tol}, C_{6tol}), 129.7 ($C_{3tol,}$ C_{5tol}), 131.2 (C_{1tol}), 132.9 (C_{1Ar}), 144.7 (C_{4tol}), 148.5, 149.3 (C_{4Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 463 (MH^+, 5), 277 (26), 91 (25). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{20}IO_5S$ [MH^+]: 463.0076; found: 463.0089.



[6] Bilbao-Ramos, P.; Sifontes-Rodríguez, S.; Dea-Ayuela, M. A.; Bolás-Fernández, F. *J. Microbiol. Methods* **2012**, *89*, 8.
[7] Galiana-Roselló, C.; Bilbao-Ramos, P.; Dea-Ayuela, M. A.; Rolón, M.; Vega, C.; Bolás-Fernández, F.; García-España, E.; Alfonso, J.; Coronel, C.; González-Rosende, M. E. *J. Med. Chem.* **2013**, *56*, 8984.
[8] Ruiz, A.; Ardeo, A.; Ignacio, R.; Sotomayor, N.; Lete, E. *Tetrahedron* **2005**, *61*, 3311.

3-(2-iodo-4,5-dimethoxyphenyl)propyl methanesulfonate (1b).[8] Mesyl chloride (1.5 mL, 19.76 mmol) and Et_3N (2.7 mL, 19.76 mmol) were added over a solution of 3-(2-iodo-4,5-dimethoxyphenyl)propan-1-ol (5.30 g, 16.46 mmol) in dry CH_2Cl_2 (30 mL) at 0 ºC. The reaction was stirred at rt for 16 h and then washed with HCl 5 M (10 mL). The resulting aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford **1b** as a brown solid (6.24 g, 95%): **m.p.** (CH_2Cl_2): 127-130 °C; **IR** (ATR): 1345 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.79-1.90 (m, 2H, C*H*$_2$CH$_2$OMs), 2.75 (t, *J* = 7.8 Hz, 2H, ArCH$_2$), 2.91 (s, 3H, CH_3), 3.71 (t, *J* = 6.3 Hz, 2H, CH_2OMs), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.75 (s, 1H, H_{6Ar}), 7.20 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 33.2 (ArCH$_2$), 36.5 (C*H*$_2$CH$_2$OMs), 37.1 (CH_3SO_3), 55.8 (OCH_3), 56.0 (OCH_3), 65.8 (CH_2OMs), 87.8 (C_{2AR}), 112.1 (C_{6Ar}), 121.5 (C_{3Ar}), 136.7 (C_{1Ar}), 147.6, 149.2 (C_{4Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 400 (M^+, 100), 304 (22), 277 (92), 177 (39). **HRMS** (ESI-TOF): calcd. for $C_{12}H_{18}IO_5S$ [MH^+]: 400.9920; found: 400.9903.

1-(1-(2-iodo-4,5-dimethoxyphenethyl)-1*H*-pyrrol-2-yl)ethan-1-one (3a). 2-acetylpyrrole (**2**) (2.04 g, 18.53 mmol) was added over a suspension of powered KOH (1.22 g, 18.53 mmol) in DMSO (50 mL) at room temperature and the mixture was stirred for 30 min. Tosylate **1a** (10.27 g, 22.24 mmol) was added and the resulting reaction mixture was stirred at rt for 6 h. The reaction was quenched with H_2O (20mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (3 x 20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (neutral alumina, petroleum ether/EtOAc 8/2) afforded *N*-phenethylpyrrole **3a** as a white solid (6.38 g, 86%): **m.p.** (petroleum ether/EtOAc): 102-103 °C; **IR** (ATR): 1645 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.46 (s, 3H, CH_3), 3.08 (t, *J* = 7.1 Hz, 2H, ArCH$_2$), 3.75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.46 (t, *J* = 7.1 Hz, 2H, CH_2N), 6.05 (dd, *J* = 4.1, 2.5 Hz, 1H, $H_{4pyrrole}$), 6.50 (s, 1H, H_{6Ar}), 6.63 (dd, *J* = 2.5, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.97 (dd, *J* = 4.1, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.18 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.3 (CH_3), 41.9 (ArCH$_2$), 49.8 (CH_2N), 55.8 (OCH_3), 56.1 (OCH_3), 88.0 (C_{2Ar}), 108.0 ($C_{4pyrrole}$), 112.8 (C_{6Ar}), 120.5 ($C_{3pyrrole}$), 121.4 (C_{3Ar}), 129.9 ($C_{2pyrrole}$), 130.7 ($C_{5pyrrole}$), 133.6 (C_{1Ar}), 148.2, 149.3 (C_{4Ar}, C_{5Ar}), 188.2 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 400 (MH^+, 86), 274 (14), 273 (100), 164 (23). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{19}INO_3$ [MH^+]: 400.0410; found: 400.0415.

1-iodo-4,5-dimethoxy-2-vinylbenzene (4).[9] Isolated in the previous experimental procedure as a by-product (798 mg, 12%): **m.p.** (petroleum ether/EtOAc): 72-73 °C; **IR** (ATR): 1645 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.20 (dd, J = 10.9, 0.8 Hz, 1H, C$H_a$$H_b$=$CH_c$), 5.50 (dd, J = 17.2, 0.8 Hz, 1H, $CH_a$$H_b$=C$H_c$), 6.79 (dd, J = 17.2, 10.9 Hz, 1H, $CH_a$$H_b$=C$H_c$), 7.00 (s, 1H, H_{6Ar}), 7.20 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 55.9 (OCH_3), 56.2 (OCH_3), 88.4 (C_{2Ar}), 108.5 (C_{6Ar}), 114.9 (CH=*C*H_2), 121.4 (C_{3Ar}), 133.1 (*C*H=CH_2), 140.2 (C_{1Ar}), 149.4, 149.5 (C_{4Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 291 (MH^+, 60), 291 (M^+, 100), 164 (35). **HRMS** (ESI-TOF): calcd. for $C_{10}H_{12}IO_2$ [MH^+]: 290.9882; found: 290.9896.

1-(1-(3-(2-iodo-4,5-dimethoxyphenyl)propyl)-1*H*-pyrrol-2-yl)ethan-1-one (3b). 2-acetylpyrrole (**2**) (1.55 g, 14.04 mmol) was added over a suspension of powered KOH (1.85 g, 28.08 mmol) in DMSO (50 mL) at room temperature and the mixture was stirred for 30 min. Mesylate **1a** (6.74 g, 16.85 mmol) was added and the resulting reaction mixture was stirred at rt for 6 h. The reaction was quenched with H_2O (20mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (3 x 20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (neutral alumina, petroleum ether/EtOAc 8/2) afforded *N*-phenylpropylpyrrole **3b** as a yellow solid (4.18 g, 72%): **m.p.** (petroleum ether/EtOAc): 60-63 °C; **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.95-2.03 (m, 2H, C$H_2$$CH_2$N), 2.42 (s, 3H, CH_3), 2.60-2.65 (m, 2H, ArCH_2), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.38 (t, J = 7.2 Hz, 2H, CH_2N), 6.11 (dd, J = 4.1, 2.5 Hz, 1H, $H_{4pyrrole}$), 6.70 (s, 1H, H_{6Ar}), 6.86 (dd, J = 2.5, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.94 (dd, J = 4.1, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.17 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.4 (*C*$H_2$$CH_2$N), 32.1 (Ar$CH_2$), 37.5 ($CH_3$), 49.3 ($CH_2$N), 56.0 ($OCH_3$), 56.2 ($OCH_3$), 88.0 ($C_{2Ar}$), 108.1 ($C_{4pyrrole}$), 112.1 ($C_{6Ar}$), 120.4 ($C_{3pyrrole}$), 121.7 ($C_{3Ar}$), 130.2 ($C_{5pyrrole}$, $C_{2pyrrole}$), 136.3 (C_{1Ar}), 147.8, 149.4 (C_{4Ar}, C_{5Ar}), 188.1 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 414 (MH^+, 84), 288 (18), 287 (100), 244 (12). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{21}INO_3$ [MH^+]: 414.0566; found: 414.0571.

[9] Gagnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804.

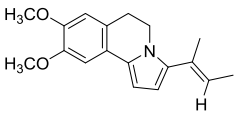
(*E*)-2-(but-2-en-2-yl)-1-(2-iodo-4,5-dimethoxyphenethyl)-1*H*-pyrrole (5a). EtMgBr (1.8 mL, 1.81 mmol, 1M in THF) was added over a solution of *N*-(*o*-iodophenetyl)pyrrole **3a** (481 mg, 1.21 mmol) in dry THF (10 mL) and the mixture as stirred at rt for 16 h. After cooling to -60 ºC, the mixture was quenched by addition of HCl 5M (7.5 mL) and stirred for 2 h. The resulting aqueous phase was extracted with Et_2O (3 x 15 mL) and washed with brine (3 x 15 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, petroleum ether/EtOAc 8/2) obtaining **5a** as a yellow oil (266 mg, 54%): **IR** (ATR): 1505 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.73 (d, *J* = 6.8 Hz, 3H, CH_3C=CHCH_3), 1.84 (s, 3H, CH_3C=CHCH_3), 3.00 (t, *J* = 6.9 Hz, 2H, ArCH_2), 3.71 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.08 (t, *J* = 6.9 Hz, 2H, CH_2N), 5.31-5.38 (m, 1H, CH_3C=C*H*CH_3), 5.91 (dd, *J* = 3.5, 1.8 Hz, 1H, $H_{4pyrrole}$), 6.06-6.08 (m, 1H, $H_{3pyrrole}$), 6.24 (s, 1H, H_{6Ar}), 6.56 (dd, *J* = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.19 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 14.1 (CH_3C=CH*C*H_3), 17.6 (*C*H_3C=CHCH_3), 42.3 (ArCH_2), 47.0 (CH_2N), 55.8 (OCH_3), 56.2 (OCH_3), 87.8 (C_{2Ar}), 106.8 ($C_{4pyrrole}$), 107.4 ($C_{3pyrrole}$), 112.7 (C_{6Ar}), 121.0 (C_{3Ar}), 121.4 ($C_{5pyrrole}$), 124.7 (CH_3C=*C*HCH_3), 128.0 (CH_3C=CHCH_3), 133.5 ($C_{2pyrrole}$), 137.8 (C_{2Ar}), 148.2 (C_{4Ar}), 149.2 (C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 413 (MH^+, 16) 412 (100), 284 (11). **HRMS** (ESI-TOF): calcd. for $C_{18}H_{23}INO_2$ [MH^+] 412.0773; found: 412.0789.

(*E*)-2-(but-2-en-2-yl)-1-(3-(2-iodo-4,5-dimethoxyphenyl)propyl)-1*H*-pyrrole (5b). EtMgBr (1.7 mL, 1.75 mmol, 1M in THF) was added over a solution of *N*-(*o*-iodophenylpropyl)pyrrole **3b** (482 mg, 1.17 mmol) in dry THF (10 mL) and the mixture as stirred at rt for 16 h. After cooling to -60 ºC, the mixture was quenched by addition of HCl 5M (7.5 mL) and stirred for 2 h. The resulting aqueous phase was extracted with Et_2O (3 x 15 mL) and washed with brine (3 x 15 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, petroleum ether/EtOAc 8/2) obtaining **5b** as a yellow oil (213 mg, 43%): **IR** (ATR): 1545 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.64 (d, *J* = 6.8 Hz, 3H, CH_3C=CHCH_3), 1.83 (s, 3H, CH_3C=CHCH_3), 1.82-1.94 (m, 2H, CH_2CH_2N), 2.51 (t, *J* = 7.9 Hz, 2H, ArCH_2), 3.74 (s, 6H, 2 x OCH_3), 3.83 (t, *J* = 7.5 Hz, 2H, CH_2N), 5.37-5.46 (m, 1H, CH_3C=C*H*CH_3), 5.88 (dd, *J* = 3.5, 1.8 Hz, 1H, $H_{4pyrrole}$), 6.00-6.02 (m, 1H, $H_{3pyrrole}$), 6.53- 6.56 (m, 1H, $H_{5pyrrole}$), 6.56 (s, 1H, H_{6Ar}), 7.11 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5

MHz, $CDCl_3$): δ = 14.1 (CH_3C=CHCH_3), 17.7 (CH_3C=$CHCH_3$), 32.3 (CH_2CH_2N), 37.7 ($ArCH_2$), 46.8 (CH_2N), 56.0 (OCH_3), 56.2 (OCH_3), 87.9 (C_{2Ar}), 106.9 ($C_{4pyrrole}$), 107.2 ($C_{3pyrrole}$), 112.1 (C_{6Ar}), 121.1 (C_{3Ar}), 121.7 ($C_{5pyrrole}$), 124.5 (CH_3C=$CHCH_3$), 128.2 (CH_3CH=$CHCH_3$) 136.4 ($C_{2pyrrole}$), 137.4 (C_{2Ar}), 147.9 (C_{4Ar}), 149.4 (C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 427 (MH^+, 18) 426 (100), 228 (16). **HRMS** (ESI-TOF): calcd. for $C_{18}H_{23}INO_2$ [MH^+] 426.0930; found: 426.0929.

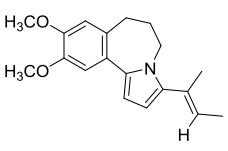
2.1.2. Intramolecular Mizoroki-Heck reaction of 2-alkenyl substituted N-(o-iodoarylalkyl)pyrroles ***5a,b***

(*E*)-3-(but-2-en-2-yl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (8).



$Pd(OAc)_2$ (4.9 mg, 0.02 mmol) was added to a solution of **5a** (88.2 mg, 0.22 mmol), PPh_3 (15.8 mg, 0.06 mmol) and Et_3N (60 µL, 0.43 mmol) in dry THF (5 mL) at rt. The reaction mixture was stirred under reflux for 6 h. The reaction mixture was diluted with 50 mL of EtOAc and washed with saturated NH_4Cl (1 x 20 mL) and H_2O (2 x 20 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under pressure. The oil crude was purified by flash chromatography (silica gel, hexane/EtOAc 8/2) to afford **8** as a yellow oil (57.4 mg, 93%): **IR** (ATR): 1510 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.80 (d, *J* = 6.8 Hz, 3H, CH_3C=CHCH_3), 1.98 (s, 3H, CH_3C=$CHCH_3$), 2.94 (t, *J* = 6.5 Hz, 2H, ArCH_2), 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.02 (t, *J* = 6.5 Hz, 2H, CH_2N), 5.30-5.53 (m, 1H, CH_3C=C$H$$CH_3$), 6.08 (d, *J* = 3.7 Hz, 1H, H_1), 6.38 (d, *J* = 3.7 Hz, 1H, H_2), 6.70 (s, 1H, H_7), 7.02 (s, 1H, H_{10}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 14.1 (CH_3C=CHCH_3), 17.2 (CH_3C=$CHCH_3$), 29.4 ($ArCH_2$), 42.0 (CH_2N), 56.0 (OCH_3), 56.0 (OCH_3), 102.2 (C_1), 106.0 (C_8), 107.2 (C_2), 111.1 (C_{11}), 123.0 (C_{11a}), 123.1 (C_{7a}), 124.2 (CH_3C=$CHCH_3$), 127.6 (CH_3CH=$CHCH_3$) 130.1 (C_3), 136.8 (C_{11b}), 147.2, 148.3 (C_9, C_{10}) ppm; **MS** (ESI) *m/z* (rel intensity): 284 (MH^+, 100), 283 (M^+, 38). **HRMS** (ESI-TOF): calcd. for $C_{18}H_{22}NO_2$ [MH^+] 284.1651; found: 284.1651.

(*E*)-3-(but-2-en-2-yl)-9,10-dimethoxy-6,7-dihydro-5*H*-benzo[*c*]pyrrolo[1,2-*a*]azepine

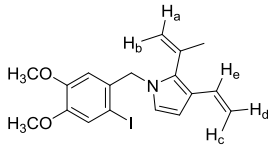


(9). $Pd(OAc)_2$ (6.5 mg, 0.03 mmol) was added to a solution of **5b** (121 mg, 0.28 mmol), PPh_3 (6.5 mg, 0.03 mmol) and *n*Bu_4NOAc (132 mg, 0.43 mmol) in dry DMF (5 mL) at rt. The reaction mixture was stirred at 60 ºC for 48 h and then diluted with 50 mL

of EtOAc and washed with saturated NH_4Cl (1 x 20 mL) and H_2O (2 x 20 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under pressure. Purification by column chromatography (silica gel, hexano/EtOAc) afforded a inseparable mixture of **9** and starting material **5b** in a 3.3:1 ratio in favor to **9** (54.2 mg, 90%) (51% conversion): **IR** (ATR): 1505 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.82 (d, J = 6.8 Hz, 3H, CH_3C=CHCH_3), 2.01 (s, 3H, CH_3C=CHCH_3), 2.17-2.30 (m, 2H, CH_2CH_2N) 2.72 (t, J = 7.0 Hz, 2H, ArCH_2), 3.82 (t, J = 6.1 Hz, 2H, CH_2N), 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.51-5.61 (m, 1H, CH_3C=CHCH_3), 6.12 (d, J = 3.6 Hz, 1H, H_1), 6.24 (d, J = 3.6 Hz, 1H, H_2), 6.77 (s, 1H, H_8), 6.96 (s, 1H, H_{11}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 14.1 (CH_3C=CH*C*H_3), 17.1 (*C*H_3C=CHCH_3), 30.7 (*C*H_2CH_2N), 32.8 (ArCH_2), 43.1 (CH_2N), 55.9 (OCH_3), 56.0 (OCH_3), 105.4 (C_1), 106.5 (C_8), 111.5 (C_2), 112.6 (C_8), 122.6 (C_{11a}), 126.7 (C_{7a}), 128.1 (CH_3C=*C*HCH_3), 129.7 (CH_3*C*=CHCH_3) 136.1 (C_3), 138.2 (C_{11b}), 147.7, 147.8 (C_9, C_{10}) ppm; **MS** (ESI) *m/z* (rel intensity): 298 (MH^+, 100), 297 (M^+, 11). **HRMS** (ESI-TOF): calcd. for $C_{19}H_{24}NO_2$ [MH^+] 298.1807; found: 298.1808.

2.2. Heck-Heck cascade reactions. Access to tetracyclic core of the Lycorane alkaloids

1-(2-iodo-4,5-dimethoxybenzyl)-2-(prop-1-en-2-yl)-3-vinyl-1*H*-pyrrole (10).[10]

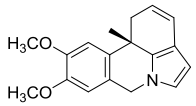


Potassium *tert*-butoxide (270 mg, 0.75 mmol) was added to a solution of methyltriphenylphosphonium bromide (86.0 mg, 0.75 mmol) in dry THF (10 mL) at 0 ºC. The reaction mixture was stirred at room temperature for 30 min and then cooled at 0 ºC. A solution of 1-(2-iodo-4,5-dimethoxybenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole-3-carboxaldehyde (467 mg, 1.31 mmol) in THF (10 mL) was added *via* canula and heated under reflux for 24 h. The reaction mixture was allowed to warm and it was filtered under vacuum. The filtrate was diluted with Et_2O (15 mL) and washed with saturated $NaHSO_3$ (15 mL), saturated Na_2CO_3 (15 mL) and brine (15 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column cromatography (silica gel, hexane/EtOAc 8/2) afforded **10** as a white solid (82.2 mg, 53%): **m.p.:** 88-90 ºC (hexane/EtOAc); **IR** (ATR): 1500 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.93 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.90 (s, 2H, CH_2), 4.96 (dd, J = 11.0, 1.6

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

Hz, 1H, H_b), 4.98-5.00 (m, 1H, H_d), 5.39-5.46 (m, 2H, H_a, H_e), 6.12 (s, 1H, H_{3Ar}), 6.42 (d, *J* = 2.8 Hz, 1H, $H_{4pyrrole}$), 6.57 (d, *J* = 2.8 Hz, 1H, $H_{5pyrrole}$), 6.65 (dd, *J* = 17.5, 10.9 Hz, 1H, H_c), 7.24 (s, 1H, H_{6Ar}) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 ($CH_3C=CH_aH_b$), 55.3 (CH_2), 55.7 (OCH_3), 56.2 (OCH_3), 84.6 (C_{2Ar}), 105.1 ($C_{4pyrrole}$), 108.8 ($CH_cH_d=CH_e$), 110.7 (C_{3Ar}), 120.3 ($C_{2pyrrole}$), 120.4 ($CH_3C=CH_aH_b$), 121.3 (C_{6Ar}), 121.8 ($C_{5pyrrole}$), 129.9 ($CH_cH_d=CH_e$), 133.2 (C_{1Ar}), 134.3 ($C_{3pyrrole}$), 135.6 ($CH_3C=CH_aH_b$), 148.7 (C_{4Ar}), 149.7 (C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 410 (MH^+, 67), 409 (M^+, 59), 284 (11), 283 (18), 276 (100). **HRMS** (ESI-TOF): calcd. for $C_{18}H_{21}INO_2$ $[MH^+]$ 410.0617; found: 410.0596.

(*S*)-9,10-dimethoxy-11b-methyl-7,11b-dihydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (11).[10]



$Pd(dba)_2$ (5.9 mg, 0.01 mmol) was added to a solution of *N*-benzylpyrrole **10** (42.0 mg, 0.10 mmol), (*S*)-P-Phos (1.8 mg, 0.03 mmol) and PMP (0.04 mL, 0.20 mmol) in EtOH (5 mL) and the reaction mixture was heated under reflux for 24 h. The reaction mixture was then diluted with EtOAc (50 mL) and washed with saturated NH_4Cl (10 mL) and H_2O (10 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The oil crude was purified by column chromatography (silica gel, hexane/EtOAc 8/2) to give **11** as a brown oil (14.9 mg, 52%): **IR** (ATR): 1510 cm^{-1}; **^1H NMR** (300 MHz, $CDCl_3$): δ = 1.28 (s, 3H, CH_3), 2.74 (m, 2H, H_1), 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.01 (d, *J* = 15.4 Hz, 1H, H_{7a}), 5.04 (d, *J* = 15.4 Hz, 1H, H_{7b}), 5.52-5.70 (m, 1H, H_2), 6.10 (d, *J* = 2.6 Hz, 1H, H_4), 6.49 (dd, *J* = 9.4, 3.1 Hz, 1H, H_3), 6.61 (d, *J* = 2.6 Hz, 1H, H_5), 6.72 (s, 1H, H_{11}), 6.86 (s, 1H, H_8) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 27.4 (CH_3), 34.1 (C_{11b}), 37.1 (C_1), 47.0 (C_7), 56.4 (2 x OCH_3), 105.7 (C_4), 107.8 (C_{11}), 109.9 (C_8), 113.4 (C_{3a}), 117.0 (C_5), 117.8 (C_2), 122.9 (C_{11a}), 123.1 (C_3), 132.0 (C_{11c}), 135.6 (C_{7a}), 147.3 (C_9), 148.8 (C_{10}) ppm; **MS** (ESI) *m/z* (rel intensity): 282 (MH^+, 100), 281 (M^+, 67), 266 (78). **HRMS** (ESI-TOF): calcd. for $C_{18}H_{20}NO_2$ $[MH^+]$ 282.1494; found: 282.1489. **$[\alpha]_D^{20}$:** + 22.7 (c = 0.32, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be -73% [Chiralcel OZ3, hexane/*i*PrOH 99/1, 0.8 mL/min, t_r (major) = 20.9 min (87%), t_r (minor) = 23.3 min (13%)].

2.3. Intramolecular carbopalladation/cyanation cascade

*2.3.1. Synthesis of 2-alkenyl N-(o-iodoarylalkyl)pyrroles **15a-o***

2.3.1.1. Alkylation reactions. Synthesis of **14a-m**

General procedure A: 2-Acylpyrrole (1 mmol) was added over a suspension of powdered KOH (2 mmol) in DMSO (3 mL) and the mixture was stirred at rt for 2 h. The corresponding bromide **12a-m** (1.2 mmol) was added, and the reaction mixture was stirred until the reaction was completed. H_2O (5 mL) was added and the resulting aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography afforded the corresponding 2-acylpyrroles **14a-m**.

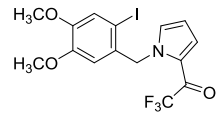
General procedure B: 2-Acylpyrrole (1 mmol) was added over a suspension of powdered NaH (2 mmol) in dry DMF (5 mL). The mixture was stirred at 60 ºC for 1 h. The corresponding bromide **12a-m** (1.5 mmol) was added and the reaction mixture was stirred until the reaction is completed. H_2O (10 mL) was added and the resulting aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried over anhydrous Na2SO4 and concentrated *in vacuo*. Flash column chromatography afforded the corresponding 2-acylpyrroles **14a-m**.

1-[1-(2-Iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl]ethan-1-one (14a).[11] According to general procedure A, 2-acetylpyrrole (**2**) (854 mg, 7.82 mmol) was treated with benzylbromide **12a** (3.34 g, 9.39 mmol) and KOH (1.03 g, 15.65 mmol) in DMSO (20 mL). The mixture was stirred at rt for 4 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **14a** as a white solid (2.45 g, 81%): **m.p. (**petroleum ether/EtOAc): 121-124 °C; **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H, CH_3CO), 3.64 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.51 (s, 2H, CH_2), 6.16-6.18 (m, 1H, $H_{4pyrrole}$), 6.25 (s, 1H, H_{6Ar}), 6.85-6.86 (m, 1H, $H_{3pyrrole}$), 7.00-7.02 (m, 1H, $H_{5pyrrole}$), 7.22 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.2 (*C*H_3CO), 55.6 (OCH_3), 56.1 (OCH_3), 56.9 (CH_2), 86.2 (C_{2Ar}), 108.6 ($C_{4pyrrole}$), 111.1 (C_{3Ar}), 120.3 ($C_{3pyrrole}$), 121.5 (C_{6Ar}), 130.0 ($C_{5pyrrole}$), 130.3 ($C_{2pyrrole}$), 132.9 (C_{1Ar}), 148.8 (C_{4Ar}),

[11] Rebolledo-Azcargorta, A.; Coya, E.; Barbolla, I.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2016**, 2054.

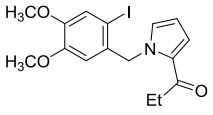
149.6 (C_{5Ar}), 188.4 (CO) ppm; **MS** (CI) *m/z* (rel intensity): 386 (MH^+,65), 276 (71), 259 (100). **HRMS** (CI-TOF): calcd. for $C_{15}H_{17}INO_3$ [MH^+] 386.0248; found: 386.0237.

2,2,2-trifluoro-1-(1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl)ethan-1-one (14b).



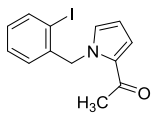
According to general procedure A, **13a** (1.09 g, 6.66 mmol) was treated with benzylbromide **12a** (2.84 g, 7.99 mmol) and KOH (439 mg, 6.66 mmol) in DMSO (30 mL). The mixture was stirred at rt for 2 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **14b** as a white solid (2.51 g, 86%): **m.p.** (petroleum ether/EtOAc): 93-95 ºC; **IR** (ATR): 1665 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.67 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.51 (CH_2), 6.27 (s, 1H, H_{6Ar}), 6.32 (dd, *J* = 4.3, 2.5 Hz, 1H, $H_{4pyrrole}$), 7.07-7.08 (m, 1H, $H_{3pyrrole}$), 7.26 (s, 1H, H_{3Ar}), 7.30-7.33 (m, 1H, $H_{5pyrrole}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 55.7 (OCH_3), 56.2 (OCH_3), 57.5 (CH_2), 86.6 (C_{2Ar}), 110.8 ($C_{4pyrrole}$), 111.1 (C_{3Ar}), 117.0 (q, *J* = 290.5 Hz, CF_3), 121.8 (C_{6Ar}), 124.4 ($C_{2pyrrole}$), 124.6 (q, *J* = 4.0 Hz, $C_{3pyrrole}$), 131.4 (C_{1Ar}), 134.0 ($C_{5pyrrole}$), 149.2, 149.8 (C_{4Ar}, C_{5Ar}), 169.9 (q, *J* = 35.4 Hz, 1H, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 440 (MH^+, 31), 314 (12), 313 (100). **HRMS** (ESI-TOF): calcd. for $C_{15}H_{14}F_3INO_3$ [MH^+] 439.9965; found: 439.9978.

1-(1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrol-2-yl)propan-1-one (14c).



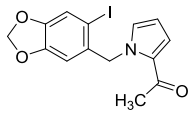
According to general procedure A, **13b** (194 mg, 1.57 mmol) was treated with benzylbromide **12a** (674 mg, 1.89 mmol) and KOH (208 mg, 3.15 mmol) in DMSO (5 mL). The mixture was stirred at rt for 2 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **14c** as a yellow solid (475 mg, 76%): **m.p.** (petroleum ether/EtOAc): 114-116 ºC; **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 2.78 (q, *J* = 7.4 Hz, 2H, CH_2CH_3), 3.60 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.49 (s, 2H, CH_2N), 6.14 (dd, *J* = 4.1, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.19 (s, 1H, H_{3Ar}), 6.83 (dd, *J* = 2.6, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.99 (dd, *J* = 4.1, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.19 (s, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 9.2 (CH_2CH_3), 32.4 (CH_2N), 55.7 (OCH_3), 56.2 (OCH_3), 56.9 (CH_2CH_3), 86.1 (C_{2Ar}), 108.7 ($C_{4pyrrole}$), 110.1 (C_{3Ar}), 119.4 ($C_{3pyrrole}$), 121.6 (C_{6Ar}), 129.9 ($C_{5pyrrole}$), 130.0 ($C_{2pyrrole}$), 133.2 (C_{1Ar}), 148.8, 149.7 (C_{4Ar}, C_{5Ar}), 191.9 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 400 (MH^+, 36), 274 (13), 273 (100). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{19}INO_3$ [MH^+] 400.0404; found: 400.0413.

1-(1-(2-iodobenzyl)-1*H*-pyrrol-2-yl)ethan-1-one (14d).[12] According to general procedure



A, 2-acetylpyrrole (**2**) (933 mg, 8.55 mmol) was treated with benzylbromide **12d** (3.05 g, 10.25 mmol) and KOH (1.13 g, 17.09 mmol) in DMSO (30 mL). The mixture was stirred at rt for 4 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **14d** as a white solid (2.32 g, 83%): **m.p.** (petroleum ether/EtOAc): 95-97 °C; **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3), 5.56 (s, 2H, CH_2), 6.24 (dd, J = 4.1, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.47 (dd, J = 7.8, 1.6 Hz, 1H, H_{3Ar}), 6.84-6.85 (m, 1H, $H_{3pyrrole}$), 6.90-6.96 (m, 1H, H_{4Ar}), 7.06 (dd, J = 4.1, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.17-7.22 (m, 1H, H_{5Ar}), 7.83 (dd, J = 7.8, 1.6 Hz, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.3 (CH_3), 57.8 (CH_2Ar), 97.6 (C_{2Ar}), 108.9 ($C_{4pyrrole}$), 120.4 ($C_{3pyrrole}$), 127.2, 128.6, 129.0, 130.5 (C_{4Ar}, C_{5Ar}, C_{6Ar}, $C_{5pyrrole}$), 130.5 ($C_{2pyrrole}$), 139.3 (C_{3Ar}), 140.8 (C_{1Ar}), 188.2 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 326 (MH^+, 100), 199 (10). **HRMS** (ESI^+): calcd. for $C_{13}H_{13}INO$ [MH^+] 326.0036; found: 326.0048.

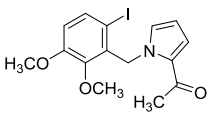
1-(1-((6-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-1*H*-pyrrol-2-yl)ethan-1-one (14e).



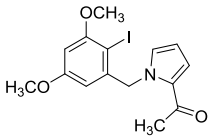
According to general procedure A, 2-acetylpyrrole (**2**) (2.46 g, 22.56 mmol) was treated with benzylbromide **12e** (9.20 g, 27.07 mmol) and KOH (2.98 g, 45.12 mmol) in DMSO (50 mL). The mixture was stirred at rt for 4 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **14e** as a yellow solid (6.95 g, 84%): **m.p.** (petroleum ether/EtOAc): 123-125 °C; **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3), 5.49 (s, 2H, CH_2), 5.91 (s, 2H, OCH_2O), 6.09 (s, 1H, H_{6Ar}), 6.23 (dd, J = 4.1, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.87 (dd, J = 2.6, 1.7 Hz, 1H, $H_{3pyrrole}$), 7.05 (dd, 1H, J = 4.1, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.26 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.3 (CH_3), 57.4 (CH_2Ar), 85.5 (C_{2Ar}), 101.7 (OCH_2O), 107.8 ($C_{4pyrrole}$), 108.9 (C_{3Ar}), 118.5 ($C_{3pyrrole}$), 120.4 (C_{6Ar}), 130.2 ($C_{5pyrrole}$), 130.4 ($C_{2pyrrole}$), 134.2 (C_{1Ar}), 147.7, 148.8 (C_4, C_5), 188.4 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 370 (MH^+, 100), 243 (10). **HRMS** (ESI-TOF): calcd. for $C_{14}H_{13}INO_3$ [MH^+] 369.9935; found: 369.9942.

[12] Nayack, M.; Kang, Y. K; Kim, I. *Org. Lett*. **2017**, 1474-1477.

1-(1-(6-iodo-2,3-dimethoxybenzyl)-1H-pyrrol-2-yl)ethan-1-one (14f). According to general procedure A, 2-acetylpyrrole (**2**) (741 mg, 6.79 mmol) was treated with benzylbromide **12f** (2.91 g, 8.15 mmol) and KOH (897 mg, 13.58 mmol) in DMSO (30 mL). The mixture was stirred at rt for 4 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **14f** as a colorless oil (1.82 g, 69%): **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.46 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.71 (s, 2H, CH_2), 6.01 (dd, *J* = 4.0, 2.7 Hz, 1H, $H_{4pyrrole}$), 6.45-6.47 (m, 1H, $H_{3pyrrole}$), 6.67 (d, *J* = 8.7 Hz, 1H, H_{4Ar}), 6.95 (dd, *J* = 4.1, 1.6 Hz, 1H, $H_{5pyrrole}$), 7.52 (s, *J* = 8.7 Hz, 1H, H_{5Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.6 (CH_3), 51.9 (CH_2), 55.9 (OCH_3), 61.0 (OCH_3), 90.3 (C_{2Ar}), 108.1 ($C_{4pyrrole}$), 114.7 (C_{4Ar}), 120.0 ($C_{3pyrrole}$), 128.0 ($C_{5pyrrole}$), 131.0 ($C_{2pyrrole}$), 133.0 (C_{1Ar}), 134.7 (C_{5Ar}), 149.0 (C_{3Ar}), 153.3 (C_{2Ar}), 188.6 (CO) ppm; **MS** (ESI): *m*/*z* (%) = 386 (MH^+, 40), 277 (41), 259 (14). **HRMS** (ESI-TOF): calcd. for $C_{15}H_{17}INO_3$ [MH^+] 386.0248; found: 386.0253.



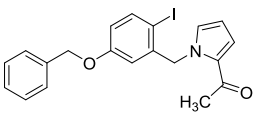
1-(1-(2-iodo-6-methoxybenzyl)-1H-pyrrol-2-yl)ethan-1-one (14g). According to general procedure A, 2-acetylpyrrole (**2**) (35.6 mg, 0.33 mmol) was treated with benzylbromide **12g** (140 mg, 0.39 mmol) and KOH (43.0 mg, 0.65 mmol) in DMSO (10 mL). The mixture was stirred at rt for 4 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **14g** as a white solid (94.3 mg, 75%): **m.p.** (petroleum ether/EtOAc): 142-144 °C; **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.57 (s, 2H, CH_2), 5.70 (d, *J* = 2.7 Hz, 1H, H_4), 6.21 (dd, *J* = 4.0, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.32 (d, *J* = 2.7 Hz, 1H, H_6), 6.85 (dd, *J* = 2.6, 1.7 Hz, 1H, $H_{3pyrrole}$), 7.03 (dd, *J* = 4.0, 1.7 Hz, 1H, $H_{5pyrrole}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.2 (CH_3), 55.3 (OCH_3), 56.5 (OCH_3), 58.1 (CH_2), 78.6 (C_{2Ar}), 97.3 (C_{4Ar}), 104.9 (C_{6Ar}), 108.8 ($C_{4pyrrole}$), 120.3 ($C_{3pyrrole}$), 130.5 ($C_{5pyrrole}$), 130.5 ($C_{2pyrrole}$), 142.9 (C_{1Ar}), 158.8, 161.4 (C_{3Ar}, C_{5Ar}), 188.3 (CO) ppm; **MS** (ESI) *m*/*z* (rel intensity): 386 (MH^+, 100), 259 (85). **HRMS** (ESI-TOF): calcd. for $C_{15}H_{17}INO_3$ [MH^+] 386.0248; found: 386.0255.



1-(1-(5-fluoro-2-iodobenzyl)-1*H*-pyrrol-2-yl)ethan-1-one (14h). According to general procedure B, 2-acetylpyrrole (**2**) (179 mg, 1.64 mmol) was added over a suspension of NaH (131 mg, 3.28 mmol) in dry DMF (10 mL) and the mixture was stirred at 60 ºC for 30 min. Benzylbromide **12h** (620 mg, 1.97 mmol) was added, and the reaction mixture was stirred at 60 ºC for 4 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **14h** as a white solid (556 mg, 99%): **m.p.** (petroleum ether/EtOAc): 122-124 °C; **IR** (ATR): 1640 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3), 5.51 (s, 2H, CH_2), 6.08-6.11 (m, 1H, H_{3Ar}), 6.26 (dd, *J* = 4.1, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.68-6.71 (m, 1H, H_{4Ar}), 6.88 (dd, *J* = 2.6, 1.7 Hz, 1H, $H_{3pyrrole}$), 7.07 (dd, *J* = 4.1, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.75-7.78 (m, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.2 (CH_3), 57.7 (CH_2), 89.5 (d, *J* = 3.4 Hz, C_{2Ar}), 109.2 ($C_{4pyrrole}$), 114.3 (d, *J* = 23.9 Hz, C_{4Ar}), 116.2 (d, *J* = 22.1 Hz, C_{6Ar}), 120.6 ($C_{3pyrrole}$), 130.3 ($C_{2pyrrole}$), 130.5 ($C_{5pyrrole}$), 140.3 (d, *J* = 7.3 Hz, C_{3Ar}), 143.4 (d, *J* = 7.3 Hz, C_{1Ar}), 163.6 (d, *J* = 247.4 Hz, C_{5Ar}), 188.3 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 344 (MH^+, 100), 302 (24), 235 (8), 217 (10). **HRMS** (ESI-TOF): calcd. for $C_{13}H_{12}FINO$ [MH^+] 343.9942; found: 343.9957.

