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Palladium catalyzed cross-coupling reactions with sulfonylhydrazones: New cascade reactions and coupling processes

Miguel Paraja Ramos

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Palladium catalyzed cross-coupling reactions with sulfonylhydrazones: New cascade reactions and coupling processes

Miguel Paraja Ramos

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RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español/Otro Idioma: Reacciones de acoplamiento cruzado con sulfonilhidrazonas catalizadas por paladio: Nuevas reacciones en cascada y procesos de acoplamiento.	Inglés: Palladium catalyzed cross-coupling reactions with sulfonylhydrazones: New cascade reactions and coupling processes.

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RESUMEN (en español)

En esta Memoria se recogen los resultados que se han obtenido durante el desarrollo de nuevas reacciones de acoplamiento cruzado con *N*-tosilhidrazonas catalizadas por paladio. Los contenidos se han dividido en una introducción general y tres capítulos que engloban los avances alcanzados en nuevas reacciones en cascada y auto-tandem, así como en la síntesis de dienos conjugados. Finalmente se incluye una parte experimental donde se describen en detalle todos los experimentos realizados, así como la caracterización de todos los productos que aparecen en la tesis.

La introducción general presenta una breve revisión de la situación actual y los avances más recientes en el contexto de las reacciones de acoplamiento catalizadas por metales de transición, y en particular, en las reacciones de acoplamiento cruzado que emplean N-sulfonilhidrazonas.

En el Capítulo 1 se presenta una nueva reacción de ciclación en cascada que es iniciada con un acoplamiento cruzado entre *N*-tosilhidrazonas y ioduros de arilo para luego dar lugar a una reacción de carbopaladación intramolecular. El paso clave en esta reacción consiste en la generación de una especie de bencil paladio la cual no puede experimentar la β-eliminación de hidrogeno. De esta manera, el complejo intermedio puede evolucionar a través de una carbopaladación intramolecular, gracias a la presencia de un fragmento alilo adyacente, en una reacción de ciclación 5-*exo*-trig. El empleo de esta reacción aportó nuevas rutas para la preparación de derivados de indanos, benzofuranos, indoles e isoquinolinas.

En el Capítulo 2, se mostran los resultados obtenidos tras el desarrollo de una nueva reacción auto-tandem que consiste en el acoplamiento entre una tosilhidrazona y un halogenuro de bencilo, seguida de una reacción de tipo Heck intramolecular. La reacción de tipo Heck es promovida gracias al doble enlace generado tras el primer acoplamiento con la tosilhidrazona. De este modo se sintetizaron una importante variedad de fluorenos, xantenos e isoquinolinas.

Por último, en el Capítulo 3 se expone una nueva reacción de acoplamiento cruzado entre tosilhidrazonas y bromuros de alquenilo para dar lugar a dienos conjugados. Esta transformación permite la preparación de dienos conjugados altamente funcionalizados. La utilidad de estos productos se puso de manifiesto realizando una reacción de cicloadición [4+2] para dar lugar a un precursor de pentaheliceno.

RESUMEN (en Inglés)

The results presented in this Memory belong to the field of palladium catalyzed cross-coupling reactions with *N*-tosylhydrazones. The contents have been divided in a general introduction and three chapters, organized attending to the different topics covered along the research: cascade cyclization reactions, auto-tandem cyclization processes and synthesis of conjugated dienes. Finally, an experimental part is included where all the experiments carried out are described in detail, as well as the characterization of all the products that appear in the thesis.

The general introduction presents a brief review of the stae of the art and the most recent advances in the context of coupling reactions catalyzed by transition metals, and in particular, in cross-coupling reactions employing *N*-sulfonylhydrazones. In Chapter 1, a novel palladium catalyzed cascade cyclization was developed. This transformation is based on the coupling between *N*-tosylhydrazones and aryl halides followed by an intramolecular carbopalladation reaction. The key step of this process consists in the generation of a benzyl palladium species which cannot undergo a β-hydride elimination. In this way, the reaction evolves through a carbopalladation taking advantage of the presence of an adjacent allyl fragment, in a formal 5-*exo*-trig cyclization. The implementation of this reaction allowed the preparation of indane, benzofuran, indole and isoquinoline derivatives.

In Chapter 2 is presented the development of a new auto-tandem cyclization reaction based on the cross-coupling between a *N*-tosylhydrazone and a benzyl bromide, followed by an intramolecular Heck reaction. In this case, the Heck reaction is enabled as a consequence of the double bond generated after the first cross-coupling. Thus, using this new transformation a wide variety of fluorenes, xantenes and acridines were prepared.

In Chapter 3, it was developed a new methodology for the preparation of conjugated dienes *via* cross-coupling reaction between *N*-tosylhydrazones and alkenyl bromides. Employing this transformation, highly substituted conjugated dienes can be prepared. In order to demonstrate the usefulness of some of these products, a [4+2] cycloaddition was carried out providing the corresponding pentahelicene precursor.

Abbreviations and Acronyms

A

Ac	acetyl
acac	acetylacetone
AIBN	2,2'-Azobis(2-methylpropionitrile)
aq	aqueous
Ar	aryl group

B

Bn	benzyl group
Boc	*tert*-butyloxycarbonyl
BQ	1,4-Benzoquinone
BTAC	behentrimonium chloride

C

°C	degree Celsius
cat	catalyst
CPME	cyclopentenyl methyl ether
COSY	Correlation Spectrscopy
Cy	cyclohexyl

D

Davephos	2-Dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
dba	dibenzylideneacetone
DCE	dichloroethane
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)-propane
d.r.	diastereoisimer ratio
DTBP	Di-*tert*-butyl peroxide
δ	chemical shift

E

E	electrophile
ee	enantiomeric excess
Eds.	Editor/s
EI	electron ionization
ESI	electrospray ionization
equiv	equivalents
Et	ethyl

EWG	electron-withdrawing group
G	
g	grams
GC-MS	Gas chomatography-mass spectrometry
H	
h	Hours
HMBC	Heteronuclear Multiple-Bond Correlation Spectroscopy
HRMS	High-Resolution Mass Spectroscopy
HSQC	Heteronuclear Single-Quantum Correlation Spectroscopy
Hz	Hertz
I	
*i*Pr	*Iso*-propyl
J	
J	coupling constant
L	
L	ligand
M	
M	metal
Me	methyl
MeTHF	2-Methyltetrahydrofuran
mg	milligram
MHZ	megahertz
min	minutes
ml	mililitres
mmol	milimoles
mol	moles
m.p.	melting point
MW	microwave
N	
N	normality
Nf	nonafluorobutanesulfonyl group
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	Nucleophile
P	
Pag.	page
PAH	Polycyclic Aromatic Hydrocarbons
Ph	phenyl
PMP	*p*-methoxyphenyl

ppm	parts per million
PTC	Phase Transfer Catalyst
R	
rt	room temperature
ref	reference
S	
Sphos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
T	
T	temperature
t	Time
Tf	trifluoromethanesulfonyl group
t-Bu	*tert*-butyl
t-BuXphos	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
THF	tetrahydrofuran
TLC	Thin-Layer Cromatography
TMS	trimethylsilyl group
Tol	tolyl group
Ts	tosyl group
X	
Xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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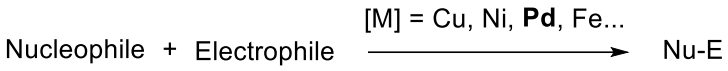
General Introduction

Transition metal catalyzed cross-coupling reactions

Cross-coupling processes involving transition metals have a rich and intriguing history commencing in the 19th century. At the present, these transformations can be regarded as some of the most reliable, efficient, accurate and powerful methods for the formation of carbon-carbon and carbon-heteroatom bonds in Organic Chemistry.

Transition metal catalysed cross-cross coupling reactions are based on the combination of nucleophilic and electrophilic species in the presence of a metal catalyst. In this way, a new cross-coupling product is achieved with the consequent generation of a new bond (Scheme I.1).



Scheme I.1. General metal catalyzed cross-coupling reaction.

The metal complex which catalyzes these reactions can be based on several transition metals, mainly Ni, Cu, Fe and Pd.[1] Nevertheless nowadays, catalysts based on palladium are the most used, being the palladium catalyzed cross-coupling reactions the most powerful tool for the generation of new C-C and C-heteroatoms bonds.[2]

Considering the topic of this doctoral thesis, the introduction will be oriented towards Pd-catalyzed cross-coupling reactions. Nevertheless, a brief revision of the origins of cross-coupling reactions will be addressed with the intention of showing a global vision of the field.

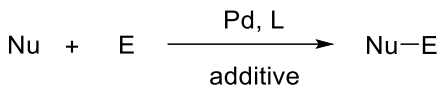
[1] A. de Mejeire, S. Brase, *Metal Catalyzed Cross-Coupling Reactions and More*, Eds. M. Oestreich Wiley-VCH, Weinheim, **2014**.
[2] E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley, New York, **2002**.

I.1 Palladium catalyzed cross-coupling reactions

I.1.1 General considerations of palladium catalyzed cross-coupling reactions

During the 1970s, metal catalyzed reactions experimented a remarkable growth, new metals like nickel were used to combine Grignard reagents with aryl and alkenyl halogens in a coupling method.[3] Shortly after, this metal was substituted by palladium,[4] which originated a new era in organometallic chemistry.

Since then, the palladium catalyzed cross-coupling reactions have represented one of the most general synthetic tools for the formation of C-C and C-heteroatom bonds[1,2,5] As a recognition of the importance of these reactions, the 2010 Nobel Prize in Chemistry was awarded to the organic chemists Richard F. Heck, Ei-ichi Negishi and Akira Suzuki, for their seminal contributions in the discovery and development of the main C-C bond forming palladium catalyzed cross-coupling methodologies (Scheme I.2).[6]



Scheme I.2. Palladium catalyzed cross-coupling reaction.

Pd-catalyzed cross-coupling reactions are based on the assembly of species with different electronic nature, electrophile (E) and nucleophile (Nu). The electrophilic partners are usually aryl, alkenyl or alkyl halides. In addition, over the years, the repertoire of electrophiles has been increased to include, pseudohalides such as sulfonates (triflates, mesylates and nanoflates), phosphates and diazonium salts among others.

---

[3] a) R. J. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Commun.* **1972**, 144–144; b) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376; c) K. Tamao, Y. Kiso, K. Sumitani, M. Kumada*, J. Am. Chem. Soc.* **1972**, *94*, 9268–9269; d) E. Negishi, S. Baba, *J. Chem. Soc. Chem. Commun.* **1976**, 596–597; e) K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, M. Kumada*, Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958–1969; f) E. Negishi, D. E. Van Horn, *J. Am. Chem. Soc.* **1977**, *99*, 3168–3170.

[4] a) M. Yamamura, I. Moritani, S.-I. Murahashi, *J. Organomet. Chem.* **1975**, *91*, 39–42; b) S. Baba, E. Negishi, *J. Am. Chem. Soc.* **1976**, *98*, 6729–6731; c) E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821–1823.

[5] J. Tsuji, *Palladium Reagents and Catalysts*; Wiley, Weinheim, **2004**.

[6] X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chemie Int. Ed.* **2010**, *49*, 9047–9050.

Regarding the nucleophilic species, there is a wide variety of possibilities which renders an enormous versatility to these processes. Organometallic reagents derived from Magnesium, Zinc, Tin, Boron or Silicon, unsaturated systems and diazo compounds are used as standard nucleophilic partners in these reactions. In the next section, different nucleophilic agents will be discussed.

In relation to the source of palladium, in most of the cases the palladium catalysts which is used comes from:

- Pd(0) complexes, like $[Pd(PPh_3)_4]$, $[Pd_2(dba)_3]$ or $[Pd(dba)_2]$.
- Pd(II) complexes, like $[Pd(OAc)_2]$ or $[PdCl_2(PPh_3)_2]$. In this case, the palladium species must be reduced to initiate the catalytic cycle.

Another important aspect is the presence of a ligand, which in many cases is essential for the appropriate outcome of the reaction. The nature of the ligand plays a key role in the stability and reactivity of the catalyst. Along the last two decades, different families of ligands have been designed and introduced providing highly active and robust catalysts that have expanded the generality of the processes, as well as allowed milder reaction conditions and lower catalyst loadings.

Finally, most of these coupling reactions require the presence of additives, usually of basic nature, to active the nucleophilic substrate.

I.1.2 Classification of C-C bond forming palladium catalyzed cross-coupling reactions

Pd-catalyzed cross-coupling reactions can be classified considering in the nature of the nucleophile, which can be of three main types:

A. An organometallic reagent.

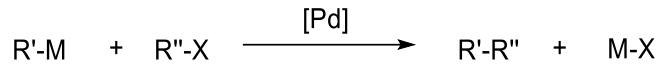
B. An unsaturated system.

C. A diazo compound.

In the following paragraphs, the different classes of reactions will be described with special emphasis on their reaction mechanisms.

A. Reactions in which the nucleophilic agent is an organometallic reagent.

Over the years, high number of organometallic reagents have been employed successfully as nucleophilic agents in cross-coupling reactions. The next equation can be used to summarize in a general manner these type of reactions (Scheme I.3).



Scheme I.3. Cross-coupling reactions which employ organometallic reagent as nucleophiles.

In this equation, R`-M represent the organometallic species, where M can be different metals, and R``-X would be the electrophilic species, where X can be different halogens or pseudohalogens.

This category can be divided in two subgroups:

- Processes in which the organometallic agent is used in stoichiometric amounts.
- Processes in which the organometallic agent is generated *in situ*, like Sonogashira reaction,[7] α-arylation of carbonyl compounds and related systems[8] and the decarboxylative cross-coupling reactions.[9]

The conventional classification of cross-coupling reactions is based on the nature of the metal (Table I.1 and Scheme I.4). Moreover, as a recognition of their relevance and popularity, all these reactions are known by the name of their discoverers.

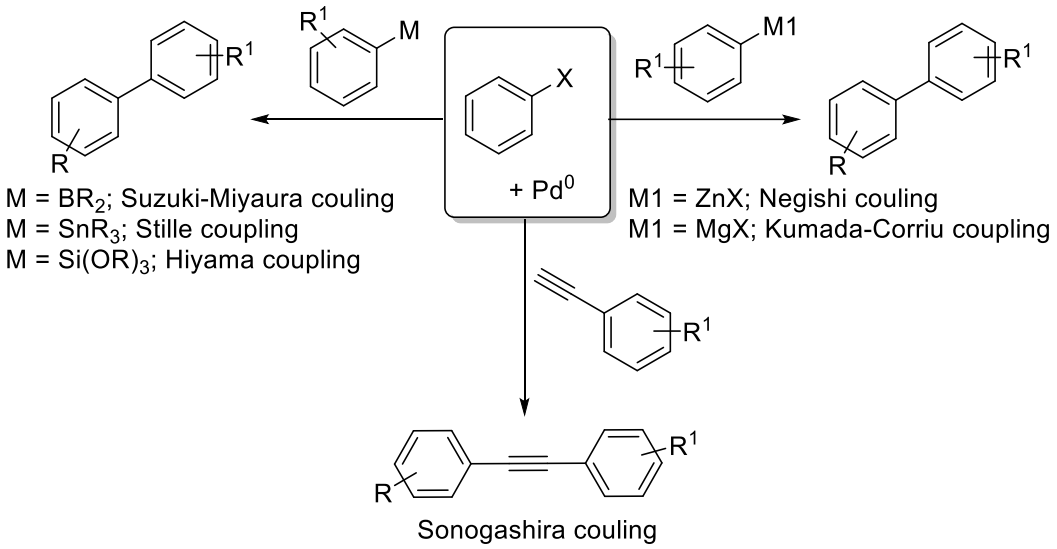
[7] For some reviews on the Sonogashira reaction, see: a) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922; b) M. S. Viciu, S. P. Nolan, *Modern Arylation Methods*, (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**, 183-200.

[8] For a review, see: C. C. C. Johansson, T. J. Colacot, *Angew. Chemie Int. Ed.* **2010**, *49*, 676–707.

[9] a) L. J. Gooßen, G. Deng, L. M. Levy, *Science.* **2006**, *313*, 662–664; b) L. J. Goossen, N. Rodríguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833.

Reaction	**Year**	**Organometallic species**	
Kumada-Corriu[3a-c,10]	(1972)	R-**Mg**X, R-**Li**	(sp^2, sp^3)
Sonogashira[7]	(1973)	R-**C≡C-H**	(sp)
Negishi[4c,11]	(1977)	R-**Zn**X, R**Al**R'$_2$, R-**Zr**R'$_2$X	(sp, sp^2, sp^3)
Stille[12]	(1977)	R-**Sn**R'$_3$	(sp, sp^2, sp^3)
Suzuki-Miyaura[13]	(1979)	R-**B**R'$_2$, R-**B**(OH)$_2$, R-**B**(OR)$_2$, R-**B**F$_3$X	(sp^2, sp^3)
Hiyama[14]	(1988)	R-**Si**R'$_3$	(sp^2)

Table I.1. Classification of palladium catalyzed cross-coupling reactions based on the nucleophilic agent.



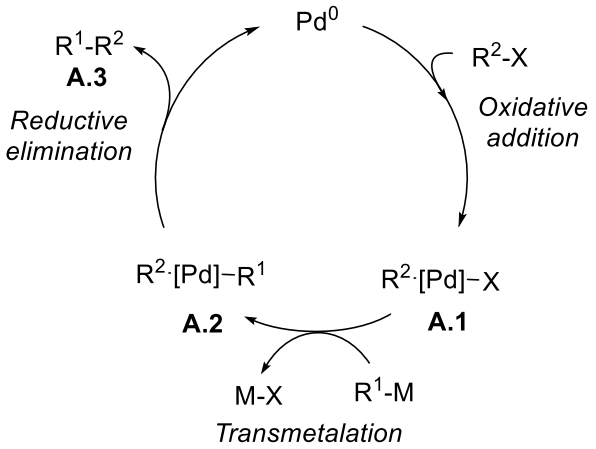
Scheme I.4. Selected examples of palladium-catalyzed C-C coupling reactions.

[10] For reviews on Kumada-Corriu Coupling, see: a) M. Kumada, *Pure Appl. Chem.* **1980**, *52*, 669-679; b) M. M. Heravi, P. Hajiabbasi, *Monatshefte für Chemie - Chem. Mon.* **2012**, *143*, 1575–1592.
[11] For reviews on Negishi coupling reaction, see: a) A. O. King, N. Okukado, E. Negishi, *J. Chem. Soc. Chem. Commun.* **1977**, 683–684; b) E. Negishi, N. Okukado, A. O. King, D. E. Van Horn, B. I. Spiegel, *J. Am. Chem. Soc.* **1978**, *100*, 2254–2256.
[12] For reviews on Stille reaction, see: a) J. K. Stille, *Angew. Chemie Int. Ed. English* **1986**, *25*, 508–524; b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.*, **2002**, *102*, 1359–1470
[13] For reviews on Suzuki-Miyaura couping, see: a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168; c) G. A. Molander, B. Canturk, *Angew. Chemie Int. Ed.* **2009**, *48*, 9240–9261.
[14] a) For reviews on Hiyama coupling, see: a) T. Hiyama, Y. Hatanaka, *Pure Appl. Chem.* **1994**, 66, 1471-1478; b) T. Hiyama, *J. Organomet. Chem.* **2002**, *653*, 58–61.

Mechanistic considerations:

In general, palladium catalyzed cross-coupling reactions feature complicated mechanisms which are still nowadays objective of study.[15]

Nevertheless, in a simplified way, palladium catalyzed cross-coupling reactions which employ organometallic reagents as nucleophiles present a mechanism with three fundamental stages.



Scheme I.5. Catalytic cycle for palladium catalyzed cross-coupling reactions with organometallic nucleophiles.

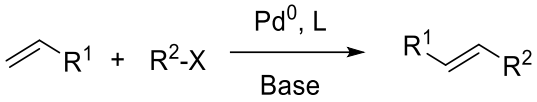
It is generally accepted that all palladium catalyzed cross-coupling reactions present the same first step in their catalytic cycle, the *oxidative addition* of the organic halide (or pseudohalide) R^2-X to the Pd(0) catalyst to generate the Pd(II) species **A.1**. Then, depending on the specific transformation, the following steps of the catalytic cycle are different.

[15] Computational studies on Negishi reaction: B. Fuentes, M. García-Melchor, A. Lledós, F. Maseras, J. A. Casares, G. Ujaque, P. Espinet, *Chem. Eur. J.* **2010**, *16*, 8596–8599. Mechanistic studies on the Stille coupling reaction: P. Espinet, A. M. Echavarren, *Angew. Chemie Int. Ed.* **2004**, *43*, 4704–4734.

In the case of palladium catalyzed cross-coupling reactions with organometallic nucleophiles, the second step consists in the *transmetallation*. In this stage, the organometallic nucleophile is incorporated to the Pd coordination sphere, to promote the formation of the Pd complex **A.2**. Finally, the *reductive elimination* step provides the R^1-R^2 coupling product **A.3** and regenerates the Pd(0) catalyst.

B. Reactions in which the nucleophilic agent is a multiple bond. Heck type reactions.

In Heck reactions an organic halide and an alkene (or in general whatever species which bears a multiple bond) are reacted to give a coupling product.[16] The multiple bond acts as nucleophile, thus this transformation can be considered the first example of Pd-catalyzed cross-coupling reactions without the employment of organometallic reagents (Scheme I.6).

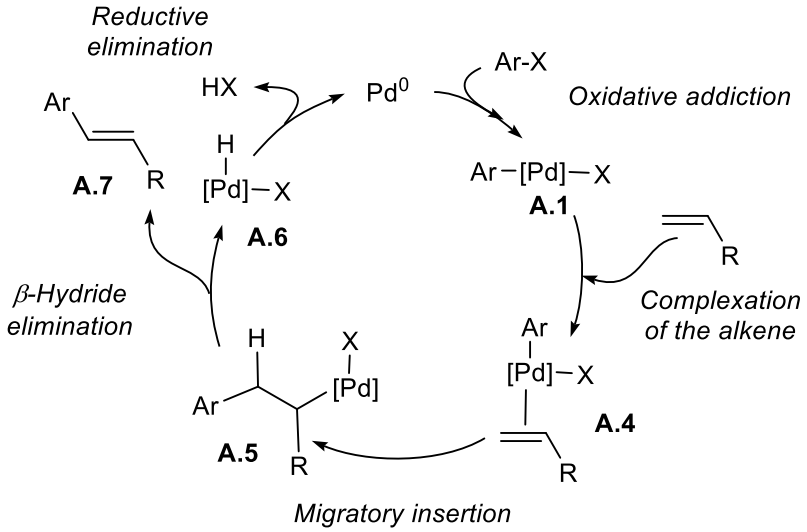


Scheme I.6. Cross-coupling reactions which employ alkenes as nucleophiles.

[16] For reviews on Heck-Mizoroki reaction, see: a) T. Mizoroki, K. Mori, A. Ozaki, Bull. Chem. Soc. Jpn. 1971, 44, 581–581; b) R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320–2322; c) M. Oestreich, *The Mizoroki- Heck Reaction*, Wiley, Chichester, **2009**.

Mechanistic considerations:

The catalytic cycle for Heck type reaction is different from that described for organometallic-based cross-couplings discussed before.

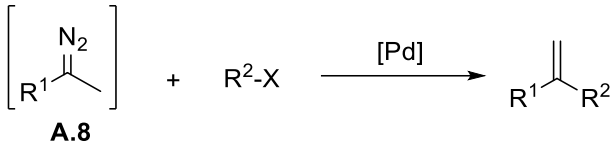


Scheme I.7. Catalytic cycle for the Heck type reactions.

In this case, the first step is again the oxidative addition, but now, the Pd(II) complex **A.1** evolves through the *complexation of the alkene* to give the Pd(II) species **A.4**. Then, *migratory insertion* of the alkene in the Pd-C bond provides the alkyl palladium complex **A.5**, in which a new C-C bond has been generated. Finally, a β-*hydride elimination* takes place to release the final unsaturated product **A.7**, and the palladium hydride **A.6**, that undergoes a reductive elimination to regenerate the Pd(0) catalyst.

C. Reaction in which the nucleophilic agent is a diazo compound.

In the last decade, a new type of palladium catalyzed cross-coupling reaction which employs diazo compounds **A.8** as standard nucleophiles has emerged as an innovative process for the formation of C-C bonds (Scheme I.8). This remarkable transformation which features the diazo compound as key reagent, represents the starting point of the work presented in this memory. Therefore, the cross-coupling reaction with diazo compounds will be explained in detail in the next sections.



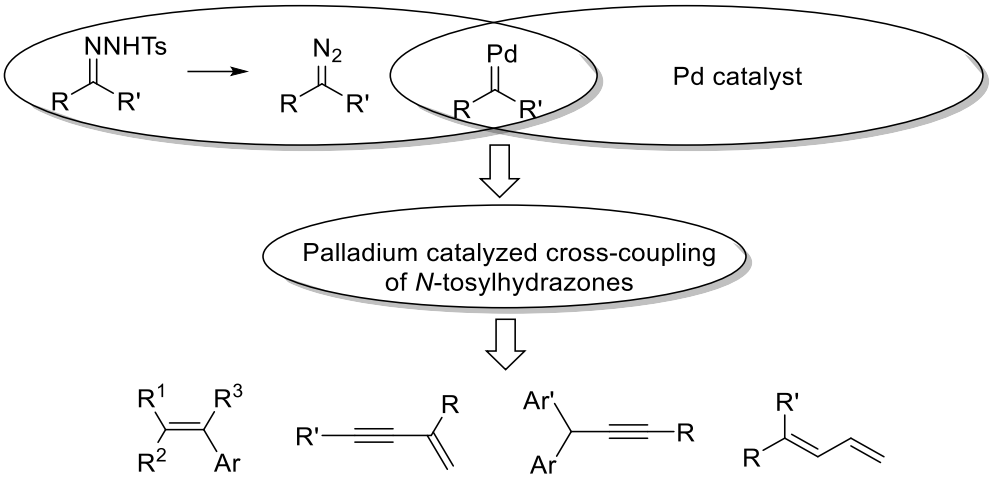
Scheme I.8. Cross-coupling reactions which employ diazo compounds as nucleophiles.

Mechanistic considerations:

The mechanism of these reactions resembles the Heck type reactions discussed above. The differential steps in the catalytic cycle of the Heck reaction are the alkene complexation and the migratory insertion of the alkene in the Pd-C bond. Quite similarly, as will be discussed in detail later on, in the reactions with diazo compounds, the differential steps are the formation of a Pd-carbene complex, and the migratory insertion of the carbene in the Pd-C bond. Thus, while in the Heck reaction a C-C species is incorporated, the reactions with diazo compounds add one C fragment by an otherwise similar mechanism. Noteworthy, these reactions can be compared with the well-known Pd-catalyzed carbonylations.

I.2 Palladium catalyzed cross-coupling reactions with diazo compounds and *N*-tosylhydrazones

Transition-metal-catalyzed carbene transformations and cross-couplings represent two major reaction types in organometallic chemistry and organic synthesis. The combination of these two types of process for the generation of C-C bonds have been for years one of the principal objective in this area of study. In this context, Pd complexes have emerged as very efficient catalysts to couple diazo compounds with a wide variety of organic halides. Despite of the usefulness of diazo compounds, their intrinsic unstability and handling difficulties have limited their synthetic applications to the so called stabilized diazo compounds: such as trimethylsilyl diazo methane or diazo compounds substituted with electronwithdrawing groups. It is for this reason that the employment of *N*-tosylhydrazones as a very convenient and general source of diazo compound has led to the development of new class of palladium-catalyzed cross-coupling reactions with remarkably wide scope (Scheme I.9).



Scheme I.9. Principal application of palladium catalyzed cross-coupling with diazo compounds and *N*-tosylhydrazones.

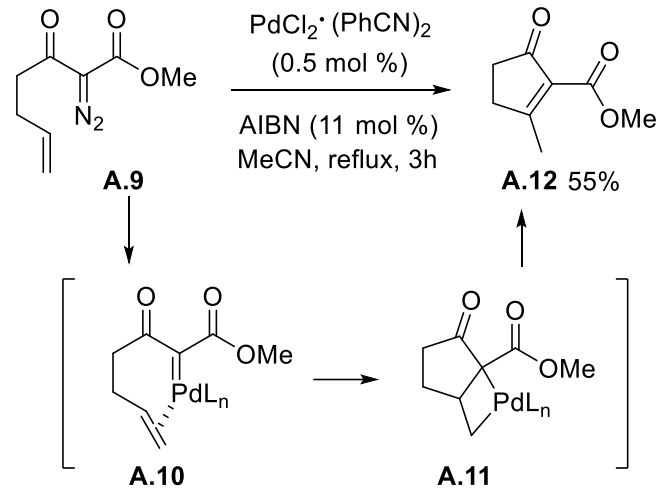
Although palladium has been the most prolific catalyst in promoting cross-coupling reactions employing diazo compounds or tosylhydrazones, recent studies employing Cu, Rh, Ni, and Co as catalysts have led to the discovery of other highly appealing transformations. Nevertheless, this short revision will be mostly restricted to the Pd-catalyzed processes.