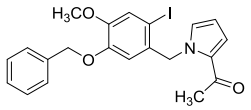
1-(1-(2-iodo-5-methoxybenzyl)-1*H*-pyrrol-2-yl)ethan-1-one (14i). According to general procedure A, 2-acetylpyrrole (**2**) (173 mg, 1.58 mmol) was treated with benzylbromide **12i** (621 mg, 1.90 mmol) and KOH (209 mg, 3.16 mmol) in DMSO (10 mL). The mixture was stirred at rt for 4 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **14i** as a colorless crystal (523 mg, 93%): **m.p.** (petroleum ether/EtOAc): 77-79 °C; **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 5.52 (s, 2H, CH_2), 6.06 (d, *J* = 3.0 Hz, 1H, H_{6Ar}), 6.23 (dd, *J* = 4.0, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.53 (dd, *J* = 8.6, 3.0 Hz, 1H, H_{4Ar}), 6.86 (dd, *J* = 2.6, 1.7 Hz, 1H, $H_{3pyrrole}$), 7.04 (dd, *J* = 4.0, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.69 (d, *J* = 8.6 Hz, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.2 (CH_3), 55.2 (OCH_3), 57.6 (CH_2), 85.8 (C_{2Ar}), 108.9 ($C_{4pyrrole}$), 114.0 (C_{4Ar}), 114.4 (C_{6Ar}), 120.4 ($C_{3pyrrole}$), 130.4 ($C_{2pyrrole}$), 130.4 ($C_{5pyrrole}$), 139.8 (C_{3Ar}), 141.9 (C_{1Ar}), 160.4 (C_{5Ar}), 188.3 (CO) ppm; **MS** (ESI): *m/z* (%) = 356 (MH^+, 100), 270 (5), 229 (3). **HRMS** (ESI-TOF): calcd. for $C_{14}H_{15}INO_2$ [MH^+]: 356.0147; found: 356.0157.

1-(1-(5-(benzyloxy)-2-iodobenzyl)-1*H*-pyrrol-2-yl)ethan-1-one (14j). According to



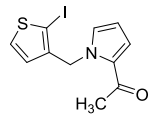
general procedure B, 2-acetylpyrrole (**2**) (140 mg, 1.28 mmol) was added over a suspension of powdered NaH (103 mg, 2.57 mmol) in dry DMF (10 mL) and the mixture was stirred at rt for 30 min. Benzylbromide **12j** (620 mg, 1.97 mmol) was added, and the reaction mixture was stirred at 60 ºC for 16 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **14j** as a white solid (462 mg, 83%): **m.p.** (petroleum ether/EtOAc): 79-81 ºC; **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3), 4.90 (s, 2H, CH_2), 5.53 (s, 2H, OCH_2), 6.13 (d, *J* = 3.0 Hz, 1H, H_{6Ar}), 6.25 (dd, *J* = 4.1, 2.5 Hz, 1H, $H_{4pyrrole}$), 6.63 (dd, *J* = 8.6, 3.0 Hz, 1H, H_{4Ar}), 6.85-6.86 (m, 1H, $H_{3pyrrole}$), 7.05 (dd, *J* = 4.1, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.31-7.38 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.71 (d, *J* = 8.6 Hz, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.3 (CH_3), 57.7 (CH_2), 70.0 (-OCH_2-), 86.0 (C_{2Ar}), 108.9 ($C_{4pyrrole}$), 114.4 (C_{4Ar}), 115.6 (C_{6Ar}), 120.4 ($C_{3pyrrole}$), 127.5 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 130.4 ($C_{2pyrrole}$), 130.5 ($C_{5pyrrole}$), 136.4 ($C_{1'}$), 139.8 (C_{3Ar}), 141.9 (C_{1Ar}), 159.5 (C_{5Ar}), 188.3 (CO) ppm; **MS** (ESI): *m/z* (%) = 432 (MH^+, 100), 305 (10). **HRMS** (ESI-TOF): calcd. for $C_{20}H_{19}INO_2$ [MH^+]: 432.0460; found: 432.0459.

1-(1-(5-(benzyloxy)-2-iodo-4-methoxybenzyl)-1*H*-pyrrol-2-yl)ethan-1-one (14k).



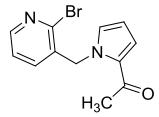
According to general procedure A, 2-acetylpyrrole (**2**) (255 mg, 2.34 mmol) was treated with benzylbromide **12k** (1.21 g, 2.80 mmol) and KOH (308 mg, 4.67 mmol) in DMSO (20 mL). The mixture was stirred at rt for 16 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **14k** as a colorless oil (709 mg, 66%): **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.37 (s, 3H, CH_3), 3.85 (OCH_3), 4.95 (OCH_2), 5.45 (CH_2), 6.14 (s, 1H, H_{6Ar}), 6.19 (dd, *J* = 4.0, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.79 (dd, *J* = 2.6, 1.7 Hz, 1H, $H_{3pyrrole}$), 6.99 (dd, *J* = 4.0, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.25-7.33 (m, 6H, $H_{3Ar,}$ $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.3 (CH_3), 56.3 (OCH_3), 57.0 (CH_2), 70.7 (OCH_2), 86.4 (C_{2Ar}), 108.8 ($C_{4pyrrole}$), 113.2 (C_{6Ar}), 120.4 ($C_{3pyrrole}$), 122.1 (C_{3Ar}), 127.3 ($C_{2'}$, $C_{6'}$), 127.9 ($C_{4'}$), 128.5 ($C_{3'}$, $C_{5'}$), 130.2 ($C_{5pyrrole}$), 130.3 ($C_{2pyrrole}$), 133.0 ($C_{1'}$), 136.5 (C_{1Ar}), 148.6, 149.4 (C_{4Ar}, C_{5Ar}), 188.2 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 462 (MH^+, 58), 336 (14), 335 (93). **HRMS** (ESI-TOF): calcd. for $C_{21}H_{21}INO_3$ (MH^+): 462.0566; found: 462.0565.

1-(1-((2-iodothiophen-3-yl)methyl)-1*H*-pyrrol-2-yl)ethan-1-one (14l). According to



general procedure A, 2-acetylpyrrole (**2**) (753 mg, 6.90 mmol) was treated with thiophenylbromide **12l** (2.51 g, 8.28 mmol) and KOH (911 mg, 13.8 mmol) in DMSO (30 mL). The mixture was stirred at rt for 16 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-thiophenylpyrrole **14l** as a white solid (1.75 g, 77%): **m.p.** (petroleum ether/EtOAc): 93-95 ºC; **IR** (ATR): 1645 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.46 (s, 3H, CH_3), 5.51 (s, 2H, CH_2), 6.17 (dd, J = 4.0, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.60 (d, J = 5.5 Hz, 1H, $H_{4thiophene}$), 6.93 (dd, J = 2.6, 1.7 Hz, 1H, $H_{3pyrrole}$), 7.01 (dd, J = 4.0, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.35 (d, J = 5.5 Hz, 1H, $H_{5thiophene}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.4 (CH_3), 49.5 (CH_2), 75.4 ($C_{2thiophene}$), 108.8 ($C_{4pyrrole}$), 120.5 ($C_{3pyrrole}$), 127.9 ($C_{4thiophene}$), 130.1 ($C_{5pyrrole}$), 130.3 ($C_{2pyrrole}$), 131.3 ($C_{5thiophene}$), 142.8 ($C_{3thiophene}$), 188.6 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 332 (MH^+, 84), 223 (30), 204 (100), 122 (31). **HRMS** (ESI-TOF): calcd. for $C_{11}H_{11}INOS$ [MH^+] 331.9606; found: 331.9619.

1-(1-((2-bromopyridin-3-yl)methyl)-1*H*-pyrrol-2-yl)ethan-1-one (14m'). According to



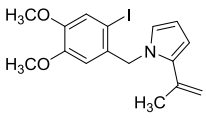
general procedure A, 2-acetylpyrrole (**2**) (175 mg, 1.61 mmol) was treated with 2-bromo-3-(bromomethyl)pyridine **12m** (604 mg, 2.41 mmol) and KOH (424 mg, 6.42 mmol) in DMSO (10 mL). The mixture was stirred at rt for 2 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded bromopyridine **14m'** as a yellow solid (269 mg, 60%): **m.p.** (petroleum ether/EtOAc): 125-127 ºC; **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 5.53 (s, 2H, CH_2), 6.22 (dd, J = 4.1, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.66-6.70 (m, 1H, $H_{5pyridine}$), 6.90 (dd, J = 2.6, 1.7 Hz, 1H, $H_{3pyrrole}$), 7.02 (dd, J = 4.1, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.07 (dd, J = 7.6, 4.7 Hz, 1H, $H_{4pyridine}$), 8.15 (dd, J = 4.7, 1.9 Hz, 1H, $H_{6pyridine}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.1 (CH_3), 51.9 (CH_2), 109.3 ($C_{4pyrrole}$), 120.6 ($C_{3pyrrole}$), 123.2 ($C_{5pyridine}$), 130.2 ($C_{2pyrrole}$), 130.7 ($C_{5pyrrole}$), 135.6 ($C_{4pyridine}$), 135.7 ($C_{3pyridine}$), 141.4 ($C_{2pyridine}$), 148.5 ($C_{6pyridine}$), 188.2 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 279 (MH^+, 6), 199 (100). **HRMS** (ESI-TOF): calcd. for $C_{12}H_{12}BrN_2O$ [MH^+] 279.0133; found: 279.0142.

1-(1-((2-iodopyridin-3-yl)methyl)-1*H*-pyrrol-2-yl)ethan-1-one (14m). 1-(1-((2-bromopyridin-3-yl)methyl)-1H-pyrrol-2-yl)ethan-1-one (**14m'**) (174 mg, 0.62 mmol) in dry dioxane (10 mL) was added *via* canula to a suspension of CuI (5.9 mg, 0.03 mmol), N,N´- dimethylethylenediamine (6 µL, 0.06 mmol) and NaI (186 mg, 1.24 mmol) in dry dioxane (10 mL) under an inert atmosphere. The mixture was heated to reflux for 16 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, petroleum ether/EtOAc 7/3) obtaining product **14m** as a white solid (184 mg, 91 %): **m.p.** (petroleum ether/EtOAc): 108-110 ºC; **IR** (ATR): 1650 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3), 5.52 (s, 2H, CH_2), 6.27 (dd, J = 4.1, 2.6 Hz, 1H, $H_{4pyrrole}$), 6.56-6.60 (m, 1H, $H_{5pyridine}$), 6.92 (dd, J = 2.6, 1.7 Hz, 1H, $H_{3pyrrole}$), 7.06-7.13 (m, 2H, $H_{4pyridine}$, $H_{5pyrrole}$), 8.20-8.22 (m, 1H, $H_{6pyridine}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.2 (CH_3), 56.0 (CH_2), 109.4 ($C_{4pyrrole}$), 120.6 ($C_{3pyrrole}$), 121.0 ($C_{2pyridine}$), 123.3 ($C_{5pyridine}$), 130.3 ($C_{2pyrrole}$), 130.5 ($C_{5pyrrole}$), 134.2 ($C_{4pyridine}$), 138.9 ($C_{3pyridine}$), 149.2 ($C_{6pyridine}$), 188.3 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 327 (MH^+, 25), 199 (100). **HRMS** (ESI-TOF): calcd. for $C_{12}H_{12}IN_2O$ [MH^+] 326.9994; found: 327.0009.

2.3.1.2. Wittig Reaction. Synthesis of 2-alkenylpyrroles **15a-o**

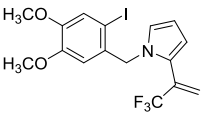
General procedure: Potassium *tert*-butoxide (2 mmol) was added to a solution of methyltriphenylphosphonium bromide (2 mmol) in dry THF (10 mL) at 0 ºC. The reaction mixture was stirred at room temperature under argon for 30 min and then cooled at 0 ºC. A solution of *N*-arylalkylpyrrole **14a-m** (1 mmol) in dry THF (10 mL) was added over 5 min and the mixture was heated under reflux for 24 h. The reaction mixture was allowed to reach room temperature and filtered under vacuum. The filtrate was diluted with Et_2O (10 mL) and sequentially washed with $NaHSO_3$ sat. (10 mL), Na_2CO_3 sat. (10 mL) and brine (10 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude was subjected to flash chromatography (silica gel) obtaining **15a-m**.

1-(2-iodo-4,5-dimethoxybenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15a). According to



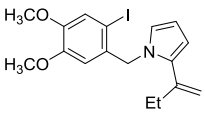
general procedure, **14a** (1.00 g, 2.61 mmol) in dry THF (20 mL) was treated with potassium *tert*-butoxide (598 mg, 5.22 mmol) and methyltriphenylphosphonium bromide (1.90 g, 5.22 mmol) in dry THF (20 mL). After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 7/3) afforded *N*-benzylpyrrole **15a** as a yellow solid (856 mg, 86%): **m.p.** (petroleum ether/EtOAc): 96-98 °C; **IR** (ATR): 1590 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.05 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.73 (s, 1H, CH_aH$_b$=C), 4.98-4.99 (m, 1H, CH$_a$$H_b$=C), 5.08 (s, 2H, CH_2), 6.00 (s, 1H, H_{6Ar}), 6.20-6.23 (m, 1H, $H_{4pyrrole}$), 6.25-6.27 (m, 1H, $H_{3pyrrole}$), 6.64-6.65 (m, 1H, $H_{5pyrrole}$), 7.24 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 55.7 (OCH_3), 56.2 (CH_2), 56.2 (OCH_3), 84.2 (C_{2Ar}), 108.2 ($C_{3pyrrole}$), 109.2 ($C_{4pyrrole}$), 110.6 (C_{3Ar}), 112.1 (*C*H$_a$H$_b$=C), 121.4 ($C_{5pyrrole}$), 123.9 (C_{6Ar}), 133.5 (CH$_a$H$_b$=*C*), 134.8 (C_{2Ar}), 135.3 ($C_{2pyrrole}$), 148.8, 149.7 (C_{4Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 384 (MH^+, 17), 276 (100), 256 (54). **HRMS** (CI-TOF): calcd. for $C_{16}H_{19}INO_2$ [MH^+] 384.0455; found: 384.0442.

1-(2-iodo-4,5-dimethoxybenzyl)-2-(3,3,3-trifluoroprop-1-en-2-yl)-1*H*-pyrrole (15b).

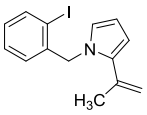


According to general procedure, **14b** (818 mg, 1.86 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (418 mg, 3.72 mmol) and methyltriphenylphosphonium bromide (1.33 g, 3.72 mmol) in dry THF (20 mL). After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **15b** as a yellow solid (491 mg, 60%): **m.p.** (petroleum ether/EtOAc): 72-74 °C; **IR** (ATR): 1505 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.62 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.01 (s, 2H, CH_2), 5.38 (dd, *J* = 3.5, 1.7 Hz, 1H, CH_aH$_b$=C), 5.95-5.97 (m, 2H, CH$_a$$H_b$=C, H_{6Ar}), 6.26 (dd, *J* = 3.8, 2.8 Hz, 1H, $H_{4pyrrole}$), 6.41-6.43 (m, 1H, $H_{3pyrrole}$), 6.74 (dd, *J* = 2.8, 1.7 Hz, 1H, $H_{5pyrrole}$), 7.23 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 55.7 (CH_2), 56.2 (OCH_3), 84.3 (C_{2Ar}), 108.8 ($C_{3pyrrole}$), 110.4 ($C_{4pyrrole}$), 112.0 (C_{3Ar}), 120.9 (q, *J* = 5.4 Hz, *C*H$_a$H$_b$=C), 121.4 ($C_{5pyrrole}$), 122.8 (q, *J* = 273.9 Hz, CF_3), 124.9 (C_{6Ar}), 125.2 (C_{1Ar}), 130.4 (q, *J* = 31.6 Hz, CH$_a$H$_b$=*C*), 132.7 ($C_{2pyrrole}$), 148.9, 150.0 (C_{4Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 438 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{16}F_3INO_2$ [MH^+] 438.0172; found: 438.0182.

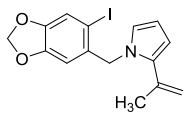
2-(but-1-en-2-yl)-1-(2-iodo-4,5-dimethoxybenzyl)-1*H*-pyrrole (15c). According to general procedure, **14c** (195 mg, 0.49 mmol) in dry THF (5 mL) was treated with potassium *tert*-butoxide (110 mg, 0.98 mmol) and methyltriphenylphosphonium bromide (350 mg, 0.98 mmol) in dry THF (10 mL). After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **15c** as a colorless oil (139 mg, 72%): **IR** (ATR): 1500 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 2.35 (q, *J* = 7.4 Hz, 2H, CH_2CH_3), 3.62 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.80-4.81 (m, 1H, CH_aH_b=C), 5.04-5.05 (m, 3H, CH_aH_b=C, CH_2), 6.00 (s, 1H, H_{3Ar}), 6.19-6.23 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.63-6.65 (m, 1H, $H_{5pyrrole}$), 7.23 (s, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 13.2 (CH_2CH_3), 30.4 (CH_2CH_3), 55.7 (OCH_3), 55.8 (CH_2), 56.2 (OCH_3), 84.3 (C_{2Ar}), 108.2 ($C_{3pyrrole}$), 108.6 ($C_{4pyrrole}$), 110.6 (C_{3Ar}), 111.5 (CH_aH_b=C), 121.4 ($C_{5pyrrole}$), 123.4 (C_{6Ar}), 133.7 (CH_aH_b=*C*), 134.7 (C_{1Ar}), 141.8 ($C_{2pyrrole}$), 148.7, 149.8 (C_{4Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 398 (MH^+, 100), 277 (56), 242 (10). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{21}INO_2$ [MH^+] 398.0611; found: 398.0614.



1-(2-iodobenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15d). According to general procedure, **14d** (603 mg, 1.85 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (416 mg, 3.71 mmol) and methyltriphenylphosphonium bromide (1.32 g, 3.71 mmol) in dry THF (20 mL). After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **15d** as a colorless oil (556 mg, 93%): **IR** (ATR): 1740 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.08 (s, 3H, CH_3), 4.69 (s, 1H, CH_aH_b=C), 4.98-4.99 (m, 1H, CH_aH_b=C), 5.18 (s, 2H, CH_2), 6.26-6.33 (m, 2H, $H_{3pyrrole}$, $H_{4pyrrole}$), 6.53-6.56 (m, 1H, H_{3Ar}), 6.67-6.68 (m, 1H, $H_{5pyrrole}$), 6.96-7.02 (m, 1H, H_{4Ar}), 7.25-7.30 (m, 1H, H_{5Ar}), 7.86-7.89 (m, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 56.7 (CH_2), 96.5 (C_{2Ar}), 108.3 ($C_{3pyrrole}$), 109.1 ($C_{4pyrrole}$), 111.9 (CH_aH_b=C), 124.0 ($C_{5pyrrole}$), 127.5, 128.8, 129.0, (C_{4Ar}, C_{5Ar}, C_{6Ar}), 134.7 (CH_aH_b=*C*), 135.3 ($C_{2pyrrole}$), 139.2 (C_{3Ar}), 141.0 (C_{1Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 324 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{14}H_{15}IN$ [MH^+] 324.0244; found: 324.0250.



1-((6-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15e).



According to general procedure, **14e** (661 mg, 1.79 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (402 mg, 3.58 mmol) and methyltriphenylphosphonium bromide (1.28 g, 3.58 mmol) in dry THF (20 mL). After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **15e** as a yellow solid (428 mg, 65%): **m.p.** (petroleum ether/EtOAc): 114-116 °C; **IR** (ATR): 1620 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 2.06 (s, 3H, CH_3), 4.69 (s, 1H, C$H_a$$H_b$=C), 4.97-4.98 (m, 1H, CH_aH_b=C), 5.06 (s, 2H, CH_2), 5.93 (s, 2H, OCH_2O), 6.05 (s, 1H, H_{3Ar}), 6.22-6.27 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.62-6.63 (m, 1H, $H_{5pyrrole}$), 7.26 (s, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 56.5 (CH_2), 84.0 (C_{2Ar}), 101.7 (OCH_2O), 108.0 ($C_{3pyrrole}$), 108.3 ($C_{4pyrrole}$), 109.2 (C_{3Ar}), 111.8 ($C$$H_aH_b$=C), 118.4 ($C_{5pyrrole}$), 123.9 ($C_{6Ar}$), 134.5, 134.6, 135.2 ($CH_aH_b$=*C*, C_{1Ar}, $C_{2pyrrole}$), 147.7, 149.0 (C_{4Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 368 (MH^+, 100), 261 (28). **HRMS** (ESI-TOF): calcd. for $C_{15}H_{15}INO_2$ [MH^+] 368.0142; found: 368.0152.

1-(6-iodo-2,3-dimethoxybenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15f). According to general procedure, **14f** (599 mg, 1.56 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (351 mg, 3.11 mmol) and methyltriphenylphosphonium bromide (1.12 g, 3.11 mmol) in dry THF (20 mL). After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **15f** as a yellow solid (508 mg, 85%): **m.p.** (petroleum ether/EtOAc): 54-56 °C; **IR** (ATR): 1570 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.24 (s, 3H, CH_3), 3.57 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.16 (s, 1H, C$H_a$$H_b$=C), 5.29-5.30 (m, 1H, CH_aH_b=C), 5.35 (s, 2H, CH_2), 6.07-6.10 (m, 1H, $H_{4pyrrole}$), 6.19-6.21 (m, 1H, $H_{3pyrrole}$), 6.37-6.39 (s, 1H, $H_{5pyrrole}$), 6.72 (d, J = 8.6 Hz, 1H, H_{4Ar}), 7.60 (d, J = 8.6 Hz, 1H, H_{5Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.4 (CH_3), 51.0 (CH_2), 56.0 (OCH_3), 60.7 (OCH_3), 90.2 (C_{2Ar}), 107.4 ($C_{3pyrrole}$), 107.7 ($C_{4pyrrole}$), 113.3 ($C$$H_aH_b$=C), 114.5 ($C_{4Ar}$), 121.1 ($C_{5pyrrole}$), 134.1 ($C_{1Ar}$), 134.7 ($C_{5Ar}$), 135.6 ($CH_aH_b$=*C*), 136.2 ($C_{2pyrrole}$), 148.8 ($C_{3Ar}$), 153.4 ($C_{2Ar}$) ppm; **MS** (ESI) *m/z* (rel intensity): 384 (MH^+, 100), 277 (14), 242 (20). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{19}INO_2$ [MH^+] 384.0455; found: 384.0462.

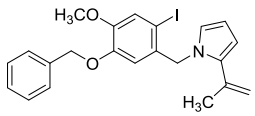
1-(2-iodo-3,5-dimethoxybenzyl)-2-(prop-1-en-2-yl)-1H-pyrrole (15g). According to general procedure, **14g** (283 mg, 0.73 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (165 mg, 1.47 mmol) and methyltriphenylphosphonium bromide (524 mg, 1.47 mmol) in dry THF (10 mL). After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded *N*-benzylpyrrole **15g** as a colorless oil (185 mg, 66%): **IR** (ATR): 1585 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.07 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.69 (s, 1H, C$H_a$$H_b$=C), 4.96-4.97 (m, 1H, CH_aH_b=C), 5.17 (s, 2H, CH_2), 5.75 (d, J = 2.7 Hz, 1H, H_{4Ar}), 6.23-6.29 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.36 (d, J = 2.7 Hz, 1H, H_{6Ar}), 6.67 (t, J = 2.3 Hz, 1H, $H_{5pyrrole}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 55.4 (OCH_3), 56.5 (OCH_3), 57.2 (CH_2), 77.1 (C_{2Ar}), 97.6 (C_{4Ar}), 104.7 ($C_{3pyrrole}$), 108.2 (C_{6Ar}), 109.0 ($C_{4pyrrole}$), 111.8 (CH_aH_b=C), 124.2 ($C_{5pyrrole}$), 134.8 (CH_aH_b=*C*), 135.2 ($C_{2pyrrole}$), 143.3 (C_{1Ar}), 158.7, 161.6 (C_{3Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 384 (MH^+, 100), 257 (42), 242 (56). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{19}INO_2$ [MH^+] 384.0455; found: 384.0465.

1-(5-fluoro-2-iodobenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15h). According to general procedure, **14h** (204 mg, 0.59 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (133 mg, 1.19 mmol) and methyltriphenylphosphonium bromide (424 mg, 1.19 mmol) in dry THF (10 mL). After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **15h** as a colorless oil (188 mg, 93%): **IR** (ATR): 1460 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.08 (s, 3H, CH_3), 4.66 (s, 1H, C$H_a$$H_b$=C), 4.99-5.00 (m, 1H, CH_aH_b=C), 5.14 (s, 2H, CH_2), 6.25-6.33 (m, 3H, $H_{4pyrrole}$, $H_{3pyrrole}$, H_{6Ar}), 6.68 (dd, J = 2.7, 1.9 Hz, 1H, $H_{5pyrrole}$), 6.73-6.80 (m, 1H, H_{4Ar}), 7.78-7.83 (m, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 56.5 (CH_2), 88.7 (d, J = 3.0 Hz, C_{2Ar}), 108.7 ($C_{3pyrrole}$), 109.4 ($C_{4pyrrole}$), 111.9 (CH_aH_b=C), 115.1 (d, J = 24.2 Hz, C_{4Ar}), 116.4 (d, J = 22.0 Hz, C_{6Ar}), 123.9 ($C_{5pyrrole}$), 134.6 (CH_aH_b=*C*), 135.2 ($C_{2pyrrole}$), 140.3 (d, J = 7.7 Hz, C_{3Ar}), 143.6 (d, J = 7.1 Hz, C_{1Ar}), 163.8 (d, J = 248.1 Hz, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 342 (MH^+, 85), 160 (33), 158 (100). **HRMS** (ESI-TOF): calcd. for $C_{14}H_{14}FIN$ [MH^+] 342.0149; found: 342.0161.

1-(2-iodo-5-methoxybenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15i). According to general procedure, **14i** (337 mg, 0.95 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (213 mg, 1.90 mmol) and methyltriphenylphosphonium bromide (678 mg, 1.90 mmol) in dry THF (10 mL). The mixture was heated under reflux for 3 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded *N*-benzylpyrrole **15i** as a colorless crystal (272 mg, 81%): **m.p.** (petroleum ether/EtOAc): 55-57 ºC; **IR** (ATR): 1590, 1465 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.07 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 4.69-4.70 (m, 1H, C$H_a$$H_b$=C), 4.97-4.99 (m, 1H, CH_aH_b=C), 5.12 (s, 2H, CH_2), 6.11 (d, J = 3.1 Hz, 1H, H_{6Ar}), 6.24-6.31 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.58 (dd, J = 8.6, 3.1 Hz, 1H, H_{4Ar}), 6.66 (dd, J = 2.8, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.71 (d, J = 8.6 Hz, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 55.2 (OCH_3), 56.6 (CH_2), 84.6 (C_{2Ar}), 108.4 ($C_{3pyrrole}$), 109.2 ($C_{4pyrrole}$), 111.9 (*C*H_aH_b=C), 113.8 (C_{4Ar}), 114.9 (C_{6Ar}), 124.0 ($C_{5pyrrole}$), 134.7 (CH_aH_b=*C*), 135.3 ($C_{2pyrrole}$), 139.6 (C_{3Ar}), 142.2 (C_{1Ar}), 160.6 (C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 354 (MH^+, 100), 212 (24). **HRMS** (ESI-TOF): calcd. for $C_{15}H_{17}INO$ [MH^+]: 354.0355; found: 354.0354.

1-(5-(benzyloxy)-2-iodobenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15j). According to general procedure, **14j** (379 mg, 0.88 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (197 mg, 1.76 mmol) and methyltriphenylphosphonium bromide (627 mg, 1.76 mmol) in dry THF (10 mL). The mixture was heated under reflux for 2 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded *N*-benzylpyrrole **15j** as a yellow solid (290 mg, 77%): **m.p.** (petroleum ether/EtOAc): 62-64 ºC; **IR** (ATR): 1590, 1460 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.07 (s, 3H, CH_3), 4.66-4.67 (m, 1H, C$H_a$$H_b$=C), 4.91 (s, 2H, OCH_2), 4.97-4.98 (m, 1H, CH_aH_b=C), 5.12 (s, 2H, CH_2), 6.11 (d, J = 3.0 Hz, 1H, H_{6Ar}), 6.24-6.31 (m, 2H, $H_{3pyrrole}$), 6.31 (dd, J = 3.7, 1.7 Hz, 1H, $H_{4pyrrole}$), 6.65-6-68 (m, 2H, H_{4Ar}, $H_{5pyrrole}$), 7.32-7.39 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.71 (d, J = 8.6 Hz, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 56.6 (CH_2), 70.0 (OCH_2), 84.9 (C_{2Ar}), 108.4 ($C_{3pyrrole}$), 109.2 ($C_{4pyrrole}$), 111.9 (*C*H_aH_b=C), 114.5 (C_{4Ar}), 116.1 (C_{6Ar}), 124.0 ($C_{5pyrrole}$), 127.7 ($C_{2'}$, $C_{6'}$), 128.1 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 134.7 (CH_aH_b=*C*), 135.2 ($C_{1'}$), 136.3 ($C_{2pyrrole}$), 139.7 (C_{3Ar}), 142.2 (C_{1Ar}), 159.7 (C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 430 (MH^+, 100), 288 (26). **HRMS** (ESI-TOF): calcd. for $C_{21}H_{21}INO$ [MH^+]: 430.0668; found: 430.0663.

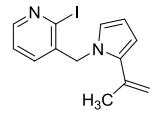
1-(5-(benzyloxy)-2-iodo-4-methoxybenzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15k).



According to general procedure, **14k** (443 mg, 0.96 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (215 mg, 1.92 mmol) and methyltriphenylphosphonium bromide (686 mg, 1.92 mmol) in dry THF (10 mL). The mixture was heated under reflux for 3 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **15k** as a yellow oil (242 mg, 55%): **IR** (ATR): 1500 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.03 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.64 (s, 1H, C$H_a$$H_b$=C), 4.94-4.96 (m, 1H, $CH_a$$H_b$=C), 4.96 (s, 2H, -$OCH_2$-), 5.05 (s, 2H, CH_2), 6.11 (s, 1H, H_{6Ar}), 6.27 (dd, *J* = 3.6, 2.7 Hz, 1H, $H_{4pyrrole}$), 6.30 (dd, *J* = 3.7, 1.8 Hz, 1H, $H_{3pyrrole}$), 6.58 (dd, *J* = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.28-7.35 (m, 6H, H_{3Ar}, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 56.1 (CH_2), 56.4 (OCH_3), 70.6 (-OCH_2-), 84.5 (C_{2Ar}), 108.3 ($C_{3pyrrole}$), 109.2 ($C_{4pyrrole}$), 112.0 (*C*$H_a$$H_b$=C), 113.0 ($C_{6Ar}$), 122.0 ($C_{5pyrrole}$), 123.9 ($C_{3Ar}$), 127.6 ($C_{2'}$, $C_{6'}$), 128.0 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 133.3 ($CH_a$$H_b$=*C*), 134.6 ($C_{1'}$), 135.2 ($C_{1Ar}$), 136.3 ($C_{2pyrrole}$), 148.8, 149.3 ($C_{4Ar}$, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 460 (MH^+, 100), 353 (25), 318 (17). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{23}INO_2$ [MH^+]: 460.0773; found: 460.0781.

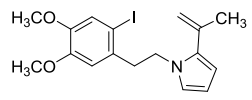
1-((2-iodothiophen-3-yl)methyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15l). According to general procedure, **14l** (718 mg, 2.17 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (488 mg, 4.35 mmol) and methyltriphenylphosphonium bromide (1.55 g, 4.35 mmol) in dry THF (20 mL). The mixture was heated under reflux for 16 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded *N*-benzylpyrrole **15l** as a colorless oil (593 mg, 83%): **IR** (ATR): 1625, 1400 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.08 (s, 3H, CH_3), 4.84 (s, 1H, C$H_a$$H_b$=C), 5.07-5.11 (m, 3H, CH_2, $CH_a$$H_b$=C), 6.19-6.24 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.39 (d, *J* = 5.5 Hz, 1H, $H_{4thiophene}$), 6.67 (dd, *J* = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.38 (d, *J* = 5.5 Hz, 1H, $H_{5thiophene}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 49.3 (CH_2), 72.9 ($C_{2thiophene}$), 108.1 ($C_{3pyrrole}$), 108.8 ($C_{4pyrrole}$), 112.7 (*C*$H_a$$H_b$=C), 123.4 ($C_{5pyrrole}$), 127.4 ($C_{4thiophene}$), 131.3 ($C_{5thiophene}$), 134.9 ($CH_a$$H_b$=*C*), 135.6 ($C_{2pyrrole}$), 143.5 ($C_{3thiophene}$) ppm; **MS** (ESI) *m/z* (rel intensity): 330 (MH^+, 100), 203 (19). **HRMS** (ESI-TOF): calcd. for $C_{12}H_{13}INS$ [MH^+] 329.9813; found: 329.9821.

2-iodo-3-((2-(prop-1-en-2-yl)-1*H*-pyrrol-1-yl)methyl)pyridine (15m). According to



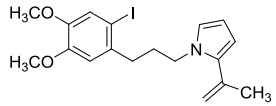
general procedure, **14m** (178 mg, 0.55 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (122 mg, 1.09 mmol) and methyltriphenylphosphonium bromide (390 mg, 1.09 mmol) in dry THF (20 mL). The mixture was heated under reflux for 16 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **15m** as a yellow oil (154 mg, 87%): **IR** (ATR): 1570, 1395 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.04 (CH_3), 4.65-4.66 (m, 1H, CH_aH$_b$=C), 4.97-4.99 (m, 1H, CH$_a$$H_b$=C), 5.14 (s, 2H, CH_2), 6.25-6.31 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.60-6.67 (m, 2H, $H_{5pyridine}$, $H_{5pyrrole}$), 7.17 (dd, J = 7.7, 4.7 Hz, 1H, $H_{4pyridine}$), 8.23-8.26 (m, 1H, $H_{6pyridine}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 54.8 (CH_2), 108.8 ($C_{3pyrrole}$), 109.6 ($C_{4pyrrole}$), 112.1 (*C*H$_a$H$_b$=C), 120.4 ($C_{2pyridine}$), 123.5, 123.8 ($C_{5pyridine}$, $C_{5pyrrole}$), 134.6 (CH$_a$H$_b$=*C*), 134.8 ($C_{4pyridine}$), 135.2 ($C_{2pyrrole}$), 139.1 ($C_{3pyridine}$), 149.4 ($C_{6pyridine}$) ppm; **MS** (ESI) *m/z* (rel intensity): 325 (MH^+, 1), 197 (100). **HRMS** (ESI-TOF): calcd. for $C_{13}H_{14}IN_2$ [MH^+] 325.0202; found: 325.0213.

1-(2-iodo-4,5-dimethoxyphenethyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15n). According to



general procedure, **3a** (168 mg, 0.42 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (94.6 mg, 0.84 mmol) and methyltriphenylphosphonium bromide (301 mg, 0.84 mmol) in dry THF (20 mL). The mixture was heated under reflux for 16 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **15n** as a colorless oil (131 mg, 78%): **IR** (ATR): 1500 cm^{-1}**; ^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.05 (s, 3H, CH_3), 3.07 (t, J = 7.0 Hz, 2H, $ArCH_2$), 3.73 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.22 (t, J = 7.0 Hz, 2H, CH_2N), 4.94-4.95 (m, 1H, CH_aH$_b$=C), 5.11-5.13 (m, 1H, CH$_a$$H_b$=C), 6.09 (dd, J = 3.6, 2.7 Hz, 1H, $H_{4pyrrole}$), 6.14 (dd, J = 3.6, 1.8 Hz, 1H, $H_{3pyrrole}$), 6.29 (s, 1H, H_{6Ar}), 6.57 (dd, J = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.23 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 42.0 ($ArCH_2$), 47.6 (CH_2N), 55.8 (OCH_3), 56.2 (OCH_3), 88.0 (C_{2Ar}), 107.4 ($C_{3pyrrole}$), 108.8 ($C_{4pyrrole}$), 112.4 (*C*H$_a$H$_b$=C), 112.7 (C_{6Ar}), 121.5 ($C_{5pyrrole}$), 123.2 (C_{3Ar}), 133.4 (CH$_a$H$_b$=*C*), 134.6 (C_{1Ar}), 136.1 ($C_{2pyrrole}$), 148.3, 149.2 (C_{4Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 398 (MH^+, 100), 271 (35), 164 (14). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{21}INO_2$ [MH^+]: 398.0617; found: 398.0623.

1-(3-(2-iodo-4,5-dimethoxyphenyl)propyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (15o).

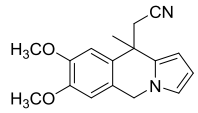


According to general procedure, **3b** (660 mg, 1.60 mmol) in dry THF (10 mL) was treated with potassium *tert*-butoxide (359 mg, 3.20 mmol) and methyltriphenylphosphonium bromide (1.14 g, 3.20 mmol) in dry THF (20 mL). The mixture was heated under reflux for 16 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded *N*-benzylpyrrole **15n** as a colorless oil (302 mg, 46%): **IR** (ATR): 1495 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.99-2.11 (m, 2H, CH_2CH_2N), 2.10 (s, 3H, CH_3), 2.66 (t, J = 7.7 Hz, 2H, $ArCH_2$), 3.86 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.08 (t, J = 7.7 Hz, 2H, CH_2N), 4.94-4.95 (m, 1H, CH_aH_b=C), 5.08-5.10 (m, 1H, CH_aH_b=C), 6.14-6.18 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.68 (s, 1H, H_{6Ar}), 6.71 (dd, J = 2.6, 1.9 Hz, 1H, $H_{5pyrrole}$), 7.23 (s, 1H, H_{3Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 32.1 (CH_2CH_2N), 37.6 ($ArCH_2$), 47.2 (CH_2N), 56.0 (OCH_3), 56.2 (OCH_3), 88.0 (C_{2Ar}), 107.3 ($C_{3pyrrole}$), 108.6 ($C_{4pyrrole}$), 112.1 (C_{6Ar}), 112.2 (CH_aH_b=C), 121.8 ($C_{5pyrrole}$), 123.0 (C_{3Ar}), 134.4 (C_{1Ar}), 136.1 (CH_aH_b=*C*), 136.3 ($C_{2pyrrole}$), 148.0, 149.4 (C_{4Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 412 (MH^+, 40), 285 (16). **HRMS** (ESI-TOF): calcd. for $C_{18}H_{23}INO_2$ [MH^+]: 412.0773; found: 412.0779.

*2.3.2. Intramolecular carbopalladation/cyanation cascade on **15a-o***

General procedure. $Pd(OAc)_2$ (0.1 mmol) was added to a mixture of *N*-(*o*-iodobenzyl)pyrrole **15** (1 mmol), potassium hexacyanoferrate(II) trihydrate (0.22 mmol), sodium carbonate (1.3 mmol) and tetrabutylammonium chloride (1 mmol) in DMF/H_2O 8/2 (3 mL). The mixture was stirred at 120 ºC for the time indicated in each case. H_2O (15 mL) was added and the resulting aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel) of the resulting residue afforded the corresponding pyrroloisoquinoline **16** and direct aryl halide cyanation product **17**.

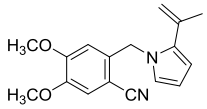
2-(7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetonitrile



(16a). According to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15a** (115 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol),

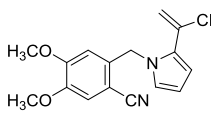
sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **16a** as a yellow solid (54.9 mg, 65%): **m.p.** (petroleum ether/EtOAc): 132-134 ºC; **IR** (ATR): 2935, 2245, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.88 (s, 3H, CH_3), 2.72 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.07 (d, J = 15.9 Hz, 1H, H_{5a}), 5.18 (d, J = 15.9 Hz, 1H, H_{5b}), 6.20 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.26 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.74-6.75 (m, 2H, H_3, H_6), 7.05 (s, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.4 (CH_3), 34.2 (CH_2), 37.5 (C_{10}), 47.1 (C_5), 56.0 (OCH_3), 56.2 (OCH_3), 103.5 (C_1), 108.4 (C_2), 108.8 (C_6), 109.2 (C_9), 117.8 (CN), 119.3 (C_3), 124.0 (C_{5a}), 129.8 (C_{10a}), 132.5 (C_{9a}), 148.4, 148.6 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 283 (MH^+, 100), 242 (46). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{19}N_2O_2$ [MH^+] 283.1447; found: 283.1450.

4,5-dimethoxy-2-((2-(prop-1-en-2-yl)-1*H*-pyrrol-1-yl)methyl)benzonitrile (17a).



According to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15a** (114 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (3.4 mg, 0.02 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (31.8 mg, 0.30 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 5 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **17a** as a yellow oil (42.9 mg, 51%): **IR** (ATR): 2935, 2220, 1510 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.02 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.78-4.79 (m, 1H, C$H_a$$H_b$=C), 5.02-5.04 (m, 1H, CH_aH_b=C), 5.35 (s, 2H, CH_2), 6.12 (s, 1H, H_{3Ar}), 6.19-6.25 (m, 2H, $H_{3pyrrole}$, $H_{4pyrrole}$), 6.67 (dd, J = 2.8, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.04 (s, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 49.2 (CH_2), 55.9 (OCH_3), 56.3 (OCH_3), 101.0 (C_{1Ar}), 108.6 ($C_{3pyrrole}$), 109.4 ($C_{4pyrrole}$), 109.6 (C_{3Ar}), 112.8 (CH_aH_b=C), 114.1 (C_{6Ar}), 117.5 (CN), 124.0 ($C_{5pyrrole}$), 135.1 (C_{2Ar}), 135.5 (CH_aH_b=*C*), 137.4 ($C_{2pyrrole}$), 148.2 (C_{5Ar}), 153.4 (C_{4Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 283 (MH^+, 100), 176 (17). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{19}N_2O_2$ [MH^+] 283.1447; found: 283.1449.

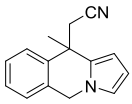
4,5-dimethoxy-2-((2-(3,3,3-trifluoroprop-1-en-2-yl)-1H-pyrrol-1-yl)methyl)benzonitrile (17b).



According to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15b** (133 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II)

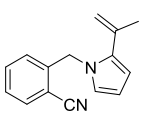
trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **17b** as a yellow solid (50.3 mg, 49%): **m.p.** (petroleum ether/EtOAc): 62-64 ºC; **IR** (ATR): 2940, 2220, 1520 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.69 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.28 (s, 2H, CH_2), 5.49-5.50 (m, 1H, C*H*$_a$H$_b$=C), 6.05-6.06 (m, 2H, CH$_a$*H*$_b$=C, H_{3Ar}), 6.26-6.27 (m, 1H, $H_{4pyrrole}$), 6.41-6.42 (m, 1H, $H_{3pyrrole}$), 6.78-6.79 (m, 1H, $H_{5pyrrole}$), 7.04 (s, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 48.7 (CH_2), 55.8 (OCH_3), 56.2 (OCH_3), 101.2 (C_{1Ar}), 109.2 ($C_{3pyrrole}$), 109.5 ($C_{4pyrrole}$), 112.4 (C_{3Ar}), 113.9 (C_{6Ar}), 117.4 (CN), 122.0 (q, J = 5.0 Hz, *C*H$_a$H$_b$=C), 122.6 (q, J = 273.6 Hz, CF_3), 125.0 ($C_{5pyrrole}$), 125.4 (C_{2Ar}), 130.3 (q, J = 31.9 Hz, CH$_a$H$_b$=*C*), 136.3 ($C_{2pyrrole}$), 148.4 (C_{5Ar}), 153.5 (C_{4Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 337 (MH^+, 100), 176 (6). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{16}F_3N_2O_2$ [MH^+] 337.1164; found: 337.1153.

2-(10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetonitrile (16d). According



to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15d** (101 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 4 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **16d** as a colorless oil (17.4 mg, 23%): **IR** (ATR): 2925, 2250, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.89 (s, 3H, CH_3), 2.74 (s, 2H, CH_2), 5.14 (d, J = 16.1 Hz, 1H, H_{5a}), 5.24 (d, J = 16.1 Hz, 1H, H_{5b}), 6.21 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.26 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.76 (dd, J = 2.7, 1.7 Hz, 1H, H_3), 7.28-7.40 (m, 3H, H_6, H_7, H_8), 7.56-7.59 (m, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.0 (CH_3), 33.8 (CH_2), 37.8 (C_{10}), 47.5 (C_5), 103.7 (C_1), 108.8 (C_2), 117.5 (CN), 119.4 (C_9), 125.2 (C_3), 126.6 (C_8), 127.5, 128.1 (C_6, C_7), 131.8, 132.4 (C_{10a}, C_{5a}), 137.9 (C_{9a}) ppm; **MS** (ESI) *m/z* (rel intensity): 223 (MH^+, 65), 182 (100). **HRMS** (ESI-TOF): calcd. for $C_{15}H_{15}N_2$ [MH^+] 223.1235; found: 223.1237.

2-((2-(prop-1-en-2-yl)-1*H*-pyrrol-1-yl)methyl)benzonitrile (17d). Isolated as byproduct



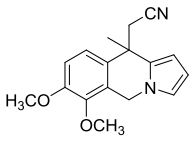
in the reaction of **15d** as a yellow oil (28.2 mg, 41%): **IR** (ATR): 2930, 2225, 1650, 1450 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.03 (s, 3H, CH_3), 4.71-4.72 (m, 1H, C*H*$_a$H$_b$=C), 5.01-5.02 (m, 1H, CH$_a$*H*$_b$=C), 5.45 (s,

2H, CH_2), 6.24-6.27 (m, 2H, $H_{3pyrrole}$, $H_{4pyrrole}$), 6.68 (dd, J = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 6.74-6.75 (m, 1H, H_{3Ar}), 7.34-7.38 (m, 1H, H_{5Ar}), 7.49-7.52 (m, 1H, H_{4Ar}), 7.67-7.69 (m, 1H, H_{6Ar}) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 49.4 (CH_2), 108.6 ($C_{3pyrrole}$), 109.3 ($C_{4pyrrole}$), 110.0 (C_{1Ar}), 112.6 (CH_aH_b=C), 117.0 (CN), 123.9 ($C_{5pyrrole}$), 127.0 (C_{5Ar}), 127.8 (C_{3Ar}), 132.7 (C_{6Ar}), 133.4 (C_{4Ar}), 135.0 (CH_aH_b=*C*), 135.5 ($C_{2pyrrole}$), 142.9 (C_{2Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 223 (MH^+, 100), 182 (4). **HRMS** (ESI-TOF): calcd. for $C_{15}H_{15}N_2$ [MH^+] 223.1235; found: 223.1241.

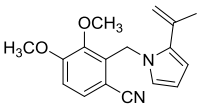
2-(10-methyl-5,10-dihydro-[1,3]dioxolo[4,5-*g*]pyrrolo[1,2-*b*]isoquinolin-10-yl)acetonitrile (16e). According to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15e** (110 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **16e** as a yellow oil (29.5 mg, 37%): **IR** (ATR): 2915, 2250, 1485 cm^{-1}; **^1H NMR** (300 MHz, $CDCl_3$): δ = 1.84 (s, 3H, CH_3), 2.66 (d, J = 16.4 Hz, 1H, CH_aH$_b$), 2.73 (d, J = 16.4 Hz, 1H, CH$_a$$H_b$), 5.03 (d, J = 15.9 Hz, 1H, H_{5a}), 5.15 (d, J = 15.9 Hz, 1H, H_{5b}), 6.00 (s, 2H, OCH_2O), 6.18 (dd, J = 3.7, 1.7 Hz, 1H, H_1), 6.25-6.26 (m, 1H, H_2), 6.70-6.74 (m, 2H, H_6, H_3), 7.01 (s, 1H, H_9) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 26.3 (CH_3), 34.0 (CH_2), 37.8 (C_{10}), 47.5 (C_5), 101.5 (OCH_2O), 103.6 (C_1), 105.4 (C_2), 106.4 (C_6), 108.8 (C_9), 117.5 (CN), 119.2 (C_3), 125.3 (C_{5a}), 131.3 (C_{10a}), 132.3 (C_{9a}), 147.0, 147.6 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 267 (MH^+, 100), 226 (76). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{15}N_2O_2$ [MH^+] 267.1134; found: 267.1137.

6-((2-(prop-1-en-2-yl)-1*H*-pyrrol-1-yl)methyl)benzo[*d*][1,3]dioxole-5-carbonitrile (17e). Isolated as byproduct in the reaction of **15e** as a white solid (29.7 mg, 38%): **m.p.** (petroleum ether/EtOAc): 94-96 ºC; **IR** (ATR): 2915, 2220, 1480 cm^{-1}; **^1H NMR** (300 MHz, $CDCl_3$): δ = 2.04 (s, 3H, CH_3), 4.73-4.75 (m, 1H, CH_aH$_b$=C), 5.02-5.04 (m, 1H, CH$_a$$H_b$=C), 5.34 (s, 2H, CH_2), 6.02 (s, 2H, OCH_2O), 6.17 (s, 1H, H_{3Ar}), 6.21-6.26 (m, 2H, $H_{3pyrrole}$, $H_{4pyrrole}$), 6.64-6.66 (m, 1H, $H_{5pyrrole}$), 7.02 (s, 1H, H_{6Ar}) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 49.2 (CH_2), 102.0 (C_{1Ar}), 102.4 (OCH_2O), 107.6 ($C_{3pyrrole}$), 108.7 ($C_{4pyrrole}$), 109.4 (C_{3Ar}), 111.3 (C_{6Ar}), 112.6 (CH_aH_b=C), 117.2 (CN), 123.8 ($C_{5pyrrole}$), 134.9 (C_{2Ar}), 135.4 (CH_aH_b=*C*),

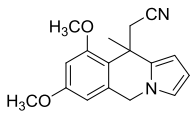
139.8 ($C_{2pyrrole}$), 147.0 (C_{5Ar}), 152.4 (C_{4Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 267 (MH^+, 100), 160 (4). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{15}N_2O_2$ [MH^+] 267.1134; found: 267.1136.

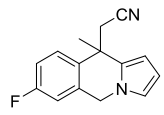
2-(6,7-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetonitrile (16f). 

According to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15f** (113 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 2 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **16f** as a brown oil (32.4 mg, 39%): **IR** (ATR): 2935, 2250, 1495 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.86 (s, 3H, CH_3), 2.70 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.05 (d, *J* = 16.9 Hz, 1H, H_{5a}), 5.35 (d, *J* = 16.9 Hz, 1H, H_{5b}), 6.17 (dd, *J* = 3.6, 1.7 Hz, 1H, H_1), 6.24-6.26 (m, 1H, H_2), 6.78-6.79 (m, 1H, H_3), 6.96 (d, *J* = 8.7 Hz, 1H, H_8), 7.26 (d, *J* = 8.7 Hz, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.1 (CH_3), 34.2 (CH_2), 37.4 (C_{10}), 42.7 (C_5), 55.8 (OCH_3), 60.5 (OCH_3), 103.4 (C_1), 108.7 (C_2), 111.7 (C_8), 117.6 (CN), 119.7 (C_9), 120.6 (C_3), 126.1 (C_{5a}), 130.8 (C_{10a}), 132.5 (C_{9a}), 144.8 (C_7), 151.2 (C_6) ppm; **MS** (ESI) *m/z* (rel intensity): 283 (MH^+, 100), 242 (30). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{19}N_2O_2$ [MH^+] 283.1447; found: 283.1453.

3,4-dimethoxy-2-((2-(prop-1-en-2-yl)-1H-pyrrol-1-yl)methyl)benzonitrile (17f). Isolated as byproduct in the reaction of **15f** 

as a colorless oil (24.1 mg, 29%): **IR** (ATR): 2940, 2225, 1490 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.16 (s, 3H, CH_3), 3.50 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.07-5.08 (m, 1H, C$H_a$$H_b$=C), 5.27-5.29 (m, 1H, $CH_a$$H_b$=C), 5.36 (s, 2H, CH_2), 6.08 (dd, *J* = 3.6, 2.8 Hz, 1H, $H_{4pyrrole}$), 6.14 (dd, *J* = 3.6, 1.8 Hz, 1H, $H_{3pyrrole}$), 6.39 (dd, *J* = 2.8, 1.8 Hz, 1H, $H_{5pyrrole}$), 6.97 (d, *J* = 8.6 Hz, 1H, H_{5Ar}), 7.47 (d, *J* = 8.6 Hz, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.3 (CH_3), 44.6 (CH_2), 56.0 (OCH_3), 60.5 (OCH_3), 105.6 (C_{1Ar}), 107.7, 107.9, 112.5 ($C_{3pyrrole}$, $C_{4pyrrole}$, C_{5Ar}), 113.9 ($CH_a$$H_b$=C), 117.5 (CN), 121.3 ($C_{5pyrrole}$), 129.8 ($C_{6Ar}$), 134.8 ($C_{2Ar}$), 135.9 ($CH_a$$H_b$=*C*), 136.2 ($C_{2pyrrole}$), 148.4 ($C_{4Ar}$), 156.8 ($C_{3Ar}$) ppm; **MS** (ESI) *m/z* (rel intensity): 283 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{19}N_2O_2$ [MH^+] 283.1447; found: 283.1453.

2-(7,9-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetonitrile (16g). 
According to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15g** (115 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 48 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **16g** as a yellow solid (18.1 mg, 21%) (63% conversion): **m.p.** (petroleum ether/EtOAc): 167-169 ºC; **IR** (ATR): 2935, 2250, 1460 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.80 (s, 3H, CH_3), 2.97 (d, J = 16.3 Hz, 1H, CH_aH$_b$), 3.54 (d, J = 16.3 Hz, 1H, CH$_a$$H_b$), 3.83 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.13 (d, J = 16.3 Hz, 1H, H_{5a}), 5.25 (d, J = 16.3 Hz, 1H, H_{5b}), 6.20 (dd, J = 3.7, 1.7 Hz, 1H, H_1), 6.33 (dd, J = 3.7, 2.7 Hz, 1H, H_2), 6.35 (d, J = 2.5 Hz, 1H, H_8), 6.47 (d, J = 2.5 Hz, 1H, H_6), 6.68 (dd, J = 2.7, 1.7 Hz, 1H, H_3) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 28.9 (CH_3), 31.5 (CH_2), 37.8 (C_{10}), 47.2 (C_5), 55.3, 55.4 (2 x OCH_3), 98.8 (C_8), 102.2 (C_6), 103.2 (C_1), 109.3 (C_2), 117.2 (CN), 117.9 (C_3), 118.8 (C_{9a}), 133.6 (C_{10a}), 134.6 (C_{5a}), 159.2, 159.7 (C_7, C_9) ppm; **MS** (ESI) *m/z* (rel intensity): 283 (MH^+, 100), 242 (33). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{19}N_2O_2$ [MH^+] 283.1447; found: 283.1440.

2-(7-fluoro-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetonitrile (16h). 
According to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15h** (102 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 48 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **16h** as a yellow oil (11.8 mg, 16%): **IR** (ATR): 2925, 2250, 1500 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.90 (s, 3H, CH_3), 2.68-2.80 (m, 2H, CH_2), 5.14 (d, J = 16.3 Hz, 1H, H_{5a}), 5.25 (d, J = 16.3 Hz, 1H, H_{5b}), 6.21-6.29 (m, 2H, H_1, H_2), 6.77-6.78 (m, 1H, H_3), 7.01 (dd, J = 8.8, 2.7 Hz, 1H, H_6), 7.11 (td, J = 8.8, 2.7 Hz, 1H, H_8), 7.57 (dd, J = 8.8, 5.3 Hz, 1H, H_8) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.2 (CH_3), 34.0 (CH_2), 37.6 (C_{10}), 47.4 (d, J = 2.2 Hz, C_5), 103.9 (C_1), 109.1 (C_2), 113.3 (d, J = 22.4 Hz, C_8), 115.1 (d, J = 21.4 Hz, C_6), 117.4 (CN), 119.4 (C_3), 127.2 (d, J = 8.3 Hz, C_9), 132.2 (C_{10a}), 133.7 (d, J = 3.3 Hz, C_{9a}), 134.1 (d, J = 7.7 Hz,

C_{5a}), 161.6 (d, J = 247.5 Hz, C_7) ppm; **MS** (ESI) *m/z* (rel intensity): 241 (MH^+, 59), 200 (100). **HRMS** (ESI-TOF): calcd. for $C_{15}H_{14}FN_2$ [MH^+] 241.1141; found: 241.1145.

4-fluoro-2-((2-(prop-1-en-2-yl)-1*H*-pyrrol-1-yl)methyl)benzonitrile (17h). Isolated as byproduct in the reaction of **15h** as a colorless oil (12.8 mg, 18%): **IR** (ATR): 2925, 2225, 1485 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.95 (s, 3H, CH_3), 4.61-4.62 (m, 1H, C$H_a$$H_b$=C), 4.93-4.94 (m, 1H, $CH_a$$H_b$=C), 5.35 (s, 2H, CH_2), 6.17-6.21 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.33 (dd, J = 9.3, 2.6 Hz, 1H, H_{3Ar}), 6.59 (dd, J = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 6.97 (ddd, J = 8.6, 7.7, 2.6 Hz, 1H, H_{5Ar}), 7.60 (dd, J = 8.6, 2.6 Hz, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.1 (CH_3), 49.4 (CH_2), 55.5 (OCH_3), 101.4 (C_{1Ar}), 108.7 ($C_{3pyrrole}$), 109.4 ($C_{4pyrrole}$), 112.6 (*C*$H_a$$H_b$=C), 112.7 ($C_{5Ar}$), 113.3 ($C_{3Ar}$), 117.5 (CN), 124.0 ($C_{5pyrrole}$), 134.6 ($C_{6Ar}$), 135.0 ($CH_a$$H_b$=*C*), 135.4 ($C_{2pyrrole}$), 145.3 ($C_{2Ar}$), 163.6 ($C_{4Ar}$) ppm; **MS** (ESI) *m/z* (rel intensity): 241 (MH^+, 100), 200 (5). **HRMS** (ESI-TOF): calcd. for $C_{15}H_{14}FN_2$ [MH^+] 241.1141; found: 241.1140.

2-(7-methoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetonitrile (16i). According to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15i** (106 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 6 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **16i** as a colorless oil (17.4 mg, 23%) (94% conversion): **IR** (ATR): 2930, 2250, 1500 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.88 (s, 3H, CH_3), 2.73 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 5.12 (d, J = 16.1 Hz, 1H, H_{5a}), 5.23 (d, J = 16.1 Hz, 1H, H_{5b}), 6.21 (dd, J = 3.7, 1.7 Hz, 1H, H_1), 6.27 (dd, J = 3.7, 2.7 Hz, 1H, H_2), 6.76 (dd, J = 2.7, 1.7 Hz, 1H, H_3), 6.80 (d, J = 2.7 Hz, 1H, H_6), 6.94 (dd, J = 8.7, 2.7 Hz, 1H, H_8), 7.50 (d, J = 8.7 Hz, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.2 (CH_3), 34.1 (CH_2), 37.3 (C_{10}), 47.6 (C_5), 55.4 (OCH_3), 103.6 (C_1), 108.8 (C_2), 111.6 (C_8), 113.6 (C_6), 117.6 (CN), 119.3 (C_3), 126.5 (C_9), 130.0 (C_{10a}), 132.8 (C_{5a}), 133.2 (C_{9a}), 158.6 (C_7) ppm; **MS** (ESI) *m/z* (rel intensity): 253 (MH^+, 94), 212 (100). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{17}N_2O$ [MH^+] 253.1341; found: 253.1339.

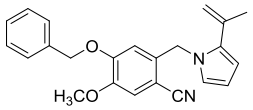
4-methoxy-2-((2-(prop-1-en-2-yl)-1*H*-pyrrol-1-yl)methyl)benzonitrile (17i). Isolated as byproduct in the reaction of **15i** as a colorless oil (20.9 mg, 28%) (94% conversion): **IR** (ATR): 2950, 2220, 1495 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.05 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.74-4.75 (m, 1H, C*H*$_a$H$_b$=C), 5.03-5.04 (m, 1H, CH$_a$*H*$_b$=C), 5.41 (s, 2H, CH_2), 6.20-6.29 (m, 3H, $H_{3pyrrole}$, $H_{4pyrrole}$, H_{3Ar}), 6.69 (dd, *J* = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 6.84 (dd, *J* = 8.6, 2.6 Hz, 1H, H_{5Ar}), 7.61 (d, *J* = 8.6 Hz, 1H, H_6) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 49.4 (CH_2), 55.5 (OCH_3), 101.4 (C_{1Ar}), 108.7 ($C_{3pyrrole}$), 109.4 ($C_{4pyrrole}$), 112.6 (*C*H$_a$H$_b$=C), 112.7 (C_{5Ar}), 113.3 (C_{3Ar}), 117.5 (CN), 124.0 ($C_{5pyrrole}$), 134.6 (C_{6Ar}), 135.0 (CH$_a$H$_b$=*C*), 135.4 ($C_{2pyrrole}$), 145.3 (C_{2Ar}), 163.6 (C_{4Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 253 (MH^+, 100), 252 (5). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{17}N_2O$ [MH^+] 253.1341; found: 253.1335.

2-(7-(benzyloxy)-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetonitrile (16j). According to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15j** (128 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 98/2) afforded **16j** as a yellow oil (22.5 mg, 23%): **IR** (ATR): 2975, 2245, 1500 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.88 (s, 3H, CH_3), 2.70 (d, *J* = 16.4 Hz, 1H, C*H*$_a$H$_b$), 2.74 (d, *J* = 16.4 Hz, 1H, CH$_a$*H*$_b$), 5.10 (d, *J* = 16.0 Hz, 1H, H_{5a}), 5.11 (s, 2H, -OCH_2-), 5.21 (d, *J* = 16.0 Hz, 1H. H_{5b}), 6.21 (dd, *J* = 3.6, 1.7 Hz, 1H, H_1), 6.27 (dd, *J* = 3.6, 2.7 Hz, 1H, H_2), 6.75 (dd, *J* = 2.7, 1.7 Hz, 1H, H_3), 6.88 (d, *J* = 2.6 Hz, 1H, H_6), 7.01 (dd, *J* = 8.7, 2.7 Hz, 1H, H_8), 7.35-7.50 (m, 6H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{5'}$, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.2 (CH_3), 34.1 (*C*H_2CN), 37.3 (C_{10}), 47.6 (C_5), 70.2 (-OCH_2-), 103.6 (C_1), 108.8 (C_2), 112.6 (C_8), 114.5 (C_6), 117.6 (CN), 119.3 (C_3), 126.5 (C_9), 127.5 ($C_{2'}$, $C_{6'}$), 128.2 ($C_{4'}$), 128.7 ($C_{3'}$, $C_{5'}$), 130.3 (C_{10a}), 132.7 (C_{5a}), 133.2 ($C_{1'}$), 136.7 (C_{9a}), 157.8 (C_7) ppm; **MS** (ESI) *m/z* (rel intensity): 329 (MH^+, 100), 288 (18). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{21}N_2O$ [MH^+] 329.1654; found: 329.1648.

4-(benzyloxy)-2-((2-(prop-1-en-2-yl)-1*H*-pyrrol-1-yl)methyl)benzonitrile (17j). Isolated as byproduct in the reaction of **15j** as a colorless oil (14.8 mg, 15%) (94% conversion): **IR** (ATR): 2920, 2220, 1495 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.02 (s, 3H, CH_3), 4.68-4.69 (m, 1H, CH_aH$_b$=C), 4.97 (s, 2H, OCH_2), 4.99-5.01 (m, 1H, CH_aH_b=C), 5.40 (s, 2H, CH_2), 6.24-6.30 (m, 3H, $H_{3pyrrole}$, $H_{4pyrrole}$, H_{3Ar}), 6.66 (dd, J = 2.6, 1.9 Hz, 1H, $H_{5pyrrole}$), 6.91 (dd, J = 8.6, 2.6 Hz, 1H, H_{5Ar}), 7.30-7.45 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.59 (d, J = 8.6 Hz, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.1 (CH_3), 49.4 (CH_2), 70.2 (-OCH_2-), 101.6 (C_{1Ar}), 108.7 ($C_{3pyrrole}$), 109.3 ($C_{4pyrrole}$), 112.6 (CH_aH_b=C), 113.3 (C_{5Ar}), 114.4 (C_{3Ar}), 117.4 (CN), 123.9 ($C_{5pyrrole}$), 127.6 ($C_{2'}$, $C_{6'}$), 128.4 ($C_{4'}$), 128.7 ($C_{3'}$, $C_{5'}$), 134.5 (C_{6Ar}), 135.0 (CH_aH_b=*C*), 135.3 ($C_{1'}$), 135.4 ($C_{2pyrrole}$), 145.3 (C_{2Ar}), 162.7 (C_{4Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 329 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{21}N_2O$ [MH^+] 329.1654; found: 329.1656.

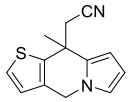
2-(7-(benzyloxy)-8-methoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetonitrile (16k). According to General Procedure, *N*-(*o*-iodobenzyl)pyrrole **15k** (138 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 24 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 98/2) afforded **16k** as a yellow oil (16.7 mg, 16%): **IR** (ATR): 2930, 2250, 1510 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.90 (s, 3H, CH_3), 2.72 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3), 5.00 (d, J = 15.8 Hz, 1H, H_{5a}), 5.12 (d, J = 15.8 Hz, 1H, H_{5b}), 5.23 (s, 2H, -OCH_2-), 6.19 (dd, J = 3.7, 1.7 Hz, 1H, H_1), 6.26 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.73 (dd, J = 2.7, 1.7 Hz, 1H, H_3), 6.76 (s, 1H, H_6), 7.09 (s, 1H, H_9), 7.32-7.48 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.1 (CH_3), 34.2 (CH_2), 37.5 (C_{10}), 47.1 (C_5), 56.4 (OCH_3), 71.2 (OCH_2), 103.5 (C_1), 108.7 (C_2), 109.1 (C_6), 111.9 (C_9), 117.6 (CN), 119.3 (C_3), 123.9 (C_{5a}), 127.2 ($C_{2'}$, $C_{6'}$), 128.0 ($C_{4'}$), 128.7 ($C_{3'}$, $C_{5'}$), 130.4 (C_{10a}), 132.4 ($C_{1'}$), 136.8 (C_{9a}), 147.6, 149.3 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 359 (MH^+, 100), 318 (6). **HRMS** (ESI-TOF): calcd. for $C_{23}H_{23}N_2O_2$ [MH^+] 359.1760; found: 359.1760.

4-(benzyloxy)-5-methoxy-2-((2-(prop-1-en-2-yl)-1*H*-pyrrol-1-yl)methyl)benzonitrile



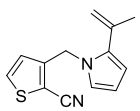
(17k). Isolated as byproduct in the reaction of **15k** as a yellow oil (32.6 mg, 30%): **IR** (ATR): 2930, 2220, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.97 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.65 (t, J = 1.1 Hz, 1H, CH_aH$_b$=C), 4.96-4.99 (m, 1H, CH$_a$$H_b$=C), 4.99 (s, 2H, -$OCH_2$-), 5.31 (s, 2H, CH_2), 6.18 (s, 1H, H_{3Ar}), 6.22-6.26 (m, 2H, $H_{3pyrrole}$, $H_{4pyrrole}$), 6.58-6.60 (m, 1H, $H_{5pyrrole}$), 7.07 (s, 1H, H_{6Ar}), 7.25-7.37 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.1 (CH_3), 49.1 (CH_2), 56.3 (OCH_3), 70.7 (-OCH_2-), 101.0 (C_{1Ar}), 108.6 ($C_{3pyrrole}$), 109.4 ($C_{4pyrrole}$), 111.5 (C_{3Ar}), 112.7 (*C*H$_a$H$_b$=C), 114.5 (C_{6Ar}), 117.4 (CN), 123.8 ($C_{5pyrrole}$), 127.5 ($C_{2'}$, $C_{6'}$), 128.2 ($C_{4'}$), 128.7 ($C_{3'}$, $C_{5'}$), 134.9 (C_{2Ar}), 135.3 (CH$_a$H$_b$=*C*), 135.4 ($C_{1'}$), 137.1 ($C_{2pyrrole}$), 148.6 (C_{5Ar}), 152.3 (C_{4Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 381 (100), 359 (MH^+, 58). **HRMS** (ESI-TOF): calcd. for $C_{23}H_{23}N_2O_2$ [MH^+] 359.1760; found: 359.1761.

2-(9-methyl-4,9-dihydrothieno[3,2-*f*]indolizin-9-yl)acetonitrile (16l). According to



General Procedure, *N*-(*o*-iodothiophenyl)pyrrole **15l** (98.6 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 24 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **16l** as a brown oil (16.3 mg, 24%): **IR** (ATR): 2925, 2250, 1455 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.89 (s, 3H, CH_3), 2.82 (d, J = 16.3 Hz, 1H, CH_aH$_b$), 2.89 (d, J = 16.3 Hz, 1H, CH$_a$$H_b$), 5.15 (d, J = 15.9 Hz, 1H, H_{4a}), 5.24 (d, J = 15.9 Hz, 1H, H_{4b}), 6.24 (dd, J = 3.7, 1.7 Hz, 1H, H_8), 6.32 (dd, J = 3.7, 2.8 Hz, 1H, H_7), 6.75 (dd, J = 2.8, 1.7 Hz, 1H, H_6), 6.93 (d, J = 5.2 Hz, 1H, H_3), 7.36 (d, J = 5.2 Hz, 1H, H_2) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 29.8 (CH_3), 36.3 (CH_2), 37.6 (C_9), 45.5 (C_4), 103.4 (C_8), 109.4 (C_7), 117.3 (CN), 119.5 (C_6), 124.8 (C_2), 125.1 (C_3), 131.6 (C_{8a}), 131.9 (C_{9a}), 139.5 (C_{2a}) ppm; **MS** (ESI) *m/z* (rel intensity): 229 (MH^+, 100), 188 (85). **HRMS** (ESI-TOF): calcd. for $C_{13}H_{13}N_2S$ [MH^+] 229.0799; found: 229.0798.

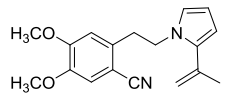
3-((2-(prop-1-en-2-yl)-1H-pyrrol-1-yl)methyl)thiophene-2-carbonitrile (17l). Isolated as



byproduct in the reaction of **15l** as a brown oil (14.0 mg, 20%): **IR** (ATR): 2920, 2215, 1415 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.05 (s, 3H, CH_3), 4.82-4.83 (m, 1H, CH_aH$_b$=C), 5.11-5.13 (m, 1H, CH$_a$$H_b$=C), 5.35 (s, 2H,

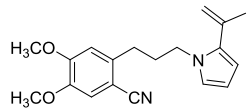
CH_2), 6.20-6.24 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.62 (d, J = 5.1 Hz, 1H, $H_{4thiophene}$), 6.69-6.70 (m, 1H, $H_{5pyrrole}$), 7.48 (d, J = 5.1 Hz, 1H, $H_{5thiophene}$) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 24.1 (CH_3), 46.1 (CH_2), 105.3 ($C_{2thiophene}$), 108.7 ($C_{3pyrrole}$), 109.3 ($C_{4pyrrole}$), 113.1 (CH_aH_b=C), 113.2 (CN), 123.5 ($C_{5pyrrole}$), 127.4 ($C_{4thiophene}$), 132.5 ($C_{5thiophene}$), 135.1 (CH_aH_b=*C*), 135.6 ($C_{2pyrrole}$), 150.8 ($C_{3thiophene}$) ppm; **MS** (ESI) *m/z* (rel intensity): 229 (MH^+, 100), 188 (3). **HRMS** (ESI-TOF): calcd. for $C_{13}H_{13}N_2S$ [MH^+] 229.0799; found: 229.0797.

4,5-dimethoxy-2-(2-(2-(prop-1-en-2-yl)-1*H*-pyrrol-1-yl)ethyl)benzonitrile (17n).



According to General Procedure, *N*-(*o*-iodophenethyl)pyrrole **15n** (119 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 2 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **17n** as a yellow oil (55.5 mg, 63%): **IR** (ATR): 2935, 2220, 1515 cm^{-1}; **^1H NMR** (300 MHz, $CDCl_3$): δ = 2.00 (s, 3H, CH_3), 3.15 (t, J = 6.6 Hz, 2H, $ArCH_2$), 3.76 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.30 (t, J = 6.6 Hz, 2H, CH_2N), 4.89-4.90 (m, 1H, CH_aH_b=C), 5.09-5.11 (m, 1H, CH_aH_b=C), 6.06 (dd, J = 3.6, 2.7 Hz, 1H, $H_{4pyrrole}$), 6.12 (dd, J = 3.6, 1.8 Hz, 1H, $H_{3pyrrole}$), 6.15 (s, 1H, H_{3Ar}), 6.50 (dd, J = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 7.02 (s, 1H, H_{6Ar}) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 24.1 (CH_3), 35.8 ($ArCH_2$), 48.1 (CH_2N), 56.0 (OCH_3), 56.2 (OCH_3), 103.3 (C_{1Ar}), 107.6 ($C_{3pyrrole}$), 109.1 ($C_{4pyrrole}$), 112.5 (C_{3Ar}), 112.6 (CH_aH_b=C), 114.0 (C_{6Ar}), 118.3 (CN), 123.3 ($C_{5pyrrole}$), 134.6 (CH_aH_b=*C*), 136.0 ($C_{2pyrrole}$), 136.7 (C_{2Ar}), 147.8 (C_{5Ar}), 152.5 (C_{4Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 297 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{18}H_{21}N_2O_2$ [MH^+] 297.1603; found: 297.1603.

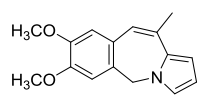
4,5-dimethoxy-2-(3-(2-(prop-1-en-2-yl)-1*H*-pyrrol-1-yl)propyl)benzonitrile (17o).



According to General Procedure, *N*-(*o*-iodophenylpropyl)pyrrole **15o** (123 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), potassium hexacyanoferrate(II) trihydrate (27.9 mg, 0.07 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in DMF/H_2O 8/2 (1 mL) for 48 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **17n** as a colorless oil (23.5 mg, 25%) (33% conversion): **IR** (ATR): 2935, 2220, 1515 cm^{-1}; **^1H NMR** (300

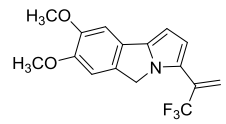
MHz, $CDCl_3$): δ = 1.97-2.08 (m, 2H, CH_2CH_2N), 2.00 (s, 3H, CH_3), 2.64-2.70 (m, 2H, ArCH_2), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.96-4.01 2.64-2.70 (m, 2H, CH_2CH_2N), 4.81-4.82 (m, 1H, CH_aH$_b$=C), 4.98-5.00 (m, 1H, CH$_a$$H_b$=C), 6.04-6.09 (m, 2H, $H_{3pyrrole}$, $H_{4pyrrole}$), 6.59-6.60 (m, 2H, H_{3Ar}, $H_{5pyrrole}$), 6.94 (s, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 31.4 (ArCH_2), 32.4 (CH_2CH_2N), 47.2 (CH_2N), 56.1 (OCH_3), 56.2 (OCH_3), 103.3 (C_{1Ar}), 107.4 ($C_{3pyrrole}$), 108.8 ($C_{4pyrrole}$), 111.8 (C_{3Ar}), 112.2 (*C*H$_a$H$_b$=C), 114.2 (C_{6Ar}), 118.3 (CN), 123.0 ($C_{5pyrrole}$), 134.4 (CH$_a$H$_b$=*C*), 136.1 (C_{2Ar}), 139.7 ($C_{2pyrrole}$), 147.6 (C_{5Ar}), 152.8 (C_{4Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 311 (MH^+, 29). **HRMS** (ESI-TOF): calcd. for $C_{19}H_{23}N_2O_2$ [MH^+] 311.1760; found: 311.1757.