I.2.1 Early examples of diazo compounds in palladium catalyzed cross-coupling reactions

Diazo compounds have emerged as reagents with wide application in organic synthesis.[17] In particular, diazo compounds have been frequently exploited as carbene or metal carbene precursors. While free carbenes have shown limited synthetic applications, due to the lack of selectivity of these highly reactive agents, metal carbenes have been found as synthetic intermediates with a remarkable diverse reactivity and selectivity.[18] Palladium carbene species have been revealed in the past few years as the key intermediate in a novel type of palladium catalyzed cross-coupling reactions. These Pd carbene intermediates, which mostly undergo migratory insertions, show unique properties that have opened the door to new possibilities for original transformations catalyzed by palladium.

[17] For selected comprehensive reviews on α-diazocarbonyl compounds, see: a) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160; b) M. P. Doyle, M. A. Mckervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**.
[18] Y. Zhang, J. Wang, *European J. Org. Chem.* **2011**, *2011*, 1015–1026.

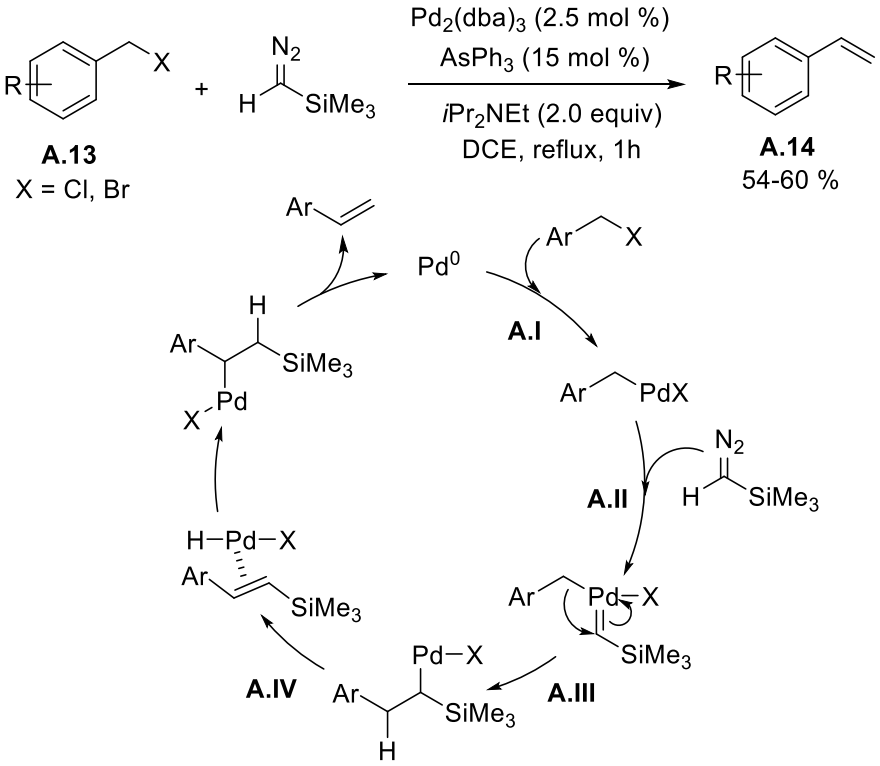
Considering the formation of a Pd-carbene as the first differential step in Pd-catalyzed cross-coupling reactions with diazo compounds, then Taber and co-workers can be considered among the pioneers in this field. Thus, in 1986 they reported a Pd(II)-catalyzed reaction of β-alkenyl α-diazoketones **A.9** for the synthesis of cyclopentenones **A.12**.[19] According to the mechanistic proposal, this transformation proceeds *via* intramolecular insertion of an alkene into the Pd-carbene **A.10**, in order to generate a palladocyclobutane intermediate **A.11** in a formal [2+2] cycloaddition (Scheme I.10).



Scheme I.10. Pd catalyzed reaction of β-alkenyl α-diazoketones.

[19] D. F. Taber, J. C. Amedio, R. G. Sherrill, *J. Org. Chem.* **1986**, *51*, 3382–3384.

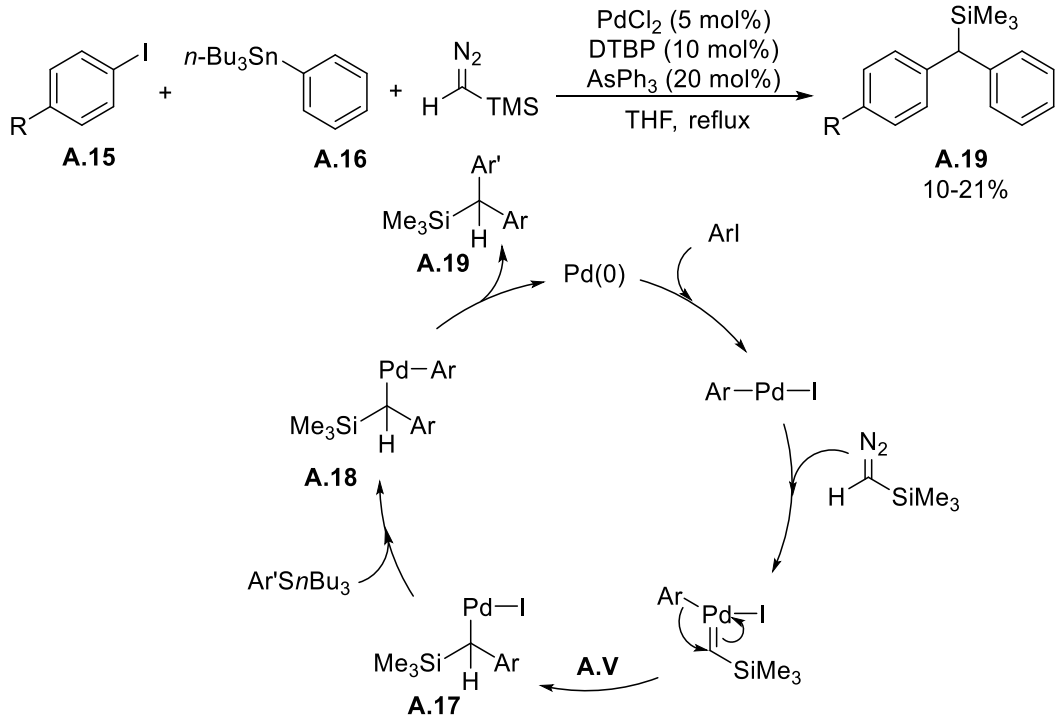
Nevertheless, the first example of a Pd-catalyzed cross-coupling employing diazo compounds was reported by Van Vranken in 2001. In their seminal paper, they reported the Pd-catalyzed reaction between benzyl bromides **A.13** and trimethylsilyl diazomethane that furnished styrene derivatives **A.14**.[20] Thus, under the appropriate reaction conditions, the reaction between benzyl halides and trimethylsilyldiazomethane (TMSD) generated the corresponding styrene derivatives. The mechanism proposed for this transformation involves the following main steps: **A.I)** oxidative addition of the benzyl halide to the Pd^0 catalyst; **A.II)** coordination of the diazo compound for the formation of the Pd-carbene complex; **A.III)** migratory insertion of the carbene into the Pd-C(sp^3) bond; and **A.IV)** β-hydride elimination of the alkyl palladium species that releases the olefin and regenerates the Pd(0) catalyst (Scheme I.11).



Scheme I.11. Pd-catalyzed cross-coupling between benzyl halides and trimethylsilyldiazomethane.

[20] K. L. Greenman, D. S. Carter, D. L. Van Vranken, *Tetrahedron* **2001**, *57*, 5219–5225.

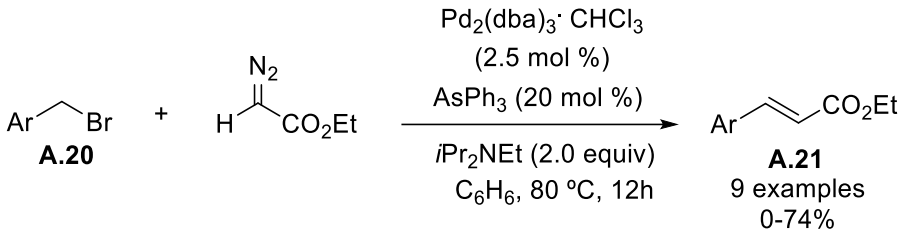
In the same publication, a new Pd-catalyzed three-component reaction between trimethylsilyldiazomethane, aryl iodides **A.15** and tributylphenyltin **A.16** was also reported.[20] Although this reaction was very limited in scope and yield, it represents the first example of the migratory insertion of a carbene ligand in the Pd-C(Ar) bond **A.V** (Scheme I.12).



Scheme I.12. Pd-carbene migratory insertion/Stille coupling sequence.

Regarding the mechanism of this transformation, it was proposed an interesting cascade reaction. After the migratory insertion of the carbene, the palladium complex **A.17** reacts with the stannane through a transmetallation reaction to give **A.18**. Then, reductive elimination on **A.18** releases the product **A.19** and regenerates the Pd(0) catalyst (Scheme I.12). A remarkable aspect in this transformation is the formation of two separate C-C bonds on the carbenic carbon in one single synthetic step.

Additionally, in 2005 the same research group described an expansion of the initial work. Thus, substituted cinamates **A.21** were furnished using ethyl diazoacetate and benzyl bromides **A.20** as coupling partners (Scheme I.13).[21]



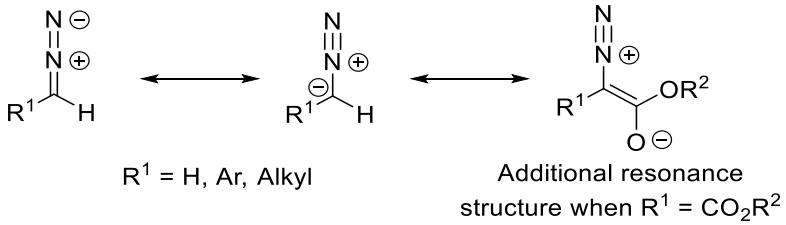
Scheme. I.13. Further expansions of benzyl migratory insertion.

[21] K. L. Greenman, D. L. Van Vranken, *Tetrahedron* **2005**, *61*, 6438–6441.

I.2.2 *N*-Tosylhydrazones in palladium catalyzed cross-coupling reactions

I.2.2.1 *In situ* generation of diazo compounds from *N*-tosylhydrazones in metal-catalyzed reactions

As it has been shown in the examples of the previous section, the synthetic utility of diazo compounds cannot be overlooked. However, diazo compounds are inherently dangerous.[22] Their toxicity and tendency to explode are indeed serious hazards to be taken into account when working with them.[23] In this sense, diazo esters arise as more stable and safer alternatives due to the resonance stabilization of the ester functional group (Scheme I.14) but at the same time, it limits the applicability of diazo compounds chemistry to a very restrigted range of substrates.[24] For this reason, it became necessary to look for ways of in situ generation of diazo compounds without such structural restrictions.



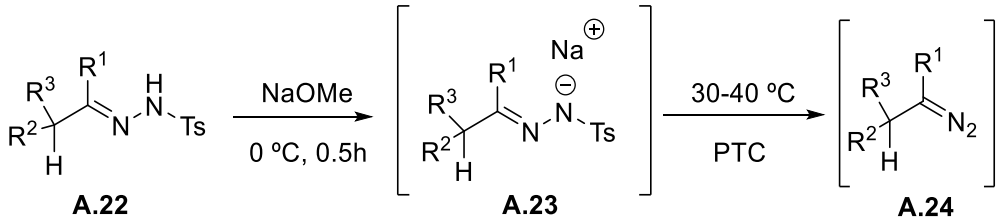
Scheme I.14. Example of stabilized diazo compound by delocalization of negative charge.

[22] a) C. D. Gutsche, in *Org. React. Vol. 8*, Eds.: R. Adams, A. H. Blatt, A. C. Cope, D. Y. Curtin, F. C. McGrew, C. Niemann, John Wiley & Sons, Inc., New York, **1954**, pp. 364; b) M. Regitz*, The chemistry of Diazonium and Diazo Groups, vol. 2,* Ed.: S. Patai*,* Wiley, New York*,* **1978**, pp. 659*;* c) D. S. Wulfman*,* G. Linstrumelle*,* C. F. Cooper*, The chemistry of Diazonium and Azo Groups,* Interscience, New York*,* **1978***;* d) M. Regitz, G. Maas, *Diazo Compounds; Properties and Synthesis,* Academic Press, Orlando, **1986**.

[23] T. Nozoe, T. Asao, M. Yasunami, H. Wakui, T. Suzuki, M. Ando, *J. Org. Chem.* **1995**, *60*, 5919–5924.

[24] R. S. Hosmane, J. F. Liebman, *Struct. Chem.* **2002**, *13*, 501–503.

In this context, *N*-tosylhydrazones emerged as useful synthetic reagents for the *in situ* formation of diazo compounds. Despite the fact that the utility of *N*-tosylhydrazones in organic synthesis has a long history,[25] their usefulness as precursors of diazo compounds in transition metal-catalyzed reactions was not reported until the beginning of 21st century. Thus, in 2001 the research group led by Professor Aggarwal disclosed a new method for the *in situ* generation of diazo compounds **A.24** from *N*-tosylhydrazone salts **A.23**.[26] Aggarwal showed an innovative protocol that relied on the formation of a *N*-tosylhydrazone salt **A.23** that could be decomposed into the diazo compound **A.24** by gentle warming in the presence of a phase transfer catalyst (PTC) (Scheme I.15).



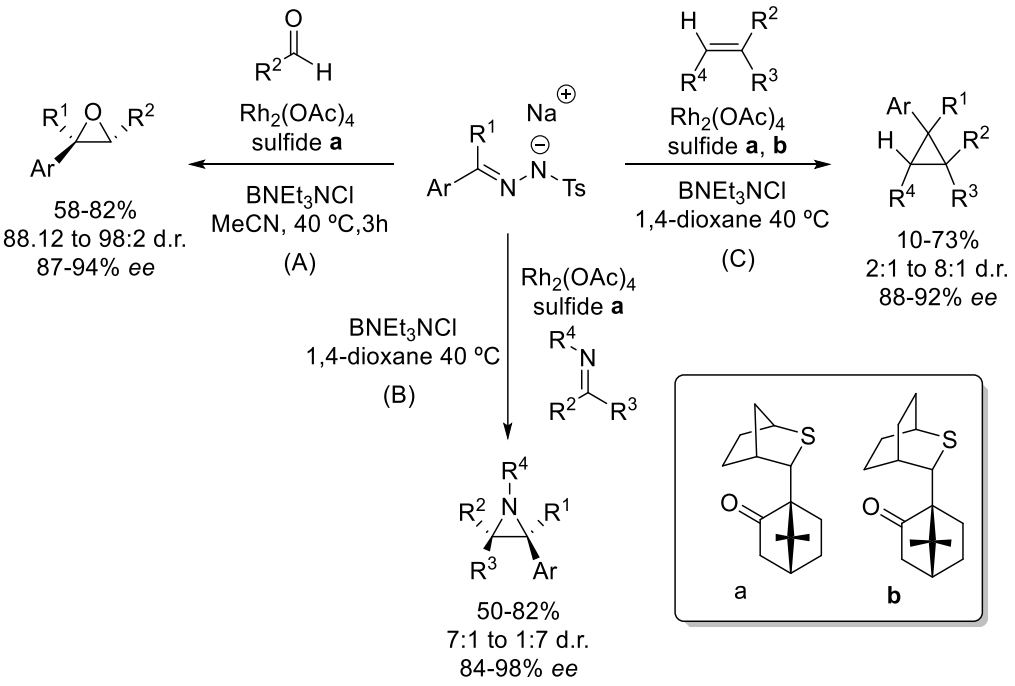
Scheme I.15. *In situ* generation of diazo compounds from *N*-tosylhydrazones.

In addition, another remarkable benefit of this *in situ* technology is the possibility to keep low the concentration of the diazo compounds. Therefore, the hazards associated with concentrated diazo solutions[22,23] and the formation of side products through dimerization reactions are limited.

Aggarwal and co-workers first applied this new *in situ* methodology in the sulfur-mediated epoxidation of aldehydes (Scheme I.16, A).[26,27] Under the reaction conditions, the diazo compound generated from the tosylhydrazone reacts with the Rh catalyst to form a Rh carbene, that in the presence of the sulfide leads to the sulfur ylide which participates in the cyclopropanation. The employment of chiral sulfides as precursors of sulfur ylides supplied high diastereo- and enantioselectivities to the reaction. After this first approximation to explore the scope of the *in situ* process, the same group extended

[25] a) W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, 4675–4678; b) R. H. Shapiro, M. F. Lipton, K. J. Kolonko, R. L. Buswell, L. A. Capuano, *Tetrahedron Lett.* **1975**, *16*, 1811–1814.
[26] V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chemie Int. Ed.* **2001**, *40*, 1430–1433.
[27] a) V. K. Aggarwal, I. Bae, H.-Y. Lee, J. Richardson, D. T. Williams, *Angew. Chemie Int. Ed.* **2003**, *42*, 3274–3278; b) V. K. Aggarwal, M. Patel, J. Studley, *Chem. Commun.* **2002**, 1514–1515; c) V. K. Aggarwal, J. N. Harvey, J. Richardson, *J. Am. Chem. Soc.* **2002**, *124*, 5747–5756; d) M. Catasús, A. Moyano, V. K. Aggarwal, *Tetrahedron Lett.* **2002**, *43*, 3475–3479.

the application to the Rh catalyzed sulfur ylide-mediated aziridination of imines (Scheme I.16, B)[28] and to the sulfur-mediated cyclopropanation of electron deficient alkenes (Scheme I.16, C).[29]



Scheme I.16. Aggarwal`s contributions for the development of new rhodium catalyzed reactions employing *N*-tosylhydrazones.

It is important to highlight that these were the first examples where metal carbenes were generated from tosylhydrazones and participated in a catalytic process. However, the application of this *in situ* technology developed by Aggarwal presented restrictions when hydrazones derived from non-enolizable carbonyls were used.

[28] a) V. K. Aggarwal, M. Ferrara, C. J. O'Brien, A. Thompson, R. V. H. Jones, R. Fieldhouse, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1635–1643; b) V. K. Aggarwal, J.-L. Vasse, *Org. Lett.* **2003**, *5*, 3987–3990; c) V. K. Aggarwal, J.-L. Vasse, *Org. Lett.* **2003**, *5*, 3987–3990.

[29] V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd, M. Porcelloni, *Angew. Chemie Int. Ed.* **2001**, *40*, 1433–1436

I.2.2.2 Discovery and expansion of palladium catalyzed cross-coupling reactions with *N*-tosylhydrazones

In 2007, our research group reported the Pd-catalyzed cross-coupling reaction between *N*-tosylhydrazones and aryl halides.[30] The development of this reaction was considered a remarkable achievement not only in the field of Pd-catalyzed cross-couplings, but also for the improvement of the methodology for the *in situ* generation of the diazo compounds from *N*-tosylhydrazones.[31] As will be shown in the following brief revision, this discovery had a great impact and triggered the interest of many research groups.

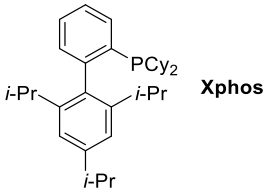
In the seminal contribution was reported the reaction between an aryl halide **A.26** and a tosylhydrazone **A.25** in presence of Li*O*t*Bu as base and a catalytic system built from $[Pd_2(dba)_3]$ and the ligand Xphos[32] that led to the formation of substituted olefins **A.27**. In the process a new C-C bond is formed between the former hydrazonic carbon and the carbon that supported the halogen of the aryl halide (Scheme I.17).

[30] J. Barluenga, P. Moriel, C. Valdés, F. Aznar*, Angew. Chemie Int. Ed.* **2007**, *46*, 5587–5590.

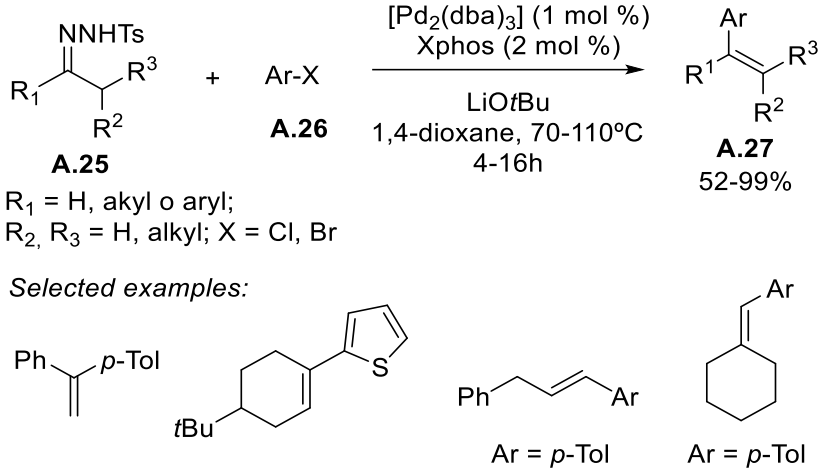
[31] With the new methodology described by our research group, the diazo compounds can be *in situ* generated directly from *N*-tosylhydrazones, employing Li*O*t*Bu as base. In this way, the preformation of the hydrazonic salts and the limitations of the method described by Aggarwal were avoided.

[32] 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) developed by Buchwald, see: X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655.

Xphos is one of the biphenyl phosphines develop by the Buchwald group, which are particularly effective as ligands in Pd-catalyzed cross-coupling reactions.



Xphos

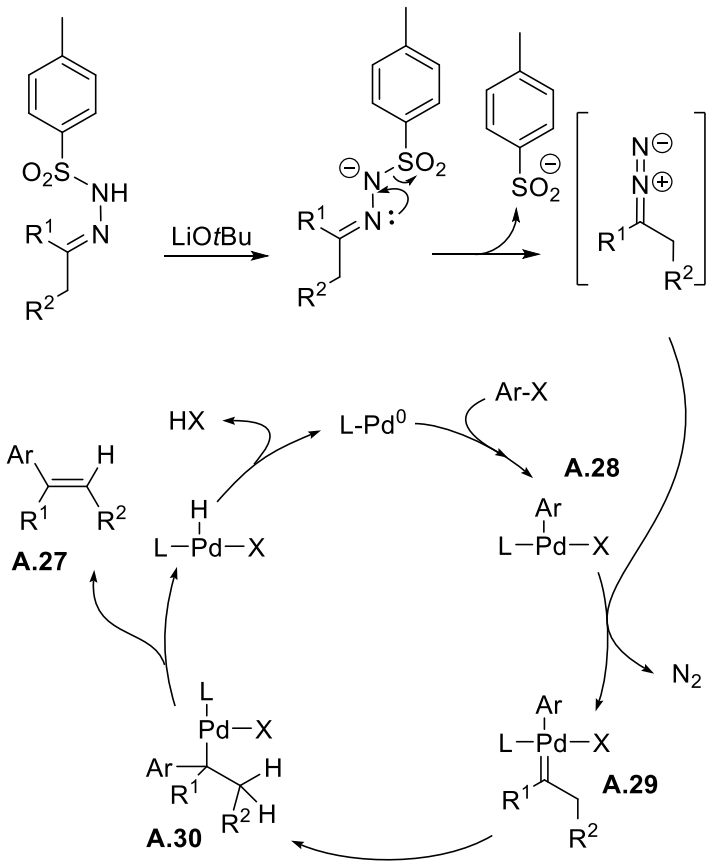


Scheme I.17. Pd-catalyzed cross-coupling reaction between tosylhydrazones and aryl halides.

Already from the very beginning, the reaction displayed a high synthetic potential. A wide variety of olefins were prepared to demonstrate the broad scope with respect to both coupling partners. Tosylhydrazones derived from aryl or alkyl ketones, either acyclic or cyclic, as well as from aldehydes could be used to carry out the reaction. Regarding the aryl halide, both bromides and chlorides were used with good results. Moreover, a variety of functional groups were tolerated on both coupling partners to provide the corresponding olefins in very high yields. Nevertheless, one particular demand of this reaction was its preference for the catalytic system and reaction conditions cited above. Especially important was the use of Xphos as ligand and Li*O*t*Bu as base to the correct operation of the reaction. Under the optimal reaction condition this reaction turned out to be very robust and highly general.

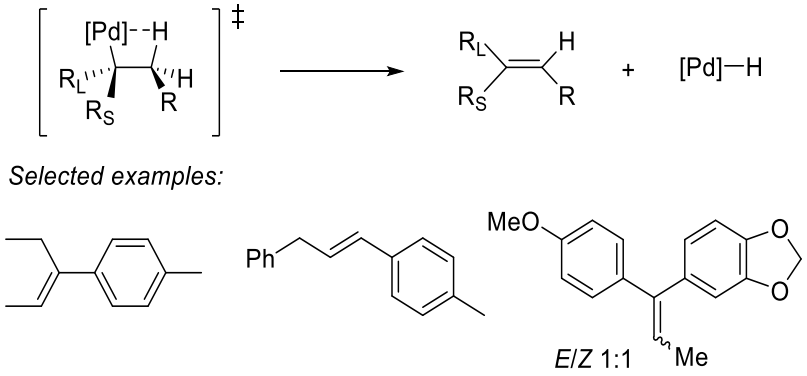
Mechanistic consideration:

The catalytic cycle postulated for this reaction is closely related with the catalytic cycle proposed for the cross-coupling between benzyl halides and diazo compounds (Scheme I.11). Herein, the first step of the transformation would be the oxidative addition of the aryl halide to the Pd(0) catalyst to give an aryl palladium complex **A.28**. Then, reaction of the diazo compound (generated from the tosylhydrazone by action of the base) with **A.28** generates the palladium carbene complex **A.29**. The unstable Pd-carbene species **A.29** undergoes a migratory insertion of the carbene ligand to produce the benzyl palladium intermediate **A.30**. Finally, the β-hydride elimination would provide the arylated olefin **A.27** and regenerate the Pd(0) catalyst (Scheme I.18).



Scheme I.18. Proposed mechanism for the Pd-catalyzed cross-coupling reaction of *N*-tosylhydrazones.

The stereochemistry of the final olefin is determined by the *syn* β-hydride elimination. Thus, in the transition state for the formation of 1,2-disubstituted and trisubstituted olefins, the bulkier group R_L would be eclipsed with the smaller substituent of the vicinal carbon atom. Therefore, trisubstituted olefin products with bulkier groups on each carbon atom, and olefins generated from hydrazones derived from aldehydes acquire a *trans* arrangement. Consequently, when R_L and R_S are similar, a 1:1 mixture of both isomers is obtained (Scheme I.19).



Scheme I.19. Justification of the final configuration present in the olefin due to the *syn* β-hydride elimination.

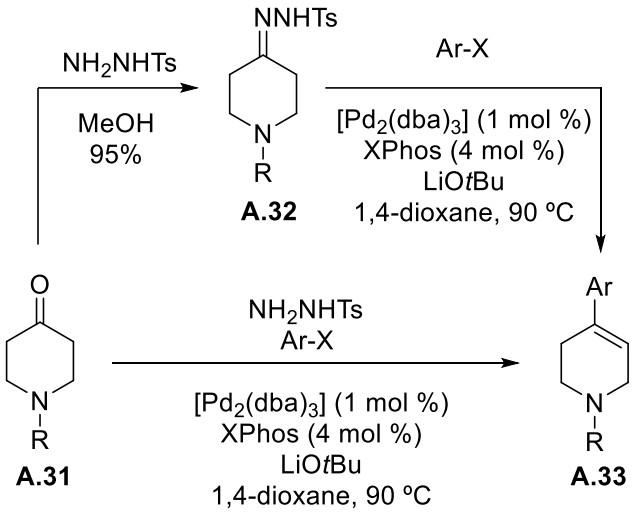
Considering the mechanism of this process, it is important to point out that the first Pd-catalyzed cross-coupling which involved a carbene-migratory insertion reaction was the transformation reported in 2001 by Van Vranken.[20] Nevertheless, in spite of the potential interest of this process, it was not investigated further in the following years, probably because of its limited scope.

Over the last years, the applications of Pd-catalyzed cross-coupling with *N*-tosylhydrazones has experimented an enormous development. An exhaustive coverage of all the new advances exceeds the limits of this memory.[33] Additionally, some specific topics will be revised in the introduction of the different chapters. For these reasons, this general introduction is restricted to present some early key contributions on the Pd-catalyzed cross-couplings with sulfonylhydrazones.

[33] For some reviews on Pd-catalyzed cross-coupling reaction with tosylhydrazones, see: a) J. Barluenga, C. Valdés, *Angew. Chemie Int. Ed.* **2011**, *50*, 7486–7500; b) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560–572; c) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236–247.

Expansion of the Pd-catalyzed cross-coupling reaction with *N*-tosylhydrazones in the synthesis of olefins.