7,8-dimethoxy-11-methyl-5*H*-benzo[*e*]pyrrolo[1,2-*a*]azepine (18). Isolated as by-product



in the reactions of **15a** (Tables 1, 2, 4 and 5) (see above): **m.p.** (petroleum ether/EtOAc): 136-138 ºC; **IR** (ATR): 2965, 1605, 1515, 1255 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.78 (s, 2H, CH_2), 6.15 (dd, *J* = 3.6, 1.6 Hz, 1H, H_1), 6.22 (td, *J* = 3.6, 2.6 Hz, 1H, H_2), 6.70 (t, *J* = 2.1 Hz, 1H, H_3), 6.76 (d, *J* = 1.5 Hz, 1H, H_{10}), 6.80 (s, 1H, H_6), 7.00 (s, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.2 (CH_3), 52.2 (CH_2), 56.0 (OCH_3), 56.1 (OCH_3), 107.4 (C_{10}), 108.5 (C_1), 110.0 (C_2), 111.4 (C_6), 120.2 (C_9), 120.5 (C_3), 128.3 (C_{5a}), 130.9 (C_{9a}), 131.3 (C_{11}), 132.4 (C_{11a}), 148.2, 148.5 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 256 (MH^+, 100), 189 (8). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{18}NO_2$ [MH^+] 256.1333; found: 2561339.

7,8-dimethoxy-3-(3,3,3-trifluoroprop-1-en-2-yl)-5*H*-pyrrolo[2,1-a]isoindole (19).

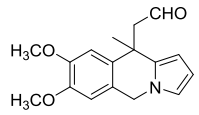


Isolated as the major compound in the reactions of **15b** using General Procedure A (Table 3) (see above): **m.p.** (petroleum ether/EtOAc): 123-125 ºC; **IR** (ATR): 2940, 1620, 1320 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.85 (s, 2H, CH_2), 5.54-5.56 (m, 1H, CH_aH$_b$=CCF_3), 5.78-5.79 (m, 1H, CH$_a$$H_b$=C$CF_3$), 6.27-6.28 (m, 1H, H_1), 6.58-6.60 (m, 1H, H_2), 6.96 (s, 1H, H_6), 7.06 (s, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 51.8 (C_5), 56.1 (OCH_3), 56.3 (OCH_3), 98.2 (C_9), 102.4 (C_1), 106.6 (C_6), 110.7 (q, *J* = 5.9 Hz, *C*H$_2$=CCF$_3$), 115.2 (q, *J* = 2.6 Hz, C_2), 122.5 (C_{5a}), 123.1 (q, *J* = 274.1 Hz, CF_3), 125.4 (C_{9a}), 130.6 (q, *J* = 30.8 Hz, CH$_2$=*C*CF$_3$), 132.4 (C_3), 141.8 (C_{9b}), 148.0, 149.6 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel

intensity): 310 (MH^+, 100), 309 (32). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{15}F_3NO_2$ [MH^+] 310.1049; found: 310.1053.

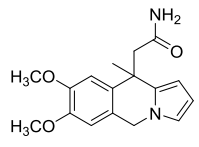
*2.3.3. Derivatization of pyrroloisoquinoline **16a***

2-(7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinolin-10-yl)acetaldehyde



(20). A solution of DIBAL (0.23 mL, 0.23 mmol, 1M in toluene) was added to a solution of **16a** (53.2 mg, 0.19 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C. The reaction mixture was stirred for 2 h and then warmed to room temperature. A saturated solution of potassium sodium tartrate (5 mL) was added and the mixture was stirred for 30 min. The mixture was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (3 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, 100 % CH_2Cl_2) of the resulting residue afforded the corresponding acetaldehyde **20** as a yellow oil (45.9 mg, 85%): **IR** (ATR): 2935, 1715, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.69 (s, 3H, CH_3), 2.94-2.95 (m, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.12 (s, 2H, H_5), 6.09 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.26 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.73-6.75 (m, 2H, H_9, H_3), 6.90 (s, 1H, H_6), 9.30 (t, J = 2.8 Hz, 1H, CHO) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 29.9 (CH_3), 37.0 (C_{10}), 47.1 (CH_2), 55.2 (C_5), 56.0 (OCH_3), 56.2 (OCH_3), 103.2 (C_1), 108.4 (C_2), 108.7 (C_9), 109.2 (C_6), 118.7 (C_3), 123.7 (C_{5a}), 131.4 (C_{10a}), 133.9 (C_{9a}), 147.9, 148.7 (C_7, C_8), 202.4 (CHO) ppm; **MS** (ESI) *m/z* (rel intensity): 286 (MH^+, 40), 242 (100). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{20}NO_3$ [MH^+] 286.1443; found: 286.1452.

2-(7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-b]isoquinolin-10-yl)acetamide



(21). A solution of **16a** (57.5 mg, 0.20 mmol) in a mixture EtOH/KOH 10M 1:1 (4 mL) was refluxed for 24 hours. The reaction was cooled to room temperature, diluted with water and acidified to pH = 1 using HCl 5M. The resulting aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (silica gel, 98% EtOAc/methanol) to afford **21** as a brown oil (52.6 mg, 86%): **IR** (ATR): 3445, 3360, 2935, 1665, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.70 (CH_3), 2.86 (d, J = 14.2 Hz, 1H, CH_aH$_b$), 2.94 (d, J = 14.2 Hz, 1H, CH$_a$$H_b$), 3.90 (s,

3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.96-5.15 (m, 4H, NH_2, H_{5a}, H_{5b}), 6.18 (dd, *J* = 3.6, 1.7 Hz, 1H, H_1), 6.28 (dd, *J* = 3.6, 2.7 Hz, 1H, H_2), 6.69 (s, 1H, H_9), 6.74 (dd, *J* = 2.7, 1.7 Hz, 1H, H_3), 7.03 (s, 1H, H_6) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 30.5 (CH_3), 38.3 (C_{10}), 47.1 (CH_2), 50.3 (C_5), 56.0 (OCH_3), 56.1 (OCH_3), 102.9 (C_1), 108.5 (C_2), 108.8, 108.9 (C_6, C_9), 119.0 (C_3), 123.0 (C_{5a}), 131.2 (C_{10a}), 134.1 (C_{9a}), 147.9, 148.7 (C_7, C_8), 172.6 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 301 (MH^+, 23), 242 (100). **HRMS** (ESI-TOF): calcd. for $C_{17}H_{21}N_2O_3$ [MH^+] 301.1552; found: 301.1546.

***tert*-butyl (2-(7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-b]isoquinolin-10-yl)ethyl)carbamate (22). 16a** (65.4 mg, 0.23 mmol) was added over a suspension of $LiAlH_4$ (17.6 mg, 0.46 mmol) in THF (1.15 mL, 0.2 M). The reaction mixture was stirred at rt for 1h and then heated under reflux for 15 min. The mixture was cooled to room temperature, carefully quenched with water and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was dissolved in dry THF (5 mL) and Boc_2O (45.3 mg, 0.21 mmol) was added. The reaction mixture was stirred at room temperature for 16 h and the solvent was then removed to afford **22** as brown oil (60.6 mg, 68%) (2 steps): **IR** (ATR): 3380, 2930, 1700, 1510 cm^{-1}; **^1H NMR** (300 MHz, $CDCl_3$): δ = 1.39 (s, 9H, $C(CH_3)_3$), 1.68 (s, 3H, CH_3), 1.97-2.14 (m, 2H, CH_2CH_2N), 2.81-2.86 (m, 2H, CH_2CH_2N), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.13 (bs, 1H, NH), 5.02-5.13 (m, 2H, H_5), 6.06 (dd, *J* = 3.6, 1.7 Hz, 1H, H_1), 6.25-6.27 (m, 1H, H_2), 6.68-6.70 (m, 2H, H_3, H_9), 6.98 (s, 1H, H_6) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 28.4 ($C(CH_3)_3$), 29.1 (CH_3), 37.5 (CH_2CH_2N), 38.1 (C_{10}), 44.7 (CH_2CH_2N), 47.0 (C_5), 56.0 (OCH_3), 56.1 (OCH_3), 78.8 ($C(CH_3)_3$), 102.6 (C_1), 108.5 (C_2), 108.6 (C_9), 108.8 (C_6), 118.1 (C_3), 123.3 (C_{5a}), 132.3 (C_{9a}), 134.8 (C_{10a}), 147.7, 148.6 (C_7, C_8), 155.8 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 387 (MH^+, 26), 331 (100). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{31}N_2O_4$ [MH^+] 387.2284; found: 387.2292.

2.4. Intramolecular carbopalladation/Suzuki coupling cascade. Synthesis of pyrrolo[1,2-b]isoquinolines 24.

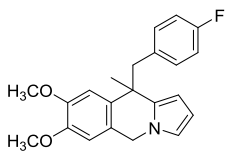
General procedure A *(Phosphane-Free Catalytic System)*. $Pd(OAc)_2$ (0.1 mmol) was added to a mixture of *N*-(*o*-iodobenzyl)pyrrole **15** (1 mmol), bororonic acid **23** (1.3 mmol), sodium carbonate (1.3 mmol) and tetrabutylammonium chloride (2 mmol) in DMF (3 ml).

The mixture was stirred at 120 ºC for the time indicated in each case. H_2O (15 mL) was added and the resulting aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel) of the resulting residue afforded the corresponding pyrroloisoquinoline **24**.

General procedure B *(with Phosphane L6)*. $Pd_2(dba)_3{\cdot}CHCl_3$ (0.1 mmol) was added to a mixture of *N*-(*o*-iodobenzyl)pyrrole **15** (1 mmol), bororonic acid **23** (1.3 mmol), sodium carbonate (1.3 mmol), tri(furan-2-yl)phosphane (**L6**) (0.2 mmol) and tetrabutylammonium chloride (2 mmol) in DMF (3 ml). The mixture was stirred at 120 ºC for 1 h. H_2O (15 mL) was added and the resulting aqueous phase was extracted with EtOAc (3 x 30 mL). The corresponding pyrroloisoquinoline **24** was obtained after workup and chromatographic purification, as indicated in General Procedure A.

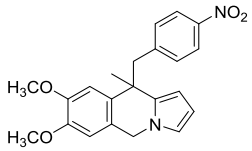
7,8-dimethoxy-10-(4-methoxybenzyl)-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24aa). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15a** (114 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-methoxyphenylboronic acid (**23a**) (59.3 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24aa** as a brown oil (66.0 mg, 61%): **IR** (ATR): 2970, 1510 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.87 (s, 3H, CH_3), 2.87 (d, J = 12.5 Hz, 1H, CH_aH$_b$), 2.99 (d, J = 12.5 Hz, 1H, CH$_a$$H_b$), 3.65-3.72 (m, 1H, H_{5a}) 3.72 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.60 (d, J = 15.4 Hz, 1H, H_{5b}), 6.16-6.29 (m, 4H, H_1, H_2, $H_{3'}$, $H_{5'}$), 6.45-6.55 (m, 4H, H_6, H_3, $H_{2'}$, $H_{6'}$), 6.97 (s, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.8 (CH_3), 41.1 (C_{10}), 46.8 (CH_2), 53.6 (C_5), 55.1 (OCH_3), 55.9 (OCH_3), 56.1 (OCH_3), 102.6 (C_1), 108.2 (C_2, C_6), 108.6 (C_9), 112.6 ($C_{3'}$, $C_{5'}$), 117.6 (C_3), 125.1 ($C_{1'}$), 130.2 (C_{5a}), 131.0 ($C_{2'}$, $C_{6'}$), 131.9 (C_{10a}), 135.0 (C_{9a}), 147.4, 148.2 (C_7, C_8), 158.2 ($C_{4'}$) ppm; **MS** (ESI) *m/z* (rel intensity): 364 (MH^+, 100), 242 (12). **HRMS** (ESI-TOF): calcd. for $C_{23}H_{26}NO_3$ [MH^+] 364.1907; found: 364.1920. [**18** (9 mg, 12%) was isolated as a byproduct. See spectroscopic data below.]

10-(4-fluorobenzyl)-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline



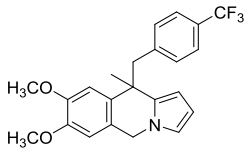
(24ab). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15a** (114 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 4-fluorophenylboronic acid (**23b**) (54.6 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 2 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24ab** as a colorless oil (56.1 mg, 54%): **IR** (ATR): 2965, 1510 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, CH_3), 2.88 (d, J = 12.5 Hz, 1H, CH_aH$_b$), 3.00 (d, J = 12.5 Hz, 1H, CH$_a$$H_b$), 3.64 (d, J = 15.4 Hz, 1H, H_{5a}), 3.86 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.62 (d, J = 15.4 Hz, 1H, H_{5b}), 6.14 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.19-6.26 (m, 3H, H_2, $H_{3'}$, $H_{5'}$), 6.43 (s, 1H, H_6), 6.50 (dd, J = 2.7, 1.7 Hz, H_3), 6.61-6.67 (m, 2H, $H_{2'}$, $H_{6'}$), 6.96 (s, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.0 (CH_3), 41.0 (C_{10}), 46.6 (CH_2), 53.6 (C_5), 55.9 (OCH_3), 56.1 (OCH_3), 102.6 (C_1), 108.0 (C_2), 108.3 (C_9), 108.4 (d, J = 7.8 Hz, $C_{2'}$, $C_{6'}$), 113.8 (d, J = 20.8 Hz, $C_{3'}$, $C_{5'}$), 117.6 (C_6), 124.9 (C_{5a}), 131.3 (C_3), 131.4 (C_{10a}), 133.7 (d, J = 3.2 Hz, $C_{1'}$), 134.5 (C_{9a}), 147.5, 148.2 (C_7, C_8), 161.7 (d, J = 244.2 Hz, $C_{4'}$) ppm; **MS** (ESI) *m/z* (rel intensity): 352 (MH^+, 100), 350 (10), 243 (13). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{23}FNO_2$ [MH^+] 352.1707; found: 352.1713.

7,8-dimethoxy-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline

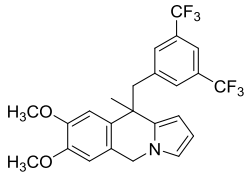


(24ac). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15a** (506 mg, 1.32 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (134 mg, 0.13 mmol), 4-nitrophenylboronic acid (**23c**) (284 mg, 1.7 mmol), sodium carbonate (180 mg, 1.7 mmol), tri(furan-2-yl)phosphane (**L6**) (60.2 mg, 0.26 mmol) and tetrabutylammonium chloride (723 mg, 2.60 mmol) in DMF (4 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24ac** as a yellow solid (470 mg, 94%): **m.p.** (petroleum ether/EtOAc): 92-94 °C; **IR** (ATR): 2970, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.90 (s, 3H, CH_3), 3.05 (d, J = 12.1 Hz, 1H, CH_aH$_b$) 3.16 (d, J = 12.1 Hz, 1H, CH$_a$$H_b$), 3.68 (d, J = 15.6 Hz, 1H, H_{5a}), 3.87 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.66 (d, J = 15.6 Hz, 1H, H_{5b}), 6.18 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.27 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.41-6.45 (m, 3H, H_6, $H_{2'}$, $H_{6'}$), 6.50 (dd, J = 2.7, 1.7 Hz, 1H, H_3), 7.02 (s, 1H, H_9), 7.80 (d, J = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.7 (CH_3), 41.0 (C_{10}), 46.6 (CH_2), 54.2 (C_5), 55.9 (OCH_3), 56.2 (OCH_3), 103.1 (C_1),

108.1, 108.2 (C_2, C_6), 108.7 (C_9), 117.9 (C_3), 122.2 ($C_{3'}$, $C_{5'}$), 124.3 (C_{5a}), 130.6 (C_{10a}), 130.6 ($C_{2'}$, $C_{6'}$), 133.6 ($C_{1'}$), 146.0 (C_{9a}), 146.6 ($C_{4'}$), 147.8, 148.5 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 379 (MH^+, 100), 243 (23). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{23}N_2O_4$ [MH^+] 379.1652; found: 379.1658.

8-dimethoxy-10-methyl-10-(4-trifluoromethylbenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24ad). 

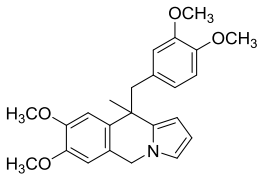
According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15a** (115 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 4-trifluoromethylphenylboronic acid (**23d**) (74.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 2 h.. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24ad** as a colorless oil (63.1 mg, 52%): **IR** (ATR): 2935, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.87 (s, 3H, CH_3), 2.97 (d, J = 12.3 Hz, 1H, CH_aH$_b$), 3.09 (d, J = 12.3 Hz, 1H, CH$_a$$H_b$), 3.66 (d, J = 15.5 Hz, 1H, H_{5a}), 3.87 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.64 (d, J = 15.5 Hz, 1H, H_{5b}), 6.16-6.17 (m, 1H, H_1), 6.26 (t, J = 3.1 Hz, 1H, H_2), 6.40-6.45 (m, 3H, $H_{2'}$, $H_{6'}$, H_6), 6.50-6.52 (m, 1H, H_3), 6.95 (s, 1H, H_9), 7.21 (d, J = 7.9 Hz, 1H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.2 (CH_3), 40.9 (C_{10}), 46.6 (CH_2), 54.0 (C_5), 55.9 (OCH_3), 56.1 (OCH_3), 102.9 (C_1), 108.1 (C_2), 108.4 (C_6, C_9), 117.8 (C_3), 123.9 (q, J = 3.8 Hz, $C_{3'}$, $C_{5'}$), 124.4 (q, J = 271.9 Hz, CF_3), 124.7 (C_{5a}), 128.4 (q, J = 32.3 Hz, $C_{4'}$), 130.2 ($C_{2'}$, $C_{6'}$), 131.1 (C_{10a}), 134.2 ($C_{1'}$), 142.2 (C_{9a}), 147.7, 148.3 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 402 (MH^+, 100), 243 (7). **HRMS** (ESI-TOF): calcd. for $C_{23}H_{23}F_3NO_2$ [MH^+] 402.1675; found: 402.1682.

10-(3,5-bis(trifluoromethy)lbenzyl)-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24ae). 

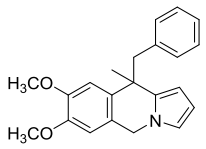
According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15a** (114 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (**23e**) (101 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **24ae** as a yellow oil (77.5 mg, 55%): **IR** (ATR): 2940, 1520 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.91 (s, 3H, CH_3), 2.99 (d, J =

12.3 Hz, 1H, C*H*$_a$H$_b$), 3.12 (d, *J* = 12.3 Hz, 1H, CH$_a$*H*$_b$), 3.46 (d, *J* = 15.9 Hz, 1H, H$_{5a}$), 3.84 (s, 3H, OCH$_3$), 3.96 (s, 3H, OCH$_3$), 4.64 (d, *J* = 15.9 Hz, 1H, H$_{5b}$), 6.18 (dd, *J* = 3.6, 1.7 Hz, 1H, H$_1$), 6.27 (dd, *J* = 3.6, 2.7 Hz, 1H, H$_2$), 6.40 (s, 1H, H$_6$), 6.46 (dd, *J* = 2.7, 1.7 Hz, 1H, H$_3$), 6.61-6.62 (m, 2H, H$_{2'}$, H$_{6'}$), 7.01 (s, 1H, H$_9$), 7.62 (s, 1H, H$_{4'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.9 (CH$_3$), 40.9 (C$_{10}$), 46.2 (CH$_2$), 54.0 (C$_5$), 56.0 (OCH$_3$), 56.3 (OCH$_3$), 103.1 (C$_1$), 108.2 (C$_2$, C$_6$), 108.8 (C$_9$), 118.0 (C$_3$), 119.9 (sept, *J* = 3.9 Hz, C$_{4'}$), 123.2 (q, *J* = 272.7 Hz, CF$_3$), 124.3 (C$_{5a}$), 130.0 (C$_{10a}$, C$_{2'}$, C$_{6'}$), 130.1 (q, *J* = 33.0 Hz, C$_{3'}$, C$_{5'}$), 133.0 (C$_{1'}$), 140.5 (C$_{9a}$), 148.2, 148.8 (C$_7$, C$_8$) ppm; **MS** (ESI) *m/z* (rel intensity): 470 (MH$^+$, 100), 360 (11). **HRMS** (ESI-TOF): calcd. for $C_{24}H_{22}F_6NO_2$ [MH$^+$] 470.1549; found: 470.1553. [**18** (12.2 mg, 16%) was isolated as a by product. See spectroscopic data below]

10-(3,4-dimethoxybenzyl)-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24af). According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15a** (114 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 3,4-dimethoxyphenylboronic acid (**23f**) (71.0 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24af** as a yellow oil (72.8 mg, 62%): **IR** (ATR): 2935, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.88 (s, 3H, CH$_3$), 2.85 (d, *J* = 12.4 Hz, 1H, C*H*$_a$H$_b$), 2.98 (d, *J* = 12.4 Hz, 1H, CH$_a$*H*$_b$), 3.51 (s, 3H, OCH$_3$), 3.54 (d, *J* = 15.4 Hz, 1H, H$_{5a}$), 3.80 (s, 3H, OCH$_3$), 3.86 (s, 3H, OCH$_3$), 3.96 (s, 3H, OCH$_3$), 4.57 (d, *J* = 15.4 Hz, 1H, H$_{5b}$), 5.72 (d, *J* = 2.0 Hz, 1H, H$_{2'}$), 5.87 (dd, *J* = 8.1, 2.0 Hz, 1H, H$_{5'}$), 6.17 (dd, *J* = 3.6, 1.7 Hz, 1H, H$_1$), 6.27 (dd, *J* = 3.6, 2.7 Hz, 1H, H$_2$), 6.42 (s, 1H, H$_6$), 6.46-6.49 (m, 2H, H$_3$,H$_{6'}$), 7.02 (s, 1H, H$_9$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.1 (CH$_3$), 41.2 (C$_{10}$), 46.7 (CH$_2$), 54.2 (C$_5$), 55.4 (OCH$_3$), 55.8 (OCH$_3$), 55.9 (OCH$_3$), 56.2 (OCH$_3$), 102.5 (C$_1$), 108.0 (C$_2$), 108.3 (C$_6$), 108.5 (C$_{5'}$), 109.9 (C$_{2'}$), 112.9 (C$_9$), 117.5 (C$_{6'}$), 121.9 (C$_3$), 125.2 (C$_{5a}$), 130.6 (C$_{1'}$), 131.7 (C$_{10a}$), 134.8 (C$_{9a}$), 147.4, 147.5, 147.6, 148.2 (C$_7$, C$_8$, C$_{3'}$, C$_{4'}$) ppm; **MS** (ESI) *m/z* (rel intensity): 394 (MH$^+$, 86), 242 (11). **HRMS** (ESI-TOF): calcd. for $C_{24}H_{28}NO_4$ [MH$^+$] 394.2013; found: 394.2017.

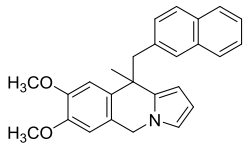


10-benzyl-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24ag).



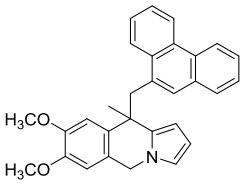
According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15a** (114 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), phenylboronic acid (**23g**) (47.5 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 4 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24ag** as a white solid (45.8 mg, 46%): **m.p.** (petroleum ether/EtOAc): 98-100 °C; **IR** (ATR): 2970, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.86 (s, 3H, CH_3), 2.90 (d, J = 12.3 Hz, 1H, CH_aH_b), 3.02 (d, J = 12.3 Hz, 1H, CH_aH_b), 3.61 (d, J = 15.3 Hz, 1H, H_{5a}), 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.59 (d, J = 15.3 Hz, 1H, H_{5b}), 6.15 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.25 (dd, J = 3.6, 2.6 Hz, 1H, H_2), 6.28-6.32 (m, 2H, $H_{2'}$, $H_{6'}$), 6.43 (s, 1H, H_6), 6.50 (dd, J = 2.6, 1.7 Hz, 1H, H_3), 6.92-6.98 (m, 3H, H_9, $H_{3'}$, $H_{5'}$), 7.06-7.11 (m, 1H, $H_{4'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.9 (CH_3), 41.0 (C_{10}), 46.7 (CH_2), 54.3 (C_5), 55.9 (OCH_3), 56.1 (OCH_3), 102.6 (C_1), 108.1 (C_2), 108.2 (C_9), 108.6 (C_6), 117.6 (C_3), 125.1 (C_{5a}), 126.1 ($C_{4'}$), 127.1 ($C_{2'}$, $C_{6'}$), 130.1 ($C_{3'}$, $C_{5'}$), 131.7 (C_{10a}), 134.9 ($C_{1'}$), 137.9 (C_{9a}), 147.4, 148.1 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 334 (MH^+, 100), 243 (11). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{24}NO_2$ [MH^+] 334.1802; found: 334.1813.

7,8-dimethoxy-10-methyl-10-(naphthalen-2-ylmethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24ah).

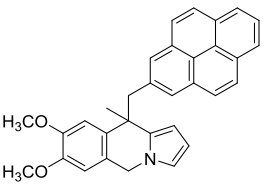


According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15a** (114 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), naphthalen-2-ylboronic acid (**23h**) (67.1 mg 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **24ah** as a colorless oil (61.0 mg, 53%): **IR** (ATR): 3010, 1275 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.91 (s, 3H, CH_3), 3.06 (d, J = 12.4 Hz, 1H, CH_aCH_b), 3.18 (d, J = 12.4 Hz, 1H, CH_aCH_b), 3.47 (d, J = 15.4 Hz, 1H, H_{5a}), 3.83 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.50 (d, J = 15.4 Hz, 1H, H_{5b}), 6.19 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.27-6.29 (m, 1H, H_2), 6.36 (s, 1H, H_6), 6.41 (dd, J = 8.4, 1.7 Hz, 1H, $H_{3'}$), 6.45-6.47 (m, 1H, H_3), 6.75 (s, 1H, $H_{1'}$), 6.98 (s, 1H, H_9), 7.35-7.43 (m, 3H, $H_{4'}$, $H_{6'}$, $H_{7'}$), 7.49-7.52 (m, 1H, $H_{5'}$), 7.70-7.73 (m, 1H, $H_{8'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.8 (CH_3), 41.1 (C_{10}), 46.8 (CH_2), 54.4 (C_5), 55.9 (OCH_3), 56.1 (OCH_3), 102.7 (C_1), 108.2 (C_2), 108.3 (C_6), 108.6 (C_9),

117.7 (C_3), 124.9 ($C_{6'}$), 125.2 (C_3), 125.4 ($C_{7'}$), 126.2 ($C_{4'}$), 127.3 ($C_{8'}$), 127.6 ($C_{5'}$), 128.6 ($C_{3'}$), 128.7 ($C_{1'}$), 131.8 ($C_{4a'}$), 132.0 ($C_{8a'}$), 132.9 (C_{10a}), 134.8 ($C_{2'}$), 135.5 (C_{9a}), 147.4, 148.2 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 384 (MH^+, 100), 242 (23). **HRMS** (ESI-TOF): calcd. for $C_{26}H_{26}NO_2$ [MH^+] 384.1958; found: 384.1964.

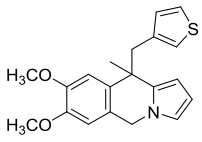
7,8-dimethoxy-10-methyl-10-(phenanthren-9-ylmethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24ai). 

According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15a** (116 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), phenenthren-9-ylboronic acid (**23i**) (86.8 mg 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24ai** as a yellow oil (82.6 mg, 63%): **IR** (ATR): 2970, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.97 (s, 3H, CH_3), 3.48-3.56 (m, 3H, CH_2, H_{5a}), 3.74 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.43 (d, J = 15.5 Hz, 1H, H_{5b}), 6.19-6.23 (m, 3H, H_1, H_2, H_6), 6.35-6.36 (m, 1H, H_3), 6.69 (s, 1H, H_9), 6.95 (s, 1H, $H_{10'}$), 7.23-7.28 (m, 1H, $H_{1'}$), 7.43-7.60 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{6'}$, $H_{7'}$, $H_{8'}$), 8.58-8.61 (m, 2H, $H_{4'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.2 (CH_3), 41.2 (C_{10}), 47.1 (CH_2), 49.5 (C_5), 56.0 (OCH_3), 56.2 (OCH_3), 102.8 (C_1), 108.2 (C_2), 108.6 (C_6), 109.1 (C_9), 118.0 (C_3), 122.2, 122.4 ($C_{4'}$, $C_{5'}$), 124.5 ($C_{8'}$), 125.3 (C_{5a}), 125.4, 125.7, 126.1, 126.3 ($C_{2'}$, $C_{3'}$, $C_{6'}$, $C_{7'}$), 128.3 ($C_{10'}$), 129.5, 129.6 ($C_{4a'}$, $C_{4b'}$, $C_{1'}$), 131.3, 131.8 ($C_{8a'}$, $C_{10a'}$), 132.3 (C_{10a}), 132.4 ($C_{9'}$), 135.2 (C_{9a}), 147.6, 148.3 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 434 (MH^+, 100), 242 (59). **HRMS** (ESI-TOF): calcd. for $C_{30}H_{28}NO_2$ [MH^+] 434.2115; found: 434.2119.

8-dimethoxy-10-methyl-10-(pyren-1-ylmethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24aj). 

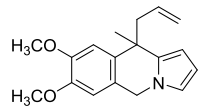
According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15a** (116 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), pyren-1-ylboronic acid (**23j**) (96.0 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24aj** as a yellow oil (114.2 mg, 83%): **IR** (ATR): 2970, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.06 (s, 3H, CH_3), 2.85 (d, J = 15.4 Hz, 1H, H_{5a}), 3.68 (s, 3H, OCH_3),

3.72-3.73 (m, 2H, CH_2), 3.91 (s, 3H, OCH_3), 4.20 (d, J = 15.4 Hz, 1H, H_{5b}), 6.09 (s, 1H, H_6), 6.25-6.33 (m, 3H, H_1, H_2, H_3), 6.99 (d, J = 7.9 Hz, 1H, $H_{10'}$), 7.08 (s, 1H, H_9), 7.51 (d, J = 9.4 Hz, 1H, $H_{2'}$), 7.71 (d, J = 9.4 Hz, 1H, $H_{3'}$), 7.79 (d, J = 7.9 Hz, 1H, $H_{9'}$), 7.92-8.13 (m, 5H, $H_{4'}$, $H_{5'}$, $H_{6'}$, $H_{7'}$, $H_{8'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.6 (CH_3), 41.7 (C_{10}), 46.8 (CH_2), 50.5 (C_5), 56.0 (OCH_3), 56.3 (OCH_3), 102.9 (C_1), 108.2 (C_2), 108.6 (C_6), 109.0 (C_9), 118.1 (C_3), 123.4, 123.7 ($C_{3'}$, $C_{10'}$), 124.2 ($C_{3a'}$), 124.5, 124.6 ($C_{2'}$, $C_{6'}$), 124.7, 125.5 ($C_{3a1'}$, $C_{5a1'}$), 125.7, 126.2, 126.9, 127.5, 129.5 ($C_{4'}$, $C_{5'}$, $C_{7'}$, $C_{8'}$, $C_{9'}$), 129.9, 130.2, 130.6, 131.3, 132.0, 132.5 ($C_{5a'}$, C_{5a}, $C_{10a'}$, $C_{8a'}$, C_{10a}, $C_{1'}$), 134.8 (C_{9a}), 147.7, 148.4 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 458 (MH^+, 100), 242 (56). **HRMS** (ESI-TOF): calcd. for $C_{32}H_{28}NO_2$ [MH^+] 458.2115; found: 458.2123.

7,8-dimethoxy-10-methyl-10-(thiophen-3-ylmethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24ak). 

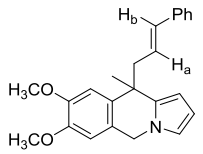
According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15a** (118 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), thiophen-3-ylboronic acid (**23k**) (49.9 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 48 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24ak** as a colorless oil (15.7 mg, 15%) (76% conversion): **IR** (ATR): 2970, 1515, 1265 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.84 (s, 3H, CH_3), 2.96 (d, J = 12.9 Hz, 1H, CH_aH_b), 3.05 (d, J = 12.9 Hz, 1H, CH_aH_b), 3.87 (s, 3H, OCH_3),* 3.92 (s, 3H, OCH_3),* 3.87-3.92 (m, 1H, H_{5a}),* 4.70 (d, J = 15.4 Hz, 1H, H_{5b}), 5.99 (dd, J = 4.9, 1.3 Hz, 1H, $H_{5'}$), 6.13-6.18 (m, 2H, H_1, $H_{2'}$), 6.24-6.26 (m, 1H, H_2), 6.48 (s, 1H, H_6), 6.54-6.55 (m, 1H, H_3), 6.90-6.92 (m, 2H, $H_{4'}$, H_9) ppm (*overlapped); **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.2 (CH_3), 40.6 (C_{10}), 46.6 (CH_2), 48.3 (C_5), 55.9 (OCH_3), 56.1 (OCH_3), 102.5 (C_1), 108.1 (C_2), 108.3 (C_6), 108.5 (C_9), 117.6 (C_3), 122.5 ($C_{2'}$), 123.3 ($C_{4'}$), 124.7 (C_{5a}), 129.6 ($C_{5'}$), 131.7 (C_{10a}), 135.0 ($C_{1'}$), 138.4 (C_{9a}), 147.4, 148.1 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 340 (MH^+, 59), 242 (100). **HRMS** (ESI-TOF): calcd. for $C_{20}H_{22}NO_2S$ [MH^+] 340.1366; found: 340.1372. [**18** (8.0 mg, 11%) and **25ak** (50.6 mg, 50%) were isolated as byproducts. See spectroscopic data below.]

10-allyl-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24al).



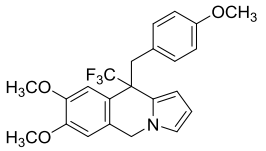
According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15a** (114 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), potasium trifluorovinylborate (52.2 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 24 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **24al** as a colorless oil (31.7 mg, 38%) (89% conversion): **IR** (ATR): 2970, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.65 (s, 3H, CH_3), 2.50-2.53 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.81-4.89 (m, 2H, CH=CH_2), 5.01 (d, J = 15.5 Hz, 1H, H_{5a}), 5.08 (d, J = 15.5 Hz, 1H, H_{5b}), 5.37-5.48 (m, 1H, CH=CH_2), 6.04 (dd, J = 3.5, 1.7 Hz, 1H, H_1), 6.23 (dd, J = 3.5, 2.7 Hz, 1H, H_2), 6.67-6.69 (m, 2H, H_3, H_6), 6.93 (s, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.2 (CH_3), 39.3 (C_{10}), 47.3 (CH_2), 49.2 (C_5), 56.0 (OCH_3), 56.1 (OCH_3), 102.6 (C_1), 108.1 (C_2), 108.8 (C_6), 108.9 (C_9), 117.4 (CH=CH$_2$), 118.0 (C_3), 124.0 (C_{5a}), 133.1 (C_{10a}), 134.8 (CH=CH$_2$), 135.5 (C_{9a}), 147.4, 148.2 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 284 (MH^+, 100), 243 (51). **HRMS** (ESI-TOF): calcd. for $C_{18}H_{22}NO_2$ [MH^+] 284.1645; found: 284.1649. [**18** (16.0 mg, 24%) was isolated as byproduct. See spectroscopic data below.]

10-cinnamyl-7,8-dimethoxy-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24am).

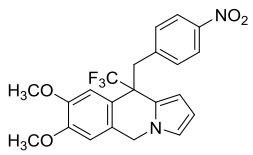


According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15a** (113 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), (*E*)-styrylboronic acid (**23m**) (57.7 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 2 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **24am** as a yellow oil (64.5 mg, 60%): **IR** (ATR): 2970, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.73 (s, 3H, CH_3), 2.55-2.68 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.01 (s, 2H, H_5), 5.82 (dt, J = 15.8, 7.4 Hz, 1H, CH_a=CH_b), 6.09-6.14 (m, 2H, H_1, CH_a=CH_b), 6.26 (dd, J = Hz, 3.6, 2.7 Hz, 1H, H_2), 6.67 (s, 1H, H_6), 6.69 (dd, J = 2.7, 1.7 Hz, 1H, H_3), 6.97 (s, 1H, H_9), 7.14-7.28 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.6 (CH_3), 39.8 (C_{10}), 47.4 (CH_2), 49.0 (C_5), 56.0 (OCH_3), 56.1 (OCH_3), 102.6 (C_1), 108.2 (C_2), 108.8 (C_6), 108.8 (C_9), 118.1 (C_3), 124.1 (C_{5a}), 126.0 ($C_{2'}$, $C_{6'}$), 126.5 (CH_a=CH$_b$), 127.0 ($C_{4'}$), 128.4 ($C_{3'}$, $C_{5'}$), 132.6 (CH$_a$=CH$_b$),

133.0 (C_{10a}), 135.5 ($C_{1'}$), 137.6 (C_{9a}), 147.4, 148.2 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 360 (MH^+, 98), 244 (11), 243 (100). **HRMS** (ESI-TOF): calcd. for $C_{24}H_{26}NO_2$ [MH^+] 360.1958; found: 360.1964.

7,8-dimethoxy-10-(4-methoxybenzyl)-10-(trifluoromethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24ba). 

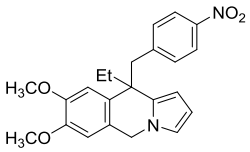
According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15b** (132 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-methoxyphenylboronic acid (**23a**) (59.3 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/dichloromethane 1/1) afforded **24ba** as a yellow oil (64.7 mg, 52%): **IR** (ATR): 2960, 1510, 1240 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.60 (d, J = 14.4 Hz, 1H, CH_aH$_b$), 3.64 (s, 3H, OCH_3), 3.75 (d, J = 14.4 Hz, 1H, CH$_a$$H_b$), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.67 (d, J = 15.8 Hz, 1H, H_{5a}), 4.99 (d, J = 15.8 Hz, 1H, H_{5b}), 6.32-6.34 (m, 1H, H_1), 6.45-6.57 (m, 6H, H_2, $H_{3'}$, $H_{5'}$, H_6, $H_{2'}$, $H_{6'}$), 6.72-6.73 (m, 1H, H_3), 7.14 (s, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 39.2 (CH_2), 46.7 (C_5), 49.6 (q, J = 25.0 Hz, C_{10}), 55.0 (OCH_3), 55.8 (OCH_3), 56.0 (OCH_3), 108.1 (C_1), 108.2 (C_2), 109.0 (C_6), 111.7 (q, J = 2.6 Hz, C_9), 113.0 ($C_{3'}$, $C_{5'}$), 119.5 (C_3), 120.9 ($C_{1'}$), 124.3 (C_{5a}), 126.0 (C_{10a}), 127.0 (q, J = 284.6 Hz, CF_3), 127.4 (C_{9a}), 130.8 ($C_{2'}$, $C_{6'}$), 147.7, 148.8 (C_7, C_8), 158.0 ($C_{4'}$) ppm; **MS** (ESI) *m/z* (rel intensity): 418 (MH^+, 100), 296 (23). **HRMS** (ESI-TOF): calcd. for $C_{23}H_{23}F_3NO_3$ [MH^+] 418.1625; found: 418.1627. [Using General Procedure A, **19** (57.1 mg, 61%) was isolated as the major compound. See spectroscopic data below.]

7,8-dimethoxy-10-(4-nitrobenzyl)-10-(trifluoromethyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24bc). 

According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15b** (133 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/dichloromethane 1/1) afforded **24bc** as

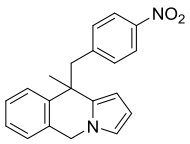
an orange solid (110 mg, 84%): **m.p.** (petroleum ether/dichloromethane): 90-92 ºC; **IR** (ATR): 2970, 1520, 1230 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 3.77-3.92 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.77 (d, J = 15.9 Hz, 1H, H_{5a}), 5.04 (d, J = 15.9 Hz, 1H, H_{5b}), 6.32-6.35 (m, 1H, H_1), 6.44-6.46 (m, 1H, H_2), 6.60 (s, 1H, H_6), 6.75-6.81 (m, 3H, H_3, $H_{2'}$, $H_{6'}$), 7.09 (s, 1H, H_3), 7.80 (d, J = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 39.7 (CH_2), 46.7 (C_5), 49.1 (q, J = 25.6 Hz, C_{10}), 55.8 (OCH_3), 56.2 (OCH_3), 108.4 (C_1), 108.5 (C_2), 109.4 (C_6), 111.2 (q, J = 2.5 Hz, C_9), 119.9 (C_{5a}), 120.0 (C_3), 122.8 ($C_{2'}$, $C_{6'}$), 123.2 (C_{10a}), 126.0 ($C_{1'}$), 126.7 (q, J = 284.5 Hz, CF_3), 130.5 ($C_{3'}$, $C_{5'}$), 143.4 (C_{9a}), 146.6 ($C_{4'}$), 148.1, 149.3 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 433 (MH^+, 100), 296 (15). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{20}F_3N_2O_4$ [MH^+] 433.1370; found: 433.1379. [Using General Procedure A, **19** (47.0 mg, 51%) was isolated as the major compound. See spectroscopic data below.]

10-ethyl-7,8-dimethoxy-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline



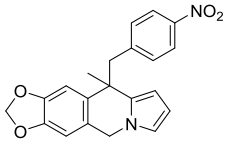
(24cc). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15c** (117 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24cc** as a yellow oil (63.5 mg, 54%): **IR** (ATR): 2970, 1520, 1265 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.64 (t, J = 7.2 Hz, 3H, CH_3CH$_2$), 2.36 (q, J = 7.2 Hz, 2H, CH$_3$CH_2), 3.06 (d, J = 12.1 Hz, 1H, CH_aH$_b$), 3.19 (d, J = 12.1 Hz, 1H, CH$_a$$H_b$), 3.64 (d, J = 15.7 Hz, 1H, H_{5a}), 3.85 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.64 (d, J = 15.7 Hz, 1H, H_{5b}), 6.15 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.28-6.31 (m, 1H, H_2), 6.37-6.40 (m, 3H, H_6, $H_{2'}$, $H_{6'}$), 6.45-6.47 (m, 1H, H_3), 6.96 (s, 1H, H_9), 7.74 (d, J = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 9.0 (*C*H$_3$CH$_2$), 33.8 (CH$_3$*C*H$_2$), 46.1 (C_{10}), 46.2 (CH_2), 54.4 (C_5), 55.8 (OCH_3), 56.2 (OCH_3), 102.9 (C_1), 108.0 (C_2), 108.2 (C_9), 109.0 (C_6), 117.7 (C_3), 122.1 ($C_{3'}$, $C_{5'}$), 125.3 (C_{5a}), 127.6 (C_{9a}), 130.5 ($C_{2'}$, $C_{6'}$), 131.8 (C_{10a}), 146.1 ($C_{1'}$), 146.4 ($C_{4'}$), 147.8, 148.7 (C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 393 (MH^+, 100), 257 (12). **HRMS** (ESI-TOF): calcd. for $C_{23}H_{25}N_2O_4$ [MH^+] 393.1809; found: 393.1815.

10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24dc).



According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15d** (97.0 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 4 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **24dc** as yellow solid (36.6 mg, 38%): **m.p.** (petroleum ether/EtOAc): 136-138 ºC; **IR** (ATR): 2935, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.93 (s, 3H, CH_3), 3.08 (d, J = 12.3 Hz, 1H, CH_aH$_b$), 3.19 (d, J = 12.3 Hz, 1H, CH$_a$$H_b$), 3.85 (d, J = 15.9 Hz, 1H, H_{5a}), 4.79 (d, J = 15.9 Hz, 1H, CH_{5b}), 6.20 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.30 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.44 (d, J = 8.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.56 (dd, J = 2.7, 1.7 Hz 1H, H_3), 7.01-7.03 (m, 1H, H_6), 7.25-7.28 (m, 1H, H_7), 7.38-7.41 (m, 1H, H_8), 7.57-7.59 (m, 1H, H_9), 7.83 (d, J = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.2 (CH_3), 41.2 (C_{10}), 47.0 (CH_2), 54.2 (C_5), 103.3 (C_1), 108.8 (C_2), 118.1 (C_9), 122.2 ($C_{3'}$, $C_{5'}$), 125.4 (C_3), 125.8 (C_8), 126.7 (C_6), 127.6 (C_7), 130.7 ($C_{2'}$, $C_{6'}$), 132.0 (C_{10a}), 133.7 (C_{5a}), 138.9 ($C_{1'}$), 145.9 ($C_{4'}$), 146.6 (C_{9a}) ppm; 319 (MH^+, 100), 183 (14). **HRMS** (ESI-TOF): calcd. for $C_{20}H_{19}N_2O_2$ [MH^+] 319.1441; found 319.1443.

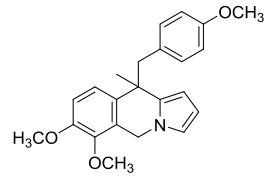
10-methyl-10-(4-nitrobenzyl)-5,10-dihydro-[1,3]dioxolo[4,5-*g*]pyrrolo[1,2-*b*]isoquinoline (24ec).



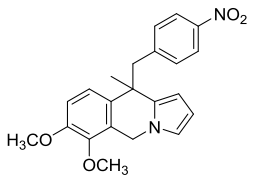
According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15e** (111 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 3 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **24ec** as a yellow solid (70.6 mg, 65%): **m.p.** (petroleum ether/EtOAc): 179-181 ºC; **IR** (ATR): 2915, 1520 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, CH_3), 3.00 (d, J = 12.2 Hz, 1H, CH_aH$_b$), 3.13 (d, J = 12.2 Hz, 1H, CH$_a$$H_b$), 3.63 (d, J = 15.8 Hz, 1H, H_{5a}), 4.61 (d, J = 15.8 Hz, 1H, H_{5b}), 5.98 (d, J = 1.4 Hz, 1H, OCH_aH$_b$O), 6.03 (d, J = 1.4 Hz, 1H, OCH$_a$$H_b$O), 6.15 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.26 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.41-6.49 (m, 4H, $H_{2'}$, $H_{6'}$, H_6, H_3), 7.02 (s, 1H, H_9), 7.82 (d, J = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.8 (CH_3), 41.3 (C_{10}), 47.0 (CH_2), 54.1 (C_5), 101.3 (OCH_2O), 103.2 (C_1),

105.3 (C_2), 105.4 (C_6), 108.8 (C_9), 117.9 (C_3), 122.2 ($C_{3'}$, $C_{5'}$), 125.3 (C_{5a}), 130.6 ($C_{2'}$, $C_{6'}$), 132.2 (C_{10a}), 133.5 ($C_{1'}$), 146.0, 146.3, 146.6, 147.5 ($C_{4'}$, C_{5a}, C_7, C_8) ppm; **MS** (ESI) *m/z* (rel intensity): 363 (MH^+, 100), 269 (40), 227 (23). **HRMS** (ESI-TOF): calcd. for $C_{21}H_{19}N_2O_4$ [MH^+] 363.1339; found 363.1346.

6,7-dimethoxy-10-(4-methoxybenzyl)-10-methyl-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24fa). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15f** (111 mg, 0.29 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 4-methoxyphenylboronic acid (**23a**) (59.3 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **24fa** as a yellow oil (23.4 mg, 22%): **IR** (ATR): 2935, 1510 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H, CH_3), 2.79 (d, J = 12.4 Hz, 1H, CH_aH$_b$), 2.95 (d, J = 12.4 Hz, 1H, CH$_a$$H_b$), 3.40 (d, J = 16.6 Hz, 1H, H_{5a}), 3.70 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.91 (d, J = 16.6 Hz, 1H, CH_{5b}), 6.11-6.15 (m, 3H, H_1, $H_{3'}$, $H_{5'}$), 6.24 (dd, J = 3.5, 2.7 Hz, 1H, H_2), 6.49-6.54 (m, 3H, $H_{2'}$, $H_{6'}$, H_3), 6.93 (d, J = 8.7 Hz, 1H, H_8), 7.21 (d, J = 8.7 Hz, 1H, H_9) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 26.6 (CH_3), 40.9 (C_{10}), 42.4 (CH_2), 54.4 (C_5), 55.1 (OCH_3), 55.8 (OCH_3), 60.1 (OCH_3), 102.4 (C_1), 108.2 (C_2), 111.2 (C_8), 112.6 ($C_{3'}$, $C_{5'}$), 117.9 (C_9), 120.7 (C_3), 127.6 (C_{5a}), 130.2 ($C_{1'}$), 130.9 ($C_{2'}$, $C_{6'}$), 133.1 (C_{10a}), 134.8 (C_{9a}), 144.0 (C_7), 150.2 (C_6), 158.2 ($C_{4'}$) ppm; **MS** (ESI) *m/z* (rel intensity): 364 (MH^+, 100), 242 (6). **HRMS** (ESI-TOF): calcd. for $C_{23}H_{26}NO_3$ [MH^+] 364.1907; found: 364.1911.

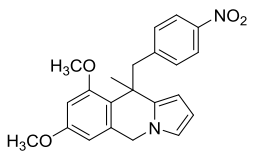


6,7-dimethoxy-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24fc). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15f** (114 mg, 0.30 mmol) was treated with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24fc** as a brown solid (41.2 mg, 37%): **m.p.** (petroluem ether/EtOAc): 102-104 ºC; **IR** (ATR): 2940, 1520 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.88 (s, 3H, CH_3), 2.98 (d, J = 12.1 Hz, 1H, CH_aH$_b$), 3.13 (d, J = 12.1 Hz, 1H, CH$_a$$H_b$), 3.59



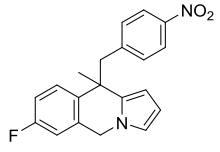
(d, J = 17.0 Hz, 1H, H_{5a}), 3.73 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.96 (d, J = 17.0 Hz, 1H, H_{5b}), 6.15 (dd, J = 3.7, 1.7 Hz, 1H, H_1), 6.26-6.28 (m, 1H, H_2), 6.40 (d, J = 8.6 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.55-6.56 (m, 1H, H_3), 6.96 (d, J = 8.7 Hz, 1H, H_8), 7.23 (d, J = 8.7 Hz, 1H, H_9), 7.81 (d, J = 8.6 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 27.3 (CH_3), 40.8 (C_{10}), 42.5 (CH_2), 54.7 (C_5), 55.8 (OCH_3), 60.1 (OCH_3), 103.0 (C_1), 108.7 (C_2), 111.6 (C_8), 118.3 (C_9), 120.7 (C_3), 122.2 ($C_{3'}$, $C_{5'}$), 126.7 (C_{5a}), 130.7 ($C_{2'}$, $C_{6'}$), 131.9 (C_{10a}), 133.6 ($C_{1'}$), 144.1 (C_{9a}), 146.1 (C_7), 146.6 ($C_{4'}$), 150.4 (C_6) ppm; **MS** (ESI) *m/z* (rel intensity): 379 (MH^+, 100), 243 (15). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{23}N_2O_4$ [MH^+] 379.1652; found: 379.1659.

7,9-dimethoxy-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-b]isoquinoline



(24gc). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15g** (92.3 mg, 0.24 mmol) was treated with $Pd(OAc)_2$ (5.4 mg, 0.02 mmol), 4-nitrophenylboronic acid (**23c**) (52.3 mg, 0.31 mmol), sodium carbonate (33.2 mg, 0.31 mmol) and tetrabutylammonium chloride (134 mg, 0.48 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **24fc** as a yellow oil (54.7 mg, 60%): **IR** (ATR): 2935, 1515 cm^{-1}; **^1H NMR** (300 MHz, $CDCl_3$): δ = 2.00 (s, 3H, CH_3), 3.09 (d, J = 12.1 Hz, 1H, CH_aH_b), 3.75-3.79 (m, 1H, CH_aH_b), 3.78 (s, 3H, OCH_3), 3.86 (d, J = 16.2 Hz, 1H, H_{5a}), 3.96 (s, 3H, OCH_3), 4.73 (d, J = 16.2 Hz, 1H, H_{5b}), 6.02 (d, J = 2.5 Hz, 1H, H_8), 6.24 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.31-6.33 (m, 1H, H_2), 6.43-6.47 (m, 4H, H_3, H_6, $H_{2'}$, $H_{6'}$), 7.74 (d, J = 8.6 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 28.9 (CH_3), 41.3 (C_{10}), 46.8 (CH_2), 49.5 (C_5), 55.2 (OCH_3), 55.3 (OCH_3), 98.6 (C_8), 101.2 (C_6), 103.1 (C_1), 109.0 (C_2), 116.6 (C_3), 118.3 (C_{9a}), 122.1 ($C_{3'}$, $C_{5'}$), 130.1 ($C_{2'}$, $C_{6'}$), 133.6 (C_{10a}), 136.1 (C_{5a}), 146.2 ($C_{1'}$), 147.8 ($C_{4'}$), 159.0, 159.5 (C_7, C_9) ppm; **MS** (ESI) *m/z* (rel intensity): 379 (MH^+, 100), 243 (14). **HRMS** (ESI^+): calcd. for $C_{22}H_{23}N_2O_4$ [MH^+] 379.1652; found: 379.1654.

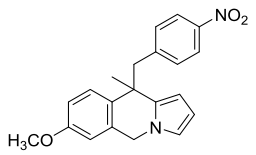
7-fluoro-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24hc).



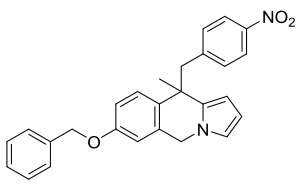
According to General Procedure B, *N*-(*o*-iodobenzyl)pyrrole **15e** (102 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in

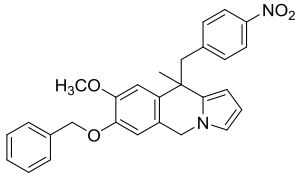
DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 98/2) afforded **24hc** as a yellow solid (57.7 mg, 57%): **m.p.** (petroleum ether/EtOAc): 171-173 ºC; **IR** (ATR): 2935, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.91 (s, 3H, CH_3), 3.03 (d, J = 12.2 Hz, 1H, CH_aH$_b$), 3.18 (d, J = 12.2 Hz, 1H, CH$_a$$H_b$), 3.78 (d, J = 16.3 Hz, 1H, H_{5a}), 4.73 (d, J = 16.3 Hz, 1H, H_{5b}), 6.20 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.30 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.43 (d, J = 8.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.54 (dd, J = 2.7, 1.7 Hz, 1H, H_3), 6.72 (dd, J = 9.0, 2.7 Hz, 1H, H_6), 7.06-7.13 (m, 1H, H_8), 7.54 (dd, J = 8.8, 5.4 Hz, 1H, H_9), 7.84 (d, J = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.4 (CH_3), 40.9 (C_{10}), 46.9 (d, J = 2.1 Hz, C_5), 54.3 (CH_2), 103.5 (C_1), 109.0 (C_2), 112.2 (d, J = 21.9 Hz, C_8), 114.8 (d, J = 21.0 Hz, C_6), 118.1 (C_3), 122.4 ($C_{3'}$, $C_{5'}$), 127.4 (d, J = 8.0 Hz, C_9), 130.7 ($C_{2'}$, $C_{6'}$), 133.4 (C_{10a}), 134.2 (d, J = 7.7 Hz, C_{5a}), 134.7 (d, J = 3.2 Hz, C_{9a}), 145.7 ($C_{1'}$), 146.7 ($C_{4'}$), 161.1 (d, J = 246.4 Hz, C_7) ppm; **MS** (ESI) *m/z* (rel intensity): 337 (MH^+, 100), 201 (14). **HRMS** (ESI-TOF): calcd. for $C_{20}H_{18}FN_2O_2$ [MH^+] 337.1347; found: 337.1357.

7-methoxy-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline



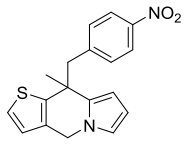
(24ic). According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15i** (82.8 mg, 0.23 mmol) was treated with $Pd(OAc)_2$ (5.3 mg, 0.02 mmol), 4-nitrophenylboronic acid (**23c**) (50.8 mg, 0.30 mmol), sodium carbonate (32.3 mg, 0.30 mmol) and tetrabutylammonium chloride (130 mg, 0.47 mmol) in DMF (0.8 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **24ic** as a colorless oil (34.3 mg, 42%): **IR** (ATR): 2935, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.89 (s, 3H, CH_3), 3.04 (d, J = 12.1 Hz, 1H, CH_aH$_b$), 3.17 (d, J = 12.1 Hz, 1H, CH$_a$$H_b$), 3.76 (d, J = 16.0 Hz, 1H, H_{5a}), 3.83 (s, 3H, OCH_3), 4.72 (d, J = 16.0 Hz, 1H, H_{5b}), 6.18 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.28 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.44 (d, J = 8.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.50-6.53 (m, 2H, H_3, H_6), 6.94 (dd, J = 8.7, 2.7 Hz, 1H, H_8), 7.47 (d, J = 8.7 Hz, 1H, H_9), 7.82 (d, J = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.5 (CH_3), 40.7 (C_{10}), 47.1 (CH_2), 54.3 (C_5), 55.3 (OCH_3), 103.2 (C_1), 108.7 (C_2), 110.2 (C_8), 113.8 (C_6), 117.9 (C_3), 122.2 ($C_{3'}$, $C_{5'}$), 126.7 (C_9), 130.7 ($C_{2'}$, $C_{6'}$), 130.9 (C_{10a}), 133.3 (C_{5a}), 134.0 (C_{9a}), 146.2 ($C_{1'}$), 146.6 ($C_{4'}$), 158.0 (C_7) ppm; **MS** (ESI) *m/z* (rel intensity): 349 (MH^+, 100), 213 (27). **HRMS** (ESI-TOF): calcd. for $C_{21}H_{21}N_2O_3$ [MH^+] 349.1552; found: 349.1554.

7-(benzyloxy)-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24jc).  According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15j** (108 mg, 0.25 mmol) was treated with $Pd(OAc)_2$ (5.7 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (54.7 mg, 0.33 mmol), sodium carbonate (34.7 mg, 0.33 mmol) and tetrabutylammonium chloride (140 mg, 0.50 mmol) in DMF (0.8 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **24jc** as a colorless oil (24.9 mg, 23%): **IR** (ATR): 2930, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.90 (s, 3H, CH_3), 3.03 (d, J = 12.1 Hz, 1H, CH_aH$_b$), 3.16 (d, J = 12.1 Hz, 1H, CH$_a$$H_b$), 3.75 (d, J = 16.0 Hz, 1H, H_{5a}), 4.70 (d, J = 16.0 Hz, 1H, H_{5b}), 5.10 (s, 2H, OCH_2), 6.19 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.28-6.30 (m, 1H, H_2), 6.43 (d, J = 8.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.52 (dd, J = 2.7, 1.7 Hz, 1H, H_3), 6.59 (d, J = 2.7 Hz, 1H, H_6), 7.02 (dd, J = 8.7, 2.7 Hz, 1H, H_8), 7.35-7.48 (m, 6H, H_9, H_{2Bn}, H_{3Bn}, H_{4Bn}, H_{5Bn}, H_{6Bn}), 7.81 (d, J = 8.7 Hz, 1H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 27.5 (CH_3), 40.7 (C_{10}), 47.1 (CH_2), 54.4 (C_5), 70.1 (OCH_2), 103.2 (C_1), 108.8 (C_2), 111.4 (C_8), 114.8 (C_6), 117.9 (C_3), 122.2 ($C_{3'}$, $C_{5'}$), 126.7 (C_9), 127.5 (C_{2Bn}, C_{6Bn}), 128.1 (C_{4Bn}), 128.6 (C_{3Bn}, C_{5Bn}), 130.7 ($C_{2'}$, $C_{6'}$), 131.2 (C_{10a}), 133.3 (C_{5a}), 134.0 (C_{1Bn}), 136.7 (C_{9a}), 146.1 ($C_{1'}$), 146.6 ($C_{4'}$), 157.1 (C_7) ppm; **MS** (ESI) *m/z* (rel intensity): 425 (MH^+, 100), 374 (7), 288 (6). **HRMS** (ESI-TOF): calcd. for $C_{27}H_{25}N_2O_3$ [MH^+] 425.1865; found: 425.1866.

7-(benzyloxy)-8-methoxy-10-methyl-10-(4-nitrobenzyl)-5,10-dihydropyrrolo[1,2-*b*]isoquinoline (24kc).  According to General Procedure A, *N*-(*o*-iodobenzyl)pyrrole **15j** (77.6 mg, 0.17 mmol) was treated with $Pd(OAc)_2$ (3.8 mg, 0.02 mmol), 4-nitrophenylboronic acid (**23c**) (36.7 mg, 0.22 mmol), sodium carbonate (23.3 mg, 0.22 mmol) and tetrabutylammonium chloride (93.9 mg, 0.50 mmol) in DMF (0.6 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) afforded **24kc** as a brown oil (22.9 mg, 30%): **IR** (ATR): 2930, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.90 (s, 3H, CH_3), 3.03 (d, J = 12.1 Hz, 1H, CH_aH$_b$), 3.15 (d, J = 12.1 Hz, 1H, CH$_a$$H_b$), 3.58 (d, J = 15.7 Hz, 1H, H_{5a}), 3.98 (s, 3H, OCH_3), 4.58 (d, J = 15.7 Hz, 1H, H_{5b}), 5.15 (s, 2H, -OCH_2-), 6.18 (dd, J = 3.6, 1.7 Hz, 1H, H_1), 6.27 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.40 (d, J = 8.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 6.46-6.48 (m, 2H, H_6, H_3), 7.04 (s, 1H, H_9), 7.32-7.46 (m, 5H, H_{2Bn}, H_{3Bn},

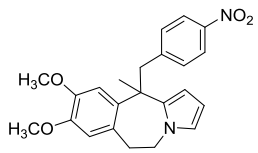
H_{4Bn}, H_{5Bn}, H_{6Bn}), 7.77 (d, J = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 27.5 (CH_3), 41.0 (C_{10}), 46.5 (CH_2), 54.3 (C_5), 56.4 (OCH_3), 71.0 (-OCH_2-), 103.1 (C_1), 108.7 (C_2), 109.0 (C_9), 111.1 (C_6), 117.9 (C_3), 122.2 ($C_{3'}$, $C_{5'}$), 124.4 (C_{5a}), 127.4 (C_{2Bn}, C_{6Bn}), 128.0 (C_{4Bn}), 128.6 (C_{3Bn}, C_{5Bn}), 130.6 ($C_{2'}$, $C_{6'}$), 131.2 (C_{10a}), 133.6 (C_{1Bn}), 136.7 (C_{9a}), 146.0 ($C_{1'}$), 146.6, 146.8 (C_8, $C_{4'}$), 149.3 (C_7) ppm; **MS** (ESI) *m/z* (rel intensity): 455 (MH^+, 100), 318 (7). **HRMS** (ESI-TOF): calcd. for $C_{28}H_{27}N_2O_4$ [MH^+] 455.1971; found: 455.1960.

9-methyl-9-(4-nitrobenzyl)-4,9-dihydrothieno[3,2-*f*]indolizine (24lc). According to



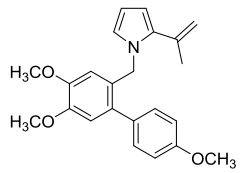
General Procedure B, *N*-(*o*-iodothiophenyl)pyrrole **15l** (98.9 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 2 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 99/1) afforded **24lc** as a yellow solid (44.9 mg, 46%): **m.p.** (petroleum ether/EtOAc): 112-114 ºC; **IR** (ATR): 2925, 1520 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.96 (s, 3H, CH_3), 3.13 (d, J = 12.1 Hz, 1H, CH_aH$_b$), 3.27 (d, J = 12.1 Hz, 1H, CH$_a$$H_b$), 3.61 (d, J = 15.6 Hz, 1H, H_{4a}), 4.70 (d, J = 15.6 Hz, 1H, H_{4b}), 6.24 (dd, J = 3.6, 1.7 Hz, 1H, H_8), 6.31 (dd, J = 3.6, 2.7 Hz, 1H, H_7), 6.44-6.48 (m, 3H, H_6, $H_{2'}$, $H_{6'}$), 6.66 (d, J = 5.2 Hz, 1H, H_3), 7.28 (d, J = 5.2 Hz, 1H, H_2), 7.81 (d, J = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 30.4 (CH_3), 41.2 (C_9), 45.0 (CH_2), 55.0 (C_4), 102.6 (C_8), 109.1 (C_7), 118.3 (C_6), 122.2 ($C_{3'}$, $C_{5'}$), 124.2 (C_2), 124.3 (C_3), 130.2 ($C_{2'}$, $C_{6'}$), 131.5 (C_{8a}), 133.3 (C_{9a}), 140.7 (C_{3a}), 145.9 ($C_{1'}$), 146.7 ($C_{4'}$) ppm; **MS** (ESI) *m/z* (rel intensity): 325 (MH^+, 100), 189 (33). **HRMS** (ESI-TOF): calcd. for $C_{18}H_{17}N_2O_2S$ [MH^+] 325.1011; found: 325.1015.

8,9-dimethoxy-11-methyl-11-(4-nitrobenzyl)-6,11-dihydro-5*H*-benzo[*d*]pyrrolo[1,2-*a*]azepine (24nc). According to General Procedure B, *N*-(*o*-iodophenethyl)pyrrole **15n** (120 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum

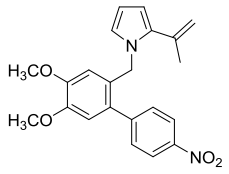


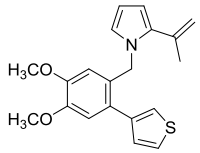
ether/EtOAc 8/2) afforded **24nc** as a yellow oil (32.2 mg, 27%): **IR** (ATR): 2935, 1510 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.77 (s, 3H, CH_3), 3.00-3.09 (m, 1H, H_{6a}), 3.17-3.26 (m, 2H, H_{6b}, CH_aH$_b$), 3.47 (d, J = 13.1 Hz, 1H, CH$_a$$H_b$), 3.87 ($OCH_3$), 3.90 ($OCH_3$), 4.01-4.15 (m, 2H, H_{5a}, H_{5b}), 6.00 (dd, J = 3.7, 1.9 Hz, 1H, H_1), 6.05 (dd, J = 3.7, 2.7 Hz, 1H, H_2), 6.59-6.62 (m, 2H, H_7, H_3), 6.69 (d, J = 8.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 7.01 (s, 1H, H_{10}), 7.95 (d, J = 8.7 Hz, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 29.1 (CH_3), 36.6 (C_6), 45.2 (C_{11}), 49.1 (CH_2), 52.6 (C_5), 55.8 (OCH_3), 56.3 (OCH_3), 106.8 (C_1), 110.1 (C_2), 112.5 (C_{10}), 114.2 (C_7), 122.5 ($C_{3'}$, $C_{5'}$), 122.8 (C_3), 131.0 ($C_{2'}$, $C_{6'}$), 131.7 (C_{6a}), 135.0 (C_{11a}), 135.8 ($C_{1'}$), 146.2 (C_{10a}), 146.5 ($C_{4'}$), 147.2 (C_8, C_9) ppm; **MS** (ESI) *m/z* (rel intensity): 393 (MH^+, 100), 257 (47). **HRMS** (ESI-TOF): calcd. for $C_{23}H_{25}N_2O_4$ (MH^+): 393.1814; found: 393.1810.

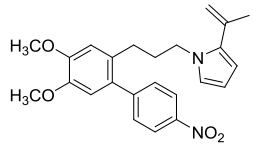
2-(prop-1-en-2-yl)-1-((4,4',5-trimethoxy-[1,1'-biphenyl]-2-yl)methyl)-1*H*-pyrrole

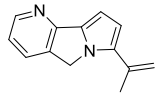


(25aa). (Table 1, entry 3)**.** $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) was added to a mixture of *N*-(*o*-iodobenzyl)pyrrole **15a** (114 mg, 0.30 mmol), 4-methoxyphenylboronic acid **23a** (59.3 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol) and tetrabutylammonium chloride (83.4 mg, 0.30 mmol) in a mixture DMF/H_2O 8/2 (1 mL). The mixture was stirred at 120 ºC for 2 h. H_2O (5 mL) was added and the resulting aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, petroleum ether/EtOAc 95/5) of the resulting residue afforded **25aa** as a yellow solid (35.6 mg, 33%)**: m.p.** (petroleum ether/EtOAc): 77-79 ºC; **IR** (ATR): 2945, 1610, 1235 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.01 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.75 (s, 1H, CH_aH$_b$=C), 4.94-4.95 (m, 1H, CH$_a$$H_b$=C), 5.06 (s, 2H, CH_2), 6.15-6.23 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.33 (s, 1H, H_{3Ar}), 6.58-6.59 (m, 1H, $H_{5pyrrole}$), 6.79 (s, 1H, H_{6Ar}), 6.96 (d, J = 8.5 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.19 (d, J = 8.5 Hz, 2H, $H_{2'}$, $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.1 (CH_3), 49.6 (CH_2), 55.3 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 107.7 ($C_{3pyrrole}$), 108.8 ($C_{4pyrrole}$), 110.4 (C_{3Ar}), 111.9 (*C*H$_a$H$_b$=C), 113.3 (C_{6Ar}), 113.8 ($C_{3'}$, $C_{5'}$), 123.7 ($C_{5pyrrole}$), 128.3 (C_{2Ar}), 130.3 ($C_{2'}$, $C_{6'}$), 132.8, 132.9 (C_{1Ar}, $C_{1'}$), 134.8 (*C*H$_a$H$_b$=*C*), 135.6 ($C_{2pyrrole}$), 147.8, 148.5 (C_{4Ar}, C_{5Ar}), 158.8 ($C_{4'}$) ppm; **MS** (ESI) *m/z* (rel intensity): 364 (MH^+, 5), 258 (12), 257 (100). **HRMS** (ESI-TOF): calcd. for $C_{23}H_{26}NO_3$ [MH^+] 364.1907; found: 364.1901.

1-((4,5-dimethoxy-4'-nitro-[1,1'-biphenyl]-2-yl)methyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (25ac).  Isolated as byproduct in the reaction of **15a** with **23c** in the presence of phosphoramidite **L7** (Table 6, entry 1: 23%; entry 2: 7%): **m.p.** (petroleum ether/EtOAc): 145-147 ºC; **IR** (ATR): 2965, 1510 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.96 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.69 (s, 1H, C$H_a$$H_b$=C), 4.93-4.94 (m, 1H, CH_aH_b=C), 5.03 (s, 2H, CH_2), 6.14-6.20 (m, 2H, $H_{4pyrrole}$, $H_{3pyrrole}$), 6.43 (s, 1H, H_{3Ar}), 6.55-6.56 (m, 1H, $H_{5pyrrole}$), 6.78 (s, 1H, H_{6Ar}), 7.39 (d, J = 8.7 Hz, 2H, $H_{2'}$, $H_{6'}$), 8.26 (d, J = 8.7 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.0 (CH_3), 49.4 (CH_2), 55.9 (OCH_3), 56.1 (OCH_3), 108.0 ($C_{3pyrrole}$), 109.0 ($C_{4pyrrole}$), 111.1 (C_{3Ar}), 112.0 (*C*H_aH_b=C), 112.8 (C_{6Ar}), 123.4 ($C_{5pyrrole}$), 123.6 ($C_{3'}$, $C_{5'}$), 128.2 (C_{1Ar}), 130.1 ($C_{2'}$, $C_{6'}$), 130.9 (C_{2Ar}), 134.9 (CH_aH_b=*C*), 135.6 ($C_{2pyrrole}$), 147.0 ($C_{1'}$), 147.2 ($C_{4'}$), 148.2 (C_{5Ar}), 149.5 (C_{4Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 379 (MH^+, 51), 272 (100), 226 (36). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{23}N_2O_4$ [MH^+] 379.1652; found: 379.1653.

1-(4,5-dimethoxy-2-(thiophen-3-yl)benzyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (25ak).  Isolated as byproduct in the reaction of **15a** with **23k** using General Procedure B (Table 5) (see above): **IR** (ATR): 2935, 1505 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.02 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.76 (s, 1H, C$H_a$$H_b$=C), 4.95-4.96 (m, 1H, CH_aH_b=C), 5.08 (s, 2H, CH_2), 6.15 (dd, J = 3.6, 2.7 Hz, 1H, $H_{4pyrrole}$), 6.21 (dd, J = 3.6, 1.8 Hz, 1H, $H_{3pyrrole}$), 6.36 (s, 1H, H_{3Ar}), 6.54 (dd, J = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 6.84 (s, 1H, H_{6Ar}), 7.03-7.05 (m, 2H, $H_{4thiophene}$, $H_{2thiophene}$), 7.37 (dd, J = 4.6, 3.3 Hz, 1H, $H_{5thiophene}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.1 (CH_3), 49.7 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 107.7 ($C_{3pyrrole}$), 108.8 ($C_{4pyrrole}$), 110.9 (C_{6Ar}), 112.0 (*C*H_aH_b=C), 113.1 (C_{3Ar}), 122.7 ($C_{5pyrrole}$), 123.4 ($C_{2thiophene}$), 125.5 ($C_{4thiophene}$), 128.0 (C_{2Ar}), 128.4 (C_{1Ar}), 128.7 ($C_{5thiophene}$), 134.8 (CH_aH_b=*C*), 135.6 ($C_{3thiophene}$), 140.5 ($C_{2pyrrole}$), 147.9, 148.7 (C_{4Ar}, C_{5Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 340 (MH^+, 10), 234 (10), 233 (100). **HRMS** (ESI-TOF): calcd. for $C_{20}H_{22}NO_2S$ [MH^+] 340.1366; found: 340.1372.

1-(3-(4,5-dimethoxy-4'-nitro-[1,1'-biphenyl]-2-yl)propyl)-2-(prop-1-en-2-yl)-1*H*-pyrrole (25oc).  According to General Procedure B, *N*-(*o*-iodophenylpropyl)pyrrole **15o** (123 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 1 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 9/1) afforded **25oc** as yellow oil (77.8 mg, 64%): **IR** (ATR): 2940, 1515 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.82-1.92 (m, 2H, CH_2CH$_2$N), 2.01 (s, 3H, CH_3), 2.48-2.53 (m, 2H, ArCH_2), 3.85-3.89 (m, 2H, CH_2N), 3.89 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.74-4.75 (m, 1H, CH_aH$_b$=C), 4.97-4.99 (m, 1H, CH$_a$$H_b$=C), 6.06 (dd, J = 3.6, 2.7 Hz, 1H, $H_{4pyrrole}$), 6.11 (dd, J = 3.6, 1.8 Hz, 1H, $H_{3pyrrole}$), 6.51 (dd, J = 2.7, 1.8 Hz, 1H, $H_{5pyrrole}$), 6.70 (s, 1H, H_{3Ar}), 6.77 (s, 1H, H_{6Ar}), 7.42 (d, J = 8.8 Hz, 2H, $H_{2'}$, $H_{6'}$), 8.26 (d, J = 8.8 Hz, 2H, $H_{3'}$, $H_{5'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 24.1 (CH_3), 29.8 (ArCH_2), 33.1 (*C*H_2CH$_2$N), 47.2 (CH_2N), 56.0 (OCH_3), 56.1 (OCH_3), 107.3 ($C_{3pyrrole}$), 108.8 ($C_{4pyrrole}$), 111.8 (*C*H$_a$H$_b$=C), 112.4 (C_{3Ar}), 112.8 (C_{6Ar}), 122.9 ($C_{5pyrrole}$), 123.5 ($C_{3'}$, $C_{5'}$), 130.2 ($C_{2'}$, $C_{6'}$), 131.0 (C_{1Ar}), 131.6 (C_{2Ar}), 134.1 (CH$_a$H$_b$=*C*), 136.0 ($C_{2pyrrole}$), 146.8 ($C_{1'}$), 147.3 ($C_{4'}$), 148.4 (C_{5Ar}), 149.2 (C_{4Ar}) ppm; **MS** (ESI) *m/z* (rel intensity): 407 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{24}H_{27}N_2O_4$ [MH^+] 407.1971; found: 407.1969.

7-(prop-1-en-2-yl)-5H-pyrido[2,3-*a*]pyrrolizine (26m).  According to General Procedure B, iodopiridine **15m** (97.2 mg, 0.30 mmol) was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (31.0 mg, 0.03 mmol), 4-nitrophenylboronic acid (**23c**) (65.1 mg, 0.39 mmol), sodium carbonate (41.3 mg, 0.39 mmol), tri(furan-2-yl)phosphane (**L6**) (13.9 mg, 0.06 mmol) and tetrabutylammonium chloride (167 mg, 0.60 mmol) in DMF (1 mL) for 48 h. After workup, purification by column chromatography (silica gel, petroleum ether/EtOAc 8/2) afforded **25oc** as yellow solid (21.5 mg, 35 %) (see above): **m.p.** (dichloromethane/EtOAc): 91-93 ºC; **IR** (ATR): 1570, 1390 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.20 (s, 3H, CH_3), 5.05 (s, 2H, CH_2), 5.11-5.12 (m, 1H, CH_aH$_b$=C), 5.19 (s, 1H, CH$_a$$H_b$=C), 6.53 (d, J = 3.9 Hz, 1H, H_9), 6.73 (d, J = 3.9 Hz, 1H, H_8), 7.07 (dd, J = 7.6, 5.1 Hz, 1H, H_3), 7.70 (dd, J = 7.6, 1.5 Hz, 1H, H_4), 8.53 (dd, J = 5.1, 1.5 Hz, 1H, H_2) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 22.2 (CH_3), 50.4 (CH_2), 101.4 (C_8), 108.4 (*C*H$_a$H$_b$=C), 113.6 (C_9), 119.1 (C_3), 130.2 (C_4), 132.4 (C_{9a}), 134.1 (C_{4a}),

135.0 (CH_aH_b=*C*), 138.2 (C_7), 149.2 (C_2), 152.5 (C_{9b}) ppm; **MS** (ESI) *m/z* (rel intensity): 197 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{13}H_{13}N_2$ [MH^+] 197.1079; found: 197.1071.