In order to improve the versatility of the Pd-catalyzed cross-coupling reaction with *N*-tosylhydrazones, it was envisioned the possibility of generating the tosylhydrazone directly from the carbonyl precursor **A.31** in the reaction medium. In this manner, a new one-pot strategy was accomplished for the preparation of 4-aryltetrahydropyridines **A.33** from 4-piperidones **A.31**.[34] Under the standard conditions, the reaction between *in situ* generated *N*-tosylhydrazones **A.32** and aryl halides provided the expected products with excellent yields in most cases (Scheme I.20).



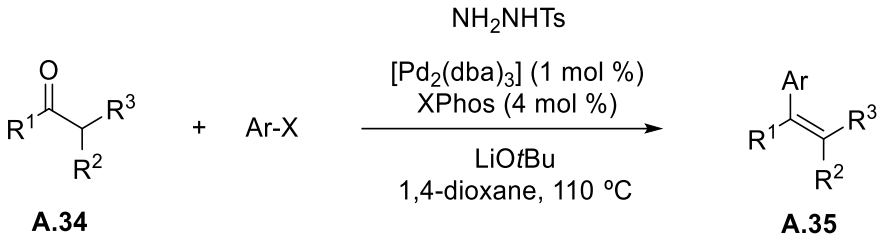
Scheme I.20. Application of Pd-catalyzed cross-coupling reaction in the synthesis of 4-aryl tetrahydropyridines.

This study provided a very efficient synthesis of a privileged scaffold[35] for medicinal chemistry employing an innovative one-pot approach.

[34] J. Barluenga, M. Tomás-Gamasa, P. Moriel, F. Aznar, C. Valdés, *Chem. Eur. J.* **2008**, *14*, 4792–4795.

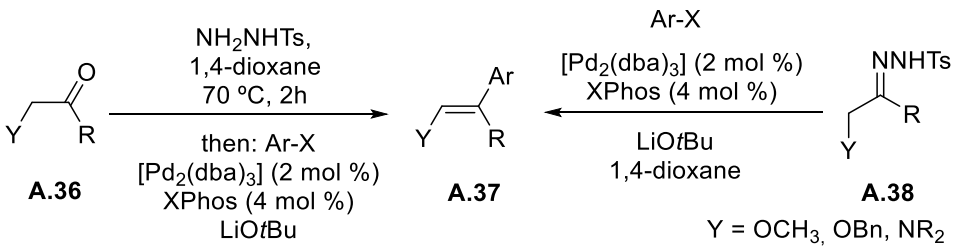
[35] a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, et al., *J. Med. Chem.* **1988**, *31*, 2235–2246; b) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930.

The one-pot multicomponent process was also successfully applied to other types of carbonyl compounds **A.34** including alkyl, aryl and cyclic ketones, as well as linear and branched aldehydes to prepare di-, tri- and tetrasubstituted alkenes **A.35** (Scheme I.21).[34,36] The result of the implementation of this procedure enabled the direct coupling of a wide variety of carbonyls to enhance the usefulness of this palladium catalyzed transformation.



Scheme I.21. General reaction for direct Pd-catalyzed cross-coupling reaction of carbonyl compounds.

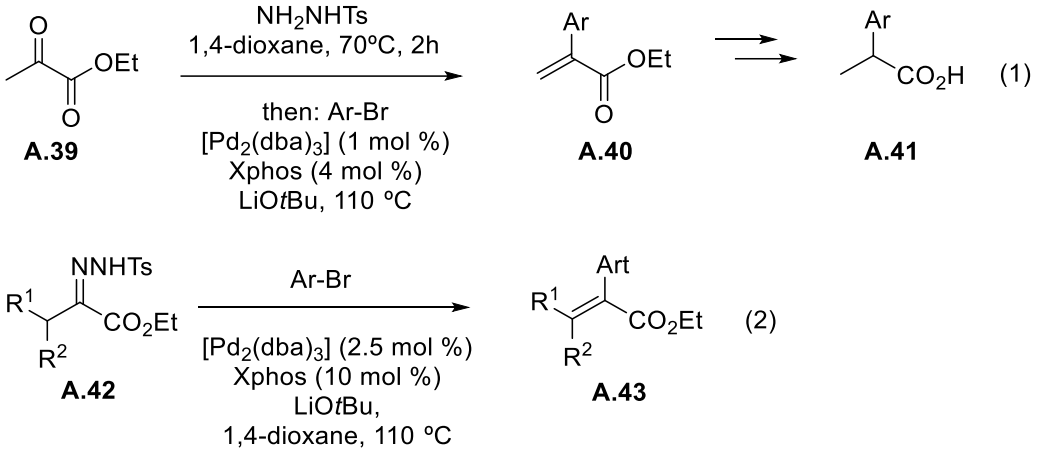
Our research group was also interested in the preparation of functionalized alkenes from the appropriate carbonyl compounds.[37] In this way, α-amino and α-alkoxy carbonyls **A.36** provided the corresponding enamines and enol ethers respectively **A.37**. This particular transformation can be conducted from the previously prepared tosylhydrazone **A.38**, or directly from the carbonyl reagent in a one-pot process (Scheme I.22).



Scheme I.22. Synthesis of enol ethers and enamines using Pd-catalyzed cross-coupling reactions.

[36] J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Adv. Synth. Catal.* **2010**, *352*, 3235–3240.
[37] J. Barluenga, M. Escribano, P. Moriel, F. Aznar, C. Valdés, *Chem. Eur. J.* **2009**, *15*, 13291–13294.

The coupling reaction could be also applied for the preparation of electron deficient olefins using tosylhydrazones derived from α-ketoesters.[38] It was particularly important the case of ethyl pyruvate **A.39**, which can be converted into 2-aryl acrylates **A.41**, versatile synthetic intermediates, and direct precursors of profen-type anti-inflammatory drugs (Scheme I.23, equation 1). In addition, tri- and tetrasubstituted olefins **A.43** can be afforded using *N*-tosylhydrazones derived from other substituted 2-oxoethers **A.42** (Scheme I.23, equation 2).

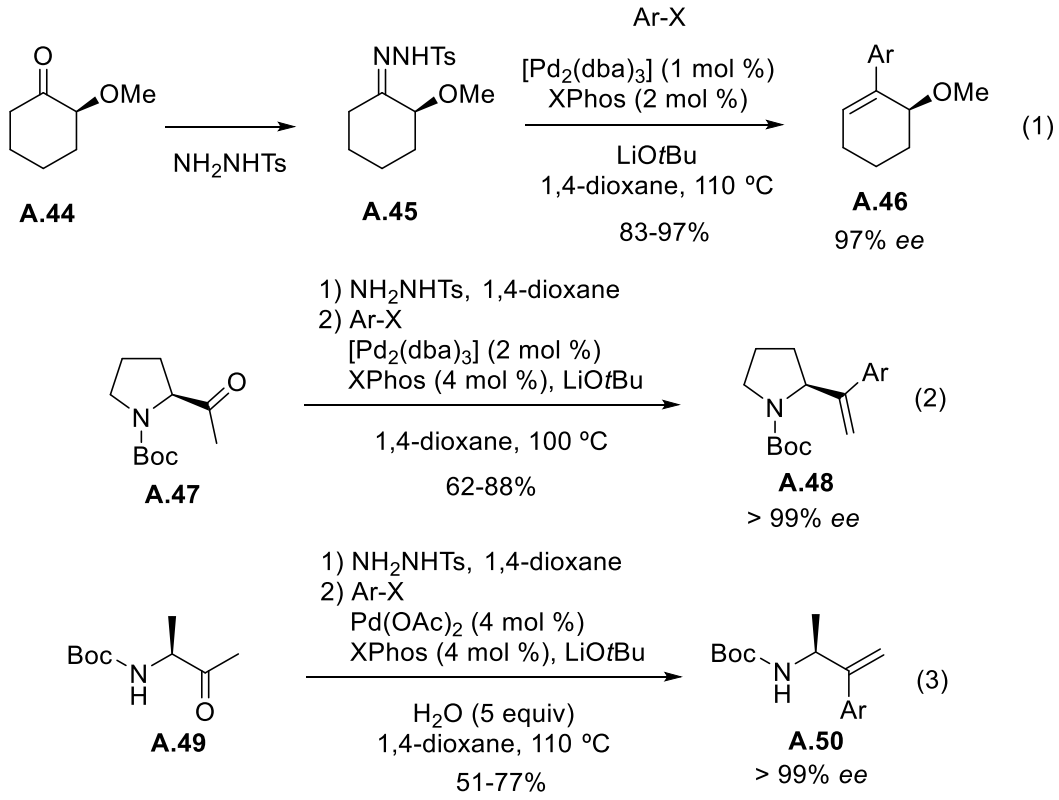


Scheme I.23. Pd-catalyzed cross-coupling reactions for the preparation of electron deficient olefins.

[38] J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Chem. Eur. J.* **2010**, *16*, 12801–12803.

Another contribution of our research group was the application of the Pd-catalyzed cross-coupling reaction with tosylhydrazones in the modification of α-chiral ketones with preservation of the configuration of the stereogenic α carbon center.

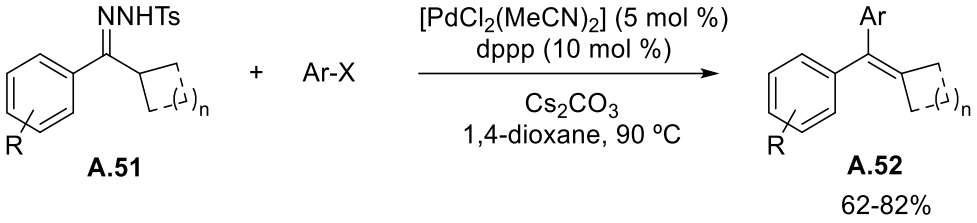
This interesting reactivity was illustrated with the reaction of enantiomerically enriched α-substituted cyclohexanones **A.44**.[39] The cross-coupling afforded allylic ethers **A.46** without erosion of α chirality (Scheme I.24, equation 1). This work was extended to α-chiral methyl ketones, derived from the α-amino acids *L*-proline **A.47** and *L*-alanine **A.48**.[39] Under the optimized reaction conditions, this methodology enabled the formation of the chiral allylic amines **A.48** and **A.50** with preservation of the configuration of the stereogenic center (Scheme I.24, equations 2 and 3).



Scheme I.24. Synthesis of enantiomerically pure allylic ethers and amines through one-pot multicomponent reaction with tosylhydrazones.

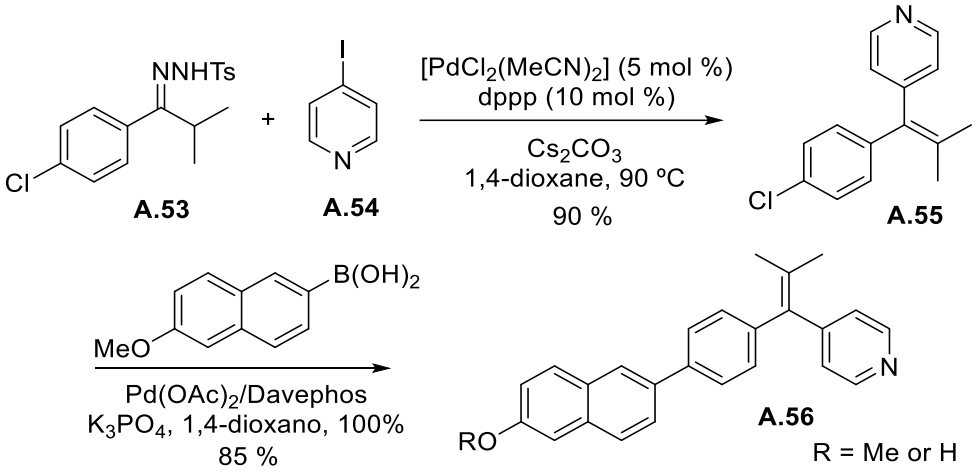
[39] J. Barluenga, M. Escribano, F. Aznar, C. Valdés, *Angew. Chemie Int. Ed.* **2010**, *49*, 6856–6859.

In 2010, Alami and co-workers reported the synthesis of a wide variety of tetrasubstituted alkenes **A.52**.[40] A different set of reaction conditions allowed for the coupling of sterically hindered tosylhydrazones **A.51** with aryl iodides and bromides. For the proper course of the reaction, it was used a catalytic system built from $[PdCl_2(MeCN)_2]$ as palladium source and the bidentate ligand 1,3-bis(diphenylphosphanyl)propane (dppp) in combination with Cs_2CO_3 as base (Scheme I.25).



Scheme I.25. Synthesis of tetrasubstituted olefins from sterically congested *N*-tosylhydrazones.

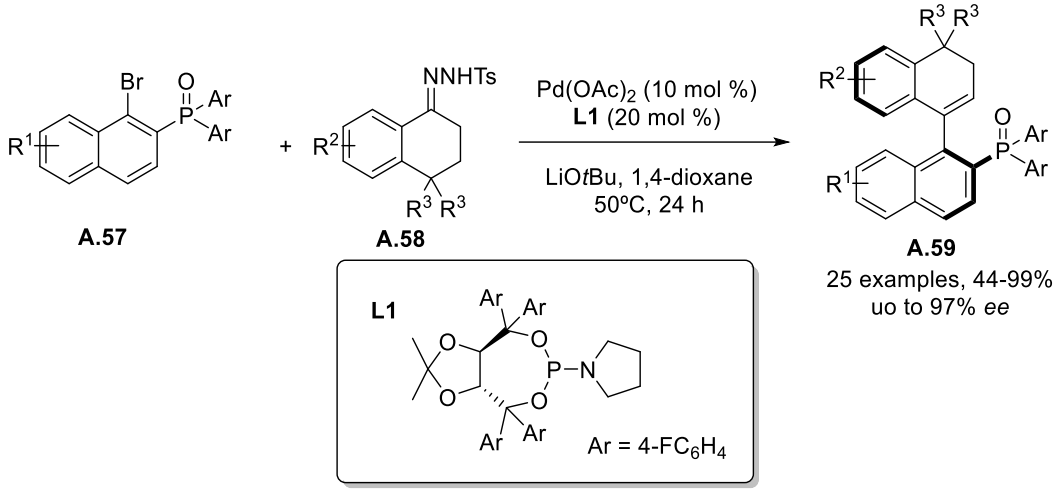
The synthetic utility of this transformation, was illustrated with the development of a very concise formal synthesis of the isopropylidene CYP17 inhibitor **A.56**. The sequence followed a two-step process consisting on a cross-coupling between the tosylhydrazone **A.53** and pyridyl iodide **A.54**, and a subsequent Suzuki reaction (Scheme I.26).



Scheme I.26. Synthesis of isopropylidene CYP17 inhibitor.

[40] E. Brachet, A. Hamze, J.-F. Peyrat, J.-D. Brion, M. Alami, *Org. Lett.* **2010**, *12*, 4042–4045.

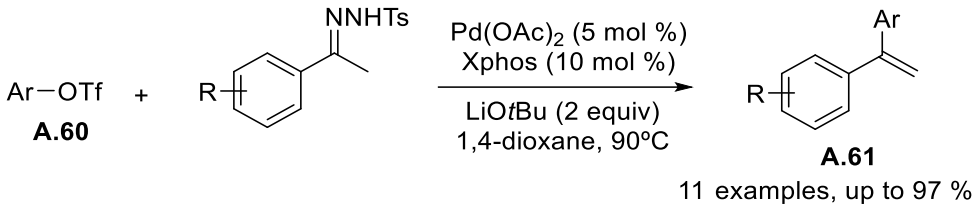
Still today, progresses are made in the context of the seminal concept of Pd-catalyzed cross-coupling reaction with tosylhydrazones. In 2016, Gu group presented the first example of an asymmetric catalytic.[41] Using this new reaction, enantiomerically enriched 1-vinylnaphthalen-2-ylphosphine oxides **A.59** featuring axial chirality were synthesized from aryl bromides **A.57** and *N*-tosylhydrazones derived from cyclic ketones **A.58**. The chirality in this transformation is transmitted by the employment of a chiral phosphoramidite ligand (**L1**). The combination of this ligand with mild reaction conditions allowed the merger between asymmetric synthesis with the Pd-carbene migratory insertion. Moreover, taking into account that the desired products are readily reduced to phosphine derivatives, this method provides and innovative way to design and synthesize phosphine ligands with axial chirality (Scheme I.27).



Scheme I.27. Enantioselective Pd-catalyzed synthesis of axial chiral vinyl arenes.

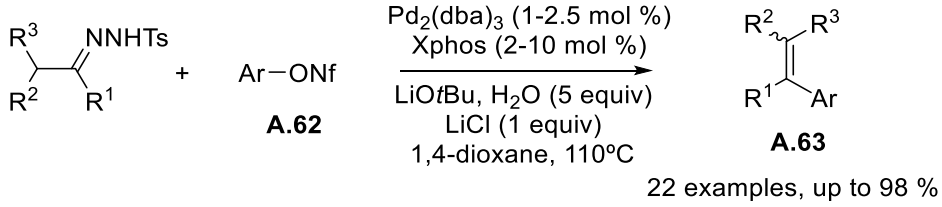
[41] J. Feng, B. Li, Y. He, Z. Gu, *Angew. Chemie Int. Ed.* **2016**, *55*, 2186–2190.

The Pd-catalyzed cross-coupling reaction with *N*-tosylhydrazones also evolved incorporating other electrophiles instead aryl halides as coupling partners. In this way, aryl sulfonates were the first electrophile incorporated in this Pd-catalyzed cross-coupling instead of aryl halides. In 2009, using an analogous conditions to those described for our research group in the reaction with aryl halides, Alami and co-worker reported a novel coupling employing aryl triflates **A.60**.[42] Although, the utilization of these pseudohalides has represented an advantage in terms of generality, the reaction described by Alami is restricted to the use of tosylhydrazones derived from acetophenones providing exclusively 1,1-diarylethylenes **A.61** (Scheme I.28).



Scheme I.28. Synthesis of 1,1-diazylethylenes from aryl triflates and *N*-tosylhydrazones.

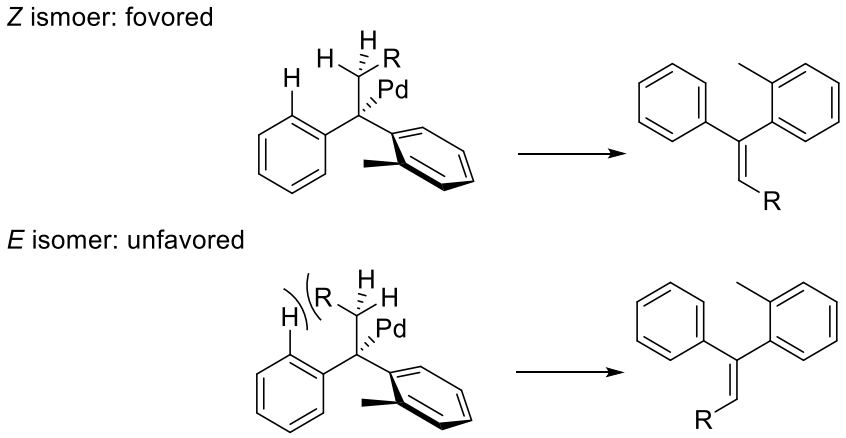
Continuing with the idea of expand the variety of electrophiles in the Pd-catalyzed cross-coupling with *N*-tosylhydrazones, our research group studied the employment of aryl nonaflates **I.62**.[43] These pseudohalides are more stable than triflates but have similar reactivity, [44] this allowed the construction of a very general version of the reaction. Suitable change of the reaction conditions were needed for the generation of di-, tri, and even tetrasubstituted alkenes **I.63** (Scheme I.29).



Scheme I.29. General synthesis of aryl alkenes from aryl nanofltes.

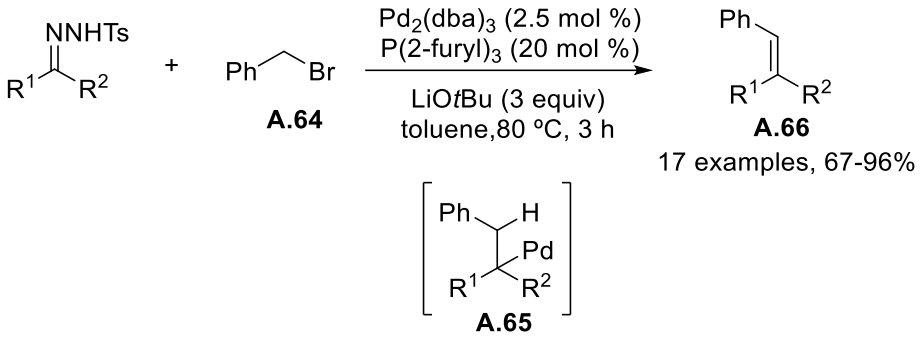
[42] B. Tréguier, A. Hamze, O. Provot, J.-D. Brion, M. Alami, *Tetrahedron Lett.* **2009**, *50*, 6549–6552.
[43] J. Barluenga, L. Florentino, F. Aznar, C. Valdés, *Org. Lett.* **2011**, *13*, 510–513.
[44] J. Högermeier, H.-U. Reissig, *Adv. Synth. Catal.* **2009**, *351*, 2747–2763.

In addition, the study of reactions with *ortho*-substituted nonaflates revealed quite interesting stereoselectivity in the synthesis of 1,1-diaryl trisubstituted olefins. The *ortho*-substituted aryl group is always in a *cis* relationship with the substituent on the other carbon atom of the newly formed double bond. This *ortho* directing effect can be explained in terms of the orientation of the *ortho*-substituted arene in the transition state for the *syn* β-hydride elimination (Scheme I.30).



Scheme I.30. Directing effect of an *ortho* substituent on the steriosectivity of the β-hydride elimination.

In 2009, Wang and co-workers described the Pd-catalyzed cross-coupling of benzyl halides **A.64** and *N*-tosylhydrazones.[45] The employment of tosylhydrazones derived from aryl or alkyl aldehydes, as well as ketones allowed the generation of di- and trisubstituted olefins **A.66**. The regioselectivity of the reaction was excellent giving in all the cases the β-hydride elimination in the benzylic position of the alkyl palladium intermediate **A.65**. The main different in the reaction conditions incorporated by Wang to carry out this coupling was the use of tri(2-furyl)phosphane as ligand to build the appropriate catalytic system (Scheme I.31).

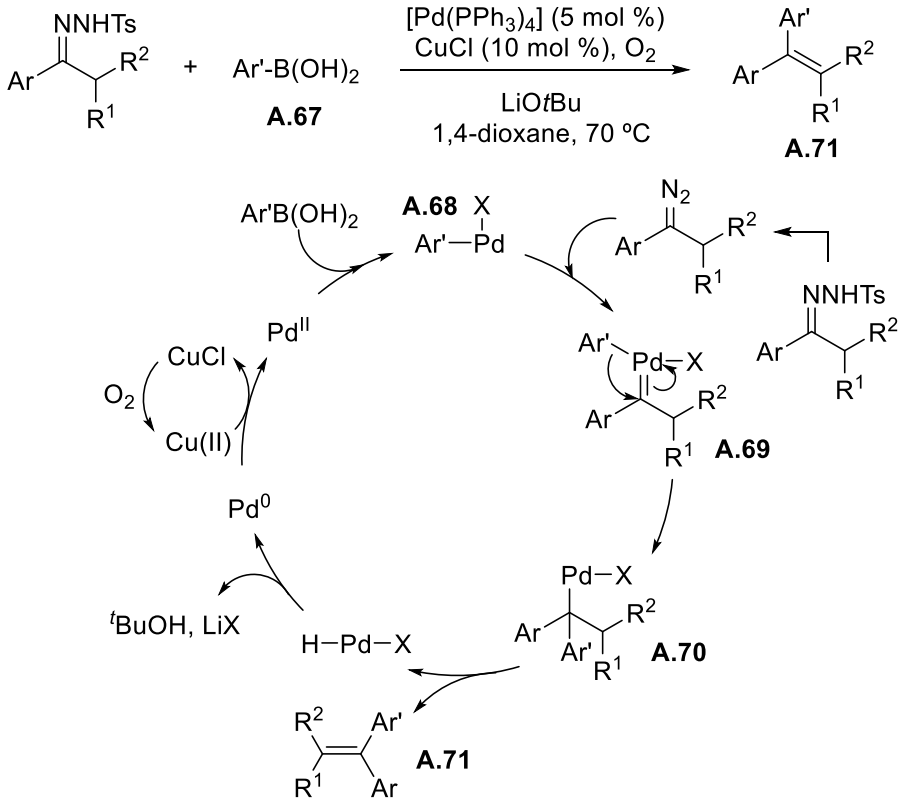


Scheme I.31. Pd-catalyzed cross-coupling reaction between benzyl bromides and *N*-tosylhydrazones.

[45] Q. Xiao, J. Ma, Y. Yang, Y. Zhang, J. Wang, *Org. Lett.* **2009**, *11*, 4732–4735.

Oxidative cross-coupling reactions with N-tosylhydrazones

The synthesis of olefins employing the Pd-catalyzed cross-coupling reaction with tosylhydrazones also evolved towards different mechanistic sequences. In this manner, in 2010 a Pd-catalyzed oxidative cross-coupling reaction with tosylhydrazones and boronic acids **A.67** was developed by Wang and co-workers. This oxidative transformation was initially discovered employing stabilized diazo compounds, and later adapted to the use of *N*-tosylhydrazones.[46] In addition to the Pd catalyst, the reaction requires the presence of an oxidant (CuCl and O_2) to reoxidized the Pd(0) to Pd(II) and close the catalytic cycle affording di-, tri- and tetrasubstituted alkenes **A.71** (Scheme I.32).[47]



Scheme I.32. Oxidative cross-coupling of tosylhydrazones with aryl boronic acids.

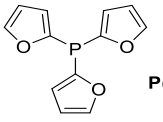
[46] C. Peng, Y. Wang, J. Wang, *J. Am. Chem. Soc.* **2008**, *130*, 1566–1567.
[47] X. Zhao, J. Jing, K. Lu, Y. Zhang, J. Wang, *Chem. Commun.* **2010**, *46*, 1724–1726.

The possible mechanism for the Pd-catalyzed oxidative coupling is initiated by the oxidation of the CuCl to Cu(II) by oxygen, which then oxidizes Pd(0) to Pd (II) species. Transmetallation of the Pd(II) species with the boronic acid affords aryl palladium species **A.68**, which reacts with the *in situ* generated diazo compound to give Pd carbene **A.69**. Migratory insertion of the aryl group to the carbenic carbon of the Pd carbene species affords the alkylpalladium intermediate **A.70**. Finally, β-hydride elimination of **A.70** provides the olefinic product **A.71** and regenerates the Pd(0) species in presence of base (Scheme I.32).

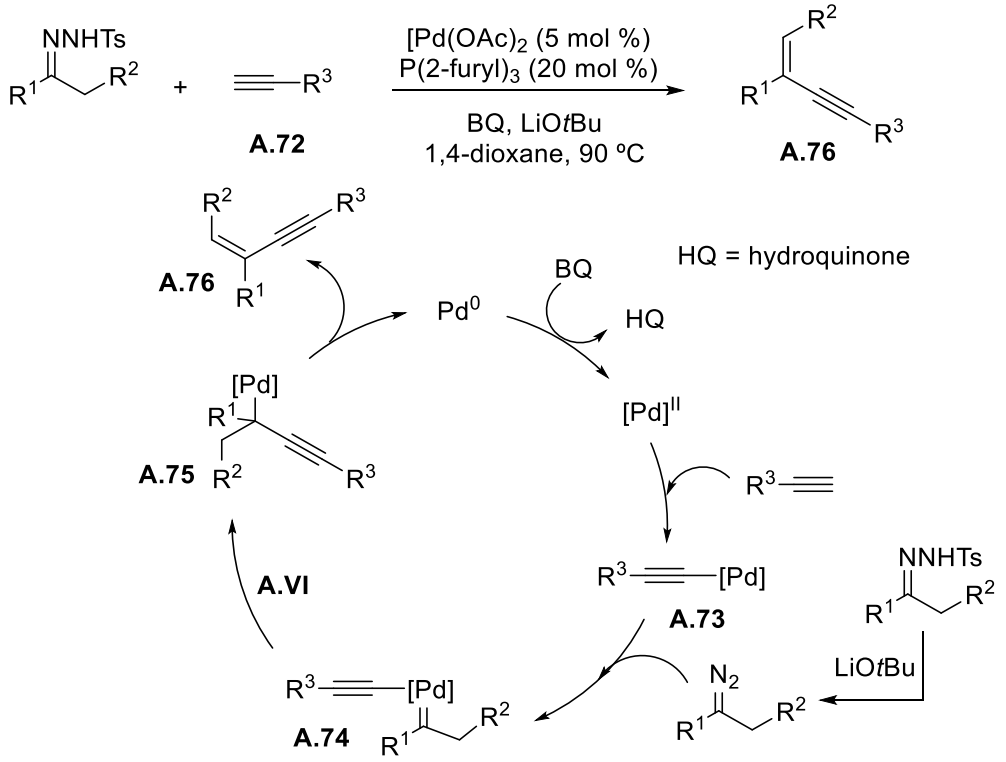
Wang also developed a synthesis of enynes **A.76** using terminal alkynes **A.72** and tosylhydrazones.[48] In this case, a catalytic system built from $Pd(OAc)_2$ and the weak electron-rich ligand $P(2\text{-furyl})_3$ was necessary for the proper course of the cross-coupling.[49] In addition, the combination of the benzoquinone (BQ) as oxidant and the LiO*t*Bu as base resulted crucial to carry out the reaction with good yields (Scheme I.33).

[48] L. Zhou, F. Ye, J. Ma, Y. Zhang, J. Wang, *Angew. Chemie Int. Ed.* **2011**, *50*, 3510–3514.

[49] For a review on tri(2-furyl)phosphine in transition-metal-catalyzed reactions, see: N. G. Andersen, B. A. Keay, *Chem. Rev.* **2001**, *101*, 997–1030.



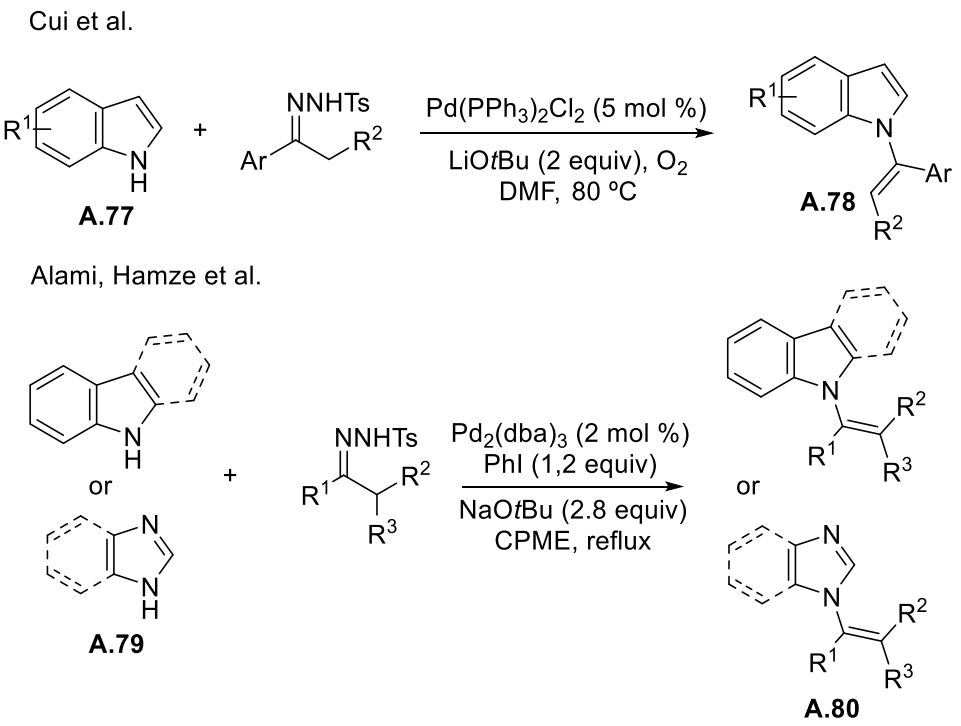
P(2-furyl)$_3$



Scheme I.33. Pd-catalyzed oxidative cross-coupling reaction of *N*-tosylhydrazones with terminal alkynes.

The proposed catalytic cycle begins with the oxidation of the Pd^0 catalyst by action of the BQ that reacts with the terminal acetylene to form the palladium acetylide **A.73**. Reaction with the diazo compound generates the Pd-carbene complex **A.74**. Then, the alkynyl migratory insertion of a palladium carbene **A.VI** takes place to give the propargylpalladium intermediate **A.75**. Finally, a β-hydride elimination releases the expected enyne **A.76** and a reductive elimination regenerates de Pd(0) catalyst (Scheme I.33).

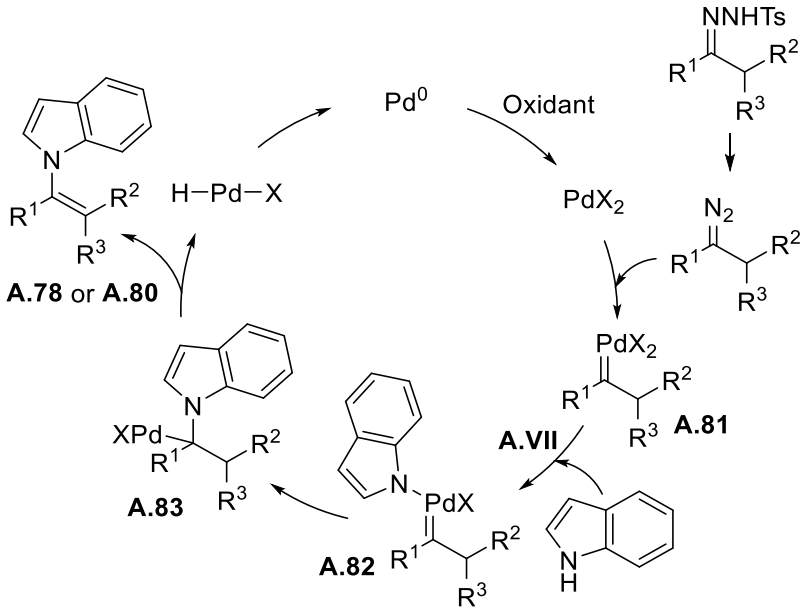
The oxidative coupling protocol have been also described for the formation of C-N bonds. In 2013, the groups of Cui,[50] and Alami and Hamze[51] independently reported different methodologies for the Pd-catalyzed oxidative *N*-alkenylation of azoles **A.77** or **A.79** with *N*-tosylhydrazones. While O_2 was used as oxidant in Cui's method, Alami and Hamze employed an excess of PhI as a sacrificial oxidant (Scheme I.34)



Scheme I.34. Pd-catalyzed oxidative alkenylation of azoles.

[50] X. Zeng, G. Cheng, J. Shen, X. Cui, *Org. Lett.* **2013**, *15*, 3022–3025.
[51] M. Roche, G. Frison, J.-D. Brion, O. Provot, A. Hamze, M. Alami, *J. Org. Chem.* **2013**, *78*, 8485–8495.

The proposed mechanism begins with the oxidation of the palladium species by action of the corresponding oxidant. Then, the coordination of the *in situ* generated diazo compounds provides the palladium carbene **A.81**, which undergoes a based-assisted ligand exchange to incorporate the indole system **A.VII**. Next, the indolyl palladium species **A.82** evolves through a migratory insertion to provide the alkyl palladium intermediate **A.83**. Finally, *syn* β-hydride elimination produces the olefinic product **A.78** or **A.80**, and reductive elimination regenerates the Pd(0) species (Scheme I.35).



Scheme I.35. Mechanistic proposal for the Pd-catalyzed oxidative alkenylation of azoles with *N*-tosylhydrazones.

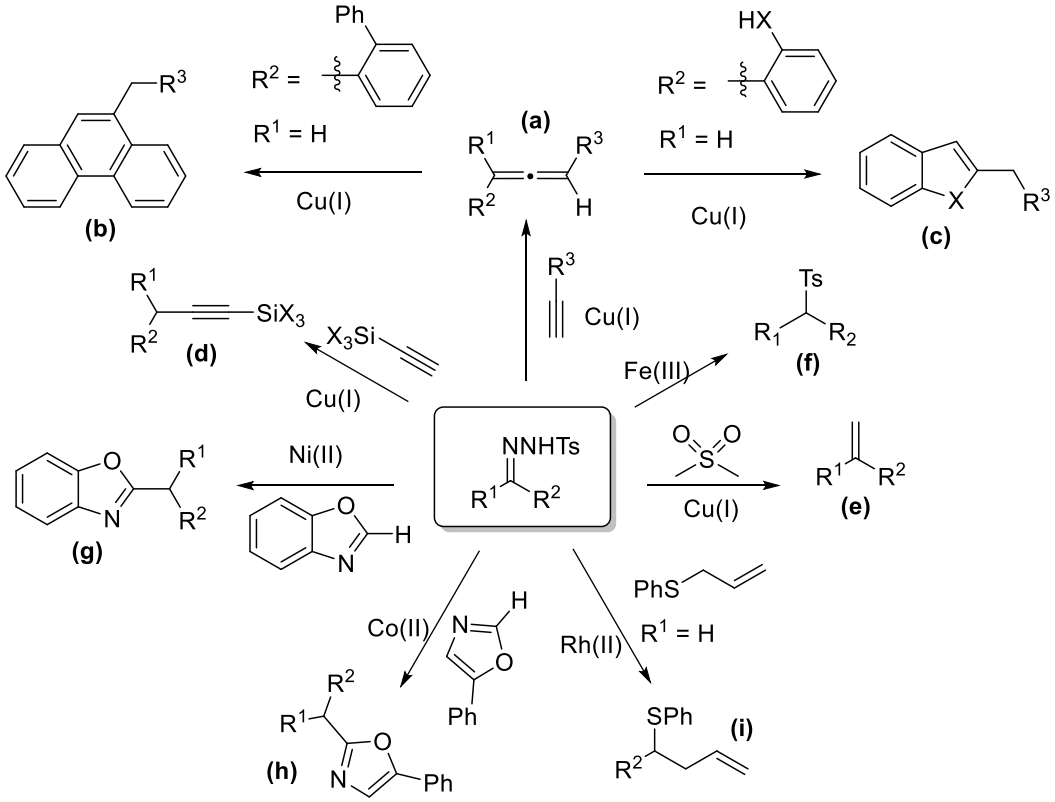
The most recent progress in Pd-catalyzed cross-couplings with *N*-sulfonylhydrazones involve the development of a variety of cascade processes. Some of these methodologies, which are relevants for the experimental work discussed in this memory, will be presented in the introduction of the specific chapter.

I.2.3 Cross-coupling reaction with *N*-tosylhydrazones catalyzed by other metals

As it has been discussed above, the versatility showed by sulfonylhydrazones as diazo compound precursors in Pd-catalyzed cross-couplings has stimulated an intensive research around these reagents in the last years. Palladium has been revealed as the most prolific transition-metal catalyst, however other metals such as nickel, iron, cobalt, rhodium, and specially copper have been employed in the development of other novel metal-catalyzed reactions based on *N*-tosylhydrazones (Scheme I.36).

Considering that the topic of this memory is focused on palladium as transition-metal catalyst, a revision of reactions catalyzed for other metals will not be included. Nevertheless, in Scheme I.36 is represented some of the most relevant transformations of transition metal catalyzed reaction with sulfonylhydrazones. Thus, with respect to the employment of Cu(I) salts or complexes, tosylhydrazones have been used to synthesize trisubstituted alenes **(a)**,[52] phenanthrenes **(b)**,[53] benzofurans **(c)**,[54] indoles **(c)**,[54] silylated terminal alkynes **(d)**[55] and very recently for the methylation of *N*-tosylhydrazones employing sulfonates as alternative to the traditional Julia olefination **(e)**.[56] In relation to other metals, can be highlighted the synthesis of sulfones by formal extrusion of nitrogen in reactions with sulfonylhydrazones catalyzed by Fe(III) salts **(f)**;[57] the alkylation of 1,3-oxazoles by Co or Ni catalyzed CH-functionalization **(g, h)**;[58] and finally, it is particularly important to underline the recent contribution by Wang regarding the Rh(II)-catalyzed asymmetric synthesis of homoalylic sulfides**(i)**.[59]

[52] Q. Xiao, Y. Xia, H. Li, Y. Zhang, J. Wang, *Angew. Chemie Int. Ed.* **2011**, *50*, 1114–1117.
[53] F. Ye, Y. Shi, L. Zhou, Q. Xiao, Y. Zhang, J. Wang, *Org. Lett.* **2011**, *13*, 5020–5023.
[54] L. Zhou, Y. Shi, Q. Xiao, Y. Liu, F. Ye, Y. Zhang, J. Wang, *Org. Lett.* **2011**, *13*, 968–971.
[55] F. Ye, X. Ma, Q. Xiao, H. Li, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 5742–5745.
[56] S. Xu, Y. Gao, R. Chen, K. Wang, Y. Zhang, J. Wang, *Chem. Commun.* **2016**, *52*, 4478–4480.
[57] J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Eur. J. Org. Chem.* **2011**, *2011*, 1520–1526.
[58] T. Yao, K. Hirano, T. Satoh, M. Miura, *Angew. Chemie Int. Ed.* **2012**, *51*, 775–779.
[59] a) Y. Li, Z. Huang, X. Wu, P.-F. Xu, J. Jin, Y. Zhang, J. Wang, *Tetrahedron* **2012**, *68*, 5234–5240; b) Z. Zhang, Z. Sheng, W. Yu, G. Wu, R. Zhang, W.-D. Chu, Y. Zhang, J. Wang, *Nat. Chem.* **2017**, *9*, 970.



Scheme I.36. Examples of reaction with *N*-tosylhydrazones catalyzed by other metals.

I.3 Conclusions of the introduction

As shown this introduction, over the last years, the Pd-catalyzed cross-coupling reactions with *N*-tosylhydrazones have experimented a tremendous growth. The combination of the *in situ* generation of diazo compounds and the palladium catalytic process based on the carbene migratory insertion, can be considered the principal differential steps for this transformation.

As a direct consequence of the attention generated by this reaction, the *N*-tosylhydrazones have become very versatile reagents for the transformation of carbonyl compounds through no conventional reactions. Their easy handling and capacity to provide diazo compounds without restrictions have placed these substrates at the forefront of cross-coupling reactions.

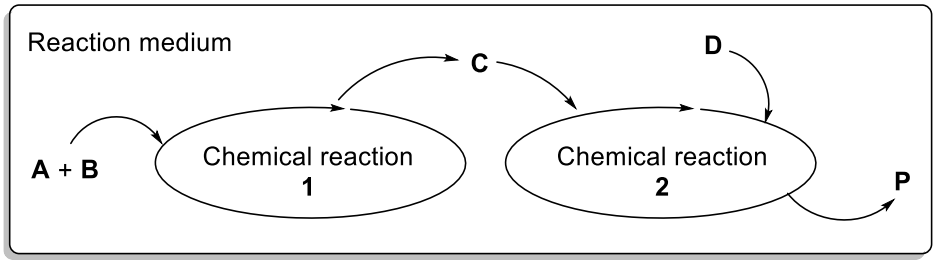
Nevertheless, despite the advances which have experimented this field during the last decade, this chemistry still holds great potential for the development of new interesting transformations. The Thesis presented herein is devoted to contribute in this particular field.

Chapter 1

New approaches in palladium catalyzed cross-couplings with *N*-tosylhydrazones: Cascade cyclization processes

1.1 Introduction

One of the most important goals of synthetic organic chemistry is the design of new methodologies to elaborate complex molecular structures from simple precursors. During the last decades, some of the most prolific areas in this sense have been transition-metal catalyzed reactions, which have been constantly evolving in terms of efficiency and versatility. It is in this context where the concept of "cascade reaction" has been incorporated within transition-metal catalyzed transformations. Conceptually the term "cascade reaction" has been used to describe a process which involves two or more chemical reactions under the same conditions. However, to be in complete accordance with this term, the second transformation must take place as a consequence of the functionality generated in the previous transformation (Scheme 1.1). Very often the expressions "tandem reaction", "domino reaction" or "sequential process" are used in a totally analogous way.[60]



Scheme 1.1. General diagram for cascade reactions with two chemical transformations.

Cascade reactions have become highly desirable transformations in organic synthesis.[61] In a typical cascade reaction, several bonds are formed in one single synthetic step, allowing for the easy generation of structural complexity from relatively simple starting materials. In the context of metal-catalyzed cascade reactions, Pd-catalyzed processes are among the most prolific and versatile transformations.[62] Depending on the role of the catalyst in the different steps of the reaction sequence, a variety of different types of metal-catalyzed cascade reactions can be distinguished.[60,63]

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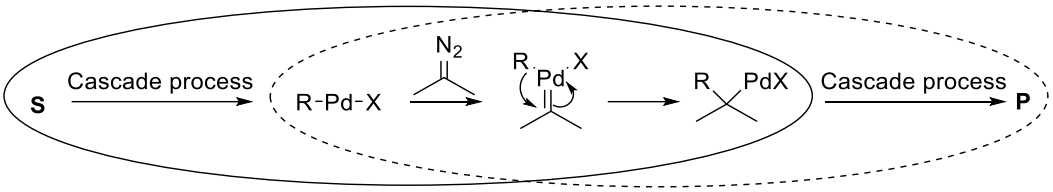
[60] D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365–2379.
[61] L. F. Yietze, *Domino Reactions: Concepts for Efficient Organic Synthesis*; Wiley, Weinheim, **2014**.
[62] P.-F. Xu, H. Wei, *Catalytic Cascade Reactions*; Eds. P.-F. Xu, W. Wang; Wiley, Hoboken, **2014**, 283.
[63] a) G. Poli, G. Giambastiani, *J. Org. Chem.* **2002**, *67*, 9456–9459; b) N. Shindoh, Y. Takemoto, K. Takasu, *Chem. Eur. J.* **2009**, *15*, 12168–12179; d) N. T. Patil, V. S. Shinde, B. Gajula, *Org. Biomol. Chem.* **2012**, *10*, 211–224.

Taking into account that the current chapter is focused on the development of new Pd-catalyzed cascade cyclization reactions with *N*-tosylhydrazones, a brief revision of the most relevant precedents will be presented.

1.1.1 Palladium catalyzed cascade cyclization reactions with *N*-sulfonylhydrazones

Over the last decades, Pd-catalyzed cascade reactions have been established as very powerful methodologies for the synthesis of carbo- and heterocycles.[64] As a consequence of the interest generated by the discovery of the Pd-catalyzed cross-coupling reaction with *N*-tosylhydrazones, many research groups have implemented this novel cross-coupling in cascade cyclization processes. The common factor in all these transformations is the metal carbene migratory insertion (Scheme 1.2).



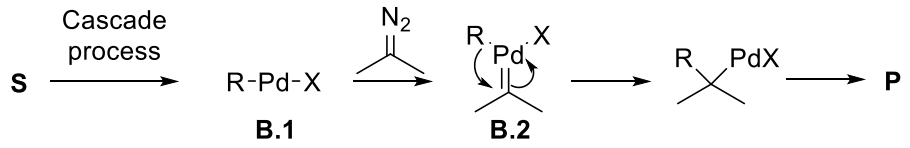
Scheme 1.2. Classification of cascade reactions with tosylhydrazones.

Pd-catalyzed cascade reactions involving diazo compounds or *N*-tosylhydrazones can be classified attending to the moment when the diazo compound is incorporated to the catalytic cycle, and therefore two main different types of rections can be distinguished: 1) Cascade cyclizations in which the reaction with the diazo compound is the terminating step, and 2) Cascade cyclizations in which the reaction with the diazo compounds is the initiation step. A third type of reactions that lay out of this classification are auto-tandem reactions, in which the same catalyst promotes two different sequential transformations with independent catalytic cycles. These type of reactions will be covered in Chapter 2 of this memory.

[64] J. J. Li, G. W. Gribble, *Palladium in Heterocyclic Chemistry*; Eds. J. J. Li, G. W. Gribble; Elsevier, Pergamon, **2006**.

Cascade cyclizations in which the cross-coupling with the diazo compound is the terminating step.

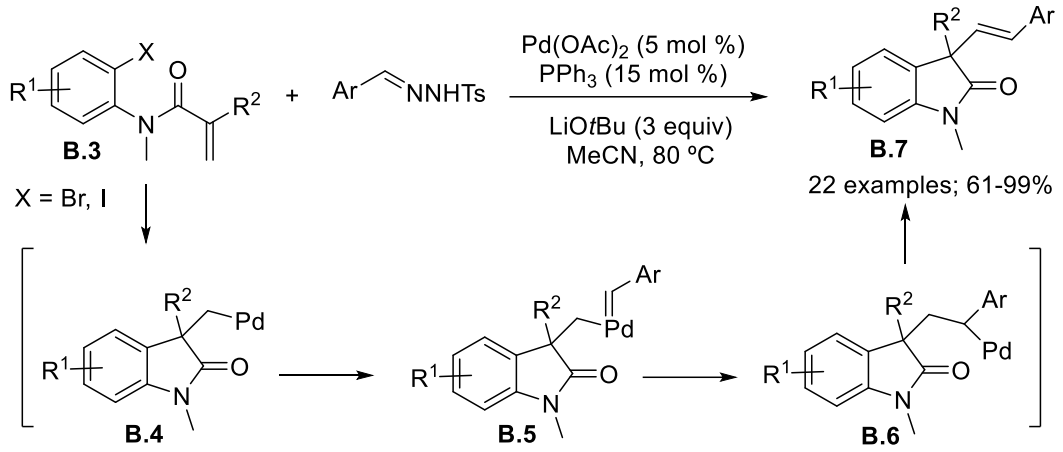
In a typical cross-coupling reaction based on diazo compounds or sulfonylhydrazones, the initial Pd(II) species **B.1** that reacts with the diazo compound to form the carbene **B.2** is generated upon oxidative addition of a Pd(0) species with an organic halide (Scheme I.37). However, the Pd(II) species **B.1** could be formed through more complex Pd-catalyzed reaction sequences, in which the cross-coupling with the diazo compound is the termination step of a cascade cyclization reaction (Scheme 1.3).



Scheme 1.3. Cascade cyclizations in which the reaction with the diazo compound takes place as terminating step.

The first example of this type of cascade cyclizations was reported by Gu and co-workers in 2013.[65] This transformation consists in a Pd-catalyzed Heck cyclization/carbene coupling cascade reaction of aryl halides **B.3** and *N*-tosylhydrazones. The reaction is initiated by a normal oxidative addition followed by a carbopalladation to generate the alkyl palladium species **B.4** that cannot suffer β-hydrogen elimination. Then the coordination of the diazo compound forms the palladium carbene **B.5**, which undergoes migratory insertion to provide the alkyl palladium intermediate **B.6**. Finally, a β-hydride elimination affords the 2-indolinone **B.7** (Scheme 1.4).

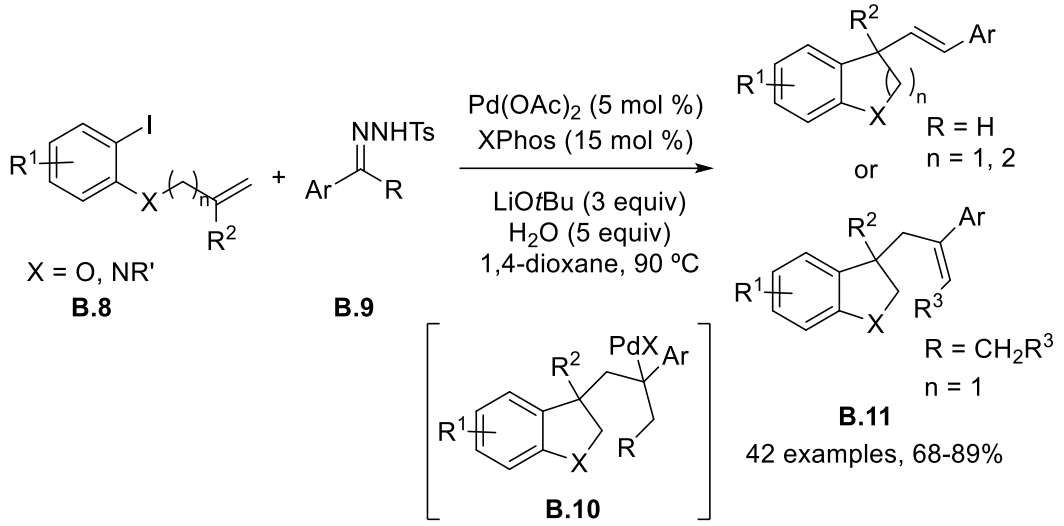
[65] X. Liu, X. Ma, Y. Huang, Z. Gu, *Org. Lett.* **2013**, *15*, 4814–4817.



Scheme 1.4. Pd catalyzed intramolecular carbopalladation/migratory insertion cascade reaction.

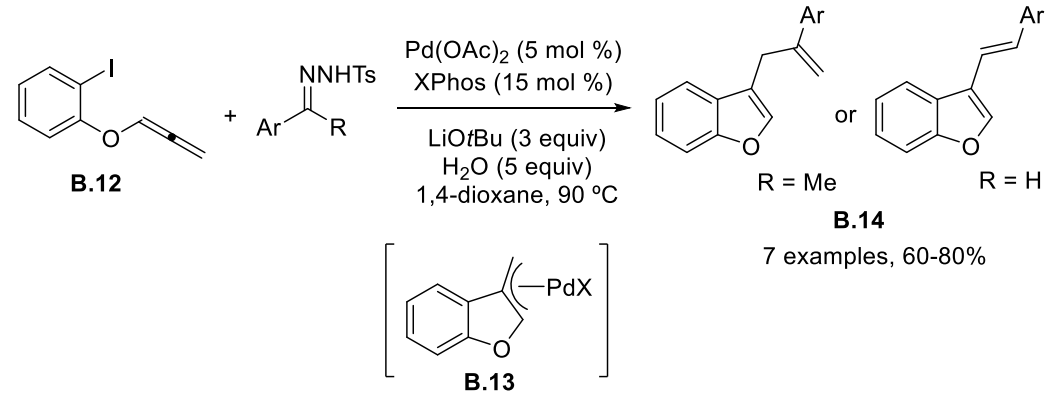
In 2015, Jiang, Wu and co-workers reported a similar Heck cyclization/carbene coupling cascade reaction.[66] In these studies the cyclization reaction is carried out using *N*-tosylhydrazones derived from aryl aldehydes or ketones **B.9**. Despite the fact that employment of *N*-tosylhydrazones derived from aryl aldehydes leads to essentially the same reaction previously described by Gu,[65] when *N*-tosylhydrazones derived from aryl ketones are used, an interesting site-selective β-hydride elimination takes place in the intermediate **B.10** to give allyl substituted heterocyclic systems **B.11** (Scheme 1.5).

[66] Y. Gao, W. Xiong, H. Chen, W. Wu, J. Peng, Y. Gao, H. Jiang, *J. Org. Chem.* **2015**, *80*, 7456–7467.



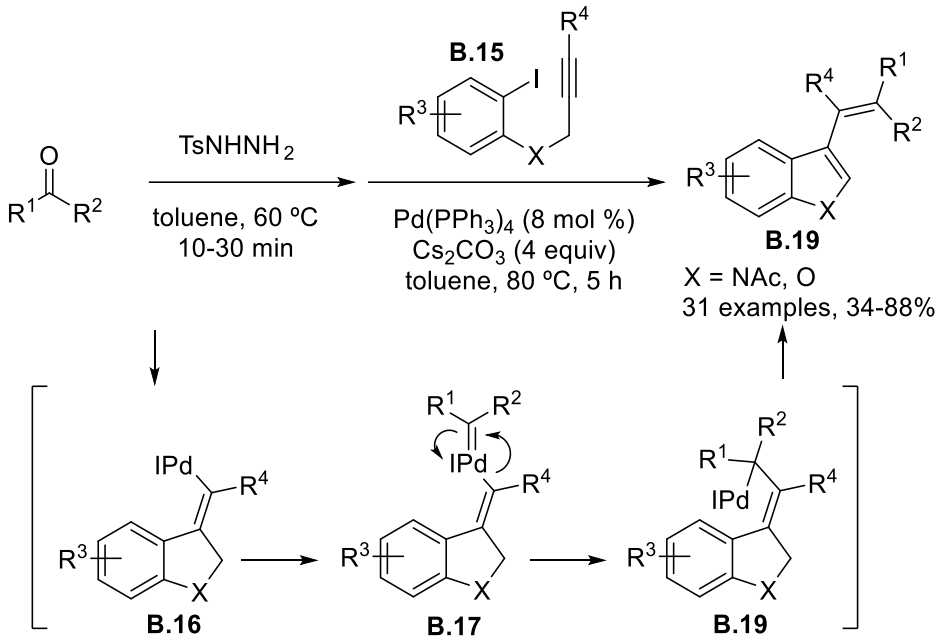
Scheme 1.5. Pd-catalyzed cascade Heck cyclization/carbene coupling reaction.

In a continuation of the early studies carried out by Jiang, Wu and co-workers, a straightforward approach for obtaining benzofuran scaffolds was described.[66] Thus, an analogous Heck cyclization/carbene coupling cascade sequence was employed taking as starting materials aryl iodides bearing allene moieties **B.12** and *N*-tosylhydrazones. The result of the employment of this new family of starting material was the generation of 2-allyl or 2-alkenyl substituted benzofurans **B.14**, through the formation of an allylic palladium intermediate **B.13** (Scheme 1.6).



Scheme 1.6. Pd-catalyzed allene-based cyclization/carbene coupling to synthesize benzofurans.