Synthesis of enantioenriched 24ac. $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) was added to a mixture of *N*-(*o*-iodobenzyl)pyrrole **15a** (115 mg, 0.30 mmol), 4-nitrophenylboronic acid (60.1 mg, 0.36 mmol), sodium carbonate (0.3 mL, 0.60 mmol, 2M in water) and phosphoramidite **L2** (32.4 mg, 0.06 mmol) in toluene (1 mL). The mixture was stirred at 110 ºC for 48 h. After work-up and column chromatography, **24ac** was obtained as a yellow solid (71.9 mg, 63%). The enantiomeric excess was determined by HPLC to be 34% [Chiralcel ADH, Hexane/2-propanol 9:1, 1 mL/min, t_R (minor) = 9.1 min (32.93 %), t_R (major) = 14.7 min (67.07 %)]. [**25ac** (26 mg, 23%) was isolated as by product].

2.5. Anti-leishmanicidal assays of pyrroloisoquinoline derivatives

Parasites and culture procedure. Promastigotes were cultured in Schneider's Insect Medium supplemented with 10% heat-inactivated Foetal Bovine Serum (FBS) and 1000 U/L of penicillin plus 100 mg/L of streptomycin in 25 mL culture flasks at 26 °C.

***In vitro* promastigote susceptibility assay.** The assay was performed as previously described.[5] Briefly, log-phase promastigotes (2.5 x 10^5 parasites/well) were cultured in 96-well plastic plates. Compounds (UA and miltefosine) were dissolved in dimethylsulfoxide (DMSO) and different concentrations of each (100, 50, 25, 12.5, 6.25 3.12, 1.56 and 0.78 µg/mL) were carried out up to 200 µL final volume. Growth control and signal-to-noise were also included. The final solvent (DMSO) concentrations never exceeded 0.5% (v/v) warranting no effect on parasites proliferation or morphology. After 48 h at 26 ºC, 20 µL of a 2.5 mM resazurin solution was added to each well and the plates were returned to the incubator for another 3 h. The Relative Fluorescence Units (RFU) (535nm - 590nm excitation-emission wavelength) was determined in a fluorometer (Infinite 200Tecan i-Control). Growth inhibition (%) was calculated by 100 - [(RFU treated wells – RFU signal-to-noise)/(RFU untreated – RFU signal-to-noise) x 100]. All tests were carried out in triplicate. Miltefosine was used as reference drug and was evaluated under the same conditions. The efficacy of each compound was estimated by calculating the IC_{50}

(concentration of the compound that produced a 50% reduction in parasites) using a multinomial probit analysis incorporated in SPSS software v21.0.

***In vitro* intracellular amastigote susceptibility assay.** The assay was carried out as previously described.[6] Briefly, 5×10^4 J774 macrophages and stationary promastigotes in a 1:5 ratio was seeded in each well of a microtiter plate, suspended in 200 µL of culture medium and incubated for 24 h at 33 °C in 5% CO_2 chamber. After this first incubation, the temperature was increased up to 37 °C for another 24h. Thereafter, cells were washed several times in culture medium by centrifugation at 1.500g for 5 min in order to remove free non-internalised promastigotes. Finally, the supernatant was replaced by 200 µL/well of culture medium containing 2-fold serial dilutions of the test compounds as in promastigotes assay. Growth control and signal-to-noise were also included. Following incubation for 48h at 37 °C, 5% CO_2, the culture medium was replaced by 200 µL/well of the lysis solution (RPMI-1640 with 0.048% HEPES and 0.01% SDS) and incubated at room temperature for 20 min. Thereafter, the plates were centrifuged at 3.500g for 5 min and the lysis solution was replaced by 200 µL/well of Schneider´s insect medium. The culture plates were then incubated at 26 °C for other 4 days to allow transformation of viable amastigotes into promastigotes and proliferation. Afterwards, 20 µL/well of 2.5mM resazurin was added and incubated for another 3 h. Finally, fluorescence emission was measured and IC_{50} was estimated as described above. All tests were carried out in triplicate. Miltefosine was used as reference drug and was evaluated at the same conditions.

Citotoxicity assay on macrophages. The assay was carried out as previously described.[7] J774 macrophages cell lines were seeded (5×10^4cells/well) in 96-well flat-bottom microplates with 100 µL of RPMI 1640 medium. The cells were allowed to attach for 24 h at 37 °C, 5% CO_2, and the medium was replaced by different concentrations of the compounds in 200 µL of medium and exposed for another 24 h. Growth controls and signal-to-noise were also included. Afterwards, a volume of 20 µL the 2.5 mM resazurin solution was added, and plates were returned to the incubator for another 3 h to evaluate cell viability. The reduction of resazurin was determined by fluorometry as in the promastigote assay. Each concentration was assayed three times. Cytotoxicity effect of compounds was defined as the 50% reduction of cell viability of treated culture cells with respect to untreated culture (CC_{50}).

3. SYNTHESIS OF CHIRAL HYDRID GUANIDINE/AMINE LIGANDS

3.1. Synthesis of new chiral hybrid guanidine/amine ligands L1/L12

formyl-*D*-valine (27a).[13] Acetic anhydride (20.31 mL, 212.75 mmol) was added to a solution of D-valine (3.79 g, 31.75 mmol) in formic acid (37 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 10 min and at rt for 4 h, and then it was treated with H_2O (15 mL). The solvent was removed, and residue was dissolved in water and evaporated i*n vacuo*. This procedure was repeated for 3 times to give **27a** as a white solid (4.85 g, 99%): **m.p.** (H_2O): 146-147 ºC [lit.[14] 148-149 ºC (H_2O)]; **^{1}H NMR** (300 MHz, DMSO-d_6): δ = 0.84-0.89 (m, 6H, CH(CH_3)$_2$), 2.01-2.12 (m, 1H, CH(CH$_3$)$_2$), 4.21 (dd, J = 5.3, 8.8 Hz, 1H, CH), 8.07 (s, 1H, CHO), 8.29 (d, J = 8.8 Hz, 1H, NH) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, DMSO-d_6): δ = 18.1 (CH(*C*H$_3$)$_2$), 19.6 (CH(*C*H$_3$)$_2$), 30.3 (*C*H(CH$_3$)$_2$), 56.1 (CH), 161.6 (CHO), 173.1 (COOH) ppm.

(*R*)-2-formamido-2-phenylacetic acid (27b).[13] Acetic anhydride (9.28 mL, 97.25 mmol) was added to a solution of D-phenylglycine (2.22 g, 14.55 mmol) in formic acid (18 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 10 min and at rt for 4 h, and then it was treated with H_2O (10 mL). The solvent was removed, and residue was dissolved in water and evaporated i*n vacuo*. This procedure was repeated for 3 times to give **27b** as a orange solid (2.45 g, 93%): **m.p.** (H_2O): 179-181 ºC [lit.[15] 185-187 ºC (MeOH/H_2O)]; **^{1}H NMR** (300 MHz, DMSO-d_6): δ = 5.42 (d, J = 7.8 Hz, 1H, CH), 7.33-7.43 (m, 5H, H_{2Ph}, H_{3Ph}, H_{4Ph}, H_{5Ph}, H_{6Ph}), 8.12 (s, 1H, CHO), 8.96 (d, J = 7.8 Hz, 1H, NH) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, DMSO-d_6): δ = 55.4 (CH), 127.9 (C_{3Ph}, C_{5Ph}), 128.5 (C_{4Ph}), 129.1 (C_{2Ph}, C_{6Ph}), 137.6 (C_{1Ph}), 161.2 (CHO), 172.0 (COOH) ppm.

formyl-*D*-alanine (27c).[16] Acetic anhydride (1.13 mL, 11.91 mmol) was added to a solution of D-alanine (162 mg, 1.78 mmol) in formic acid (2 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 10 min and at rt for 4 h, and then it was

[13] Boyle, G. A.; Govender, T. ; Kruger, H. G.; Maguire, G. E. M. *Tetrahedron: Asymmetry*, **2004**, *15*, 2661.
[14] Nyman, M. A.; Herbst, R. M. *J. Org. Chem.* **1950**, *15*, 108.
[15] Wannaporn, D.; Ishikawa, T. *Mol. Divers.* **2005**, *9*, 321.
[16] Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang, T.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem.* **1992**, *57*, 5383.

treated with H_2O (1 mL). The solvent was removed, and residue was dissolved in water and evaporated i*n vacuo*. This procedure was repeated for 3 times to give **27c** as a white solid (191 mg, 93%): **m.p.** (H_2O): 124-125 ºC [lit.[17] 125-127 ºC (MeOH/H_2O)]; **^{1}H NMR** (300 MHz, DMSO-d_6): δ = 1.25 (d, J = 7.3 Hz, 3H, CH_3), 4.20-4.30 (m, 1H, CH), 7.98 (s, 1H, CHO), 8.34 (d, J = 7.5 Hz, 1H, NH) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, DMSO-d_6): δ = 17.8 (CH_3), 46.6 (CH), 161.1 (CHO), 174.2 (COOH) ppm.

(*R*)-3-methyl-2-(methylamino)butan-1-ol (28a).[13] *N*-formylamino acid **27a** (4.48 g, 30.91 mmol) was added to a suspension of $LiAlH_4$ (4.94 g, 123.64 mmol) in dry THF (50 mL) at 0 ºC. The reaction mixture was allowed to gradually warm to rt overnight and stirred further 24 h at rt. The reaction was again cooled to 0 ºC and an equal volume of Et_2O (50 mL) was added. The mixture was quenched with saturated Na_2SO_4 aqueous solution, filtered and washed with Et_2O. The solvent was removed in vacuum to yield amino alcohol **28a** as a colorless oil (2.71 g, 75%): **IR** (ATR): 3310, 1655, 1460, 1065 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.83 (d, J = 6.9 Hz, 3H, CH(CH_3)$_2$), 0.89 (d, J = 6.9 Hz, 3H, CH(CH_3)$_2$), 1.71-1.83 (m, 1H, CH(CH$_3$)$_2$), 2.18-2.24 (m, 1H, CH), 2.35 (s, 3H, CH_3), 2.57 (brs, 2H, OH, NH), 3.30 (dd, J = 10.7, 7.1 Hz, 1H, CH_aH$_b$), 3.56 (dd, J = 10.7, 4.1 Hz, 1H, CH$_a$$H_b$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 18.3 (CH(*C*H$_3$)$_2$), 19.5 (CH(*C*H$_3$)$_2$), 28.2 (*C*H(CH$_3$)$_2$), 33.7 (CH_3), 60.2 (CH_2), 66.0 (CH) ppm. **$[\alpha]_D^{20}$:** +10.2 (c = 1, $CHCl_3$) [lit.[13] +53.0 (c = 1, $CHCl_3$)].

(*R*)-2-(methylamino)-2-phenylethan-1-ol (28b).[13] *N*-formylamino acid **27b** (1.07 g, 5.98 mmol) was added to a suspension of $LiAlH_4$ (956 mg, 23.94 mmol) in dry THF (20 mL) at 0 ºC. The reaction mixture was allowed to gradually warm to rt overnight and stirred further 24 h at rt. The reaction was again cooled to 0 ºC and an equal volume of Et_2O (50 mL) was added. The mixture was quenched with saturated Na_2SO_4 aqueous solution, filtered and washed with Et_2O. The solvent was removed in vacuum to yield amino alcohol **28b** as a colorless oil (813 mg, 90%): **IR** (ATR): 3330, 1655, 1065 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH_3), 3.69-3.83 (m, 3H, CH_2, CH), 4.09 (brs, 2H, OH, NH), 7.30-7.42 (m, 5H, H_{2Ph}, H_{3Ph}, H_{4Ph}, H_{5Ph}, H_{6Ph}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 33.5 (CH_3), 65.9 (CH_2), 66.5 (CH), 127.5 (C_{2ph},

[17] Chiacchio, U.; Casuscelli, F.; Corsavo, A.; Librando, V.; Rescifina, A.; Romeo, R.; Romero G. *Tetrahedron* **1995**, *51*, 5689.

C_{6Ph}), 128.1 (C_{4Ph}), 128.8 (C_{3ph}, C_{5Ph}), 138.4 (C_{1Ph}) ppm. **$[\alpha]_D^{20}$:** -69.8 (c = 1, EtOH), [lit.[18] -79.6 (c = 1, EtOH)].

(*R*)-2-(methylamino)propan-1-ol (28c). *N*-formylamino acid **27c** (2.26 g, 19.33 mmol) was added to a suspension of $LiAlH_4$ (3.09 g, 77.32 mmol) in dry THF (20 mL) at 0 ºC. The reaction mixture was allowed to gradually warm to rt overnight and stirred further 24 h at rt. The reaction was again cooled to 0 ºC and an equal volume of Et_2O (50 mL) was added. The mixture was quenched with saturated Na_2SO_4 aqueous solution, filtered and washed with Et_2O. The solvent was removed in vacuum to yield amino alcohol **28c** as a colorless oil (1.09 g, 63%): **IR** (ATR): 3310, 2960, 1655, 1390 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.4 Hz, 3H, CH_3), 2.39 (s, 3H, NCH_3), 2.52 – 2.85 (m, 3H, CH, NH, OH), 3.28 (dd, J = 10.7, 7.2 Hz, 1H, CH_{2a}), 3.56 (dd, J = 10.7, 3.9 Hz, 1H, CH_{2b}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 16.2 (CH_3), 33.4 (NCH_3), 56.1 (CH_2), 65.3 (CH) ppm. **$[\alpha]_D^{20}$:** -37.5 (c = 4.5, $CHCl_3$).

(*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-*N*,3-dimethylbutan-2-amine (29a). *tert*-butyldiphenylsilyl chloride (0.84 mL, 3.24 mmol) was added to a solution of amino alcohol **28a** (345 mg, 2.94 mmol) and imidazole (441 mg, 6.48 mmol) in dry DMF (20 mL) at rt. The reaction mixture was stirred at rt for 90 min and then treated with water (20 mL) and stirred at rt for 15 min. The reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (silica gel, EtOAc/MeOH 9/1) to give the *O*-protected amino alcohol **29a** as a yellow oil (1.04 g, 99%): **IR** (ATR): 2930, 1430, 1110, 1080 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.09 (s, 9H, $C(CH_3)_3$), 1.85-1.96 (m, 1H, $CH(CH_3)_2$), 2.14 (br s, 1H, NH), 2.31-2.37 (m, 1H, CH), 2.41 (s, 3H, CH_3), 3.64 (dd, J = 10.4, 6.3 Hz, 1H, CH_aH_b), 3.71 (dd, J = 10.4, 4.6 Hz, 1H, CH_aH_b), 7.37-7.44 (m, 6H, 2 x H_{3Ph}, 2 x H_{4Ph}, 2 x H_{5Ph}), 7.68-7.72 (m, 4H, 2x H_{2Ph}, 2 x H_{6Ph}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 18.6 ($CH(CH_3)_2$), 18.9 ($CH(CH_3)_2$), 19.3 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 28.6 ($CH(CH_3)_2$), 34.8 (CH_3), 62.9 (CH_2), 66.6 (CH), 127.7 (2 x $C_{3'}$, 2 x $C_{5'}$), 129.7 (2 x $C_{4'}$), 133.6 (2 x $C_{1'}$), 135.6 (2 x $C_{2'}$, 2 x $C_{6'}$) ppm; **MS** (ESI) *m/z* (rel intensity): 356 (MH^+, 57), 312 (45), 298 (64), 278 (100). **HRMS**

[18] Ito, Y.; Amino, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1983**, *105*, 1586.

(ESI-TOF): calcd. for $C_{22}H_{34}NOSi$ [MH^+] 356.2410; found: 356.2394. **$[\alpha]_D^{20}$:** +5.8 (c = 1, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 92% [Chiralcel ADH, hexane/*i*PrOH 99/1, 0.5 mL/min, t_r (minor) = 8.6 min (4%), t_r (major) = 9.1 min (96%)].

(*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-*N*-methyl-1-phenylethan-1-amine (29b). *tert*-butyldiphenylsilyl chloride (1.52 mL, 5.67 mmol) was added to a solution of amino alcohol **28b** (779 mg, 5.15 mmol) and imidazole (772 mg, 11.34 mmol) in dry DMF (20 mL) at rt. The reaction mixture was stirred at rt for 90 min and then treated with water (20 mL) and stirred at rt for 15 min. The reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (silica gel, EtOAc/MeOH 9/1) to give the *O*-protected amino alcohol **29b** as a colorless oil (1.20 g, 60%): **IR** (ATR): 3065, 2925, 1430, 1110, 1075, 700 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.11 (s, 9H, C(CH_3)$_3$), 2.18 (brs, 1H, NH), 2.38 (s, 3H, CH_3), 3.71-3.77 (m, 1H, CH), 7.24-7.33 (m, 5H, H_{2Ph}, H_{3Ph}, H_{4Ph}, H_{5Ph}, H_{6Ph}), 7.36-7.49 (m, 6H, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.64-7.70 (m, 4H, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 19.3 (*C*(CH_3)$_3$), 26.9 (C(*C*H_3)$_3$), 34.7 (CH_3), 67.1 (CH), 68.9 (CH_2), 127.4, 127.7, 127.8, 127.8, 128.3 (C_{2Ph}, C_{3Ph}, C_{4Ph}, C_{5Ph}, C_{6Ph}), 129.7, 129.8 (2 x $C_{3'}$, 2 x $C_{5'}$), 133.4, 133.5 (2 x $C_{1'}$), 135.6 (2 x $C_{2'}$, 2 x $C_{6'}$, 2 x $C_{4'}$), 140.5 (C_{1Ph}) ppm; **MS** (ESI) *m/z* (rel intensity): 390 (MH^+, 69), 332 (80), 312 (100), 120 (38). **HRMS** (ESI-TOF): calcd. for $C_{25}H_{32}NOSi$ [MH^+] 390.2253; found: 390.2245. **$[\alpha]_D^{20}$:** -2.4 (c = 1, CH_2Cl_2).

(*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-*N*-methylpropan-2-amine (29c). *tert*-butyldiphenylsilyl chloride (4.35 mL, 16.37 mmol) was added to a solution of amino alcohol **28c** (1.33 g, 14.87 mmol) and imidazole (2.25 g, 32.77 mmol) in dry DMF (15 mL) at rt. The reaction mixture was stirred at rt for 90 min and then treated with water (15 mL) and stirred at rt for 15 min. The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with H_2O (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (silica gel, EtOAc/MeOH 8/2) to give the *O*-protected amino alcohol **29c** as a colorless oil (1.20 g, 60%): **IR** (ATR): 1410, 1105, 1080, 700 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.4 Hz, 3H, CH_3), 1.09 (s, 9H, C(CH_3)$_3$), 2.44 (s, 3H, NCH_3), 2.74-2.80 (m, 1H, CH), 1.74 (brs, 1H, NH), 3.52-3.65 (m,

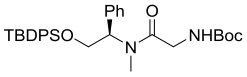
2H, CH_2), 7.38-7.46 (m, 6H, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.67-7.71 (m, 4H, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 16.1 (CH_3), 19.2 ($C(CH_3)_3$), 26.8 ($C(CH_3)_3$), 33.4 (NCH_3), 56.3 (CH), 67.2 (CH_2), 127.6, 127.7 (2 x $C_{3'}$, 2 x $C_{5'}$), 129.6, 129.7 (2 x $C_{4'}$), 133.4, 133.5 (2 x $C_{1'}$), 135.5 (2 x $C_{2'}$, 2 x $C_{6'}$) ppm; **MS** (ESI) *m/z* (rel intensity): 328 (MH^+, 19), 270 (54), 250 (100). **HRMS** (ESI-TOF): calcd. for $C_{20}H_{30}NOSi$ [MH^+] 328.2097; found: 328.2082. **$[\alpha]_D^{20}$:** -6.5 (c = 1, CH_2Cl_2).

(*tert*-butoxycarbonyl)glycine (31).[19] A solution of Boc_2O (2.64 g, 11.97 mmol) in dioxane (15 mL) was added over a solution of glycine (0.60 g, 7.98 mmol) and NaOH (0.48 g, 11.97 mmol) in a mixture 1:1 H_2O/dioxane (50 mL). The reaction mixture was stirred at rt for 24 h and then the solvent was removed. The remaining aqueous solution was washed with Et_2O (2 × 20 mL) and the organic phase is extracted with a saturated $NaHCO_3$ aqueous solution (2 × 20 mL). The aqueous phase was acidified with saturated $KHSO_4$ aqueous solution and extracted with EtOAc (2 × 20 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum to give *N*-Boc protected glycine **31** as a white solid (1.32 g, 93%): **m.p.** (EtOAc): 87-88 ºC [lit.[20] 88-90 ºC (EtOAc)]; **IR** (ATR): 3315, 1705, 1650 cm^{-1}; **^1H NMR** (300 MHz, $CDCl_3$) (ratio of rotamers 1.6:1): δ = 1.41 (s, 9H, both rotamers, $C(CH_3)_3$), 3.82-3.92 (m, 2H, both rotamers, CH_2), 5.42 (brs, 1H, major rotamer, NH), 6.67 (brs, 1H, minor rotamer, NH), 11.34 (brs, 1H, both rotamer, COOH) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, $CDCl_3$): δ = 28.1 (both rotamers, $C(CH_3)_3$), 42.1 (major rotamer, CH_2), 43.3 (minor rotamer, CH_2), 80.4 (major rotamer, $C(CH_3)_3$), 81.8 (minor rotamer, $C(CH_3)_3$), 156.2 (major rotamer, $COOC(CH_3)_3$), 157.4 (minor rotamer, $COOC(CH_3)_3$), 174.0 (minor rotamer, COOH), 174.4 (major rotamer, COOH) ppm.

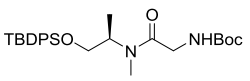
***tert*-butyl (*R*)-(2-((1-((*tert*-butyldiphenylsilyl)oxy)-3-methylbutan-2-yl)(methyl)amino)-2-oxoethyl)carbamate (32a).** A solution of *O*-protected aminoalcohol **29a** (5.20 g, 15.52 mmol) in dry CH_2Cl_2 (15 mL) was added *via* cannula over a mixture of Boc-protected glycine **31** (2.72 g, 15.52 mmol) and DMAP (47.9 mg, 0.39 mmol) in dry CH_2Cl_2 (30 mL). The reaction mixture was cooled to 0 ºC and DCC (3.23 g, 15.52 mmol) was added slowly. The

[19] Brough, P.; Klumpp, C.; Bianco, A.; Campidelli, S.; Prato, M. *J. Org. Chem.* **2006**, *71*, 2014.
[20] Ling, Y.; Ye, X.; Ji, H.; Zhang, Y.; Lai, Y.; Peng, S.; Tian, J. *Bioorg. Med. Chem.* **2010**, *18*, 3448.

reaction mixture was stirred 10 min at 0 ºC and then 4 h at rt. CH_2Cl_2 (80 mL) was added and the precipitate was filtered off. The resulting solution was washed with 10 % HCl aqueous solution (20 mL) and a saturated $NaHCO_3$ aqueous solution (20 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The crude was purified by column chromatograghy (silica gel, petroleum ether/EtAOc 7/3) to give **32a** as a colorless oil (5.47 g, 73%): **IR** (ATR): 3420, 1715, 1650, 1050, 705 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) (ratio of rotamers 1:0.83): δ = 0.79-0.86 (m, 6H, both rotamers, $CH(CH_3)_2$), 1.00 (s, 9H, major rotamer, $SiC(CH_3)_3$), 1.02 (s, 9H, minor rotamer, $SiC(CH_3)_3$), 1.45 (s, 9H, major rotamer, $OC(CH_3)_3$), 1.46 (s, 9H, minor rotamer, $OC(CH_3)_3$), 1.65-1.73 (m, 1H, rotamer$_a$, $CH(CH_3)_2$), 1.82-1.90 (m, 1H, rotamer$_b$, $CH(CH_3)_2$), 2.72 (s, 3H, major rotamer, NCH_3), 2.81 (s, 3H, minor rotamer, NCH_3), 3.27-3.34 (m, 1H, rotamer$_a$, CH), 3.46-3.52 (m, 1H, rotamer$_a$, OCH_{2a}), 3.67-3.73 (m, 1H, rotamer$_b$, OCH_{2a}), 3.77-3.83 (m, 2H, rotamer$_a$, OCH_{2b}, rotamer$_b$, OCH_{2b}), 3.84-4.04 (m, 3H, rotamer$_a$, $CH_{2a}NH$, rotamer$_a$, $CH_{2b}NH$, rotamer$_b$, $CH_{2a}NH$), 4.14-4.21 (m, 1H, rotamer$_b$, $CH_{2b}NH$), 4.29 (brs, 1H, rotamer$_b$, CH), 5.64 (brs, 1H, rotamer$_a$, NH), 5.69 (brs, 1H, rotamer$_b$, NH), 7.35-7.46 (m, 12H, both rotamers, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.59-7.64 (m, 8H, both rotamers, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 19.0 (rotamer$_a$, $C(CH_3)_3$), 19.1 (rotamer$_b$, $C(CH_3)_3$), 19.7, 19.9 (rotamer$_a$, $CH(CH_3)_2$), 19.9, 20.0 (rotamer$_b$, $CH(CH_3)_2$), 26.4 (rotamer$_a$, $CH(CH_3)_2$), 26.7 (both rotamers, $SiC(CH_3)_3$), 26.8 (rotamer$_a$, NCH_3), 27.1 (rotamer$_b$, $CH(CH_3)_2$), 28.4 (both rotamers, $OC(CH_3)_3$), 29.4 (rotamer$_b$, NCH_3), 42.7 (rotamer$_a$, CH_2NH), 42.8 (rotamer$_b$, CH_2NH), 61.7 (rotamer$_a$, OCH_2), 62.8 (rotamer$_b$, OCH_2), 64.2 (rotamer$_a$, CH), 79.3 (rotamer$_a$, $OC(CH_3)_3$), 79.4 (rotamer$_b$, $OC(CH_3)_3$), 127.8 (rotamer$_a$, 2 x $C_{3'}$, 2 x $C_{5'}$), 127.9 (rotamer$_b$, 2 x $C_{3'}$, 2 x $C_{5'}$), 129.8, 129.8 (rotamer$_a$, 2 x $C_{4'}$), 129.9, 130.0 (rotamer$_b$, 2 x $C_{4'}$), 132.6, 132.8 (rotamer$_a$, 2 x $C_{1'}$), 133.1, 133.3 (rotamer$_b$, 2 x $C_{1'}$), 135.5, 135.6 (rotamer$_a$, 2 x $C_{2'}$, 2 x $C_{6'}$), 135.7 (rotamer$_b$, 2 x $C_{2'}$, 2 x $C_{6'}$), 155.7, 155.8 (both rotamers, $COOC(CH_3)_3$), 169.1 (rotamer$_a$, CO), 169.4 (rotamer$_b$, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 513 (MH^+, 1), 457 (18), 455 (54). **HRMS** (ESI-TOF): calcd. for $C_{29}H_{45}N_2O_4Si$ [MH^+] 513.3149; found: 513.3156. **$[\alpha]_D^{20}$:** +6.2 (c = 1, CH_2Cl_2).

***tert*-butyl (*R*)-(2-((2-((*tert*-butyldiphenylsilyl)oxy)-1-phenylethyl)(methyl)amino)-2-oxoethyl)carbamate (32b).** 

A solution of *O*-protected aminoalcohol **29b** (1.36 g, 3.48 mmol) in dry CH_2Cl_2 (15 mL) was added *via* cannula over a mixture of Boc-protected glycine **31** (610 mg, 3.48 mmol) and DMAP (10.7 mg, 0.09 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was cooled to 0 ºC and DCC (731 mg, 3.48 mmol) was added slowly. The reaction mixture was stirred 10 min at 0 ºC and then 4 h at rt. CH_2Cl_2 (80 mL) was added and the precipitate was filtered off. The resulting solution was washed with 10 % HCl aqueous solution (20 mL) and a saturated $NaHCO_3$ aqueous solution (20 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The crude was purified by column chromatograghy (silica gel, petroleum ether/EtAOc 8/2) to give **32b** (1.09 g, 57%) as a colorless oil: **IR** (ATR): 3420, 1710, 1050, 700 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) (ratio of rotamers 1:0.72): δ = 1.05 (s, 9H, both rotamer, $SiC(CH_3)_3$), 1.47 (s, 9H, $rotamer_a$, $OC(CH_3)_3$), 1.48 (s, 9H, $rotamer_b$, $OC(CH_3)_3$), 2.70 (s, 3H, major rotamer, NCH_3), 2.71 (s, 3H, minor rotamer, NCH_3), 3.80-4.02 (m, 3H, $rotamer_a$, OCH_2, $rotamer_b$, OCH_{2a}), 4.07-4.18 (m, 4H, $rotamer_b$, OCH_{2b}, $rotamer_a$, C*H*$_2$NH, $rotamer_b$, C*H*$_{2a}$NH), 4.28 (dd, *J* = 16.6, 3.6 Hz, 1H, $rotamer_b$, C*H*$_{2b}$NH), 4.96-4.97 (m, 1H, minor rotamer, CH), 5.66 (brs, 1H, both rotamer, NH), 5.93-5.98 (m, 1H, major rotamer, CH), 7.06-7.32 (m, both rotamers, 5H, H_{2Ph}, H_{3Ph}, H_{4Ph}, H_{5Ph}, H_{6Ph}), 7.40-7.47 (m, 6H, both rotamers, 2 x $H_{4'}$, 2 x $H_{4'}$, 2 x $H_{5'}$,), 7.66 (d, *J* = 6.4 Hz, 4H, both rotamers, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 19.0 ($rotamer_a$, $SiC(CH_3)_3$), 19.1 ($rotamer_b$, $SiC(CH_3)_3$), 26.6 ($rotamer_a$, $SiC(CH_3)_3$), 26.8 ($rotamer_b$, $SiC(CH_3)_3$), 28.3 ($rotamer_a$, NCH_3), 28.4 (both rotamers, $OC(CH_3)_3$), 29.6 ($rotamer_b$, NCH_3), 42.8 ($rotamer_a$, CH_2NH), 42.8 ($rotamer_b$, CH_2NH), 57.5 ($rotamer_a$, CH), 60.2 ($rotamer_b$, CH), 62.2 ($rotamer_a$, OCH_2), 62.3 ($rotamer_b$, OCH_2), 79.4 ($rotamer_a$, $OC(CH_3)_3$), 79.5 ($rotamer_b$, $OC(CH_3)_3$), 127.0, 127.7, 127.8, 127.9, 128.0, 128.2, 128.6, 128.9, 129.5, 129.9, 130.1 (both rotamers, C_{2Ph}, C_{3Ph}, C_{4Ph}, C_{5Ph}, C_{6Ph}, 2 x $C_{3'}$, 2 x $C_{5'}$), 132.5, 132.7 ($rotamer_a$, 2 x $C_{1'}$), 133.0, 133.2 ($rotamer_b$, 2 x $C_{1'}$), 134.8, 135.5, 135.6, 135.7 (both rotamers, 2 x $C_{2'}$, 2 x $C_{6'}$), 136.1 ($rotamer_a$, C_{1Ph}), 137.1 ($rotamer_b$, C_{1Ph}), 155.7 ($rotamer_a$, $COOC(CH_3)_3$), 155.8 ($rotamer_b$, $COOC(CH_3)_3$), 169.1 ($rotamer_a$, CO), 169.2 ($rotamer_b$, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 547 (MH^+, 2), 489 (70), 473 (33), 447 (50). **HRMS** (ESI-TOF): calcd. for $C_{32}H_{43}N_2O_4Si$ [MH^+] 547.2992; found: 547.5984. **$[\alpha]_D^{20}$:** -3.6 (c = 0.5, CH_2Cl_2).

***tert*-butyl (*R*)-(2-((1-((*tert*-butyldiphenylsilyl)oxy)propan-2-yl)(methyl)amino)-2-oxoethyl)carbamate (32c).** 

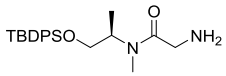
A solution of *O*-protected aminoalcohol **29c** (2.67 g, 8.16 mmol) in dry CH_2Cl_2 (15 mL) was added *via* cannula over a mixture of Boc-protected glycine **31** (1.43 g, 8.16 mmol) and DMAP (25.0 mg, 0.20 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was cooled to 0 ºC and DCC (1.70 g, 8.16 mmol) was added slowly. The reaction mixture was stirred 10 min at 0 ºC and then 4 h at rt. CH_2Cl_2 (80 mL) was added and the precipitate was filtered off. The resulting solution was washed with 10 % HCl aqueous solution (20 mL) and a saturated $NaHCO_3$ aqueous solution (20 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The crude was purified by column chromatograghy (silica gel, petroleum ether/EtAOc 7/3) to give **32c** (3.27g, 83%) as a colorless oil: **IR** (ATR): 3420, 1715, 1650, 1105, 1050, 700 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) (ratio of rotamers 1:1): δ = 1.01 (s, 9H, rotamer$_a$, $SiC(CH_3)_3$), 1.03 (s, 9H, rotamer$_b$, $SiC(CH_3)_3$), 1.06-1.09 (m, 3H, both rotamers, $CHCH_3$), 1.45 (s, 9H, rotamer$_a$, $OC(CH_3)_3$), 1.46 (s, 9H, rotamer$_b$, $OC(CH_3)_3$), 2.71 (s, 3H, rotamer$_a$, NCH_3), 2.77 (s, 3H, rotamer$_b$, NCH_3), 3.48-3.56 (m, 2H, rotamer$_a$, OCH_2), 3.59-3.67 (m, 2H, rotamer$_b$, OCH_2), 3.84-3.97 (m, 3H, rotamer$_a$, CH, rotamer$_a$, CH_2NH), 4.02-4.14 (m, 2H, rotamer$_b$, CH_2NH), 4.77-4.83 (m, 1H, rotamer$_b$, CH), 5.61 (brs, 1H, both rotamers, NH), 7.36-7.46 (m, 6H, both rotamers, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.59-7.63 (m, 4H, both rotamers, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 13.7 (rotamer$_a$, $CHCH_3$), 14.5 (rotamer$_b$, $CHCH_3$), 18.9 (rotamer$_a$, $C(CH_3)_3$), 19.1 (rotamer$_b$, $C(CH_3)_3$), 26.3 (rotamer$_a$, NCH_3), 26.7 (both rotamers, $C(CH_3)_3$), 28.3 (both rotamers, $COOC(CH_3)_3$), 28.6 (rotamer$_b$, NCH_3), 42.6 (rotamer$_a$, CH_2NH), 42.8 (rotamer$_b$, CH_2NH), 50.4 (rotamer$_b$, CH), 52.7 (rotamer$_a$, CH), 64.3 (rotamer$_a$, OCH_2), 65.0 (rotamer$_b$, OCH_2), 79.3 (rotamer$_a$, $COOC(CH_3)_3$), 79.4 (rotamer$_b$, $COOC(CH_3)_3$), 127.7 (rotamer$_a$, 2x $C_{3'}$, 2 x $C_{5'}$), 127.8 (rotamer$_b$, 2x $C_{3'}$, 2 x $C_{5'}$), 129.7, 129.8 (rotamer$_a$, 2x $C_{4'}$), 129.9 (rotamer$_b$, 2x $C_{4'}$), 132.6, 132.8 (rotamer$_a$, $C_{1'}$), 133.2, 133.3 (rotamer$_b$, $C_{1'}$), 135.5 (rotamer$_a$, 2x $C_{2'}$, 2 x $C_{6'}$), 135.6 (rotamer$_b$, 2x $C_{2'}$, 2 x $C_{6'}$), 155.7 (rotamer$_a$, $COOC(CH_3)_3$), 155.8 (rotamer$_b$, $COOC(CH_3)_3$), 168.4 (rotamer$_a$, CO), 168.7 (rotamer$_b$, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 513 ($M+C_2H_5$, 4), 429 (25), 427 (28), 413 (23), 386 (30), 385 (100), 353 (46), 333 (54), 327 (74), 307 (62). **HRMS** (ESI-TOF): calcd. for $C_{29}H_{45}N_2O_4Si$ $[M+C_2H_5]$ 513.3149; found: 513.3159. **$[\alpha]_D^{20}$:** +7.0 (c = 1, $CHCl_3$).