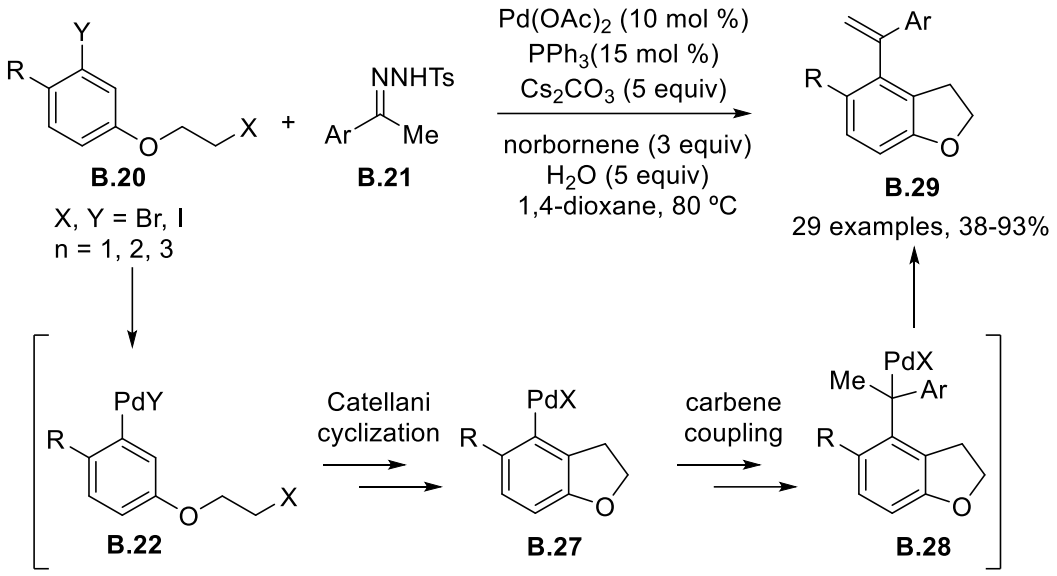
Quite similarly, the carbopalladation/tosylhydrazone cross-coupling was performed by Wang and co-workers employing *o*-iodo-*N*-propargylanilines **B.15**.[67] In this case, the carbopalladation reaction affords an alkenyl palladium complex **B.16** that is intercepted by the diazo compound generated from the tosylhydrazone. Then, migratory insertion followed by a formal δ-hydrogen elimination provides the final alkenylindoles **B.19** (Scheme 1.7).



Scheme 1.7. Pd-catalyzed alkyne insertion/carbene coupling cascade reaction.

[67] Z. Liu, Y. Xia, S. Zhou, L. Wang, Y. Zhang, J. Wang, *Org. Lett.* **2013**, *15*, 5032–5035.

Apart from the intramolecular insertion of and unsaturated bond, Xu, Liang and co-workers developed an original Pd-catalyzed cyclization/carbene coupling cascade reaction by the combination of the Catellani reaction[68] and the *N*-tosylhydrazone-based cross-coupling.[69] Under the typical conditions of the Catellani reaction (Pd catalyst in the presence of norbornene), the reaction between *m*-iodophenyl bromoalkyl ethers **B.20** and tosylhydrazones **B.21** leads to the alkenyl substituted benzofused heterocycle **B.29**. The formation of **B.29** can be explained considering that the aryl palladium species **B.27** generated *via* Catellani reaction, reacts with the diazo compound generated from the tosylhydrazone to produce the alkyl palladium intermediate **B.28**. A final β-hydride elimination provides the benzo-fused oxygen-containing five to seven membered ring systems (Scheme 1.8).

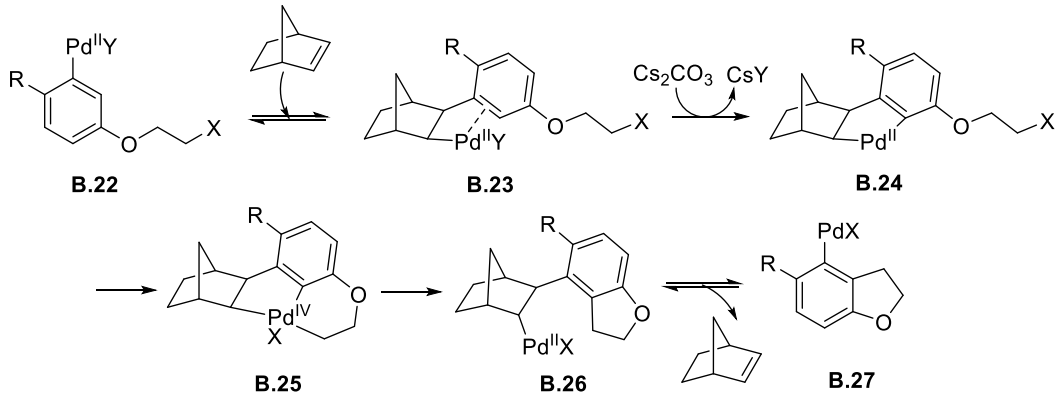


Scheme 1.8. Pd-catalyzed Catellani cyclization/carbene coupling cascade reaction.

[68] a) M. Catellani, E. Motti, N. Della Ca', *Acc. Chem. Res.* **2008**, *41*, 1512–1522; b) N. Della Ca', M. Fontana, E. Motti, M. Catellani, *Acc. Chem. Res.* **2016**, *49*, 1389–1400.

[69] X.-X. Wu, P.-X. Zhou, L.-J. Wang, P.-F. Xu, Y.-M. Liang, *Chem. Commun.* **2014**, *50*, 3882–3884.

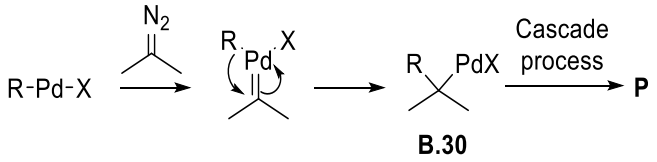
The mechanistic proposal for the Catellani cyclization in this particular reaction is initiated by the oxidative addition of the aryl halide to Pd(0) to afford the aryl Pd(II) species **B.22**. Norbornene insertion leads to complex **B.23**, which is fairly stable toward β-hydride elimination, because of geometric constraints, and evolves to the five-membered palladacycle **B.24** through intramolecular *ortho*-C-H activation in the presence of a base. Then, the oxidative addition of alkyl halide to **B.24** gives Pd(IV) complex **B.25**, which readily undergoes reductive elimination to provide norbornyl-Pd(II) species **B.26**. Finally, C-C bond cleavage occurs, through β-elimination leading to the arylpalladium intermediate **B.27** and norbornene (Scheme 1.9). At this stage, the arylpalladium complex **B.27** reacts with the diazo compound generated from the tosylhydrazone, to complete the catalytic cycle (Scheme 1.8).



Scheme 1.9. Proposed mechanism of Catellani cyclization.

Cascade cyclizations in which the cross-coupling with the diazo compound takes place as initial step.

In this second type of cyclization cascade reaction, the coupling with the diazo compound occurs in first place in order to generate a Pd(II) species **B.30**. In a typical Pd-catalyzed carbene migratory insertion coupling reaction, the alkyl metal species **B.30** generated upon carbene migratory insertion, usually undergoes β-hydride elimination.[70] However, if the alkyl palladium intermediate **B.30** cannot suffer β-hydride elimination, a further cascade process can be achieved (Scheme 1.10).

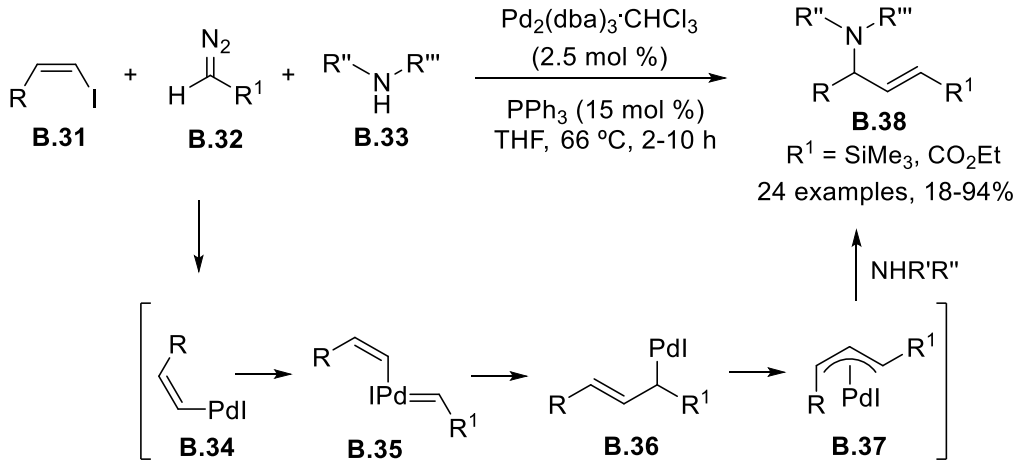


Scheme 1.10. General process of cascade reaction initiated into the alkyl palladium species **B.30**.

The first examples of cascade processes based on this principle were developed to afford the synthesis of linear molecules.

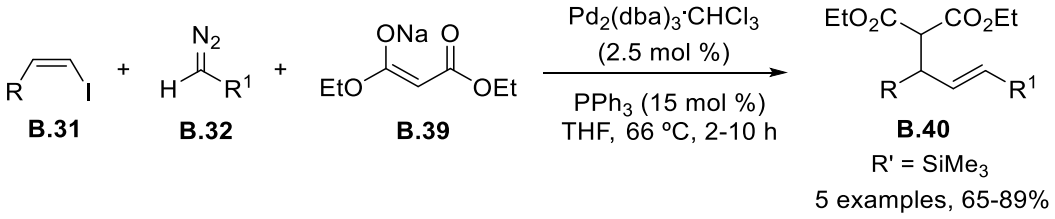
[70] a) J. Barluenga, C. Valdés, *Angew. Chemie Int. Ed.* **2011**, *50*, 7486–7500; b) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560–572; c) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236–247.

In 2007, Van Vranken and co-workers reported the first Pd-catalyzed cascade reactions based on diazo compounds through the generation of η^3-allylpalladium species **B.37** from the carbene migratory insertion process. The formation of these intermediates **B.37** was achieved by reaction of vinyl iodides **B.31** with diazo compounds **B.32.** Then, in the presence of an amine the allylic substitution takes place to afford the allylic amine **B.38** (Scheme 1.11).[71]



Scheme 1.11. Pd-catalyzed three-component cross-coupling of vinyl halides.

The reaction was later extended to involve sodium diethyl malonate **B.39** as nucleophilic partner instead of amines (Scheme 1.12).[72]

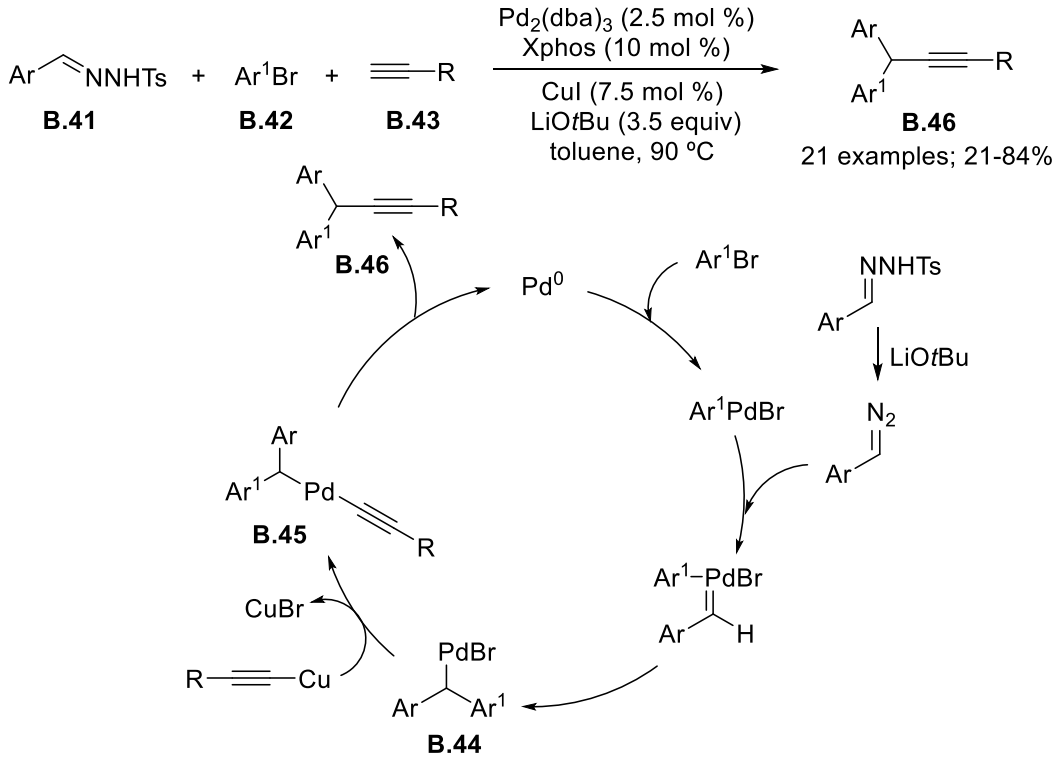


Scheme 1.12. Pd-catalyzed three-componet cross-coupling envolving sodium diethyl malonate.

[71] a) S. K. J. Devine, D. L. Van Vranken, *Org. Lett.* **2007**, *9*, 2047–2049; b) R. Kudirka, S. K. J. Devine, C. S. Adams, D. L. Van Vranken, *Angew. Chemie Int. Ed.* **2009**, *48*, 3677–3680.

[72] S. K. J. Devine, D. L. Van Vranken, *Org. Lett.* **2008**, *10*, 1909–1911.

In 2010, Wang and co-workers presented a three-component cascade reaction of *N*-tosylhydrazones, aryl halides and terminal alkynes, in which the carbene insertion reaction and the Sonogashira alkylation are combined.[73] In this reactions, after the typical previous steps for the cross-coupling reaction with tosylhydrazones, the benzyl palladium intermediate, which cannot afford a β-hydride elimination, undergoes transmetalation with the *in situ* formed copper acetylyde to give the palladium complex **B.45**. Subsequently, reductive elimination affords the benzhydryl acetylene **B.46** and regenerates the palladium catalyst (Scheme 1.13).

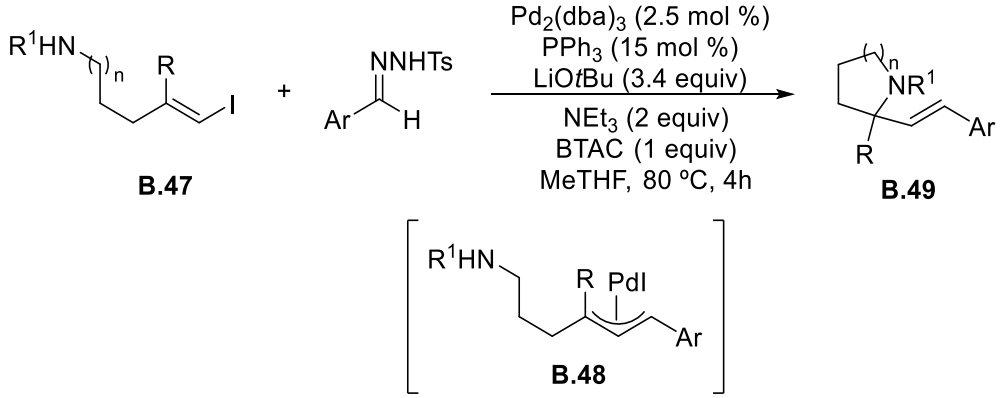


Scheme 1.13. Pd-catalyzed migratory insertion/Sonogashira coupling cascade reaction.

Considering these two transformation, in which the cascade process is promoted by the alkyl palladium species generated in a previous cross-coupling with diazo compounds, various studies were carried out to implement this idea in cascade cyclization processes.

[73] L. Zhou, F. Ye, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 13590–13591.

In 2012, Van Vranken and co-workers described the intramolecular version of their previous studies (Schemes 1.11 and 1.12),[71,72] which can be considered the first example of a Pd-catalyzed cascade cyclization reaction with *N*-tosylhydrazones which involves an allylic substitution.[74] In this novel cascade approach, vinyl iodides bearing amino groups **B.47** and *N*-tosylhydrazones derived from aldehydes were used to give pyrrolidine and piperidine ring systems **B.49**. In this case, the cyclization is enabled by the formation of η^3-allylpalladium intermediate **B.48**, which finally is trapped by the amino group in a formal intramolecular nucleophilic substitution (Scheme 1.14). The usefulness of this approach was illustrated by the successful application of this strategy in the synthesis of the natural alkaloid caulophyllumine.

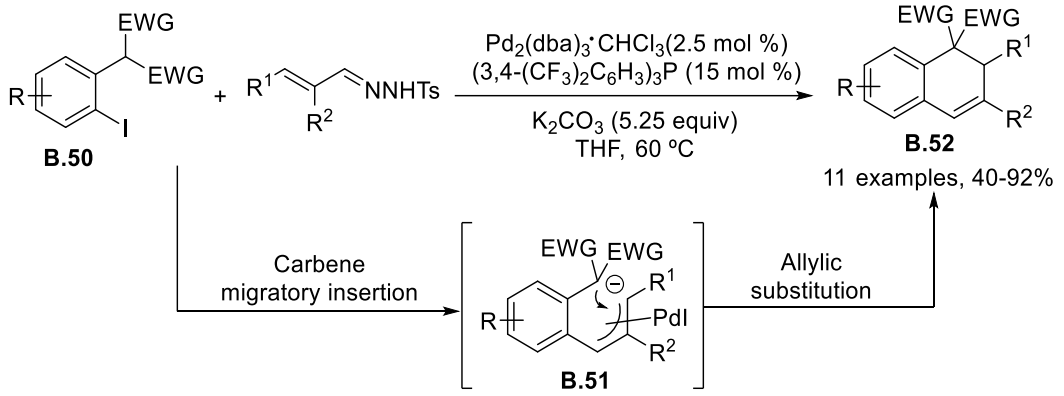


Scheme 1.14. Pd catalyzed carbenylative aminative cyclization with *N*-tosylhydrazones.

The interest for these cyclization cascade reactions involving a final allylic substitution became evident in the following years. One year after the publication of Van Vranken´s work, Liang and co-workers reported another Pd-catalyzed cascade cyclization reaction.[75] This time the reaction took place between *o*-iodoarylmalonates **B.50** and *N*-tosylhydrazones derived from α,β-unsaturated aldehydes, to form highly substituted dihydronaphthalenes **B.52**. This reaction was proposed to occur through a carbene migratory insertion to give the η^3-allylpalladium intermediate **B.51**, followed by an intramolecular allylic substitution of the internal carbon nucleophile (Scheme 1.15).

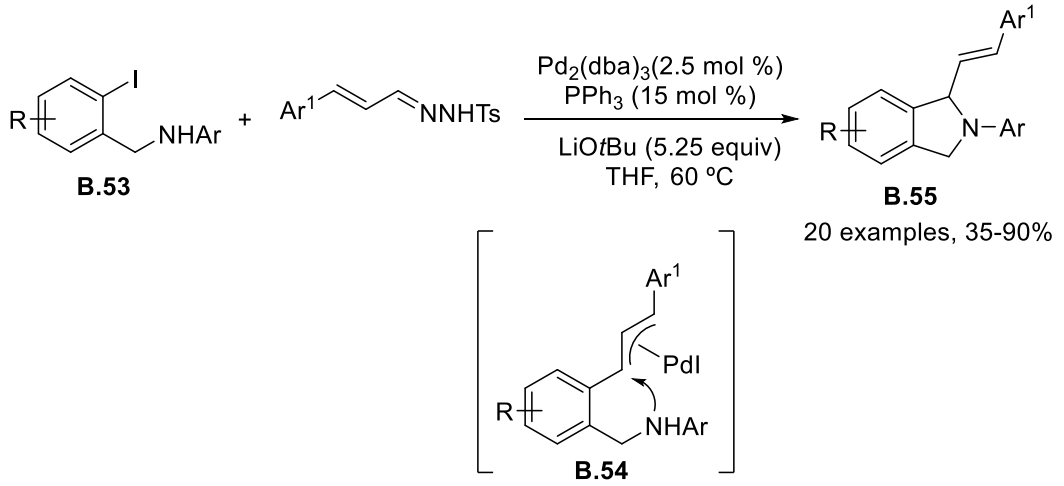
[74] A. Khanna, C. Maung, K. R. Johnson, T. T. Luong, D. L. Van Vranken, *Org. Lett.* **2012**, *14*, 3233–3235.

[75] Y.-Y. Ye, P.-X. Zhou, J.-Y. Luo, M.-J. Zhong, Y.-M. Liang, *Chem. Commun.* **2013**, *49*, 10190–10192.



Scheme 1.15. Pd-catalyzed cascade cyclization reaction of *o*-iodoarylmalonates and *N*-tosylhydrazones.

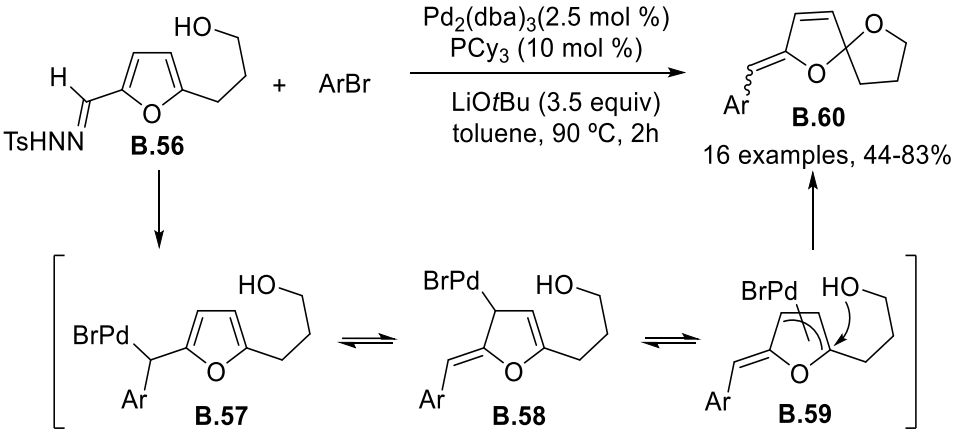
Subsequently, the same research group reported a similar Pd-catalyzed cascade cyclization reaction employing *o*-iodobenzylamines **B.53** and α,β-unsaturated *N*-tosylhydrazones for the preparation of isoindoline derivatives **B.55**.[76] The mechanism is only differs from the case explained above, in which the intramolecular allylic substitution **B.54** is carried out by the internal benzyl amino group (Scheme 1.16).



Scheme 1.16. Pd-catalyzed cascade cyclization reaction for the synthesis of isoindolines.

[76] P.-X. Zhou, J.-Y. Luo, L.-B. Zhao, Y.-Y. Ye, Y.-M. Liang, *Chem. Commun.* **2013**, *49*, 3254–3256.

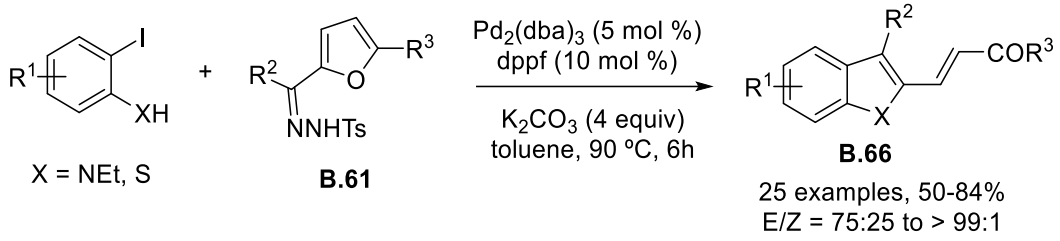
In 2014, Jiang and co-workers described a dearomatizating cascade cyclization between aryl bromides and furfural *N*-tosylhydrazones **B.56**.[77] The key of this new synthetic transformation is the presence of a hydroxyl-containing alkyl fragment in the *N*-tosylhydrazone component. Therefore, after the carbene migratory insertion and the subsequent formation of the η^3-furylmethyl palladium intermediate **B.59**, the system undergoes an intramolecular nucleophilic dearomatization to provide spiroacetal enol ethers **B.60**. The configuration showed for newly formed double bond is largely dependent on the substrates selected to carry out the reaction (Scheme 1.17).



Scheme 1.17. Pd-catalyzed cascade reaction through carbene coupling/dearomatic cyclization.

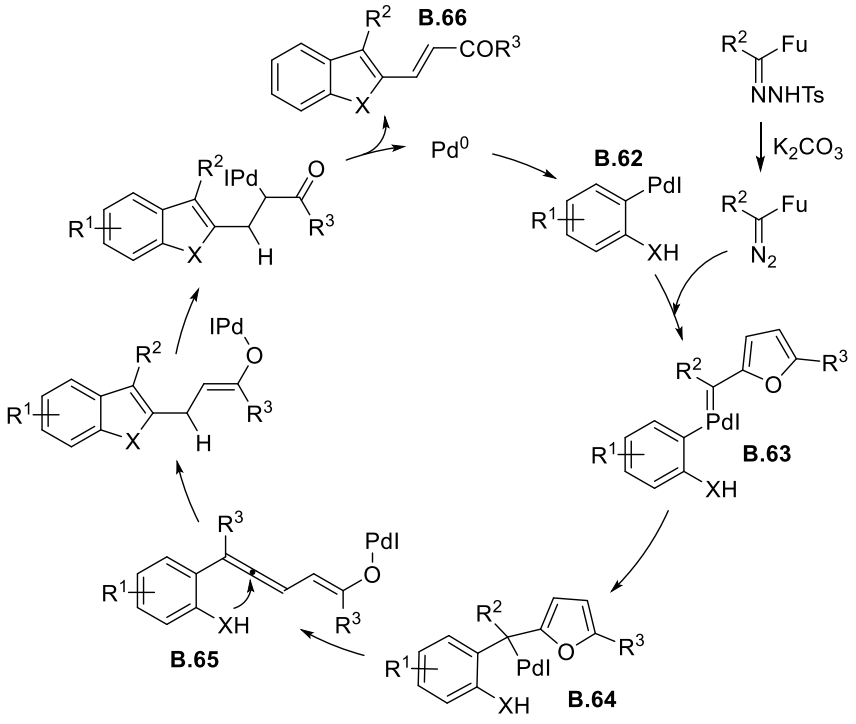
Continuing with the development of cascade cyclization relations based on furan-containing *N*-tosylhydrazones, in 2015, Jiang and co-workers introduced a transformation in which the alkyl palladium intermediate does not evolve through a η^3-allylpalladium intermediate.[78] Otherwise, it is an oxygen coordinated palladium complex **B.65** which provides the viability of the cascade cyclization process. Thus, a new Pd-catalyzed carbene cross-coupling/cyclization cascade sequence enabled the formation of benzofused heterocycles **B.66** employing *N*-tosylhydrazones **B.61** and 2-iodoanilines or 2-iodotiophenol (Scheme 1.18).

[77] B. Yin, X. Zhang, J. Liu, X. Li, H. Jiang, *Chem. Commun.* **2014**, *50*, 8113–8116.
[78] B. Yin, X. Zhang, X. Zhang, H. Peng, W. Zhou, B. Liu, H. Jiang, *Chem. Commun.* **2015**, *51*, 6126–6129.



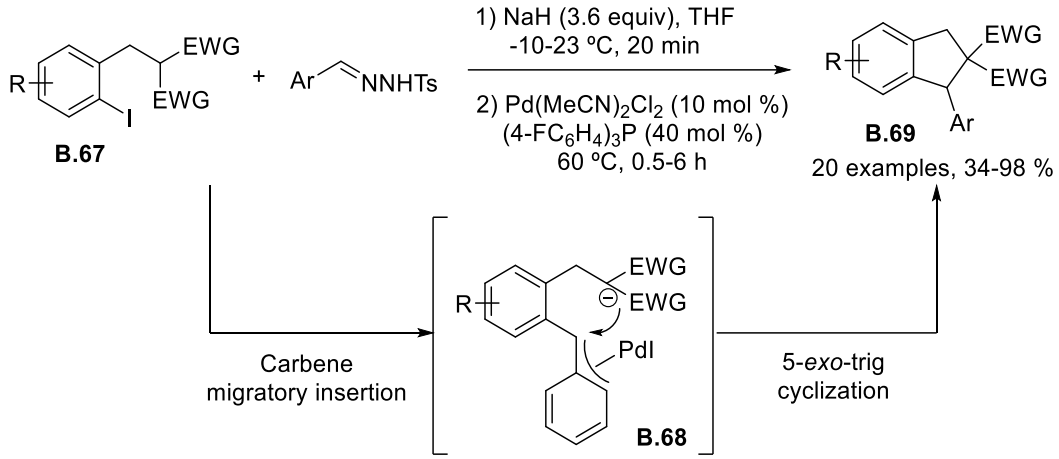
Scheme 1.18. Pd-catalyzed cascade reaction *via* ring opening furfural *N*-tosylhydrazone.

The proposed mechanism begins with the oxidative addition of the aryl iodide to the Pd(0) catalyst to give the Pd(II) complex **B.62**. Then, the coordination of the diazo compound provides the furyl palladium carbene **B.63**, which undergoes a migratory insertion to promote the formation of alkyl intermediate **B.64**. At this point a β-oxygen elimination takes place to open the furan ring and form the allene **B.65**. Subsequent intramolecular cyclization and β-hydride elimination affords polysubstituted indoles and benzothiophenes as the final products **B.66** (Scheme 1.19).



Scheme. 1.19. Proposed mechanism for Pd-catalyzed cascade formation of indoles and benzothiophenes.

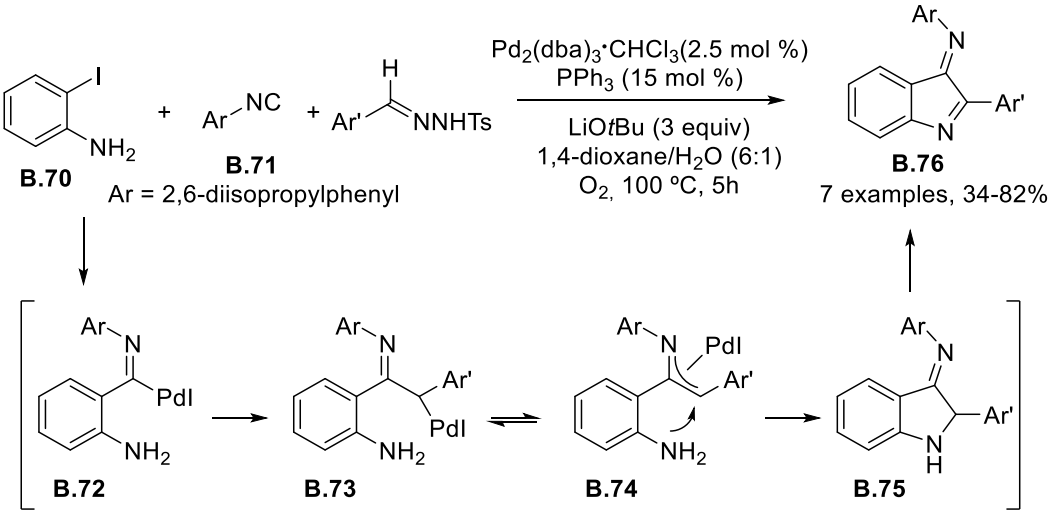
In 2014, Van Vranken and co-workers presented an innovative Pd-catalyzed cascade cyclization approach for the synthesis of indane derivatives.[79] In this study a wide variety of 1-arylindanes **B.69** are prepared using *o*-iodobenzylmalonates **B.67** and *N*-tosylhydrazones derived from aldehydes. The proposed mechanism for this reaction involves a carbene migratory insertion to give an unprecedented η^3-benzylpalladium complex **B.68**. Then, a nucleophilic attack on the carbenic carbon provides the corresponding indane **B.69** in a formal 5-*exo*-trig cyclization (Scheme 1.20).



Scheme 1.20. Synthesis of indanes through Pd-catalyzed carbene insertion/5-*exo*-trig cyclization.

Recently, Cheng and co-workers reported a Pd-catalyzed three-component cascade cyclization reaction using 2-iodoanilines **B.70**, bulky arylisonitriles **B.71** and *N*-tosylhydrazones to form 3-iminoindole derivatives **B.76**.[80] The proposed mechanism for this novel transformation occurs *via* generation of the amino palladium species **B.72** through an oxidative addition followed by isonitrile insertion. Then, the carbenic insertion provides the alkyl palladium intermediate **B.73**, which undergoes an intramolecular nucleophilic cyclization to produce the 3-iminoindole intermediate **B.75** *via* aza η^3-allylpalladium species **B.74**. Upon oxidation to the iminium intermediate **B.75** a variety of 3-iminoindole derivatives **B.76** can be obtained (Scheme 1.21).

[79] E. S. Gutman, V. Arredondo, D. L. Van Vranken, *Org. Lett.* **2014**, *16*, 5498–5501.
[80] Q. Dai, Y. Jiang, S. Guo, J.-T. Yu, J. Cheng, *Chem. Commun.* **2015**, *51*, 14781–14784.



Scheme 1.21. Pd-catalyzed multi-component cascade cyclization reaction for the synthesis of indole derivatives.

As it has been shown, most cascade cyclizations that include the migratory insertion as initiation step, rely on the formation of a η^3-allylpalladium complex followed by a nucleophilic substitution. Nervertheless, the alkylpalladium complex formed upon migratory insertion might be involved in other types of cascade reactions.

Thus, in Chapter 1 will be explored a different class of cascade cyclizations that take advantage of the reactivity of the intermediate benzylpalladium complex. The versatility of this new methodology will be illustrates by the synthesis of a variety of carbo- and heterocycles through a common approach.

Chapter 1. Part A

Synthesis of indanes and benzofurans through Pd-catalyzed cascade cyclization reactions with *N*-tosylhydrazones

1.A.1 Introduction

1.A.1.1 Indanes

Indanes and their homologous indenes are among the most important carbocylic systems because their structures are present in numerous natural products (Scheme 1.A.1).[81] The skeleton of the indane privileged substructure is formed by a benzene ring fused to a cyclopentene. It is worth noting that, many indane and indene derivatives have shown biological activities, including anticancer, anti-inflammatory, anti-hyperchorestelоremic, antiallergic, anticonvulsant, herbicidal, fungicidal, and antimicrobial.[82,83] In addition, these structures have also found application in material science,[84,85] as well as became part of ligands in metal-catalyzed transformations.[86]

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[81] a) G. G. Bianco, H. M. C. Ferraz, A. M. Costa, L. V Costa-Lotufo, C. Pessoa, M. O. de Moraes, M. G. Schrems, A. Pfaltz, L. F. Silva, *J. Org. Chem.* **2009**, *74*, 2561–2566; b) D.-C. Oh, P. G. Williams, C. A. Kauffman, P. R. Jensen, W. Fenical, *Org. Lett.* **2006**, *8*, 1021–1024; c) Y. Jung, I. Kim, *J. Org. Chem.* **2015**, *80*, 2001–2005.

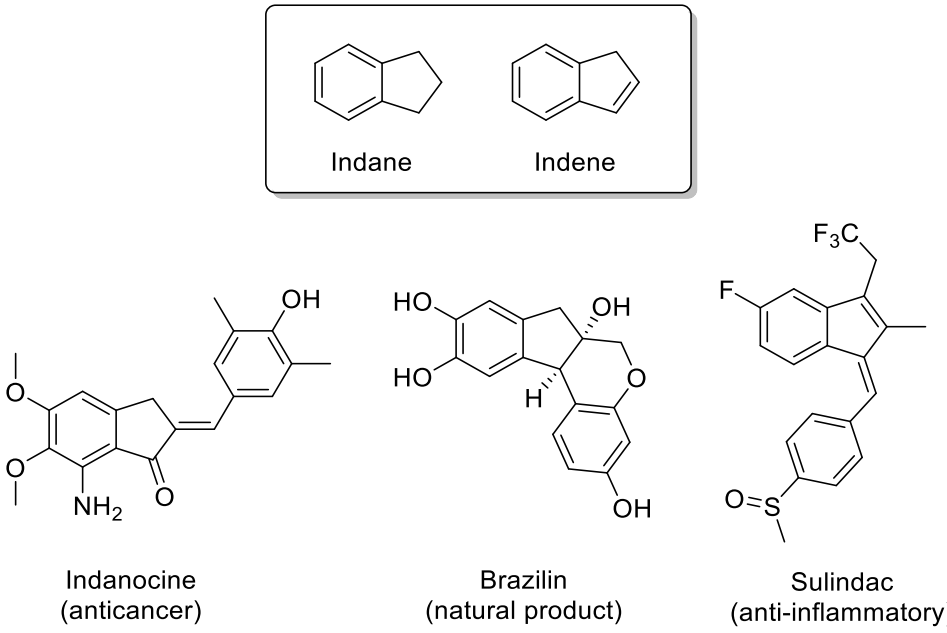
[82] For recent examples of biologically active indane derivatives, see: a) M. Sharma, S. M. Ray, *Eur. J. Med. Chem.* **2008**, *43*, 2092–2102; b) F. Lie, Y. Chen, Z. Wang, Z. Li, *Tetrahedron: Asymmetry* **2009**, *20*, 1206–1211; c) S. Kumar, A. P. Dwivedi, V. K. Kashyap, A. K. Saxena, A. K. Dwivedi, R. Srivastava, D. P. Sahu, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2404–2407; d) G. A. Tunbridge, J. Oram, L. Caggiano, *Medchemcomm* **2013**, *4*, 1452–1456; e) A. Singh, K. Fatima, A. Singh, A. Behl, M. J. Mintoo, M. Hasanain, R. Ashraf, S. Luqman, K. Shanker, D. M. Mondhe, et al., *Eur. J. Pharm. Sci.* **2015**, *76*, 57–67.

[83] For recent examples of biologically active indene derivatives, see: a) E. Alcalde, N. Mesquida, J. Frigola, S. Lopez-Perez, R. Merce, *Org. Biomol. Chem.* **2008**, *6*, 3795–3810; b) C. Huang, W. J. Moree, S. Zamani-Kord, B.-F. Li, F. C. Tucci, S. Malany, J. Wen, H. Wang, S. R. J. Hoare, C. Yang, et al., *Bioorg. Med. Chem. Lett.* **2011**, *21*, 947–951; c) H. S. El-Sheshtawy, A. M. Abou Baker, *J. Mol. Struct.* **2014**, *1067*, 225–232; d) J. Banothu, S. Basavoju, R. Bavantula, *J. Heterocycl. Chem.* **2015**, *52*, 853–860.

[84] For indane derivatives, see: a) J. Barberá, O. A. Rakitin, M. B. Ros, T. Torroba, *Angew. Chemie Int. Ed.* **1998**, *37*, 296–299; b) Yang, M. V Lakshmikantham, M. P. Cava, D. Lorcy, J. R. Bethelot, *J. Org. Chem.* **2000**, *65*, 6739–6742; c) A. R. Morales, A. Frazer, A. W. Woodward, H.-Y. Ahn-White, A. Fonari, P. Tongwa, T. Timofeeva, K. D. Belfield, *J. Org. Chem.* **2013**, *78*, 1014–1025.

[85] For indene derivatives, see: a) S. Basurto, S. García, A. G. Neo, T. Torroba, C. F. Marcos, D. Miguel, J. Barberá, M. B. Ros, M. R. de la Fuente, *Chem. Eur. J.* **2005**, *11*, 5362–5376; b) H. Seyler, W. W. H. Wong, D. J. Jones, A. B. Holmes, *J. Org. Chem.* **2011**, *76*, 3551–3556; c) J.-S. Dang, W.-W. Wang, X. Zhao, S. Nagase, *Org. Lett.* **2014**, *16*, 170–173.

[86] J. G. M. Morton, H. Al-Shammari, Y. Sun, J. Zhu, D. W. Stephan, *Dalt. Trans.* **2014**, *43*, 13219–13231.



Scheme 1.A.1. Representative examples of natural products and drugs based on indane and indene structures.

Synthesis of indanes

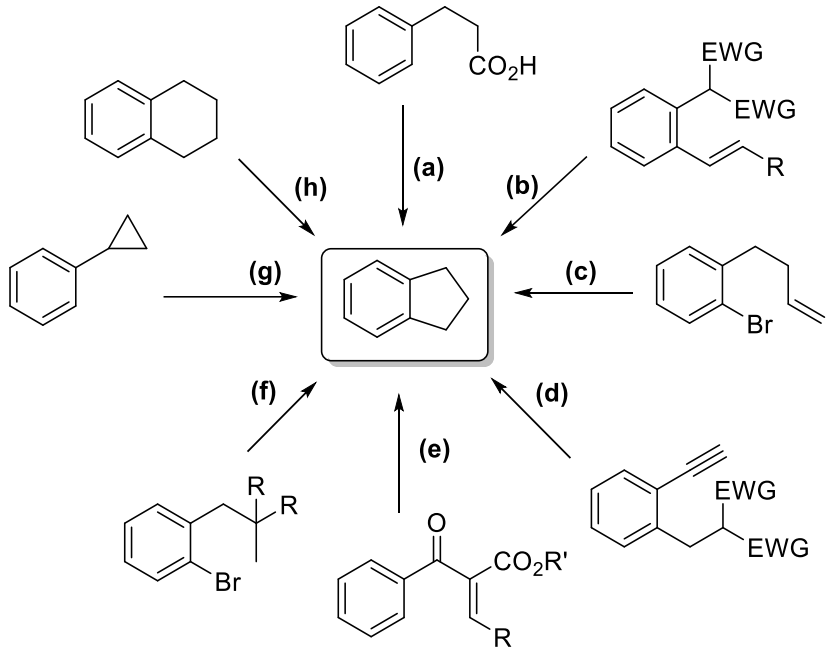
As a consequence of the great utility of indanes in a wide variety of scientific areas, continuous efforts have been devoted to the discovery of new efficient methods for their synthesis. Therefore, different methodologies have been developed, including intra- and intermolecular reactions.

There are different ways of achieving the synthesis of these structures, however, nowadays the most common approaches are based on: intramolecular Frield-Crafts-type cyclization reactions **(a)**,[87] cyclization reactions involving Michael-type addition **(b)**,[88]

[87] a) A. Saito, M. Umakoshi, N. Yagyu, Y. Hanzawa, *Org. Lett.* **2008**, *10*, 1783–1785; b) J. Wang, Y. Zhou, L. Zhang, Z. Li, X. Chen, H. Liu, *Org. Lett.* **2013**, *15*, 1508–1511; c) J.-M. Begouin, F. Capitta, X. Wu, M. Niggemann, *Org. Lett.* **2013**, *15*, 1370–1373; d) W. Yin, Y. Ma, J. Xu, Y. Zhao, *J. Org. Chem.* **2006**, *71*, 4312–4315.

[88] a) S. Fustero, E. Rodríguez, L. Herrera, A. Asensio, M. A. Maestro, P. Barrio, *Org. Lett.* **2011**, *13*, 6564–6567; b) A. Biswas, S. De Sarkar, R. Fröhlich, A. Studer, *Org. Lett.* **2011**, *13*, 4966–4969; c) C. P. Johnston, A. Kothari, T. Sergeieva, S. I. Okovytyy, K. E. Jackson, R. S. Paton, M. D. Smith, *Nat. Chem* **2015**, *7*, 171–177.

cyclizations involving Heck-type reactions **(c)**,[89] cyclizations of acetylenic substrates **(d)**,[90] metal-catalyzed Nazarov-type cyclizations **(e)**,[91] transition-metal-mediated C-H activations **(f)**,[92] and ring expansion **(g)**[93] and ring contraction methods **(h)** (Scheme 1.A.2).[94]



Scheme 1.A.2. Most common approaches for the synthesis of indane scaffolds.

[89] a) S. Kesavan, J. S. Panek, J. A. Porco, *Org. Lett.* **2007**, *9*, 5203–5206; b) A. Minatti, X. Zheng, S. L. Buchwald, *J. Org. Chem.* **2007**, *72*, 9253–9258; c) J. Ruan, J. A. Iggo, J. Xiao, *Org. Lett.* **2011**, *13*, 268–271.

[90] a) R. Shintani, K. Takatsu, T. Hayashi, *Angew. Chemie Int. Ed.* **2007**, *46*, 3735–3737; b) D. B. Ramachary, R. Mondal, C. Venkaiah, *Eur. J. Org. Chem.* **2010**, *2010*, 3205–3210; c) A.-L. Auvinet, M. Ez-Zoubir, S. Bompard, M. R. Vitale, J. A. Brown, V. Michelet, V. Ratovelomanana-Vidal, *ChemCatChem* **2013**, *5*, 2389–2394.

[91] a) J. Nie, H.-W. Zhu, H.-F. Cui, M.-Q. Hua, J.-A. Ma, *Org. Lett.* **2007**, *9*, 3053–3056; b) H. Zheng, X. Xie, J. Yang, C. Zhao, P. Jing, B. Fang, X. She, *Org. Biomol. Chem.* **2011**, *9*, 7755–7762.

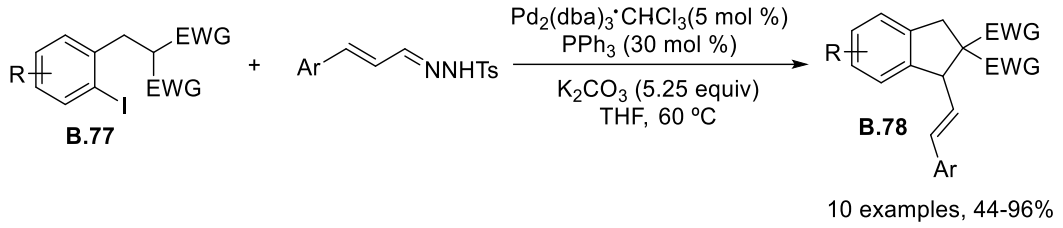
[92] a) Q. Huang, R. Hua, *Chem. – A Eur. J.* **2009**, *15*, 3817–3822; b) X.-H. Li, B.-H. Zheng, C.-H. Ding, X.-L. Hou, *Org. Lett.* **2013**, *15*, 6086–6089; c) H. Duan, Z. Chen, L. Han, Y. Feng, Y. Zhu, S. Yang, *Org. Biomol. Chem.* **2015**, *13*, 6782–6788.

[93] a) T. Seiser, O. A. Roth, N. Cramer, *Angew. Chemie Int. Ed.* **2009**, *48*, 6320–6323; b) D. Rosa, A. Orellana, *Chem. Commun.* **2012**, *48*, 1922–1924.

[94] K. O. Eyong, M. Puppala, P. S. Kumar, M. Lamshoft, G. N. Folefoc, M. Spiteller, S. Baskaran, *Org. Biomol. Chem.* **2013**, *11*, 459–468.

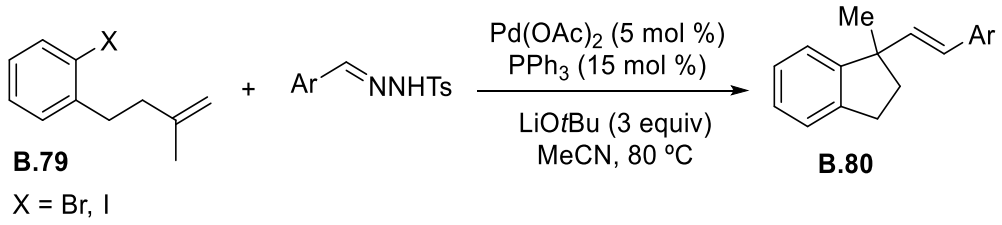
The methodology expounded above lay bare the numerous variety of transformations which can be used to produce indane derivatives. However, according with the thematic of this Memory, next it will be only explained those reactions which implicate the employment of *N*-tosylhydrazones as principal reagent.

In 2013, the first reaction for the generation of indane skeletons from *N*-tosylhydrazones was reported. This cascade transformation involves the participation of a η^3-allylpalladium intermediate as a key element of the process. Employing *o*-iodobenzylmalonates **B.77** and a *N*-tosylhydrazone derived from cinnamyl aldehyde, the reaction evolves through a 5-*exo* cyclization for the production of indane structures **B.78** (Scheme 1.A.3).[75] See also Scheme 1.20 for the extension of this methodology by Van Vranken.[79]



Scheme 1.A.3. Pd-catalyzed cascade reaction for the synthesis of indanes.

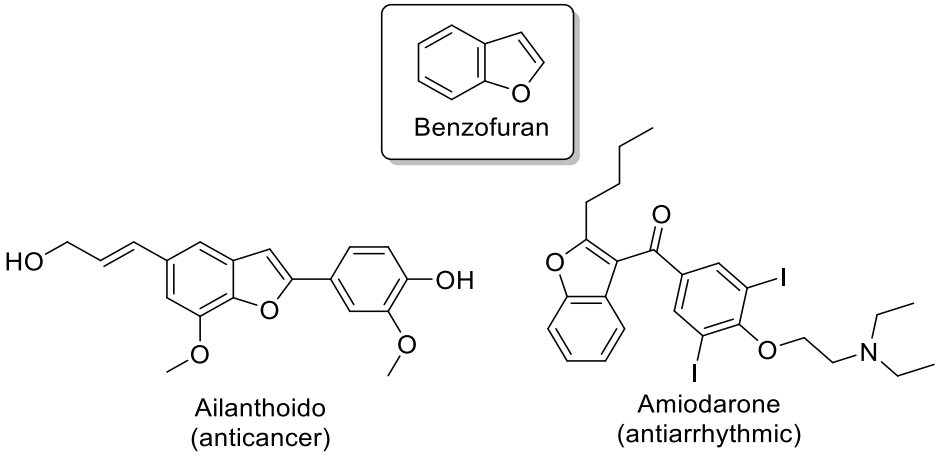
The intramolecular Heck cyclization/carbene insertion cascade sequence discussed previously in Scheme 1.5 has also been applied for the preparation of indane scaffolds. Thus, using the correct length in the chain that supports the alkene **B.79**, a 5-*exo*-trig cyclization can be promoted to give the appropriate carbocyclic system **B.80** (Scheme 1.A.4).[65]



Scheme 1.A.4. Synthesis of indanes via Heck cyclization/carbene insertion cascade reaction.

1.A.1.2 Benzofurans

Benzofurans are heterocycles built from the fusion of a benzene and a furan ring. These oxygen bearing scaffolds have drawn considerable attention over the years as a consequence of their presence in natural[95] and biologically important[96] molecules (Scheme 1.A.5). Benzofuran derivatives display a wide variety of medical applications including anti-inflammatory,[97] analgesic,[97] antiparasitic,[98] antimicrobial,[99] antitumor[100] and kinase inhibitor.[101] Moreover, the benzofuran moiety is also present in functional organic materials.[102]



Scheme 1.A.5. Representative examples of drugs based on the benzofuran scaffold.

[95] a) P. Máximo, A. Lourenço, S. S. Feio, J. C. Roseiro, *J. Nat. Prod.* **2002**, *65*, 175–178; b) B. Sritularak, K. Likhitwitayawuid, J. Conrad, B. Vogler, S. Reeb, I. Klaiber, W. Kraus, *J. Nat. Prod.* **2002**, *65*, 589–591.

[96] a) E. Tsuji, K. Ando, J. Kunitomo, M. Yamashita, S. Ohta, S. Kohno, Y. Ohishi, *Org. Biomol. Chem.* **2003**, *1*, 3139–3141; b) I. Hayakawa, R. Shioya, T. Agatsuma, H. Furukawa, S. Naruto, Y. Sugano, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 455–458.

[97] Y.-S. Xie, D. Kumar, V. D. V. Bodduri, P. S. Tarani, B.-X. Zhao, J.-Y. Miao, K. Jang, D.-S. Shin, *Tetrahedron Lett.* **2014**, *55*, 2796–2800.

[98] M. Thévenin, S. Thoret, P. Grellier, J. Dubois, *Bioorg. Med. Chem.* **2013**, *21*, 4885–4892.

[99] M. Koca, S. Servi, C. Kirilmis, M. Ahmedzade, C. Kazaz, B. Özbek, G. Ötük, *Eur. J. Med. Chem.* **2005**, *40*, 1351–1358.

[100] F. Xie, H. Zhu, H. Zhang, Q. Lang, L. Tang, Q. Huang, L. Yu, *Eur. J. Med. Chem.* **2015**, *89*, 310–319.

[101] M.-A. Bazin, L. Bodero, C. Tomasoni, B. Rousseau, C. Roussakis, P. Marchand, *Eur. J. Med. Chem.* **2013**, *69*, 823–832.

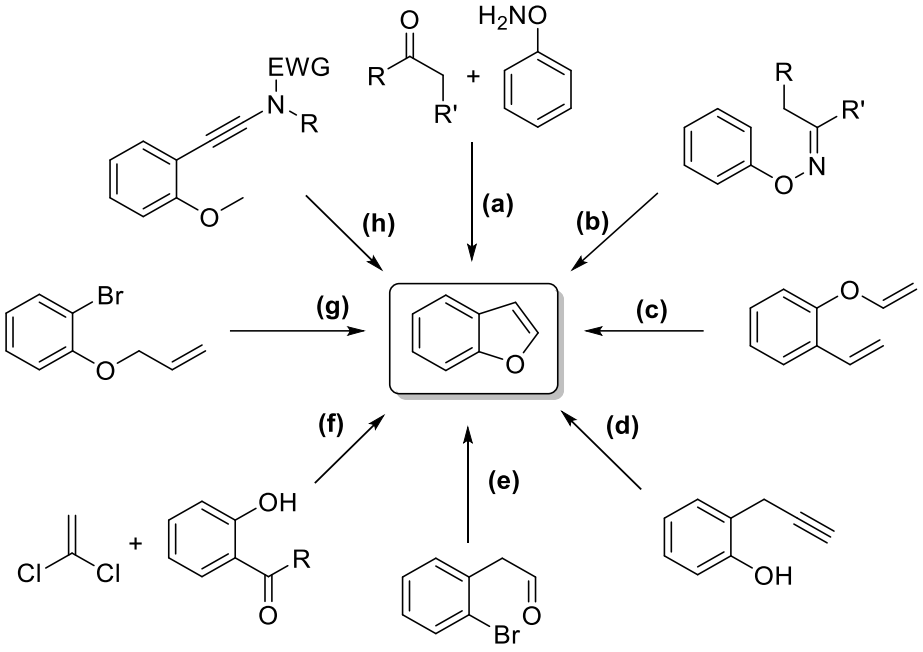
[102] a) O. Oter, K. Ertekin, C. Kirilmis, M. Koca, M. Ahmedzade, *Sensors Actuators B Chem.* **2007**, *122*, 450–456; b) J. R. Hwu, K.-S. Chuang, S. H. Chuang, S.-C. Tsay, *Org. Lett.* **2005**, *7*, 1545–1548.

Synthesis of benzofurans

Because benzofuran can be considered the "parent" of many related compound with interesting properties, numerous efforts have been made in the development of novel synthetic methodologies for their preparation.

Although the discovery of reactions for the generation of benzofurans is a process which has covered long time, herein, only the recent advances in this field will be collected. The most innovative ways to synthesize substituted benzofurans are: condensation-rearrangement-cyclization reactions **(a)**,[103] [3,3]-sigmatropic rearrangements **(b)**,[104] ring-closing metathesis **(c)**,[105] palladium-catalyzed cyclization reactions **(d)**,[106] cyclization reactions catalyzed by other metals **(e)**,[107] acid- and based-mediated cyclizations **(f)**,[108] radical cyclizations **(g)**[109] and electrophilic cyclization reactions **(h)** [110] (Scheme 1.A.6).

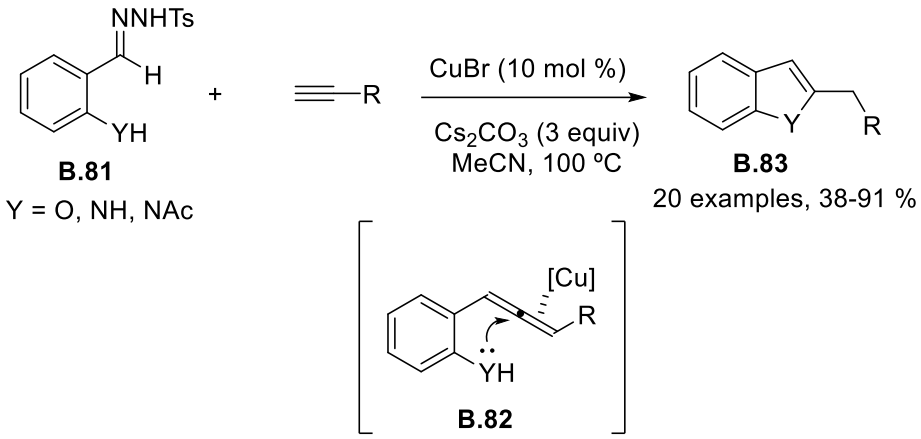
[103] F. Contiero, K. M. Jones, E. A. Matts, A. Porzelle, N. C. O. Tomkinson, *Synlett*. **2009**, *18*, 3003-3006.
[104] N. Takeda, O. Miyata, T. Naito, *European J. Org. Chem.* **2007**, *2007*, 1491–1509.
[105] W. A. L. van Otterlo, G. L. Morgans, L. G. Madeley, S. Kuzvidza, S. S. Moleele, N. Thornton, C. B. de Koning, *Tetrahedron.* **2005**, *61*, 7746–7755.
[106] a) K. W. Anderson, T. Ikawa, R. E. Tundel, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695; b) S. E. Denmark, R. C. Smith, W.-T. T. Chang, J. M. Muhuhi, *J. Am. Chem. Soc.* **2009**, *131*, 3104-3118; c) P. K. Mandali, D. K. Chand, *Synthesis*. **2015**, *47*, 1661-1668; d) M. Rajesh, N. Thirupathi, T. J. Reddy, S. Kanojiya, M. S. Reddy, *J. Org. Chem.* **2015**, *80*, 12311-12320.
[107] a) I. Nakamura, Y. Mizushima, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023; b) C. Chen, P. G. Dormer, *J. Org. Chem.* **2005**, *70*, 6964–6967; c) D.-H. Lee, K.-H. Kwon, C. S. Yi, *J. Am. Chem. Soc.* **2012**, *134*, 7325–7328; d) B. Anxionnat, D. Gomez Pardo, G. Ricci, K. Rossen, J. Cossy, *Org. Lett.* **2013**, *15*, 3876–3879; e) A. Baralle, S. Otsuka, V. Guérin, K. Murakami, H. Yorimitsu, A. Osuka, *Synlett*. **2015**, *26*, 327-330.
[108] a) J. Barluenga, H. Vázquez-Villa, I. Merino, A. Ballesteros, J. M. González, *Chem. Eur. J.* **2006**, *12*, 5790–5805; b) F. Schevenels, I. E. Markó, *Org. Lett.* **2012**, *14*, 1298–1301.
[109] S. E. Vaillard, A. Postigo, R. A. Rossi, *J. Org. Chem.* **2004**, *69*, 2037–2041.
[110] Y. Kong, L. Yu, L. Fu, J. Cao, G. Lai, Y. Cui, Z. Hu, G. Wang, *Synthesis*. **2013**, *45*, 1975-1982.