***(R)*-2-amino-*N*-(1-((*tert*-butyldiphenylsilyl)oxy)-3-methylbutan-2-yl)-*N*-methylacetamide (33a). 32a** (5.91 g, 11.53 mmol) was dissolved in a 1:1 mixture of TFA/CH_2Cl_2 (100 mL). The reaction mixture was stirred 90 min at rt. The reaction was quenched with NaOH 1 M aqueous solution and extracted with CH_2Cl_2 (1 × 20 mL). The organic phase was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The crude oil was purified by column chromatograghy (silica gel, EtOAc/MeOH 9/1) to afford **33a** (4.28 g, 90%) as a colorless oil: **IR** (ATR): 1665, 1110, 700 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) (ratio of rotamers 1:0.84): δ = 0.75-0.82 (m, 6H, both rotamers, $CH(CH_3)_2$), 1.01 (s, 9H, minor rotamer, $C(CH_3)_3$), 1.04 (s, 9H, major rotamer, $C(CH_3)_3$), 1.73-1.80 (m, 1H, minor rotamer, $CH(CH_3)_2$), 1.95-1.97 (m, 1H, major rotamer, $CH(CH_3)_2$), 2.77 (s, 3H, minor rotamer, NCH_3), 2.88 (s, 3H, major rotamer, NCH_3), 3.08-3.12 (m, 1H, rotamer$_a$, CH), 3.53-3.57 (m, 1H, rotamer$_a$, OCH_{2a}), 3.73-3.86 (m, 5H, rotamer$_a$, OCH_{2b}, rotamer$_b$, OCH_2, rotamer$_a$, CH_2NH), 3.95-4.00 (m, 2H, rotamer$_b$, CH_2NH), 4.12-4.17 (m, 1H, rotamer$_b$, CH), 7.36-7.45 (m, 6H, both rotamers, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.59-7.63 (m, 4H, both rotamers, 2 x $H_{2'}$, 2 x $H_{6'}$), 8.39 (brs, 2H, both rotamers, NH_2) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 18.8 (rotamer$_a$, $C(CH_3)_3$), 19.1 (rotamer$_b$, $C(CH_3)_3$), 19.4 (rotamer$_a$, $CH(CH_3)_2$), 19.5 (rotamer$_b$, $CH(CH_3)_2$), 25.8 (rotamer$_a$, $CH(CH_3)_2$), 26.7 (rotamer$_a$, $C(CH_3)_3$), 26.8 (rotamer$_b$, $C(CH_3)_3$), 27.0 (rotamer$_b$, $CH(CH_3)_2$), 27.9 (rotamer$_a$, NCH_3), 30.1 (rotamer$_b$, NCH_3), 40.1 (rotamer$_a$, CH_2NH_2), 40.4 (rotamer$_b$, CH_2NH_2), 63.1 (both rotamers, OCH_2), 61.9 (rotamer$_a$, CH), 63.1 (rotamer$_a$, OCH_2), 64.8 (rotamer$_b$, CH), 65.9 (rotamer$_b$, OCH_2), 127.8 (rotamer$_a$, 2x $C_{3'}$, 2 x $C_{5'}$), 127.9 (rotamer$_b$, 2x $C_{3'}$, 2 x $C_{5'}$), 129.9 (rotamer$_a$, 2x $C_{4'}$), 130.0, 130.1 (rotamer$_a$, 2x $C_{4'}$), 132.5 (rotamer$_a$, 2 x $C_{1'}$), 132.9, 133.0 (rotamer$_b$, 2 x $C_{1'}$), 135.5 (rotamer$_a$, 2x $C_{3'}$, 2 x $C_{5'}$), 135.6 (rotamer$_b$, 2x $C_{3'}$, 2 x $C_{5'}$), 166.2 (rotamer$_a$, CO), 166.7 (rotamer$_b$, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 413 (MH^+, 77), 355 (100), 335 (46). **HRMS** (ESI-TOF): calcd. for $C_{24}H_{37}N_2O_2Si$ [MH^+] 413.2624; found: 413.2607. **$[\alpha]_D^{20}$:** +8.4 (c = 1, $CHCl_3$).

(*R*)-2-amino-*N*-(2-((*tert*-butyldiphenylsilyl)oxy)-1-phenylethyl)-*N*-methylacetamide (33b). 32b (1.48 g, 2.72 mmol) was dissolved in a 1:1 mixture of TFA/CH_2Cl_2 (30 mL). The reaction mixture was stirred 2 h at rt. The reaction was quenched with NaOH 1 M aqueous solution and extracted with CH_2Cl_2 (1 × 15 mL). The organic phase was washed with brine (1 × 15 mL),

dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The crude oil was purified by column chromatograghy (silica gel, EtOAc) to afford **33b** (774 mg, 64%) as a colorless oil: **IR** (ATR): 1670, 1110, 700 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) (ratio of rotamers 1:0.67): δ = 1.00 (s, 9H, both rotamer, $C(CH_3)_3$), 2.67 (s, 3H, major rotamer, NCH_3), 2.69 (s, 3H, minor rotamer, NCH_3), 3.64-4.13 (m, 4H, both rotamer, OCH_2, CH_2NH), 4.63-4.72 (m, 1H, minor rotamer, CH), 5.74-5.78 (m, 1H, major rotamer, CH), 6.99-7.24 (m, 5H, both rotamers, H_{2Ph}, H_{3Ph}, H_{4Ph}, H_{5Ph}, H_{6Ph}), 7.33-7.45 (m, 6H, both rotamers, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.58-7.64 (m, 4H, both rotamers, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 18.8 ($rotamer_a$, $C(CH_3)_3$), 19.0 ($rotamer_b$, $C(CH_3)_3$), 26.6 ($rotamer_a$, $C(CH_3)_3$), 26.7 ($rotamer_b$, $C(CH_3)_3$), 28.9 ($rotamer_a$, NCH_3), 30.1 ($rotamer_b$, NCH_3), 40.2 ($rotamer_a$, CH_2NH), 40.2 ($rotamer_b$, CH_2NH), 58.3 ($rotamer_a$, CH), 60.8 ($rotamer_b$, CH), 62.5 (both rotamer, OCH_2), 126.9, 127.5, 127.7, 127.9, 128.0, 128.3, 128.6, 128.9, 130.0, 130.2 (both rotamers, C_{2Ph}, C_{3Ph}, C_{4Ph}, C_{5Ph}, C_{6Ph}, 2 x $C_{3'}$, 2 x $C_{5'}$), 132.3, 132.5 ($rotamer_a$, 2 x $C_{1'}$), 132.9 ($rotamer_b$, 2 x $C_{1'}$), 135.2, 135.5 (both rotamers, 2x $C_{2'}$, 2 x $C_{6'}$), 136.4 (both rotamer, C_{1Ph}), 166.7 (both rotamers, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 447 (MH^+, 13), 389 (50), 303 (100). **HRMS** (ESI-TOF): calcd. for $C_{27}H_{35}N_2O_2Si$ [MH^+] 447.2468; found: 447.2464. **$[\alpha]_D^{20}$:** -1.7 (c = 1, $CHCl_3$).

(*R*)-2-amino-*N*-(1-((tert-butyldiphenylsilyl)oxy)propan-2-yl)-*N*-methylacetamide (33c).



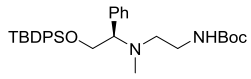
32c (223 mg, 2.72 mmol) was dissolved in a 1:1 mixture of TFA/CH_2Cl_2 (4 mL). The reaction mixture was stirred 90 min at rt. The reaction was quenched with NaOH 1 M aqueous solution and extracted with CH_2Cl_2 (1 × 5 mL). The organic phase was washed with brine (1 × 5 mL), dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum. The crude oil was purified by column chromatograghy (silica gel, EtOAc/MeOH 9/1) to afford **33c** (142 mg, 80%) as a colorless oil: **IR** (ATR): 1670, 1110, 700 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) (ratio of rotamers 1:1): δ = 1.00 (s, 9H, $rotamer_a$, $C(CH_3)_3$), 1.02 (s, 9H, $rotamer_b$, $C(CH_3)_3$), 1.05 (m, 3H, $rotamer_a$, $CHCH_3$), 1.06 (m, 3H, $rotamer_b$, $CHCH_3$), 2.68 (s, 3H, $rotamer_a$, NCH_3), 2.77 (s, 3H, $rotamer_b$, NCH_3), 3.48-3.60 (m, 3H, $rotamer_a$, OCH_2, $rotamer_b$, OCH_{2a}), 3.65-3.75 (m, 4H, $rotamer_a$, CH, $rotamer_b$, OCH_{2b}, $rotamer_a$, CH_2NH_2), 3.86-3.97 (m, 2H, $rotamer_b$, CH_2NH_2), 4.64-4.67 (m, 1H, $rotamer_b$, CH), 7.34-7.43 (m, 12H, both rotamers, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.58-7.61 (m, 8H, both rotamers, 2 x $H_{2'}$, 2 x $H_{6'}$), 8.37 (brs, 2H, both rotamers, NH_2) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 13.4 ($rotamer_a$, $CHCH_3$), 14.1 ($rotamer_b$, $CHCH_3$), 18.8 ($rotamer_a$, $C(CH_3)_3$), 19.0 ($rotamer_b$, $C(CH_3)_3$), 26.6

(rotamer$_a$, C(*C*H$_3$)$_3$), 26.7 (rotamer$_b$, C(*C*H$_3$)$_3$), 26.8 (rotamer$_a$, NCH$_3$), 29.0 (rotamer$_b$, NCH$_3$), 40.1 (both rotamers, CH$_2$NH$_2$), 51.0 (rotamer$_b$, CH), 53.4 (rotamer$_a$, CH), 64.3 (rotamer$_a$, OCH$_2$), 65.2 (rotamer$_b$, OCH$_2$), 127.7 (rotamer$_a$, 2 x C$_{3'}$, 2 x C$_{5'}$), 127.9 (rotamer$_b$, 2 x C$_{3'}$, 2 x C$_{5'}$), 129.8 (rotamer$_a$, 2 x C$_{4'}$), 130.0 (rotamer$_b$, 2 x C$_{4'}$), 132.5, 132.6 (rotamer$_a$, 2 x C$_{1'}$), 133.0 (rotamer$_b$, 2 x C$_{1'}$), 135.4 (rotamer$_a$, 2 x C$_{2'}$, 2 x C$_{6'}$), 135.5 (rotamer$_b$, 2 x C$_{2'}$, 2 x C$_{6'}$), 165.9 (both rotamers, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 385 (MH$^+$, 85), 327 (100), 307 (85). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{33}N_2O_2Si$ [MH$^+$] 385.2311; found: 385.2292. **$[\alpha]_D^{20}$:** +7.1 (c = 1, CHCl$_3$).

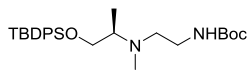
***tert*-butyl (2-bromoethyl)carbamate (36).** Di-*t*-butyl dicarbonate (3.21 g, 14.71 mmol) was added to a solution of 2-bromoethylamine hydrobromide (1.49 g, 7.35 mmol) and triethylamine (10.2 mL, 73.53 mmol) in MeOH (50 mL). The reaction mixture was stirred at 60 ºC for 1 h and at rt for 14 h. The mixture was concentrated *in vacuo* and then dissolved in CH$_2$Cl$_2$. The organic residue was successively washed with 1 M HCl (30 mL), saturated NaHCO$_3$ aqueous solution (30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, CH$_2$Cl$_2$) to give pure Boc-protected amine **36** as a colorless oil (1.36 g, 82%): **IR** (ATR): 1645 cm^{-1}; **^{1}H NMR** (300 MHz, CDCl$_3$): δ = 1.41 (s, 9H, C(C*H*$_3$)$_3$), 3.39-3.52 (m, 4H, C*H*$_2$C*H*$_2$), 5.04 (brs, 1H, NH) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, CDCl$_3$): δ = 28.3 (C(*C*H$_3$)$_3$), 32.7 (BrCH$_2$), 42.4 (CH$_2$N), 79.8 (*C*(CH$_3$)$_3$), 155.6 (CO) ppm.

***tert*-butyl (*R*)-(2-((1-((tert-butyldiphenylsilyl)oxy)-3-methylbutan-2-yl)(methyl)amino)ethyl)carbamate (37a).** A mixture of *O*-protected amino alcohol **29a** (507 mg, 1.43 mmol) and *tert*-butyl (2-bromoethyl)carbamate (**36**) (636 mg, 2.85 mmol) in presence of anhydrous K$_2$CO$_3$ (789 mg, 5.71 mmol) was refluxed in EtOAc (20 mL) for 72 h. The reaction mixture was washed with water (20 mL). The organic phase was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated to dryness. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 7/3) to afford **37a** as a colorless oil (439 mg, 62%): **IR** (ATR): 2955, 1715, 1110, 1090 cm^{-1}; **^{1}H NMR** (300 MHz, CDCl$_3$): δ = 0.83 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 0.99 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.10 (s, 9H, SiC(C*H*$_3$)$_3$), 1.48 (s, 9H, OC(C*H*$_3$)$_3$), 1.74-1.81 (m, 1H, C*H*(CH$_3$)$_2$), 2.21-2.25 (m, 1H, CH), 2.34 (s, 3H, CH$_3$), 2.72-2.86 (m, 1H, C*H*$_2$NCH$_3$), 3.19-3.22 (m, 2H, C*H*$_2$NH), 3.76 (dd, *J* =

11.1, 6.5 Hz, 1H, OCH_aH$_b$), 3.81 (dd, *J* = 11.1, 3.7 Hz, 1H, OCH$_a$$H_b$), 5.13 (brs, 1H, NH), 7.41-7.48 (m, 6H, 2 x H$_{3'}$, 2 x H$_{4'}$, 2 x H$_{5'}$), 7.70-7.73 (m, 4H, 2 x H$_{2'}$, 2 x H$_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 19.1 (Si*C*(CH$_3$)$_3$), 20.6 (CH(*C*H$_3$)$_2$), 21.1 (CH(*C*H$_3$)$_2$), 27.0 (SiC(*C*H$_3$)$_3$), 28.0 (*C*H(CH$_3$)$_2$), 28.5 (OC(*C*H$_3$)$_3$), 36.9 (NCH$_3$), 38.4 (CH$_2$NH), 54.8 (*C*H$_2$NCH$_3$), 62.0 (CH$_2$O), 70.9 (CH), 78.8 (O*C*(CH$_3$)$_3$), 127.7 (2 x C$_{3'}$, 2 x C$_{5'}$), 129.7 (2 x C$_{4'}$), 133.5 (2 x C$_{1'}$), 135.7 (2 x C$_{2'}$, 2 x C$_{6'}$), 156.2 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 499 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{29}H_{47}N_2O_3Si$ [MH^+] 499.3356; found: 499.3364. **[α]$_D^{20}$:** +7.6 (c = 1, $CHCl_3$).

***tert*-butyl** 

(*R*)-(2-((1-((tert-butyldiphenylsilyl)oxy)-3-methylbutan-2-yl)(methyl)amino)ethyl)carbamate (37b). A mixture of *O*-protected amino alcohol **29b** (1.05 g, 2.69 mmol) and *tert*-butyl (2-bromoethyl)carbamate (**36**) (721 mg, 3.23 mmol) in presence of anhydrous K_2CO_3 (745 mg, 5.39 mmol) was refluxed in acetonitrile (20 mL) for 72 h. The reaction mixture was washed with water (20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 9/1) to afford **37b** as a colorless oil (852 mg, 59%): **IR** (ATR): 3420, 2930, 1705, 1105, 1085 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.00 (s, 9H, SiC(C*H*$_3$)$_3$), 1.43 (s, 9H, OC(C*H*$_3$)$_3$), 2.20 (s, 3H, CH$_3$), 2.51-2.54 (m, 1H, C*H*$_2$NCH$_3$), 3.16-3.19 (m, 2H, C*H*$_2$NH), 3.58-3.61 (m, 1H, CH), 3.88 (dd, *J* = 10.7, 5.6 Hz, 1H, OCH_aH$_b$), 4.04 (dd, *J* = 10.7, 6.5 Hz, 1H, OCH$_a$$H_b$), 5.01 (brs, 1H, NH), 7.18-7.30 (m, 5H, H$_{2Ph}$, H$_{3Ph}$, H$_{4Ph}$, H$_{5Ph}$, H$_{6Ph}$), 7.34-7.43 (m, 6H, 2 x H$_{3'}$, 2 x H$_{4'}$, 2 x H$_{5'}$), 7.57-7.59 (m, 4H, 2 x H$_{2'}$, 2 x H$_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 19.1 (Si*C*(CH$_3$)$_3$), 26.8 (SiC(*C*H$_3$)$_3$), 28.5 (OC(*C*H$_3$)$_3$), 37.8 (CH$_2$NH), 38.2 (NCH$_3$), 53.6 (*C*H$_2$NCH$_3$), 65.0 (CH$_2$O), 70.1 (CH), 78.9 (O*C*(CH$_3$)$_3$), 127.2 (C$_{4Ph}$), 127.7, 128.1, 128.6 (C$_{2Ph}$, C$_{3Ph}$, C$_{5Ph}$, C$_{6Ph}$, 2 x C$_{3'}$, 2 x C$_{5'}$), 129.6, 129.7 (2 x C$_{4'}$), 133.5 (2 x C$_{1'}$), 135.6, 135.7 (2 x C$_{2'}$, 2 x C$_{6'}$), 139.5 (C$_{1Ph}$), 156.1 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 533 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{32}H_{45}N_2O_3Si$ [MH^+] 533.3199; found: 533.3207. **[α]$_D^{20}$:** +4.4 (c = 1, $CHCl_3$).

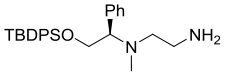
***tert*-butyl** 

(*R*)-(2-((1-((*tert*-butyldiphenylsilyl)oxy)propan-2-yl)(methyl)amino)ethyl)carbamate (37c). A mixture of *O*-protected amino alcohol **29c** (1.26 g, 3.85 mmol) and *tert*-butyl (2-bromoethyl)carbamate (**36**) (1.03 g, 4.62 mmol) in presence of

anhydrous K_2CO_3 (1.06 g, 7.69 mmol) was refluxed in EtOAc (20 mL) for 72 h. The reaction mixture was washed with water (20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc 9/1) to afford **37c** as a colorless oil (960 mg, 53%): **IR** (ATR): 3415, 2930, 1710, 1105, 1090 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.98 (d, J = 6.7 Hz, 3H, CH_3), 1.08 (s, 9H, $SiC(CH_3)_3$), 1.44 (s, 9H, $OC(CH_3)_3$), 2.20 (s, 3H, NCH_3), 2.58 (t, J = 5.7 Hz, 2H, CH_2NCH_3), 2.79-2.85 (m, 1H, CH), 3.15-3.16 (m, 2H, CH_2NH), 3.52 (dd, J = 10.4, 5.9 Hz, 1H, OCH_aH_b), 3.69 (dd, J = 10.4, 6.3 Hz, 1H, OCH_aH_b), 5.12 (brs, 1H, NH), 7.38-7.48 (m, 6H, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.67-7.72 (m, 4H, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 11.9 (CH_3), 19.2 ($SiC(CH_3)_3$), 26.9 ($SiC(CH_3)_3$), 28.5 ($OC(CH_3)_3$), 36.8 (CH_2NH), 38.0 (NCH_3), 52.8 (CH_2NCH_3), 59.8 (CH_2O), 65.8 (CH), 78.9 ($OC(CH_3)_3$), 127.7 (2 x $C_{3'}$, 2 x $C_{5'}$), 129.6 (2 x $C_{4'}$), 133.7 (2 x $C_{1'}$), 135.6 (2 x $C_{2'}$, 2 x $C_{6'}$), 156.2 (CO) ppm; **MS** (ESI) *m/z* (rel intensity): 471 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{27}H_{43}N_2O_3Si$ [MH^+] 471.3043; found: 471.3035. **$[\alpha]_D^{20}$:** +8.5 (c = 1, $CHCl_3$).

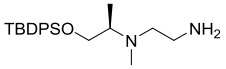
(*R*)-N^1-(1-((*tert*-butyldiphenylsilyl)oxy)-3-methylbutan-2-yl)-N^1-methylethane-1,2-diamine (38a). 37a (360 mg, 0.72 mmol) was dissolved in a 1:1 mixture of TFA/CH_2Cl_2 (8 mL) and stirred at rt for 90 min. The reaction mixture was quenched with 1 M NaOH aqueous solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was washed with a saturated NaCl aqueous solution (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (silica gel, EtOAc/MeOH 9/1) to afford **38a** as a yellow oil (279 mg, 97%): **IR** (ATR): 2930, 1470, 1430 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.72 (d, J = 6.6 Hz, 3H, $CH(CH_3)_2$), 0.88 (d, J = 6.6 Hz, 3H, $CH(CH_3)_2$), 0.98 (s, 9H, $C(CH_3)_3$), 1.58 (brs, 2H, NH_2), 1.66-1.73 (m, 1H, $CH(CH_3)_2$), 2.10-2.14 (m, 1H, CHN), 2.22 (s, 3H, NCH_3), 2.54-2.69 (m, 4H, NCH_2CH_2N), 3.64-3.71 (m, 2H, CH_2O), 7.27-7.36 (m, 6H, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.59- 7.61 (m, 4H, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 19.1 ($C(CH_3)_3$), 20.6 ($CH(CH_3)_2$), 21.1 ($CH(CH_3)_2$), 26.9 ($C(CH_3)_3$), 28.1 ($CH(CH_3)_2$), 37.0 (NCH_3), 40.0 (CH_2NH_2), 58.8 (CH_2NCH_3), 62.0 (CH_2O), 71.2 (CH), 127.6 (2 x $C_{3'}$, 2 x $C_{5'}$), 129.6 (2 x $C_{4'}$), 133.6, 133.7 (2 x $C_{1'}$), 135.7 (2 x $C_{2'}$, 2 x $C_{6'}$) ppm; **MS** (ESI) *m/z* (rel intensity): 399 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{24}H_{39}N_2OSi$ [MH^+] 399.2832; found: 399.2838. **$[\alpha]_D^{20}$:** +6.8 (c = 1, $CHCl_3$).

(*R*)-N^1-(2-((*tert*-butyldiphenylsilyl)oxy)-1-phenylethyl)-N^1-methylethane-1,2-diamine



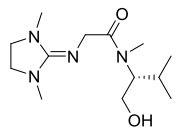
(38b). 37b (628 mg, 1.18 mmol) was dissolved in a 1:1 mixture of TFA/CH_2Cl_2 (14 mL) and stirred at rt for 90 min. The reaction mixture was quenched with 1 M NaOH aqueous solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was washed with a saturated NaCl aqueous solution (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (silica gel, EtOAc/MeOH 9/1) to afford **38b** as a yellow oil (112 mg, 22%): **IR** (ATR): 2935, 1675, 1430, 1200, 1130, 1110 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.00 (s, 9H, SiC(CH_3)$_3$), 1.60 (brs, 2H, NH_2), 2.22 (s, 3H, NCH_3), 2.44-2.55 (m, 2H, CH_2NCH_3), 2.64-2.80 (m, 2H, CH_2NH_2), 3.63 (t, J = 6.1 Hz, 1H, CH), 3.92 (dd, J = 10.5, 6.0 Hz, 1H, OCH_aH$_b$), 4.08 (dd, J = 10.5, 6.2 Hz, 1H, OCH$_a$$H_b$), 7.23-7.45 (m, 11H, H_{2Ph}, H_{3Ph}, H_{4Ph}, H_{5Ph}, H_{6Ph}, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.57-7.61 (m, 4H, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 19.1 (Si*C*(CH_3)$_3$), 26.8 (SiC(*C*H_3)$_3$), 38.7 (NCH_3), 39.5 (CH_2NH), 57.7 (*C*H_2NCH_3), 65.2 (CH_2O), 70.3 (CH), 127.0 (C_{4Ph}), 127.6 (C_{2Ph}, C_{3Ph}, C_{5Ph}, C_{6Ph}), 128.0, 128.7 (2 x $C_{3'}$, 2 x $C_{5'}$), 129.6 (2 x $C_{4'}$), 133.5, 133.6 (2 x $C_{1'}$), 135.6 (2 x $C_{2'}$, 2 x $C_{6'}$), 140.1 (C_{1Ph}) ppm; **MS** (ESI) *m/z* (rel intensity): 433 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{27}H_{37}N_2OSi$ [MH^+] 433.2675; found: 433.2687. **$[\alpha]_D^{20}$:** +2.3 (c = 1, $CHCl_3$).

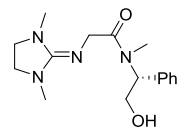
(*R*)-N^1-(1-((*tert*-butyldiphenylsilyl)oxy)propan-2-yl)-N^1-methylethane-1,2-diamine



(38c). 37c (187 mg, 0.40 mmol) was dissolved in a 1:1 mixture of TFA/CH_2Cl_2 (5 mL) and stirred at rt for 90 min. The reaction mixture was quenched with 1 M NaOH aqueous solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was washed with a saturated NaCl aqueous solution (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography (silica gel, EtOAc/MeOH 9/1) to afford **38c** as a yellow oil (94.2 mg, 64%): **IR** (ATR): 2945, 1680, 1435, 1205, 1110 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.03 (d, J = 6.7 Hz, 3H, CH_3), 1.08 (s, 9H, C(CH_3)$_3$), 2.23 (s, 3H, NCH_3), 2.56-2.68 (m, 2H, CH_2NH_2), 2.75-2.88 (m, 3H, CH_2NCH_3, CH), 3.55 (dd, J = 10.3, 6.2 Hz, 1H, OCH_aH$_b$), 3.72 (dd, J = 10.3, 5.9 Hz, 1H, OCH$_a$$H_b$), 4.10 (brs, 2H, NH_2), 7.39-7.43 (m, 6H, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.68-7.71 (m, 4H, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 12.7 (CH_3), 19.2 (*C*(CH_3)$_3$), 26.9 (C(*C*H_3)$_3$), 37.2 (NCH_3), 38.8 (CH_2NH_2), 55.1 (*C*H_2NCH_3), 59.8 (CH), 65.7 (CH_2O), 127.7 (2 x $C_{3'}$, 2 x $C_{5'}$), 129.7 (2 x $C_{4'}$), 133.6 (2 x $C_{1'}$), 135.6 (2 x $C_{2'}$, 2 x $C_{6'}$) ppm; MS (ESI) *m/z* (rel intensity): 399

(MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{22}H_{35}N_2OSi$ [MH^+] 371.2519; found: 371.2527. **$[\alpha]_D^{20}$:** +5.3 (c = 1, $CHCl_3$).

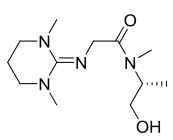
((*R*)-2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-(1-hydroxy-3-methylbutan-2-yl)-*N*-methylacetamide (L1).  TBAF (10.27 mL, 10.27 mmol) was added to a solution of protected aminoalcohol **33a** (2.12 g, 5.14 mmol) in dry THF (40 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 10 min and at rt for 90 min. The solvent was then evaporated in vacuum and the residue, without purification, was dissolved in dry CH_3CN (20 mL), and Et_3N (1.44 mL, 10.27 mmol) and 2-chloro-1,3-dimethylimidazolinium chloride (875 mg, 5.14 mmol) were added at rt. The reaction mixture was stirred at rt for 24 h and then the solvent was removed *in vacuo*. The crude was purified by column chromatograghy (aluminium oxide, CH_2Cl_2/MeOH 9.5/0.5) to afford **L1** as a yellowish oil (692 mg, 50%): **IR** (ATR): 3280, 1650, 1590 cm^{-1}; **^{1}H NMR** (300 MHz, D_2O) (ratio of rotamers 1:0.80): δ = 0.75 (d, J = 6.7 Hz, 3H, major rotamer, $CH(CH_3)_2$), 0.82 (d, J = 6.6 Hz, 3H, minor rotamer, $CH(CH_3)_2$), 0.91-0.94 (m, 6H, both rotamers, $CH(CH_3)_2$), 1.72-1.84 (m, 1H, both rotamers, $CH(CH_3)_2$), 2.78 (s, 3H, minor rotamer, NCH_3), 2.86 (s, 3H, major rotamer, NCH_3), 2.94 (s, 6H, $rotamer_a$, 2 x CH_3), 2.95 (s, 6H, $rotamer_b$, 2 x CH_3), 3.29-3.34 (m, 1H, minor rotamer, 1H, CH), 3.49-3.53 (m, 1H, $rotamer_a$, $CH_{2a}OH$), 3.57-3.62 (m, 5H, 1H, $rotamer_b$, $CH_{2a}OH$, both rotamers, CH_2CH_2), 3.77-3.83 (m, 2H, $rotamer_b$, CH_2OH), 4.09-4.14 (m, 1H, major rotamer, CH), 4.33-4.44 (m, 2H, both rotamers, CH_2N) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, D_2O): δ = 18.8, 19.0, 19.1, 19.2 (both rotamers, $CH(CH_3)_2$), 26.3 ($rotamer_a$, $CH(CH_3)_2$), 26.8 ($rotamer_b$, $CH(CH_3)_2$), 27.4 (major rotamer, NCH_3), 28.4 (minor rotamer, NCH_3), 33.4 (both rotamers, 2 x CH_3), 44.8 (major rotamer, CH_2N), 45.1 (minor rotamer, CH_2N), 49.0 (both rotamers, CH_2CH_2), 59.0 (minor rotamer, CH_2OH), 59.4 (major rotamer, CH_2OH), 62.7 (minor rotamer, CH), 65.1 (major rotamer, CH), 159.4 ($rotamer_a$, C=N), 159.6 ($rotamer_b$, C=N), 170.9 (both rotamers, CO) ppm; MS (ESI) *m/z* (rel intensity): 271 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{13}H_{26}N_4O_2$ [MH^+] 271.2129; found: 271.2134. **$[\alpha]_D^{20}$:** +14.8 (c = 1, CH_2Cl_2).

(*R*)-2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-(2-hydroxy-1-phenylethyl)-*N*-methylacetamide (L2).  TBAF (2.96 mL, 2.96 mmol) was added to a solution of the protected aminoalcohol **33b** (573 mg, 1.48 mmol) in dry THF (10 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 10

min and at rt for 90 min. The solvent was then evaporated in vacuum and the residue, without purification, was dissolved in dry CH_3CN (10 mL), and Et_3N (0.42 mL, 2.96 mmol) and 2-chloro-1,3-dimethylimidazolinium chloride (251 mg, 1.48 mmol) were added at rt. The reaction mixture was stirred at rt for 24 h and then the solvent was removed *in vacuo*. The crude was purified by column chromatograghy (aluminium oxide, CH_2Cl_2/MeOH 9/1) to afford **L2** as a yellowish oil (293 mg, 75%): **IR** (ATR): 3290, 1655, 1600 cm^{-1}; **^{1}H NMR** (300 MHz, D_2O) (ratio of rotamers 1:0.44): δ = 2.75 (s, 3H, minor rotamer, NCH_3), 2.79 (s, 3H, major rotamer, NCH_3), 2.86 (s, 6H, minor rotamer, 2 x CH_3), 2.90 (s, 6H, major rotamer, 2 x CH_3), 3.57 (s, 4H, minor rotamer, C*H*$_2$C*H*$_2$), 3.58 (s, 4H, major rotamer, C*H*$_2$C*H*$_2$), 3.98-4.13 (m, 2H, both rotamers, C*H*$_2$OH), 4.35 (s, 2H, major rotamer, CH_2N), 4.42 (s, 1H, minor rotamer, $CH_{2a}N$), 4.54 (s, 1H, minor rotamer, $CH_{2b}N$), 4.96-5.01 (m, 1H, minor rotamer, CH), 5.61-5.66 (m, 1H, major rotamer, CH), 7.22-7.38 (m, 5H, both rotamers, H_{2Ph}, H_{3Ph}, H_{4Ph}, H_{5Ph}, H_{6Ph}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, D_2O): δ = 28.8 (minor rotamer, NCH_3), 29.1 (major rotamer, NCH_3), 33.4 (minor rotamer, CH_3), 33.4 (major rotamer, CH_3), 44.9 (major rotamer, CH_2N), 45.1 (minor romater, CH_2N), 49.0 (both rotamers, *C*H$_2$*C*H$_2$), 58.8 (major rotamer, CH), 59.4 (major rotamer, CH_2OH), 59.9 (minor rotamer, CH_2OH), 60.7 (minor rotamer, CH), 127.1 (minor rotamer, C_{2Ph}, C_{6Ph}), 127.5 (major rotamer, C_{2Ph}, C_{6Ph}), 128.3 (major rotamer, C_{4Ph}), 128.5 (minor rotamer, C_{4Ph}), 128.9 (major rotamer, C_{3Ph}, C_{5Ph}), 129.1 (minor rotamer, C_{3Ph}, C_{5Ph}), 135.5 (minor rotamer, C_{1Ph}), 135.6 (major rotamer, C_{1Ph}), 159.4 (major rotamer, C=N), 159.6 (minor rotamer, C=N), 170.7 (major rotamer, CO), 170.9 (minor rotamer, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 305 (MH^+, 93), 114 (100). **HRMS** (ESI-TOF): calcd. for $C_{16}H_{25}N_4O_2$ [MH^+] 305.1978; found: 305.1971. **$[\alpha]_D^{20}$:** +4.9 (c = 1, CH_2Cl_2).

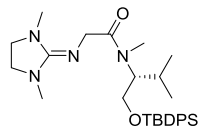
(*R*)-2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-(1-hydroxypropan-2-yl)-*N*-methylacetamide (L3). TBAF (0.83 mL, 0.83 mmol) was added to a solution of the protected aminoalcohol **33c** (162 mg, 0.42 mmol) in dry THF (5 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 10 min and at rt for 90 min. The solvent was then evaporated in vacuum and the residue, without purification, was dissolved in dry CH_3CN (5 mL), and Et_3N (0.12 mL, 0.84 mmol) and 2-chloro-1,3-dimethylimidazolinium chloride (71.0 mg, 0.42 mmol) were added at rt. The reaction mixture was stirred at rt for 24 h and then the solvent was removed *in vacuo*. The crude was purified by column chromatograghy (aluminium oxide, CH_2Cl_2/MeOH 9/1) to afford **L3** as a colorless oil (54.8 mg, 54%): **IR** (ATR): 3275, 1645,

1595 cm^{-1}; **^{1}H NMR** (300 MHz, D_2O) (ratio of rotamers 1:0.9): δ = 0.99 (d, J = 6.9 Hz, 3H, major rotamer, CHCH_3), 1.06 (d, J = 6.9 Hz, 3H, minor rotamer, CHCH_3), 2.75 (s, 3H, minor rotamer, NCH_3), 2.81 (s, 3H, major rotamer, NCH_3), 2.90 (s, 6H, minor rotamer, 2 x CH_3), 2.91 (s, 6H, 2 x rotamer, CH_3), 3.46-3.55 (m, 4H, both rotamers, CH_2OH), 3.58 (s, 8H, both rotamers, CH_2CH_2), 3.84-3.91 (m, 1H, minor rotamer, CH), 4.30 (s, 2H, rotamer$_a$, CH_2N), 4.36 (s, 1H, rotamer$_b$, $CH_{2a}N$), 4.40-4.46 (m, 1H, rotamer$_b$, $CH_{2b}N$), 4.48-4.58 (m, 1H, major rotamer, CH) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, D_2O): δ = 12.6 (rotamer$_a$, CHCH_3), 13.3 (rotamer$_b$, CHCH_3), 26.6 (rotamer$_a$, NCH_3), 27.6 (rotamer$_b$, NCH_3), 33.4 (both rotamers, 2 x CH_3), 44.8 (rotamer$_a$, CH_2N), 44.9 (rotamer$_b$, CH_2N), 49.0 (both rotamers, CH_2CH_2), 51.8 (rotamer$_a$, CH), 53.7 (rotamer$_b$, CH), 61.5 (rotamer$_a$, CH_2OH), 61.7 (rotamer$_b$, CH_2OH), 159.4 (rotamer$_a$, C=N), 159.6 (rotamer$_b$, C=N), 170.1 (rotamer$_a$, CO), 170.2 (rotamer$_b$, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 243 (MH^+, 35), 114 (100). **HRMS** (ESI-TOF): calcd. for $C_{11}H_{23}N_4O_2$ [MH^+] 243.1821; found: 243.1820. **$[\alpha]_D^{20}$:** -21.6 (c = 1, CH_2Cl_2).

(*R*)-2-((1,3-dimethyltetrahydropyrimidin-2(1*H*)-ylidene)amino)-*N*-(1-hydroxypropan-2-yl)-*N*-methylacetamide (L4). 
Oxalyl chloride (0.16 mL, 1.78 mmol) was added to a solution of 1,3-dimethyl pyrimidinone (190 mg, 1.49 mmol) in dry CCl_4 (5 mL). The reaction mixture was stirred at 60 ºC for 16 h and was evaporated in vacuum to afford 2-chloro-1,3-dimethylpyrimidinium chloride, which was hygroscopic. On the other hand, TBAF (0.74 mL, 0.74 mmol) was added to a solution of the protected aminoalcohol **33c** (0.14 g, 0.37 mmol) in dry THF (4 mL) at 0 ºC and the reaction mixture was stirred at 0 ºC for 10 min and at rt for 90 min. The solvent was then evaporated in vacuum and the resulting residue, without purification, was dissolved in dry CH_3CN (8 mL), and Et_3N (0.10 mL, 0.74 mmol) and 2-chloro-1,3-dimethylpyrimidinium chloride, previously synthesized, were added at rt. The reaction mixture was stirred 24 h at rt and then concentrated to dryness. The crude was purified by column chromatograghy (aluminium oxide, CH_2Cl_2/MeOH 9/1) to afford **L4** as a yellow oil (16.4 mg, 17%): **IR** (ATR): 3295, 1625, 1570 cm^{-1}; **^{1}H NMR** (300 MHz, D_2O) (ratio of rotamers 1:0.9): δ = 0.98 (d, J = 6.9 Hz, 3H, major rotamer, CHCH_3), 1.06 (d, J = 6.9 Hz, 3H, minor rotamer, CHCH_3), 1.89-2.00 (m, 4H, both rotamers, $CH_2CH_2CH_2$), 2.72 (s, 3H, minor rotamer, NCH_3), 2.79 (s, 3H, mayor rotamer, NCH_3), 3.02 (s, 6H, rotamer$_a$, 2 x CH_3), 3.03 (s, 6H, rotamer$_b$, 2 x CH_3), 3.22-3.27 (m, 8H, both rotamers, $CH_2CH_2CH_2$), 3.49-3.54 (m, 2H, both rotamers, CH_2OH), 3.83-3.95 (m, 1H, minor rotamer, CH), 4.07 (s,

2H, rotamer$_a$, CH_2N), 4.13-4.23 (s, 2H, rotamer$_b$, CH_2N), 4.46-4.58 (m, 1H, major rotamer, CH) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, D_2O): δ = 12.7 (rotamer$_a$, $CHCH_3$), 13.4 (rotamer$_b$, $CHCH_3$), 21.3 (both rotamers, $CH_2CH_2CH_2$), 26.4 (minor rotamer, NCH_3), 27.6 (major rotamer, NCH_3), 39.0 (both rotamers, 2 x CH_3), 45.8 (rotamer$_a$, CH_2N), 46.1 (rotamer$_b$, CH_2N), 48.2 (both rotamers, $CH_2CH_2CH_2$), 51.6 (major rotamer, CH), 53.6 (minor rotamer, CH), 61.7 (rotamer$_a$, CH_2OH), 61.7 (rotamer$_b$, CH_2OH), 158.6 (rotamer$_a$, C=N), 158.7 (rotamer$_b$, C=N), 170.5 (rotamer$_a$, CO), 170.6 (rotamer$_b$, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 257 (MH^+, 100), 128 (87). **HRMS** (ESI-TOF): calcd. for $C_{12}H_{25}N_4O_2$ [MH^+] 257.1978; found: 257.1982. **$[\alpha]_D^{20}$:** -6.4 (c = 1, CH_2Cl_2).

(*R*)-*N*-(1-((*tert*-butyldiphenylsilyl)oxy)-3-methylbutan-2-yl)-2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-methylacetamide (L5).



Et_3N (0.09 mL, 0.60 mmol) and 2-chloro-1,3-dimethylimidazolinium chloride (5.1 mg, 0.30 mmol) were added to a solution of protected aminoalcohol **33a** (124 mg, 0.30 mmol) in dry CH_3CN (10 mL) at rt. The reaction mixture was stirred at rt for 24 h and then the solvent was removed *in vacuo*. The crude was purified by column chromatograghy (aluminium oxide, CH_2Cl_2/MeOH 9/1) to afford **L5** as a colorless oil (104 mg, 68%): **IR** (ATR): 1655, 1595, 1105, 700 cm^{-1}; **^1H NMR** (300 MHz, D_2O): δ = 0.78-0.81 (m, 6H, rotamer$_a$, $CH(CH_3)_2$), 0.90 (d, *J* = 6.6 Hz, 3H, rotamer$_b$, $CH(CH_3)_2$), 0.96 (d, *J* = 6.6 Hz, 3H, rotamer$_b$, $CH(CH_3)_2$), 1.00 (s, 9H, rotamer$_a$, $C(CH_3)_3$), 1.01 (s, 1H, rotamer$_b$, $C(CH_3)_3$), 1.70-1.91 (m, 2H, both rotamers, $CH(CH_3)_2$), 2.76 (s, 3H, rotamer$_a$, NCH_3), 2.94 (s, 9H, rotamer$_b$, NCH_3, rotamer$_a$, 2 x CH_3), 3.05 (s, 6H, rotamer$_b$, 2 x CH_3), 3.39-3.45 (m, 1H, rotamer$_a$, CH), 3.54-3.65 (m, 9H, rotamer$_b$, CH, both rotamers, NCH_2CH_2N), 3.73-3.80 (m, 2H, rotamer$_a$, CH_2N), 3.86-3.91 (m, 1H, rotamer$_a$, OCH_{2a}), 4.19-4.26 (m, 3H, rotamer$_a$, OCH_{2b}, rotamer$_a$, CH_2N), 4.54-4.79 (m, 2H, rotamer$_b$, OCH_2), 7.33-7.43 (m, 12H, both rotamers, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.53-7.61 (m, 8H, both rotamers, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **$^{13}C\{^1H\}$ NMR** (75.5 MHz, D_2O): δ = 19.2 (rotamer$_a$, $C(CH_3)_3$), 19.3 (rotamer$_b$, $C(CH_3)_3$), 19.7, 19.9, 20.0 (both rotamers, $CH(CH_3)_2$), 26.4 (both rotamers, $CH(CH_3)_2$), 26.9 (rotamer$_a$, $C(CH_3)_3$), 27.0 (rotamer$_b$, $C(CH_3)_3$), 27.4 (rotamer$_a$, NCH_3), 27.9 (rotamer$_b$, NCH_3), 34.4 (rotamer$_a$, CH_3), 34.5 (rotamer$_b$, CH_3), 44.8 (rotamer$_a$, CH_2N), 44.9 (rotamer$_b$, CH_2N), 49.1 (rotamer$_a$, CH_2CH_2), 49.2 (rotamer$_b$, CH_2CH_2), 62.3 (rotamer$_a$, CH_2O), 62.9 (rotamer$_b$, CH_2O), 64.6 (both rotamers, CH), 127.8 (rotamer$_a$, 2 x $C_{3'}$, 2 x $C_{5'}$), 128.0 (rotamer$_b$, 2 x $C_{3'}$, 2 x $C_{5'}$), 129.9 (rotamer$_a$, 2 x $C_{4'}$), 130.0, 130.1 (rotamer$_b$, 2 x $C_{4'}$), 132.8 (rotamer$_a$, $C_{1'}$), 133.1 (rotamer$_b$,

$C_{1'}$), 135.3 (rotamer$_a$, 2 x $C_{2'}$, 2 x $C_{6'}$), 135.5 (rotamer$_b$, 2 x $C_{2'}$, 2 x $C_{6'}$), 159.6 (rotamer$_a$, C=N), 159.7 (rotamer$_b$, C=N), 168.3 (rotamer$_a$, CO), 168.6 (rotamer$_b$, CO) ppm; **MS** (ESI) *m/z* (rel intensity): 509 (MH^+, 49), 3340 (100), 320 (42). **HRMS** (ESI-TOF): calcd. for $C_{29}H_{45}N_4O_2Si$ [MH^+] 509.3312; found: 509.3292. **$[\alpha]_D^{20}$:** +11.3 (c = 1, CH_2Cl_2).

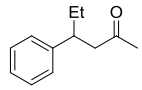
(*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-*N*-(2-(imidazolidin-2-ylideneamino)ethyl)-*N*,3-dimethylbutan-2-amine (L10). Et_3N (0.16 mL, 0.1.15 mmol) and 2-(methylthio)-4,5-dihydro-1*H*-imidazole hydroiodide (141 mg, 0.58 mmol) were added to a solution of protected aminoalcohol **33a** (230 mg, 0.58 mmol) in dry CH_3CN (10 mL) at rt. The reaction mixture was stirred at rt for 24 h and then the solvent was removed *in vacuo*. The crude was purified by column chromatograghy (aluminium oxide, CH_2Cl_2/MeOH 98/2) to afford **L10** as a colorless oil (267 mg, 99%): **IR** (ATR): 3340, 1590, 1105, 705 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.6 Hz, 3H, CH(CH_3)$_2$), 0.92 (d, *J* = 6.6 Hz, 3H, CH(CH_3)$_2$), 1.06 (s, 9H, C(CH_3)$_3$), 1.82-1.93 (m, 1H, C*H*(CH$_3$)$_2$), 2.28-2.37 (m, 1H, CHN), 2.37 (s, 3H, NCH_3), 2.82-2.85 (m, 2H, CH_2N), 3.32-3.38 (m, 2H, CH_2NCH_3), 3.62-3.82 (m, 6H, HNCH_2CH_2NH, CH_2O), 7.37-7.48 (m, 7H, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$, NH), 7.62-7.66 (m, 4H, 2 x $H_{2'}$, 2 x $H_{6'}$), 9.12 (brs, 1H, NH) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 19.2 (*C*(CH$_3$)$_3$), 20.2 (CH(*C*H$_3$)$_2$), 21.5 (CH(*C*H$_3$)$_2$), 27.0 (C(*C*H$_3$)$_3$), 27.5 (*C*H(CH$_3$)$_2$), 37.3 (NCH_3), 41.5 (*C*H_2N), 43.0, 43.4 (HN*C*H_2*C*H_2NH), 56.7 (*C*H_2NCH_3), 61.1 (CH_2O), 71.3 (CH), 127.9 (2 x $C_{3'}$, 2 x $C_{5'}$), 130.0 (2 x $C_{4'}$), 133.0 (2 x $C_{1'}$), 135.6 (2 x $C_{2'}$, 2 x $C_{6'}$), 161.7 (C=N) ppm; **MS** (ESI) *m/z* (rel intensity): 467 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{27}H_{43}N_4OSi$ [MH^+] 467.3206; found: 467.3208. **$[\alpha]_D^{20}$:** +9.3 (c = 1, CH_2Cl_2).

(*R*)-1-((*tert*-butyldiphenylsilyl)oxy)-*N*-(2-(imidazolidin-2-ylideneamino)ethyl)-*N*-methylpropan-2-amine (L12). Et_3N (0.11 mL, 0.79 mmol) and 2-(methylthio)-4,5-dihydro-1H-imidazole hydroiodide (9.7 mg, 0.40 mmol) were added to a solution of protected aminoalcohol **33a** (147 mg, 0.40 mmol) in dry CH_3CN (5 mL) at rt. The reaction mixture was stirred at rt for 24 h and then the solvent was removed *in vacuo*. The crude was purified by column chromatograghy (aluminium oxide, CH_2Cl_2/MeOH 95/5) to afford **L12** as a colorless oil (120 mg, 69%): **IR** (ATR): 3355, 1590, 1115, 700 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.7 Hz, 3H, CHCH_3), 1.06 (s, 9H, C(CH_3)$_3$), 2.33 (s, 3H, NCH_3), 2.77-2.80 (m, 2H, NCH_2), 2.91-2.97 (m, 1H, CH), 3.35-3.67 (m, 8H, *C*H_2NCH_3,

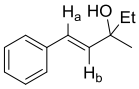
HNC*H*$_2$C*H*$_2$NH, CH_2O), 7.37-7.48 (m, 6H, 2 x $H_{3'}$, 2 x $H_{4'}$, 2 x $H_{5'}$), 7.62-7.66 (m, 4H, 2 x $H_{2'}$, 2 x $H_{6'}$) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 12.0 (CH*C*H$_3$), 19.3 (*C*(CH$_3$)$_3$), 27.0 (C(*C*H$_3$)$_3$), 36.8 (NCH_3), 41.4 (NCH_2), 42.8, 43.4 (HN*C*H$_2$*C*H$_2$NH), 55.7 (CH_2NCH_3), 60.4 (CH), 65.2 (CH_2O), 127.9 (2 x $C_{3'}$, 2 x $C_{5'}$), 130.0 (2 x $C_{4'}$), 133.0 (2 x $C_{1'}$), 135.4 (2 x $C_{2'}$, 2 x $C_{6'}$), 162.1 (C=N) ppm; **MS** (ESI) *m/z* (rel intensity): 467 (MH^+, 100). **HRMS** (ESI-TOF): calcd. for $C_{25}H_{39}N_4OSi$ [MH^+] 439.2893; found: 439.2899. **$[\alpha]_D^{20}$:** +8.7 (c = 1, CH_2Cl_2).

3.2. Screening of the new catalytic systems in Cu(I)-catalyzed asymmetric conjugate addition reactions

(*S*)-4-phenylhexan-2-one (41). $CuBr{\cdot}SMe_2$ (6.2 mg, 0.03 mmol) and **L4** (9.2 mg, 0.036 mmol) were dissolved in dry CH_2Cl_2 (3.0 mL) and the mixture was stirred at rt for 20 min. Then, *trans*-4-phenyl-3-buten-2-one **40** (87.7 mg, 0.30 mmol) was added and the mixture was cooled to – 78 ºC. Ethylmagnesium bromide (0.22 mL, 0.66 mmol, 3M in Et_2O) was added dropwise and the reaction was further stirred at -78 ºC for 90 min. MeOH (3 mL) was added and the mixture was allowed to reach rt. Then, aqueous NH_4Cl 1 M solution was added to the mixture. The organic phase was separated, and the resulting aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The reaction crude was subjected to flash chromatography (silica gel, petroleum ether/EtOAc 9/1) to yield **41** as a colorless oil (51.8 mg, 49%): **IR** (ATR): 1715, 1360, 755 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.50-1.78 (m, 2H, CH_2CH_3), 2.03 (s, 3H, $COCH_3$), 2.72-2.80 (m, 2H, CH_2), 3.00-3.04 (m, 1H, CH), 7.18-7.30 (m, 5H, H_{2Ar}, H_{3Ar}, H_{4Ar}, H_{5Ar}, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 12.2 (CH_2CH_3), 29.5 (CH_2CH_3), 30.8 ($COCH_3$), 43.1 (CH), 50.6 (CH_2), 126.1 (C_{4Ar}), 127.3 (C_{2Ar}, C_{6Ar}), 128.2 (C_{3Ar}, C_{5Ar}), 144.0 (C_{1Ar}), 207.6 (CO) ppm.



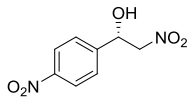
(*E*)-3-methyl-1-phenylpent-1-en-3-ol (42). Isolated in the previous procedure as by-product (20.1 mg, 19%): **IR** (ATR): 3430, 3090cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 1.34 (s, 3H, CCH_3), 1.63 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 1.84 (s, 1H, OH), 6.24 (d, *J* = 16.2 Hz, 1H, CH_a=CH_b), 6.56 (d, *J* = 16.2 Hz, 1H, CH_a=CH_b), 7.15-7.45 (m, 5H, H_{2Ar}, H_{3Ar} H_{4Ar} H_{5Ar} H_{6Ar}); **^{13}C{^{1}H} NMR** (75.5 MHz, $CDCl_3$): δ = 8.2 (CH_2CH_3), 27.4 (CCH_3), 35.2 (CH_2CH_3),



73.2 (CCH_3), 126.0 (CH_a=CH_b), 126.2 (C_{2Ar}, C_{6Ar}), 127.1 (CH_a=CH_b), 127.2 (C_{4Ar}), 128.4 (C_{3Ar}, C_{5Ar}), 136.4 (C_{1Ar}) ppm.

3.3. Screening of the new catalytic systems in copper-catalyzed asymmetric Henry reactions

(*S*)-2-nitro-1-(4-nitrophenyl)ethan-1-ol (44):[21] **L1** (13.4 mg, 0.05 mmol) and CuBr (6.4 mg, 0.04 mmol) were dissolved in methanol (1.5 mL) and the mixture was stirred for 1 h. Then, nitromethane (1.00 mL, 18.15 mmol) and 4-nitrobenzaldehyde (49.9 mg, 0.33 mmol) were added over the solution and the mixture was stirred at rt for 48 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, petroleum ether/EtOAc 7/3), affording β-nitroalcohol **44** as a colorless oil (33.4 mg, 47%) (50% conversion): **IR** (ATR): 3510, 2920, 1515, 1380, 1080, 855 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$): δ= 3.09 (d, *J* = 4.0 Hz, 1H, OH), 3.98-4.79 (m, 2H, CH_2), 5.61 (dt, 1H, *J* = 8.1, 4.1 Hz, 1H, CH), 7.63 (d, *J* = 8.7 Hz, 2H, H_{2Ar}, H_{6Ar}), 8.28 (d, *J* = 8.7 Hz, 2H, H_{3Ar}, H_{5Ar}) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 69.9 (CH), 80.6 (CH_2), 124.1 (C_{3Ar}, C_{5Ar}), 126.9 (C_{2Ar}, C_{6Ar}), 145.0 (C_{1Ar}), 148.0 (C_{4Ar}). The enantiomeric excess was determined by HPLC to be 47% [Chiralcel OD, hexane/*i*PrOH 9/1, 1 mL/min, t_r (minor) = 26.7 min (26%), t_r (major) = 33.1 min (74%)]. The absolute stereochemistry was assigned as (*S*) by comparison with literature.



[21] Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692.

4. USE OF *N*-ALKENYLNITRONES IN INVERSE-ELECTRON DEMAND DIELS-ALDER (IEDDA) REACTION

(*Z*)-but-2-en-2-ylboronic acid (46).[22] $HBBr_2 \cdot SMe_2$ (81.0 mL, 81.0 mmol) was added to a solution of 2-butyne (5.00 g, 92.4 mmol) in CH_2Cl_2 at 0 ºC and the mixture was stirred for 2 h. The reaction mixture was then transferred to 60 mL of a 10:1 mixture of diethyl ether and H_2O and allowed to stir for 15 minutes. The reaction mixture was diluted with additional diethyl ether (40 mL) and extracted with H_2O (3 x 10 mL). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the alkenylboronic acid **46** (6.61 g, 82%) as a white solid: **m.p.** (Et_2O): 77-79 ºC; **IR** (ATR): 3305, 2950, 1605, 1460, 1380 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.75 (s, 3H, CH_3C=$CHCH_3$), 1.80 (d, J = 6.5 Hz, 3H, CH_3CH=$CHCH_3$), 6.83 (q, *J* = 6.5, 1H, CH_3CH=$CHCH_3$) ppm; **^{13}C{^{1}H} NMR** (125.7 MHz, $CDCl_3$): δ = 14.2 (CH_3CH_2), 62.3 (CH_3CH_2), 126.4 (C_{3Ar}, C_{5Ar}), 128.9 (C_{2Ar}, C_{6Ar}), 130.1 (C_{1Ar}), 130.6 (C_{4Ar}), 151.9 (C=NOH), 164.0 (CO) ppm.

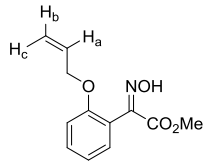
Ethyl (*E*)-2-(hydroxyimino)-2-phenylacetate (49).[23] Hydroxylamine hydrochloride (1.04 g, 15.00 mmol) was added to a solution of ethyl benzoylformate (1.78 g, 10.00 mmol) in pyridine (3.85 mL). The mixture was stirred at reflux for 2 h and then the solvent was removed. H_2O and 3 N HCl were added and the mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were washed with H_2O (20 mL) and sat. $NaHCO_3$ (20 mL), dried over anhydrous Na_2SO_4, and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, 80% hexane/EtOAc) to afford the oxime **49** as a colorless oil (1.04 g, 52%): **IR** (ATR): 3430, 2985, 1220 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.1 Hz, 3H, CH_3CH_2), 4.47 (q, *J* = 7.1 Hz, 2H, CH_3CH_2), 7.37-7.43 (m, 3H, C_{3Ar}, C_{4Ar}, C_{5Ar}), 7.57-7.59 (m, 2H, C_{2Ar}, C_{6Ar}), 9.68 (s, 1H, NOH) ppm; **^{13}C{^{1}H} NMR** (125.7 MHz, $CDCl_3$): δ = 14.2 (CH_3CH_2), 62.3 (CH_3CH_2), 126.4 (C_{3Ar}, C_{5Ar}), 128.9 (C_{2Ar}, C_{6Ar}), 130.1 (C_{1Ar}), 130.6 (C_{4Ar}), 151.9 (C=NOH), 164.0 (CO) ppm.

[22] Patil, A. S.; Mo, D.-L.; Wang, H.-Y.; Mueller, D. S.; Anderson, L. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 7799.
[23] Hata, S.; Maeda, T.; Shimizu, M. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 1203.

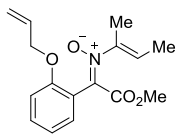
Dimethyl 2-(hydroxyimino)malonate (50).[24] A solution of dimethyl malonate (4.63 g, 35.02 mmol) in glacial acetic acid (7 mL) was added to a solution of sodium hydroxide (840 mg, 21.01 mmol) in glacial acetic acid (10 mL) at 0 ºC. Then, an aqueous solution of $NaNO_2$ 4 M (4.83 g, 70.04 mmol) was slowly added and the reaction mixture was stirred at 0 ºC for 1 h and at rt overnight. The reaction was saturated with NaCl (15 mL) and extracted with EtOAc (3 x 15 mL). The organic phase was washed with sat. $NaHCO_3$ (15 mL) and brine (2 x 15 mL) until the pH of the aqueous layer remained basic (pH 8-9). Next, the organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum, affording oxime **50** as a white solid (3.39 g, 60%): **m.p.** (petroleum ether/EtOAc): 104-105 ºC; **IR** (ATR): 3410, 1730, 1650 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 8.86 (brs, 1H, NOH) ppm; **^{13}C{^{1}H} NMR** (125.7 MHz, $CDCl_3$): δ = 53.1 (OCH_3), 53.4 (OCH_3), 143.8 (C=NOH), 160.4 (CO), 160.9 (CO) ppm.

(*E*)-N-(but-2-en-2-yl)-1,3-dimethoxy-1,3-dioxopropan-2-imine oxide (52).[25] Pyridine (0.88 mL, 10.84 mL) was added to a solution of oxime **50** (582 mg, 3.61 mmol), alkenylboronic acid **46** (1.08 g, 10.84 mmol), $Cu(OAc)_2$ (656 mg, 3.61 mmol), and anhydrous Na_2SO_4 (4.36 g, 30.72 mmol) in DCE (36 mL)and the mixture was stirred at rt for 5 h. The reaction mixture was then filtered through a plug of silica gel covered with a layer of celite and washed with EtOAc (3 x 10 mL). The filtrate was concentrated under vacuum. Purification by column chromatography (silica gel, hexane/EtOAc 9/1) of the resulting residue afforded the corresponding nitrone **52** as a yellow oil (513 mg, 66%): **IR** (ATR): 1730, 1630, 1515, 1385, 1295, 1220 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.66 (dq, J = 7.2, 1.3 Hz, 3H, CH_3C=CHCH_3), 2.00 (s, 3H, CH_3C=$CHCH_3$), 3.74 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_2), 5.60-5.65 (m, 1H, CH_3C=C*H*CH_3) ppm; **^{13}C{^{1}H} NMR** (125.7 MHz, $CDCl_3$): δ = 12.5 (CH_3C=CH*C*H_3), 14.0 (*C*H_3C=$CHCH_3$), 52.9 (OCH_3), 53.1 (OCH_3), 122.0 (CH_3C=*C*HCH_3), 131.5 (CH_3*C*=$CHCH_3$), 144.3 (C=N), 159.5 (CO), 160.7 (CO) ppm.

[24] May, D. A.; Lash, T. D. *J. Org. Chem.* **1992**, *57*, 4820.
[25] Reidl, T. W.; Son, J.; Wink; D. J.; Anderson, L. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 11579.

methyl 2-(2-(allyloxy)phenyl)-2-(hydroxyimino)acetate (53). 

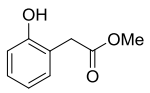
Hydroxylamine hydrochloride (147 mg, 2.12 mmol) was added to a solution of **61** (311 mg, 1.41 mmol) in pyridine (3 mL). The mixture was stirred at reflux for 2 h and then the solvent was removed. H_2O (20 mL) and 3 N HCl (20 mL) were added and the mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were washed with H_2O (20 mL) and $NaHCO_3$ sat. (20 mL), dried over Na_2SO_4, and concentrated to dryness. The crude was subjected to flash chromatography (silica gel, hexane/EtOAc 8/2) to afford the oxime **(*Z*)-53** as a colorless oil (180 mg, 54%) and **(*E*)-53** as a colorless oil (95.3 mg, 29%). **Methyl (*Z*)-2-(2-(allyloxy)phenyl)-2-(hydroxyimino)acetate ((*Z*)-53): IR** (ATR): 3420, 2985, 1645, 1325, 1220 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 4.52-4.54 (m, 2H, CH_2), 5.22-5.24 (m, 1H, H_b), 5.35 (dd, *J* = 17.2, 1.9 Hz, 1H, H_c), 5.95 (ddt, *J* = 17.2, 10.2, 4.8 Hz, 1H, H_a), 6.94-6.95 (m, 1H, H_{3Ar}), 7.02-7.05 (m, 1H, H_{5Ar}), 7.36-7.42 (m, 2H, H_{4Ar}, H_{6Ar}), 10.29 (brs, 1H, NOH) ppm; **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$): δ = 52.8 (CH_3), 69.1 (CH_2), 112.5 (C_{3Ar}), 117.1 (CH_bH_c=CH_a), 118.7 (C_{1Ar}), 120.5 (C_{5Ar}), 130.6 (C_{6Ar}), 131.2 (C_{4Ar}), 132.8 (CH_bH_c=CH_a), 148.0 (C=NOH), 155.9 (C_{2Ar}), 164.0 (CO) ppm. **Methyl (*E*)-2-(2-(allyloxy)phenyl)-2-(hydroxyimino)acetate ((*E*)-53): IR** (ATR): 3450, 2970, 1340, 1230 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 4.53 (dt, *J* = 5.6, 1.6 Hz, 2H, CH_2), 5.28 (dq, *J* = 10.7, 1.5 Hz, 1H, H_b), 5.36 (dq, *J* = 17.3, 1.5 Hz, 1H, H_c), 5.91-6.09 (m, 1H, H_a), 6.90 (d, *J* = 8.3 Hz, 1H, H_{3Ar}), 6.94-7.05 (m, 1H, H_{5Ar}), 7.36 (ddd, *J* = 8.8, 7.6, 1.8 Hz, 1H, H_{4Ar}), 7.56 (dd, *J* = 7.6, 1.8 Hz, 1H, H_{6Ar}), 9.92 (brs, 1H, NOH) ppm; **^{13}C{^{1}H} NMR** (125.7 MHz, $CDCl_3$): δ = 52.3 (CH_3), 69.7 (CH_2), 112.7 (C_{3Ar}), 118.1 (CH_bH_c=CH_a), 120.9 (C_{1Ar}), 121.3 (C_{5Ar}), 129.3 (C_{6Ar}), 131.7 (C_{4Ar}), 132.6 (CH_bH_c=CH_a), 148.8 (C=NOH), 156.5 (C_{2Ar}), 163.7 (CO) ppm.

1-(2-(allyloxy)phenyl)-N-((*E*)-but-2-en-2-yl)-2-methoxy-2-oxoethan-1-imine oxide (55). 

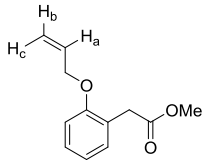
Pyridine (0.55 mL, 6.78 mL) was added to a solution of oxime **53** (532 mg, 2.26 mmol), alkenylboronic acid **46** (677 mg, 6.78 mmol), $Cu(OAc)_2$ (285 mg, 2.26 mmol) and anhydrous Na_2SO_4 (2.73 g, 19.21 mmol) in DCE (23 mL) and the reaction mixture was stirred at rt for 20 h. The reaction mixture was then filtered through a plug of silica gel covered with a layer of celite and washed with EtOAc (3 x 10 mL) and the filtrate was concentrated under vacuum to give the crude product mixture. Purification by column chromatography (silica gel, hexane/EtOAc 8/2) of the resulting residue afforded the nitrone **55** as a colorless oil (309

mg, 47%): **IR** (ATR): 2935, 1740, 1630, 1420, 1385 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.68 (d, J = 6.9 Hz, 3H, CH_3C=CHCH_3), 2.14 (s, 3H, CH_3C=CHCH_3), 3.70 (s, 3H, OCH_3), 4.51 (d, J = 5.1 Hz, 2H, CH_2), 5.24 (d, J = 10.6 Hz, 1H, H_b), 5.35 (d, J = 17.3 Hz, 1H, H_c), 5.63 (q, J = 7.1 Hz, 1H, CH_3C=CHCH$_3$), 5.91-5.99 (m, 1H, H_a), 6.89-6.90 (m, 1H, H_{3Ar}), 7.01-7.03 (m, 1H, H_{5Ar}), 7.32-7.35 (m, 1H, H_{4Ar}), 7.91-7.93 (m, 1H, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (125.7 MHz, $CDCl_3$): δ = 12.6 (CH_3C=CHCH_3), 14.1 (CH_3C=CHCH_3), 52.5 (OCH_3), 69.4 (OCH_2), 112.4 (C_{3Ar}), 117.7 (CH_bH_c=CH_a), 119.5 (C_{1Ar}), 120.0 (C_{5Ar}), 120.8 (CH_3C=$CHCH_3$), 122.1 (CH_3C=$CHCH_3$), 130.6, 131.5 (C_{4Ar}, C_{6Ar}), 132.7 (CH_bH_c=CH_a), 145.4 (C_{2Ar}), 156.4 (CO_2Me), 164.5 (C=N) ppm.

methyl 2-(2-hydroxyphenyl)acetate (59).[26] H_2SO_4 (10 drops) was added to a stirred solution of 2-hydroxyphenylacetic acid (2.05 g, 13.47 mmol) in methanol (40 mL) and the reaction mixture was heated at reflux for 3 h. The mixture was cooled, filtered through a pad of silica and washed with EtOAc. The solvent was removed *in vacuo* to afford **59** as white solid (2.15 g, 96%): **m.p.** (EtOAc): 62-63 ºC [lit.[26] 61-62 ºC (EtOAc)]; **IR** (ATR): 3410, 1725, 1470, 1360, 1205 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 3.69 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 6.36 (OH), 6.86-6.92 (m, 2H, H_{3Ar}, H_{5Ar}), 7.11 (dd, J = 7.7, 1.8 Hz, 1H, H_{6Ar}), 7.17 (td, J = 7.7, 1.8 Hz, 1H, H_{4Ar}) ppm; **^{13}C{^{1}H} NMR** (125.7 MHz, $CDCl_3$): δ = 37.2 (CH_2), 52.7 (OCH_3), 117.2 (C_{3Ar}), 120.7 (C_{1Ar}), 120.8 (C_{5Ar}), 129.1 (C_{4Ar}), 131.1 (C_{6Ar}), 154.9 (C_{2Ar}), 174.3 (CO) ppm.



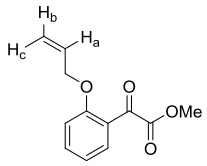
methyl 2-(2-(allyloxy)phenyl)acetate (60). Potassium carbonate (11.86 g, 85.82 mmol) and allyl bromide (3.70 mL, 42.91 mmol) were added to a solution of **59** (3.56 g, 21.45 mmol) in acetone (30 mL) and the mixture was stirred overnight at rt. The solution was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (30 mL) and the organic phase was washed with H_2O (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness. The resulting crude was purified by flash chromatography (silica gel, hexane/EtOAc 95/5) to afford **60** as a yellow oil (2.80 g, 63%): **IR** (ATR): 2955, 1750, 1510, 1245, 1170 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 3.68 (s, 2H, $ArCH_2$), 3.69 (s, 3H, OCH_3), 4.49-4.61 (m, 2H, OCH_2), 5.25-5.28 (m, 1H, H_b), 5.40-5.45 (dq, J = 17.3, 1.7 Hz, 1H, H_c), 6.03 (ddt, J = 17.3, 10.7,



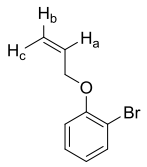
[26] Aitken, H. R. M.; Furkert, D. P.; Hubert, J. G.; Wood, J. M.; Brimble, M. A. *Org. Biomolec. Chem.* **2013**, *11*, 5147.

4.9 Hz, 1H, H_a), 6.87 (dd, *J* = 8.2, 1.1 Hz, 1H, H_{3Ar}), 6.94 (td, *J* = 7.4, 1.1 Hz, 1H, H_{5Ar}), 7.19-7.26 (m, 2H, H_{4Ar}, H_{6Ar}) ppm; **$^{13}C\{^1H\}$ NMR** (125.7 MHz, $CDCl_3$): δ = 36.1 ($ArCH_2$), 51.8 (OCH_3), 68.7 (OCH_2), 111.7 (C_{3Ar}), 116.9 (CH_bH_c=CH_a), 120.7 (C_{5Ar}), 123.5 (C_{1Ar}), 128.5 (C_{4Ar}), 131.0 (C_{6Ar}), 133.2 (CH_bH_c=CH_a), 156.5 (C_{2Ar}), 172.3 (CO) ppm.

methyl 2-(2-(allyloxy)phenyl)-2-oxoacetate (61). Magnesium turnings (488 mg, 20.08 mmol) were added to a solution of **63** (3.06 g, 14.34 mmol) in dry THF (8 mL) at -78 ºC and the mixture was stirred at -78 ºC for 2 h. A solution of methyl oxalate (2.37 g, 20.08 mmol) in THF (12 mL) was added dropwise and the reaction mixture was stirred at -78 ºC for 3h. The reaction mixture was quenched with aq. NH_4Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, affording **61** as a colorless oil (1.80 g, 57%): **IR** (ATR): 2970, 1765, 1680, 1525, 1250 cm^{-1}; **^1H NMR** (500 MHz, $CDCl_3$): δ = 3.82 (s, 3H, OCH_3), 4.53-4.55 (m, 2H, CH_2), 5.27-5.30 (m, 1H, H_b), 5.34-5.39 (m, 1H, H_c), 5.92-6.00 (m, 1H, H_a), 6.93 (d, *J* = 8.5 Hz, 1H, H_{3Ar}), 7.00-7.03 (m, 1H, H_{5Ar}), 7.51 (ddd, *J* = 8.8, 7.3, 1.8 Hz, 1H, H_{4Ar}), 7.82 (dd, *J* = 7.7, 1.8 Hz, 1H, H_{6Ar}) ppm; **$^{13}C\{^1H\}$** NMR (125.7 MHz, $CDCl_3$): δ = 52.4 (CH_3), 69.9 (CH_2), 113.0 (C_{3Ar}), 118.9 (CH_bH_c=CH_a), 121.4 (C_{5Ar}), 122.9 (C_{1Ar}), 130.7 (C_{6Ar}), 132.0 (CH_bH_c=CH_a), 136.3 (C_{4Ar}), 159.3 (C_{2Ar}), 165.6 (CO_2Me), 186.5 (ArCO) ppm.



1-(allyloxy)-2-bromobenzene (63). Potassium carbonate (7.16 g, 51.83 mmol) and allyl bromide (2.24 mL, 25.92 mmol) were added to a solution of 2-bromophenol (2.24 g, 12.96 mmol) in acetone (26 mL) and the mixture was stirred overnight at rt. The solution was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (30 mL) and the organic extracts washed with H_2O (30mL) and brine (30mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness. The resulting crude was purified by flash chromatography (silica gel, hexane/EtOAc 95/5) to afford **60** as a yellow oil (2.68 g, 97%): **IR** (ATR): 2930, 1650, 1530, 1285 cm^{-1}; **^1H NMR** (500 MHz, $CDCl_3$): δ = 4.61-4.62 (m, 2H, CH_2), 5.32 (dd, *J* = 10.6, 1.7 Hz, 1H, H_b), 5.50 (dq, *J* = 17.3, 1.7 Hz, 2H, H_c), 6.07 (ddt, *J* = 17.2, 10.4, 4.9 Hz, 1H, H_a), 6.84 (td, *J* = 7.5 Hz, 1H, H_{4Ar}), 6.90 (dd, *J* = 8.2, 1.4 Hz, 1H, H_{6Ar}), 7.25 (ddd, *J* = 8.6, 7.5, 1.7 Hz, 1H, H_{5Ar}), 7.55 (dd, *J* = 7.9, 1.6 Hz, 1H, H_{3Ar}) ppm; **$^{13}C\{^1H\}$ NMR** (125.7



MHz, $CDCl_3$): δ = 69.6 (CH_2), 112.3 (C_{2Ar}), 113.7 (C_{6Ar}), 117.7 (CH_bH_c=CH_a), 122.1 (C_{4Ar}), 128.5 (C_{5Ar}), 132.7 (CH_bH_c=CH_a), 133.4 (C_{3Ar}), 155.0 (C_{1Ar}) ppm.

(2-allylphenyl)methanol (66). 2-bromobenzyl alcohol (1.29 g, 6.92 mmol), $Pd(PPh_3)_2Cl_2$ (486 mg, 0.69 mmol), tri(butyl)tin (2.4 mL, 7.62 mmol) and PPh_3 (363 mg, 1.38 mmol) were dissolved in DMF (15 mL) and the reaction mixture was heated at 60 ºC for 24 h. The mixture was diluted with H_2O (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to dryness. Purification by column chromatography (silica gel, hexane/EtOAc 8/2) afforded **66** as a white solid (732 mg, 71%): **m.p.** (hexane/EtOAc): 69-71 ºC; **IR** (ATR): 3320, 2930, 1255 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 1.60 (t, J = 6.0 Hz, 1H, OH), 3.49 (dd, J = 6.1, 1.7 Hz, 2H, CH_2), 4.71 (d, J = 5.9 Hz, 2H, CH_2OH), 5.01 (dd, J = 17.1, 1.8 Hz, 1H, H_c), 5.08 (dd, J = 10.1, 1.6 Hz, 1H, H_b), 5.99-6.03 (m, 1H, H_a), 7.13-7.39 (m, 4H, H_{3Ar}, H_{4Ar}, H_{5Ar}, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (125.7 MHz, $CDCl_3$): δ = 36.7 (CH_2), 63.1 (CH_2OH), 115.8 (CH_bH_c=CH_a), 126.6, 128.0, 128.3, 129.8 (C_{2Ar}, C_{3Ar}, C_{4Ar}, C_{5Ar}), 137.4 (C_{2Ar}), 137.8 (CH_bH_c=CH_a), 138.6 (C_{1Ar}) ppm.

1-allyl-2-(bromomethyl)benzene (67).[27] PBr_3 (0.45 mL, 4.79 mmol) was added dropwise to a solution of (2-allylphenyl)methanol **66** (546 mg, 3.69 mmol) in DCE (10 mL) at 0 ºC. The reaction was stirred at room temperature for 1 h. Ice water was added carefully to the mixture and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography afforded **67** as a yellow oil (358 mg, 44%); **IR** (ATR): 2955, 1490, 1025 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 3.56-3.57 (m, 2H, CH_2), 4.56 (s, 2H, CH_2Br), 5.06 (dt, J = 17.1, 1.7 Hz, 1H, H_c), 5.13 (dt, J = 10.1, 1.7 Hz, 1H, H_b), 6.00-6.08 (m, 1H, H_a), 7.22-7.37 (m, 4H, H_{3Ar}, H_{4Ar}, H_{5Ar}, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (125.7 MHz, $CDCl_3$): δ = 31.7 (CH_2Br), 36.7 (CH_2), 116.3 (CH_bH_c=CH_a), 127.0 (C_{3Ar}), 129.2, 130.3, 130.6 (C_{4Ar}, C_{5Ar}, C_{6Ar}), 135.8 (C_{1Ar}), 136.5 (CH_bH_c=CH_a), 138.8 (C_{2Ar}) ppm.

[27] Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901.

methyl 2-(2-bromophenyl)-2-oxoacetate (71). H_2SO_4 (1 drop) was added to a stirred solution of 2-(2-bromophenyl)-2-oxoacetic acid (295 mg, 1.29 mmol) in methanol (3.5 mL) and the reaction mixture was heated at reflux for 3 h. The mixture was cooled, filtered through a pad of silica and washed with EtOAc. The solvent was removed *in vacuo* to afford **71** as brown oil(272 mg, 87%): **IR** (ATR): 1740, 1710, 1435, 1255, 1210 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 3.89 (s, 3H, OCH_3), 7.34-7.40 (m, 2H, H_{4Ar}, H_{5Ar}), 7.55-7.62 (m, 2H, H_{3Ar}, H_{6Ar}) ppm; **^{13}C{^{1}H} NMR** (125.7 MHz, $CDCl_3$): δ = 53.4 (OCH_3), 121.6 (C_{2Ar}), 127.8 (C_{6Ar}), 131.7, 133.7, 134.2 (C_{3Ar}, C_{4Ar}, C_{5Ar}), 135.4 (C_{1Ar}), 162.8 (CO_2Me), 186.9 (ArCO) ppm.