Scheme 1.A.6. Most common approaches for the synthesis of benzofurans.

Regarding the methodologies available for the synthesis of benzofurans employing *N*-tosylhydrazones, two of the possibilities have been already explained in the previous sections. The first approach consists in the reaction described by Jiang and Wu, in which aryl iodides bearing allene moieties and *N*-tosylhydrazones are employed to promote a Heck cyclization/carbene coupling cascade process (Scheme 1.6).[66] The second approach is the reaction developed by Wang for the formation of benzofurans or indoles systems (Scheme 1.7).[67] Using the appropriate aryl iodide precursors, the intramolecular cyclization/carbene insertion would provide corresponding benzofuran derivatives.

In 2011, Wang and co-workers reported a novel copper-catalyzed coupling reaction for the synthesis of allenes, starting from *N*-tosylhydrazones and terminal alkynes.[111] Soon after, this allene formation strategy was applied in the generation of a new cascade cyclization reaction for the formation of indole and benzofuran structures **B.83**.[112] The evolution of the coupling reaction into the cascade process was enabled by the incorporation of nucleophile (hydroxyl or amino functional groups) in the *N*-tosylhydrazone **B.81**. The mechanism of this transformation might involve the formation of an allene species **B.82**, which is activated by the copper catalyst to afford an intramolecular nucleophilic cyclization (Scheme 1.A.6).



Scheme 1.A.6. Cu-catalyzed synthesis of benzofurans and indoles from *N*-tosylhydrazones.

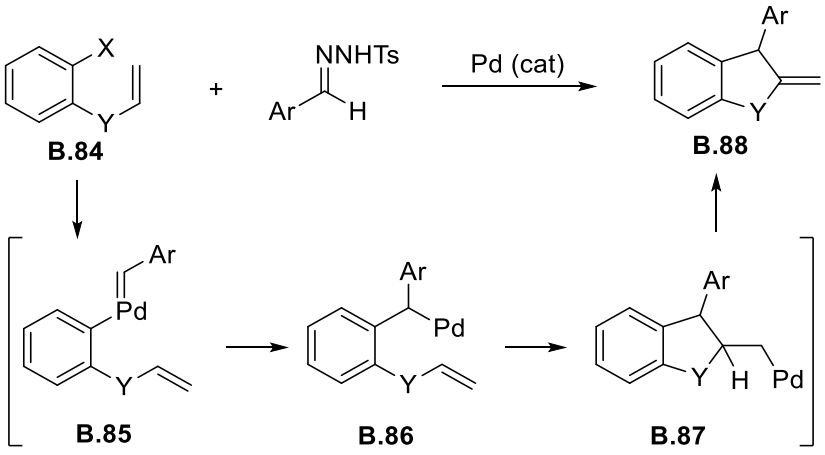
[111] Q. Xiao, Y. Xia, H. Li, Y. Zhang, J. Wang, *Angew. Chemie Int. Ed.* **2011**, *50*, 1114–1117.
[112] L. Zhou, Y. Shi, Q. Xiao, Y. Liu, F. Ye, Y. Zhang, J. Wang, *Org. Lett.* **2011**, *13*, 968–971.

1.A.2 Results and discussions

1.A.2.1 Objective and general considerations

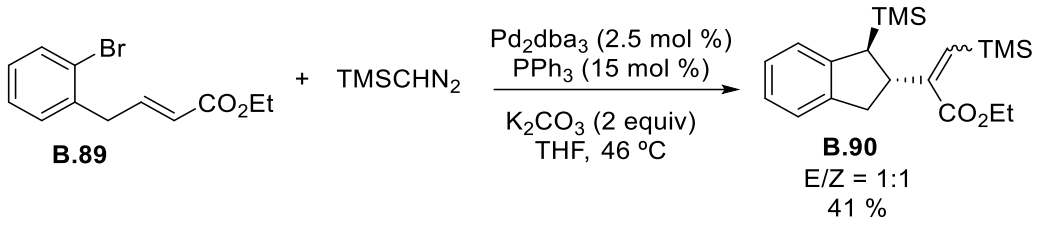
As it has been shown in the General Introduction, our research group has participated actively in the development of new Pd-catalyzed cross-coupling reactions with *N*-tosylhydrazones. Within this field, the discovery of novel cascade cyclization reactions have attracted special attention to our group.

In this context, we envisioned a new cascade cyclization process combining the C-C bond forming reaction based on the migratory insertion step, with an intramolecular Heck reaction. Thus, we decided to explore the reaction of aryl halides featuring a C-C double bond attached at the *o*-position **B.84**, with *N*-tosylhydrazones derived from aromatic aldehydes. We anticipated that after the migratory insertion, the generated benzylpalladium complex **B.86** could not decompose through a β-hydrogen elimination, and therefore, could participate in a subsequent carbopalladation step providing the alkylpalladium complex **B.87**. Finally, a β-hydrogen elimination would give the expected benzofused products **B.88** (Scheme 1.A.9).



Scheme 1.A.9. Proposed cascade cyclization reaction Chapter 1.A.

It must be noted that this approach had been previously studied by Van Vranken employing trimethylsilyldiazomethane as carbene precursor.[113] However, those reactions showed limited application and synthetic interest, due to the formation of byproducts **B.90** derived from the incorporation of more than one molecule of carbene during the cascade process (Scheme 1.A.10). For this reason, we found interesting to investigate whether the same approach could be carried out with *N*-tosylhydrazones instead of stabilized diazo compounds, and if it would be possible to find reaction conditions to overcome the limitations reported in those reactions.

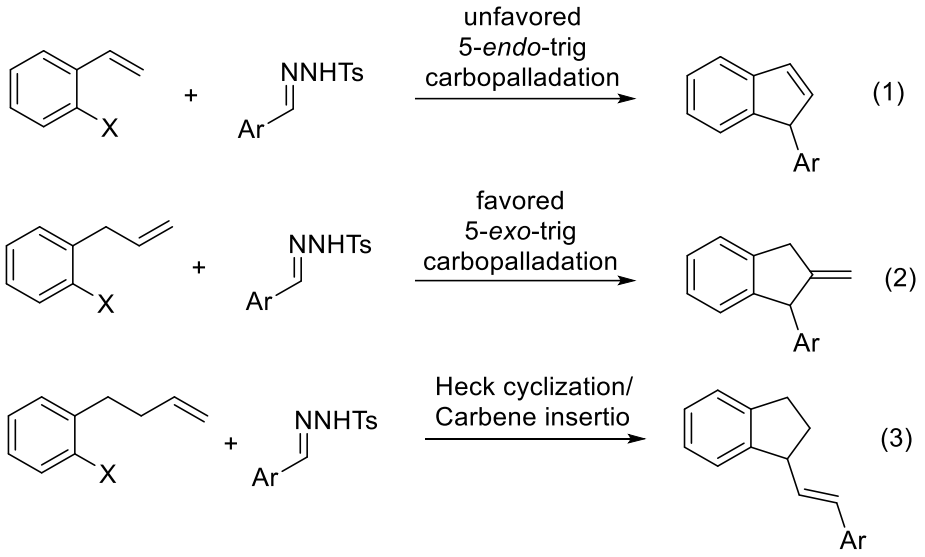


Scheme 1.A.10. Previous study $TMSCHN_2$ reported by Van Vranken.

[113] R. Kudirka, D. L. Van Vranken, *J. Org. Chem.* **2008**, *73*, 3585–3588.

1.A.2.2 Optimization

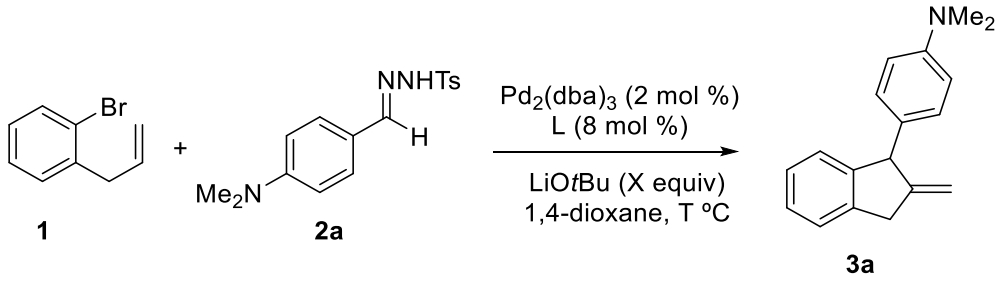
In agreement with our initial idea, various starting aryl halides could be considered differing in the length to the tether that connects the double bond to the aromatic ring. However, from the different possibilities only the *o*-allylhalobenzenes would meet the requirements for the envisioned cascade reactions (Scheme 1.A.11, equation 2). In the case of employing *o*-vinylhalobenzene, an unfavoured 5-*endo*-trig carbopalladation should occur, which is large unlikely (Scheme 1.A.11, equation 1). On the other hand, with longer tethers the intramolecular Heck reaction would be the favoured pathway as discussed in Scheme 1.4[65] and Scheme 1.5[66] (Scheme 1.A.11, equation 3).



Scheme 1.A.11. Passible starting aryl halides considering the length to the tether that connects the doble bond.

We started our research by employing 1-allyl-2-bromobenzene **1** and the tosylhydrazone derived from 4-dimethylaminobenzaldehyde **2a** as a model to develop suitable reaction conditions. We expected that upon oxidative addition, the incorporation of the diazo compound into the catalytic cycle might be favored towards the intramolecular 5-*endo*-trig Heck reaction, according with the Baldwin rules.[114] Indeed, preliminary experiments under the standard reaction conditions for cross-coupling reactions with *N*-tosylhydrazones revealed the formation of the expected indane **3a** with moderate yield (Table 1.A.1, entry 1). When Sphos[115] was used as ligand, it was observed a better yield (Table 1.A.1, entry 2). Regarding the other variable conditions, the employment of 1.1 equivalents of hydrazone, 5 equivalents of LiO*t*Bu and a temperature of 90 °C improved even more the yield of the reaction (Table 1.A.1, entry 3). The optimal reaction conditions were provided with the addition of 5 equivalents of water (Table 1.A.1, entry 4).[39]

Table 1.A.1. Optimization of reaction conditions for aryl bromides.



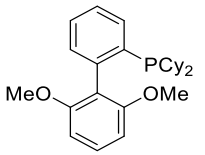
1 **2a** **3a**

Entry	Hydrazone (equiv)	Ligand	LiO*t*Bu (equiv)	H_2O (equiv)	TºC	Yield[a] (%)
1	1	Xphos	3	-	110	22
2	1	Sphos	3	-	110	51
3	1.1	Sphos	5	-	90	63
4	1.1	Sphos	5	5	90	76

[a] Yields determining by ^{1}H-NMR employing Ph_3CH as internal standard.

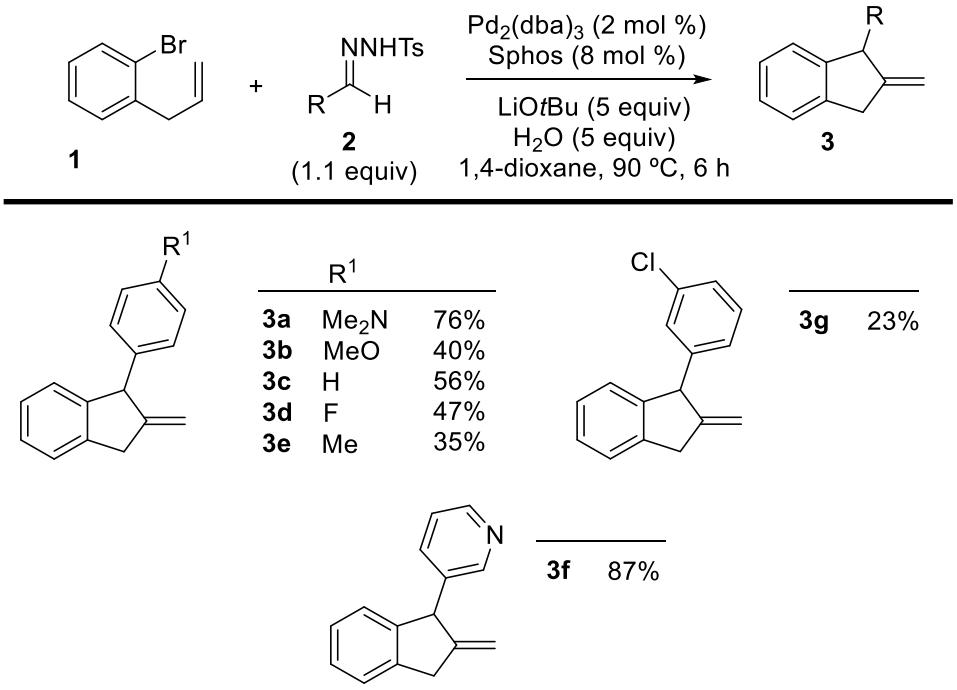
[114] K. Gilmore, R. K. Mohamed, I. V Alabugin, *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2016**, *6*, 487–514.

[115] 2-(2',6'-dimethoxybiphenyl)dicyclohexylphosphine, for reference see: T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.



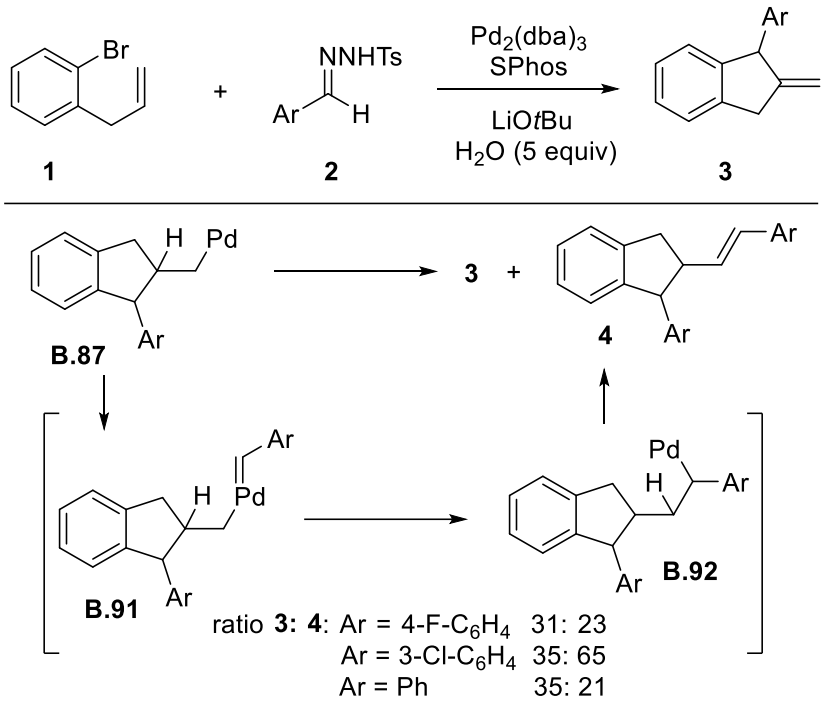
Sphos

Under the optimized conditions, the scope of the reaction was examined with a limited number of examples leading to the corresponding indanes although with moderate yields (Scheme 1.A.12).



Scheme 1.A.12. Synthesis of indanes **3** from 1-allyl-2-bromobenzene **1** and *N*-tosylhydrazones.

The relatively low yield obtained in most of the examples was due to the formation of byproduct **4**, which incorporates two diazo compound fragments (Scheme 1.A.13). The generation of **4** can be justified considering that the alkylpalladium complex **B.87** can react with a second diazo compound at a faster rate than the β-hydride elimination step, to give the Pd-carbene complex **B.91**. Then, the migratory insertion provides the alkylpalladium intermediate **B.92**, and the β-hydride elimination furnishes compound **4**.

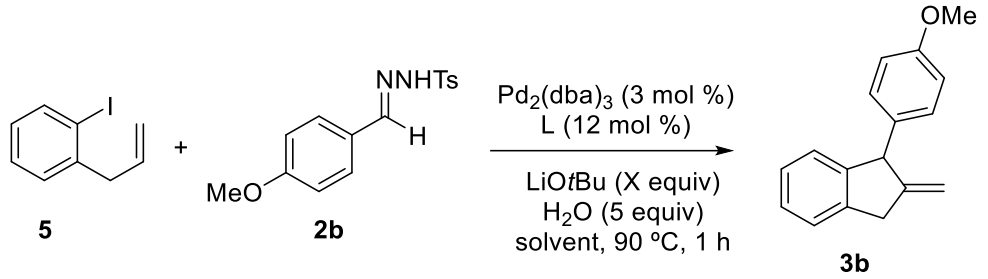


Scheme 1.A.13. Preliminary results on the synthesis of methyleneindanes **3** from 1-allyl-2-bromobenzene **1** and *N*-tosylhydrazones.

Unfortunately, after extensive experimentation, it was not possible to shut down this reaction pathway completely. Indeed, at 70 °C the formation of **4** could be minimized, but at the expense of a lower conversion. For this reason, we decided to examine the reaction with the analogous iodides, in the expectation that the higher reactivity of the aromatic iodides might allow more flexibility in the composition of the catalyst, and thus, tune the activity towards the desired indanes.

Therefore, a reoptimization was conducted with 1-allyl-2-iodobenzene **5**. In spite of the examination of other phosphines as ligands, Sphos turned out to be again the best ligand for the transformation (Table 1.A.2, entry 1, 2 and 3). The increase of the equivalents of hydrazone and base produced an improvement in the yield (Table 1.A.2, entry 4). Additionally, the best result was obtained when acetonitrile was employed as solvent, providing an almost quantitative reaction (Table 1.A.2, entry 5). The scope of the process turned out to be wider than in the case of the reaction with the bromide, giving generally much higher yields (Scheme 1.A.14). Moreover, the formation of the undesired byproduct **4** was never detected.

Table 1.A.2. Optimization of reaction conditions for aryl iodides.



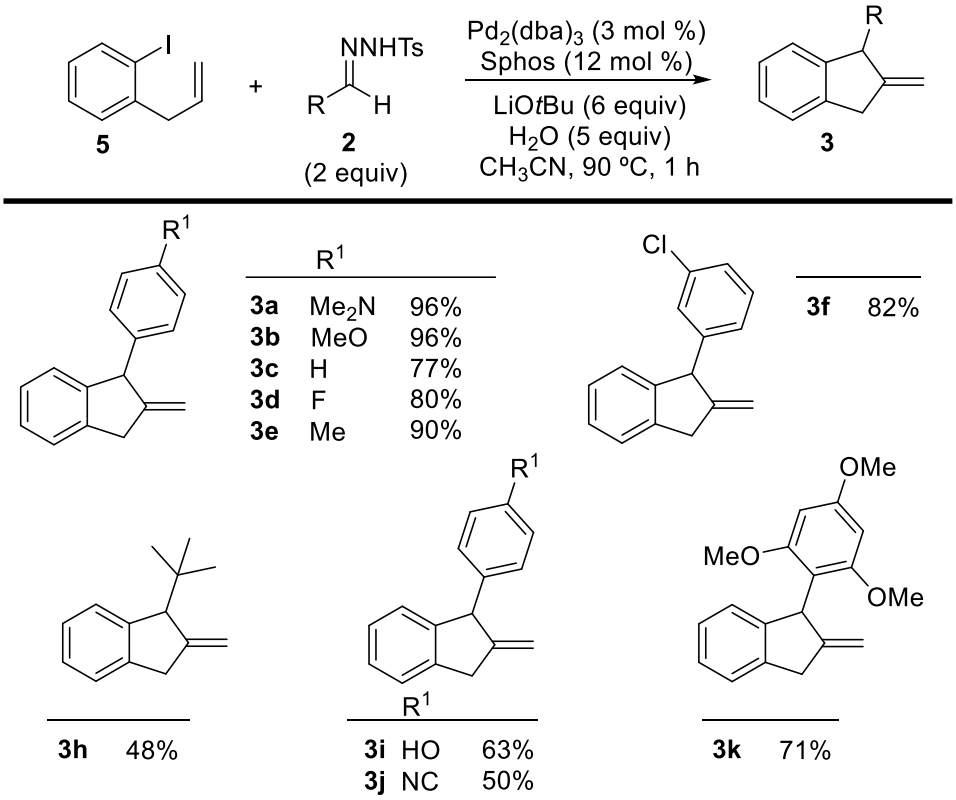
5 **2b** **3b**

Entry	Hydrazone (equiv)	Ligand	LiO*t*Bu (equiv)	Solvent	Yield[a] (%)
1	1.1	Sphos	5	1,4-dioxane	53
2	1.1	Xphos	5	1,4-dioxane	31
3	1.1	PPh_3	5	1,4-dioxane	-
4	2	Sphos	6	1,4-dioxane	63
5[b]	2	Sphos	6	acetonitrile	96

[a] Yields determining by ^{1}H-NMR employing Ph_3CH as internal pattern. [b] Isolated yield after flash chromatography.

1.A.2.3 Generalization of the reaction for the synthesis of indanes

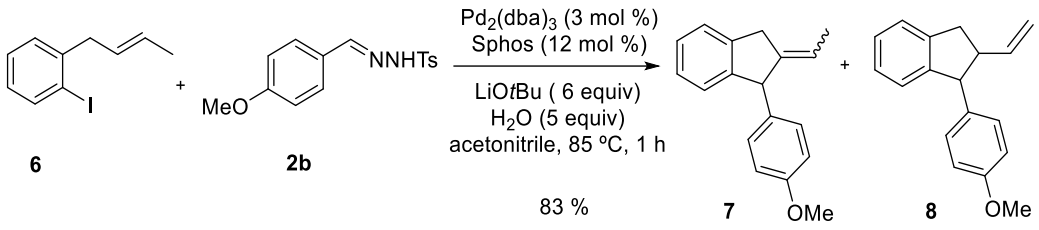
As it can see in the examples presented in Scheme 1.A.14, the reaction can be applied to a wide range of *N*-tosylhydrazones. The reaction tolerated well the employment of tosylhydrazones derived from aromatic aldehydes with a variety of functional groups (**3a-e**, **3i** and **3j**) in different positions of the ring (**3f**). It was particularly interesting the generation of the hydroxy substituted indane **3i**, which was achieved by using the tosylhydrazone of 4-acetoxybenzaldehyde. Under the reaction conditions of the cyclization reaction, the deprotection of the acetoxy group occurs, giving the indane **3i** in one single step. Moreover, tosylhydrazones derived from heteroaromatic aldehydes (**3g**), as well as the highly hindered diortho-substituted system (**3k**) provided the expected indanes with good yields. Additionally, the tosylhydrazone of pivalaldehyde was also an appropriate substrate for the cascade reaction (**3h**).



Scheme 1.A.14. Synthesis of indanes **3** from 1-allyl-2-bromobenzene **1** and 1-allyl-2-iodobenzene **5** and *N*-tosylhydrazones.

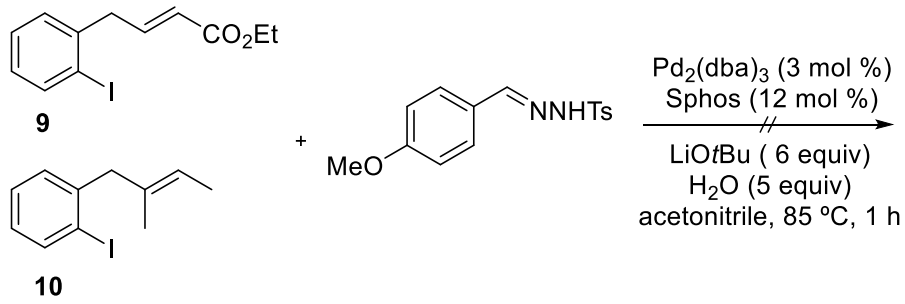
Influence of the substitution of the double bond in the synthesis of indanes

The influence of substituents in both positions of the double bound was also studied. Carrying out the cascade cyclization process with (*E*)-1-(but-2-en-1-yl)-2-iodobenzene **6** the reaction took place successfully, but gave rise to a mixture of three isomeric indanes arising from an unselective β-hydride elimination (Scheme 1.A.15).



Scheme 1.A.15. Attempt with (*E*)-1-(but-2-en-1-yl)-2-iodobenzene to promote the cascade cyclization.

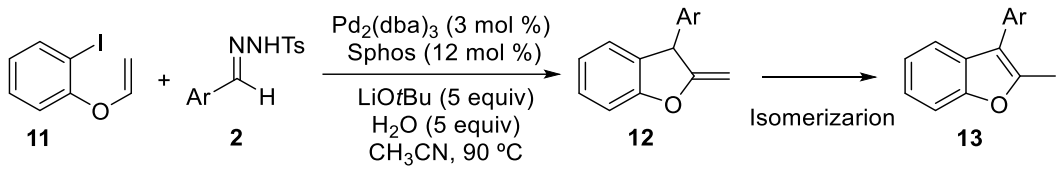
However, other type of substitution in the double bond failed to provide the indanes through the cascade cyclization reaction. Ethoxycarbonyl substitution on the terminal position of the double bond **9** or substitution at both the internal and terminal positions **10** was not tolerated, as the formation of the indanes was not detected. In both cases, the starting iodides were recovered after the reaction under the standard conditions (Scheme 1.A.16).



Scheme 1.A.16. Substitution not tolerated on the double bond.

1.A.2.4 Synthesis of benzofurans

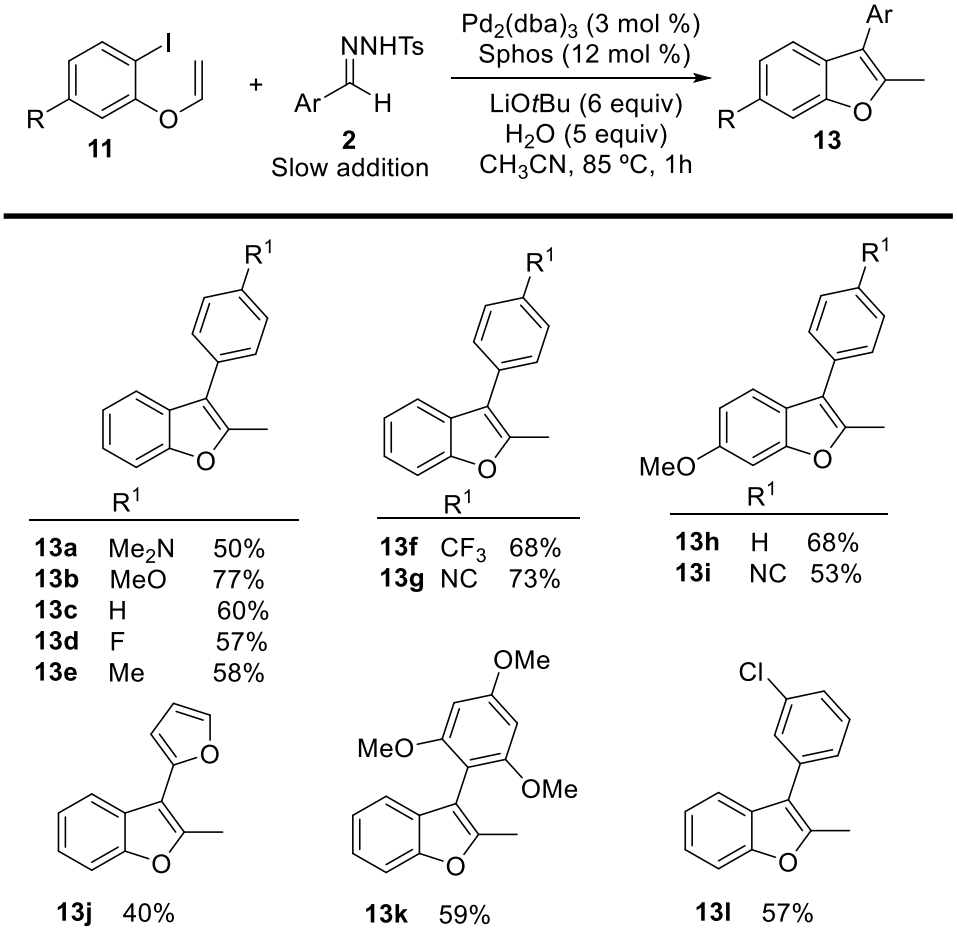
With these results in hand we turned our attention to allyl ethers **11**, which would hopefully lead to benzofuran derivatives through a similar cascade cyclization reaction. We expected that after the five-membered ring formation with the exocyclic double bond **12**, the product would suffer an isomerization of the double bond in the same reaction conditions as a consequence of higher stability of the benzofuran structure (Scheme 1.A.17).



Scheme 1.A.17. Strategy for the cascade cyclization reaction leading to benzofurans.

In our preliminary experiments, the benzofurans **13** were obtained with moderate yields, but in many cases, the undesired compound derived from the incorporation of a second unit of tosylhydrazone was again detected. Nevertheless, the formation of these byproducts could be avoided by carrying out the reaction with slow addition of the tosylhydrazone *via* a syringe-pump. In this way, the concentration of the diazo compound is kept low, and therefore the β-hydride elimination on the alkyl intermediate **B.87** occurs at a faster rate than the reaction with the transient diazo compound.

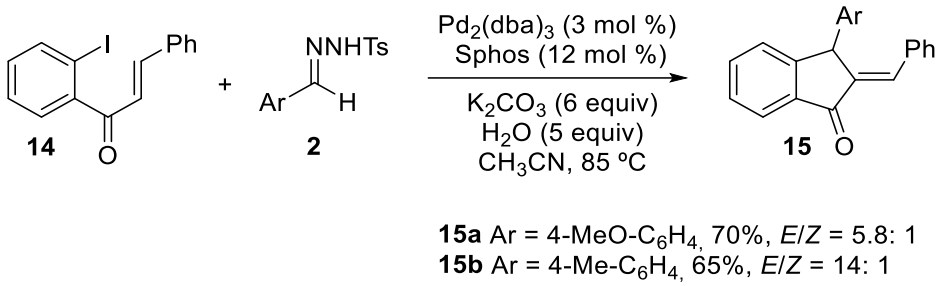
Thus, under the suitable reaction conditions, a set of 2,3-disubstituted benzofurans **13** was obtained in a very straightforward manner from readily available starting materials (Scheme 1.A.18). In the same manner, as in the synthesis of indanes, the reaction was very robust in relation with the substitution supported in the aromatic ring of the hydrazone. Electron-donating and electron-withdrawing functional groups were well tolerated in different positions of the aromatic ring, providing the corresponding benzofurans in good yields (**13a-g** and **13l**). The reaction also allowed substitution on the benzene ring of the allyl ether (**13h** and **13j**), as well as hydrazones derived from heterocyclic aldehydes (**13j**) and a highly hindered diortho-substituted system (**13k**).



Scheme 1.A.18. Preparations of benzofurans **13** from iodo allyl ethers **11** and *N*-tosylhydrazones **2**.

1.A.2.5 Synthesis of benzylideneindanones

To further illustrate the versatility of this cascade cyclization reaction as a method for the synthesis of benzofused five-membered rings, we also studied the reaction with iodoalkene **14**, a quite challenging substrate due to the presence of additional functionality as well as substitution on the double bond. Delightfully, after a slight modification of the reaction conditions (K_2CO_3 as base instead of Li*O*t*Bu*), the reaction led to the formation of the benzylideneindanones **15** derived from the cyclization reaction with good yields. It is noteworthy that the final β-hydride elimination took place with high stereoselectivity leading to the *E* stereoisomer as the major product (Scheme 1.A.19).[116]



15a Ar = 4-MeO-C_6H_4, 70%, *E*/*Z* = 5.8: 1
15b Ar = 4-Me-C_6H_4, 65%, *E*/*Z* = 14: 1

Scheme 1.A.19. Synthesis of benzylideneindanones **15** from *N*-tosylhydrazones **2** and iodoketone **14**.

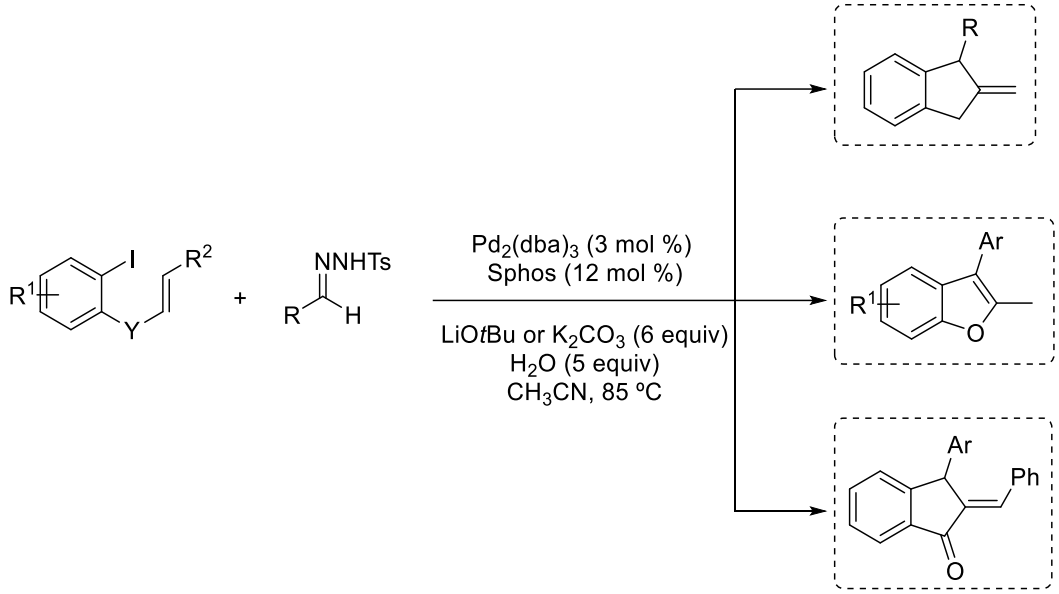
[116] Shortly after the publication of our work, Sekar and co-workers reported a similar cascade synthesis of benzylidene indanones. D. Arunprasath, P. Muthupandi, G. Sekar, *Org. Lett.* **2015**, *17*, 5448–5451.

1.A.3 Conclusions

In this Chapter 1. Part A, it has been reported a new Pd-catalyzed cascade cyclization reaction between *o*-iodoallylbenzene derivatives and *N*-tosylhydrazones derived from aldehydes. This novel cascade transformation has been further expanded for the formation of benzofused five-membered rings, such as benzofuran structures. These processes are based on a catalytic cycle that involves a migratory insertion of a Pd-carbene complex generated from a tosylhydrazone, followed by an intramolecular Heck reaction. It is especially important to remark that during this reaction two new C-C bonds are formed on the same carbon atom, and in one single synthetic step.

As a consequence of the great potential of results obtained in this section for the synthesis of indanes and benzofurans, we decided to examine the possibility of applying this reaction in the preparation of other types of heterocycles. Thus, the synthesis of indole and quinoline derivatives that will be shown in the Part B of this chapter is a direct consequence of the achievements of this first section.

1.A.4 Graphic summary



Chapter 1. Part B

Synthesis of indoles and 1,4-dihydroquinolines through Pd-catalyzed cascade cyclization reactions with *N*-tosylhydrazones

1.B.1 Introduction

1.B.1.1 Indoles

The indole ring is one of the most widely distributed heterocycles in nature, existing in different kind of plants, animals and marine organisms (Scheme 1.B.1).[117] The indole core is essential part of many biologically active natural products. For example, indole-3-acetic acid (IAA), a plant hormone of the auxin class;[118] tryptophan, an essential amino acid;[119] and the neurotransmitter serotonin.[120] The indole nucleus is also well-known as one of the most important privileged structures in drug-discovery. Nowadays, its application being part of drugs is enormous. In fact it is difficult to find a family of pharmaceuticals which do not have at least one indole-containing compound with medical activity.[121] Moreover, indole has become a privileged scaffold in other research areas such as agrochemistry[122] or material science.[123]

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[117] a) J. Barluenga, C. Valdés, in *Modern Heterocyclic Chemistry*, ed. J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, Wiley-VCH, Weinheim, vol.1 , **2011**, pp. 377–513; b) K. N. Kaushik, N. Kaushik, P. Attri, N. Kumar, H. C. Kim, K. A. Verma, H. E. Choi, *Molecules.* **2013**, *18*, 6620–6662.

[118] S. Spaepen, J. Vanderleyden, R. Remans, *FEMS Microbiol. Rev.* **2007**, *31*, 425–448.

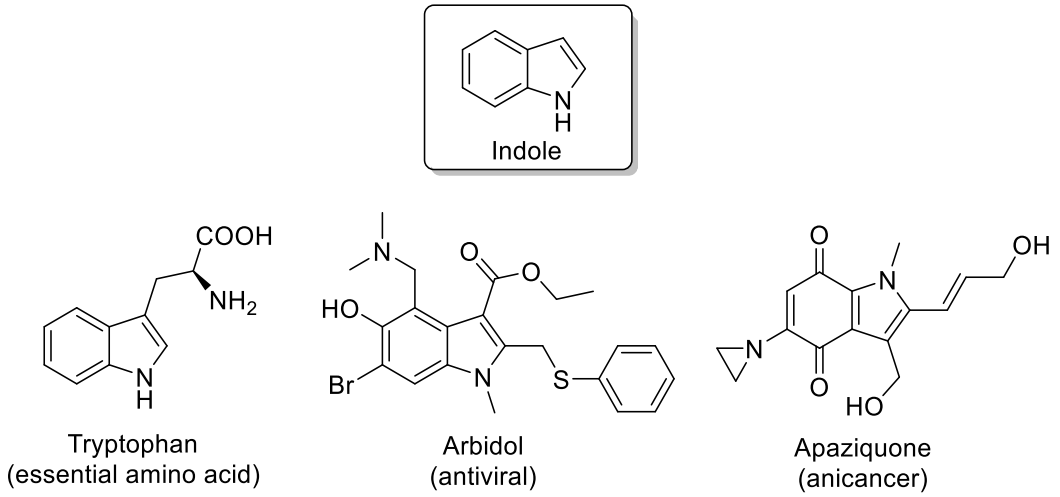
[119] D. J. Walther, J.-U. Peter, S. Bashammakh, H. Hörtnagl, M. Voits, H. Fink, M. Bader, *Science.* **2003**, *299*, 76 LP-76.

[120] I. P. Kema, E. G. E. de Vries, F. A. J. Muskiet, *J. Chromatogr. B Biomed. Sci. Appl.* **2000**, *747*, 33–48.

[121] For some pharmacologic applications, see: Anti-inflammatory or analgesic: M. A. A. Radwan, E. A. Ragab, N. M. Sabry, S. M. El-Shenawy, *Bioorg. Med. Chem.* **2007**, *15*, 3832–3841; Antimicrobial: H. Behbehani, H. M. Ibrahim, S. Makhseed, H. Mahmoud, *Eur. J. Med. Chem.* **2011**, *46*, 1813–1820; Anticancer: M.-J. R. P. Queiroz, A. S. Abreu, M. S. D. Carvalho, P. M. T. Ferreira, N. Nazareth, M. São-José Nascimento, *Bioorg. Med. Chem.* **2008**, *16*, 5584–5589; AntiHIV: I. Merino, A. Monge, M. Font, J. J. Martínez de Irujo, E. Alberdi, E. Santiago, I. Prieto, J. J. Lasarte, P. Sarobe, F. Borrás, *Farm.* **1999**, *54*, 255–264; Tranquilizing: J. L. Falcó, M. Piqué, M. González, I. Buira, E. Méndez, J. Terencio, C. Pérez, M. Príncep, A. Palomer, A. Guglietta, *Eur. J. Med. Chem.* **2006**, *41*, 985–990; Antihistaminic: S. Battaglia, E. Boldrini, F. Da Settimo, G. Dondio, C. La Motta, A. M. Marini, G. Primofiore, *Eur. J. Med. Chem.* **1999**, *34*, 93–105; Antidiabetic: Y.-Y. Li, H.-S. Wu, L. Tang, C.-R. Feng, J.-H. Yu, Y. Li, Y.-S. Yang, B. Yang, Q.-J. He, *Pharmacol. Res.* **2007**, *56*, 335–343.

[122] H. Hayashi, K. Takiuchi, S. Murao, M. Arai, *Agric. Biol. Chem.* **1989**, *53*, 461–469.

[123] R. A. Valentine, A. Whyte, K. Awaga, N. Robertson, *Tetrahedron Lett.* **2012**, *53*, 657–660.



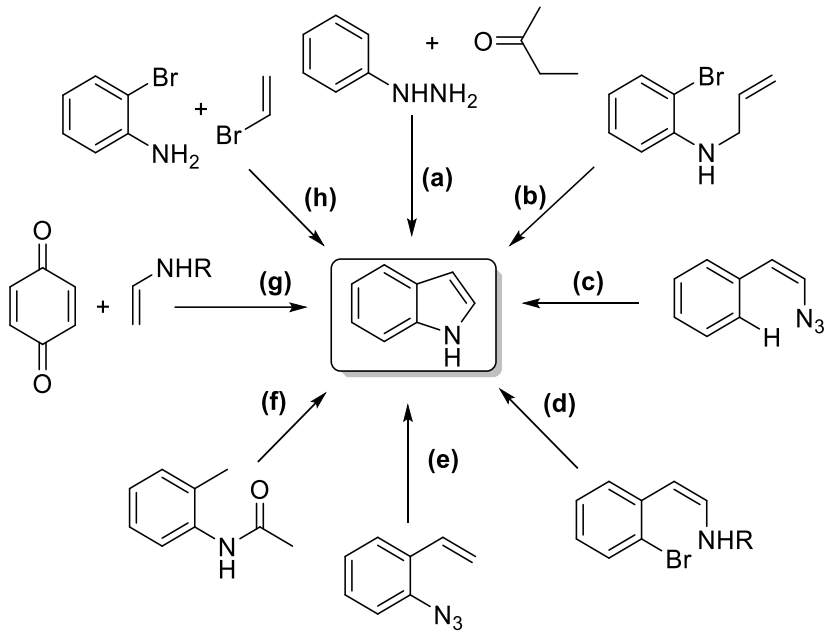
Scheme 1.B.1. Representative examples of natural products and drugs based on indole scaffold.

Synthesis of indoles

Since its first isolation in 1866 by Bayer,[124] the importance of the indole skeleton in chemistry has been growing steadily. Despite the large number of methods which have been developed to generate indoles, the interest on the development of new synthetic methods for these structures remains active nowadays.[125]

[124] R. Huisgen, *Angew. Chemie Int. Ed. English* **1986**, *25*, 297–311.
[125] a) J. Barluenga, F. Rodríguez, F. J. Fañanás, *Chem. Asian J.* **2009**, *4*, 1036–1048; b) R. Vicente, *Org. Biomol. Chem.* **2011**, *9*, 6469–6480

The most powerful methods using available to prepare indole scaffolds are based on these strategies: Fisher indole synthesis **(a)**,[126] intramolecular Heck cyclizations **(b)**,[127] Hemetsberge indole sinthesis **(c)**,[128] Buchwald strategy by transition-metal-aryl halide amination **(d)**,[129] Sundberg sinthesis **(e)**,[130] Madelung indole sinthesis **(f)**,[131] Nenitzescu synthesis from cycloalkane derivatives **(g)**[132] and strategies based on Pd-catalyzed auto-tandem cyclizations **(h)** [133] (Scheme 1.B.2).



Scheme 1.B.2. Most common approaches for the synthesis of indoles.

[126] a) J. Chae, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 3336–3339; b) E. Yasui, M. Wada, N. Takamura, *Tetrahedron Lett.* **2006**, *47*, 743–746.
[127] H. Fuwa, M. Sasaki, *Org. Lett.* **2007**, *9*, 3347–3350.
[128] T.-S. Mei, X. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806–10807.
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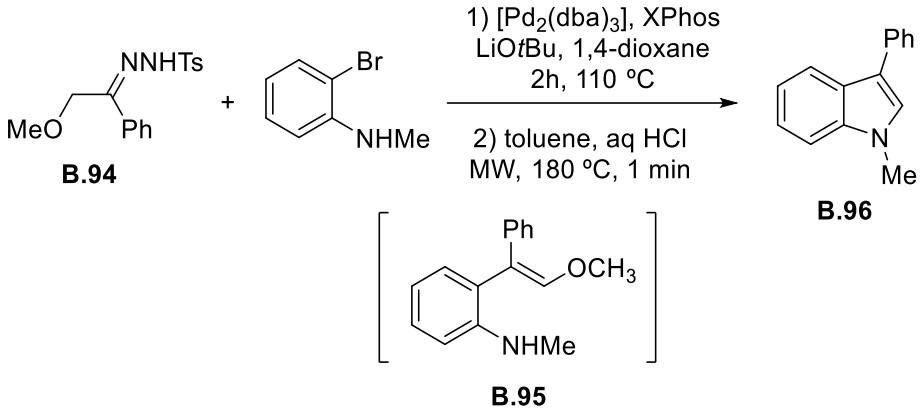
[130] M. Shen, B. E. Leslie, T. G. Driver, *Angew. Chemie Int. Ed.* **2008**, *47*, 5056–5059.
[131] L. Zhou, M. P. Doyle, *J. Org. Chem.* **2009**, *74*, 9222–9224.
[132] G. Revial, I. Jabin, S. Lim, M. Pfau, *J. Org. Chem.* **2002**, *67*, 2252–2256.
[133] a) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Eur. J.* **2005**, *11*, 2276–2283; b) J. Barluenga, A. Jiménez-Aquino, C. Valdés, F. Aznar, *Angew. Chemie Int. Ed.* **2007**, *46*, 1529–1532; c) J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *J. Am. Chem. Soc.* **2009**, *131*, 4031–4041.

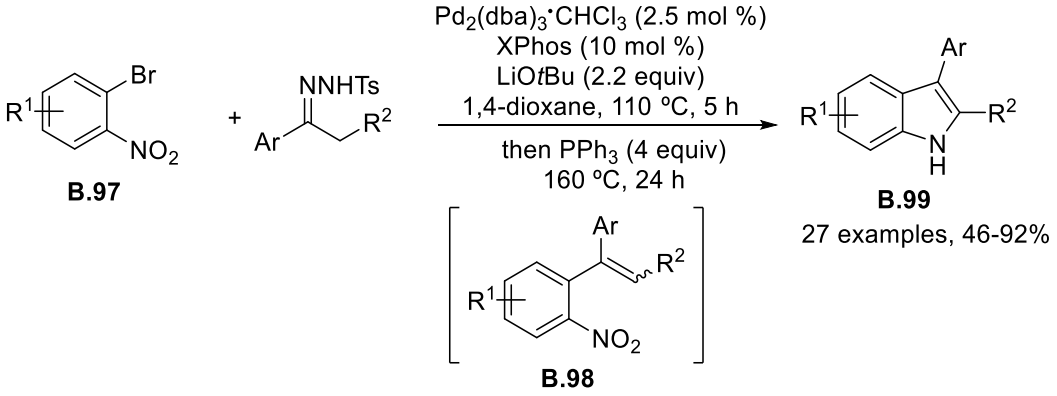
Metal-catalyzed reactions involving *N*-tosylhydrazones have been also applied to the synthesis of indoles. Some of these reactions have already been presented in the discussion of cyclization cascade processes showed before. This is the case of Wang`s copper-catalyzed cascade cyclization *via* allene formation/nucleophilic attack. With the employment of an amino group as nucleophile, the reaction allows for the formation of indole derivatives (Scheme 1.A.6).[112] Another example is the reaction described by Wang in 2013, which follows the synthetic sequence intramolecular carbopalladation/carbene coupling (Scheme 1.7).[67] The last case is the transformation developed by Yin in 2015, based on the carbene coupling/furan ring opening/nucleophilic attack (Scheme 1.15).[78]

Another approach for the synthesis of indoles was uncovered by our research group as a consequence of the preparation of enol ethers (Scheme I.43),[37] which are protected carbonyl compounds that can be deprotected under acidic media. Thus, a two-step synthetic sequence was developed, which started with the reaction between the tosylhydrazone derived from a α-methoxyacetophenone **B.94** and *o*-bromo-*N*-methylaniline to produce the enol ether **B.95**. Then, an intramolecular cyclization promoted by treatment with an aqueous acid solution led to the formation of an indole **B.96** (Scheme 1.B.3).[37]



Scheme 1.B.3. Synthesis of indoles using enols ethers generated through Pd-catalyzed reactions with tosylhydrazones.

Finally, in 2016, Alami and co-workers described a one-pot two-step reaction between *N*-tosylhydrazones and 2-nitroaryl bromides **B.97** for the synthesis of substituted indoles.[134] The first step of this transformation lie in a typical Pd-catalyzed cross-coupling with a tosylhydrazone, in which the *o*-nitrostyrene **B.98** is formed. Then, a PPh_3 promoted reductive cyclization[135] allows the formation of the desired heterocycle. This one-pot reaction is efficient to afford highly substituted indoles **B.99** regioselectively (Scheme 1.B.4).



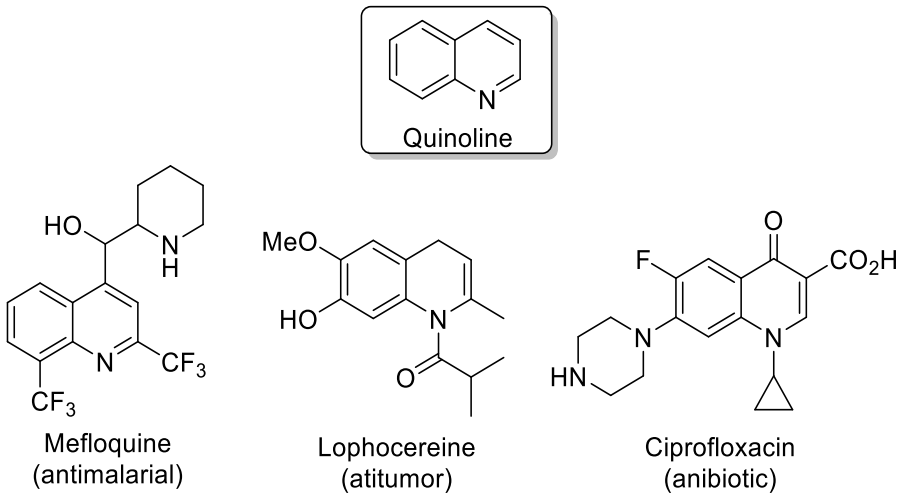
Scheme 1.B.4. Pd-catalyzed one-pot reaction of *N*-tosylhydrazones and 2-nitroaryl bromides.

[134] T. Bzeih, T. Naret, A. Hachem, N. Jaber, A. Khalaf, J. Bignon, J.-D. Brion, M. Alami, A. Hamze, *Chem. Commun.* **2016**, *52*, 13027–13030.

[135] The phosphine promoted cyclization of *o*-nitrostyrenes is known as the Cadogan-Sundberg indole synthesis. H. Majgier-Baranowska, J. D. Williams, B. Li, N. P. Peet, *Tetrahedron Lett.* **2012**, *53*, 4785–4788.

1.B.1.2 Quinolines

Quinolines and their hydrogenated forms (dihydroquinolines and tetrahydroquinolines) are also important nitrogenated heterocycles. Quinoline skeleton is present in many natural products and pharmacologically active compounds displaying a broad range of biological activities (Scheme 1.B.5).[136] Over the years, quinoline derivatives have been found to possess a broad range of application in medicinal,[137] bioorganic[138] and materials chemistry.[139]



[136] a) J. P. Michael, *Nat. Prod. Rep.* **1999**, *16*, 697–709; b) R. Musiol, J. Jampilek, K. Kralova, D. R. Richardson, D. Kalinowski, B. Podeszwa, J. Finster, H. Niedbala, A. Palka, J. Polanski, *Bioorg. Med. Chem.* **2007**, *15*, 1280–1288.

[137] For some medical applications, see: Antimalarial: A. Dorn, S. R. Vippagunta, H. Matile, C. Jaquet, J. L. Vennerstrom, R. G. Ridley, *Biochem. Pharmacol.* **1998**, *55*, 727–736; Antibacterial: R. Cormier, W. N. Burda, L. Harrington, J. Edlinger, K. M. Kodigepalli, J. Thomas, R. Kapolka, G. Roma, B. E. Anderson, E. Turos, et al., *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6513–6520; R. Musiol, J. Jampilek, V. Buchta, L. Silva, H. Niedbala, B. Podeszwa, A. Palka, K. Majerz-Maniecka, B. Oleksyn, J. Polanski, *Bioorg. Med. Chem.* **2006**, *14*, 3592–3598; O. Afzal, S. Kumar, M. R. Haider, M. R. Ali, R. Kumar, M. Jaggi, S. Bawa, *Eur. J. Med. Chem.* **2015**, *97*, 871–910; Anticonvulsant: Z.-F. Xie, K.-Y. Chai, H.-R. Piao, K.-C. Kwak, Z.-S. Quan, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4803–4805; Anti-inflammatory: A. Baba, N. Kawamura, H. Makino, Y. Ohta, S. Taketomi, T. Sohda, *J. Med. Chem.* **1996**, *39*, 5176–5182; Analgesic: E. Rajanarendar, M. Nagi Reddy, S. Rama Krishna, K. Rama Murthy, Y. N. Reddy, M. V Rajam, *Eur. J. Med. Chem.* **2012**, *55*, 273–283.

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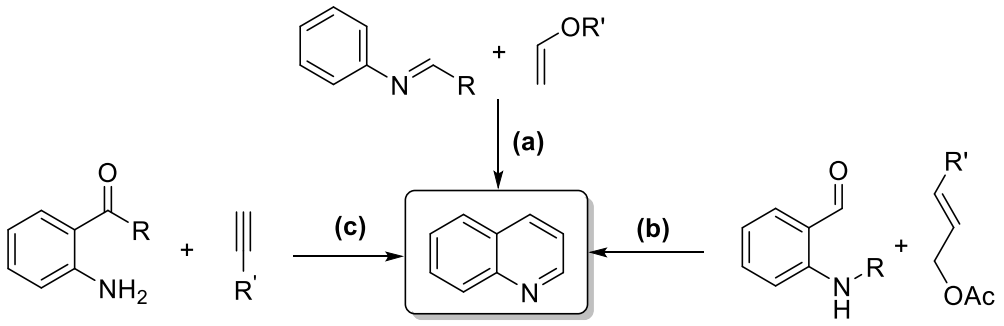
Scheme 1.B.5. Representative examples drugs based on quinoline derivatives.

Synthesis of quinolines

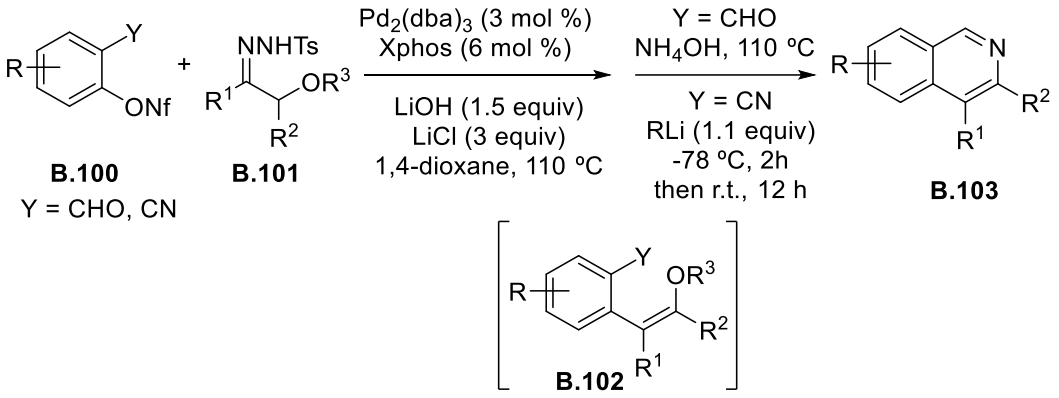
A number of synthetic methodologies have appeared since the late 1800s for the synthesis of quinolines and their derivatives. The structural core of quinoline has been generally synthesized by various conventional named reactions such as Skraup,[140] Doebner-Von Miller,[141] Friedlander,[142] Pfitzinger,[143] Conrad-Limpach[144] or Combes synthesis.[145] Although many of these methods are very efficient, they often involve the use of reagents which are not environmentally friendly, produce a large amount of waste and require long reaction times. Thus, many efforts to develop new approaches in the synthesis of quinolines have been made in order to avoid the deficiencies present in the traditional methodology. Nowadays, some of the most powerful strategies for the synthesis of quinoline cores are based on: Povarov reaction and related **(a)**,[146] reaction between 2-aminobenzaldehydes and allylic acetates *via* allic amination/Stetter reaction **(b)**[147] and reaction from amines and alkynes through hydroamination/condensation or hydroaminarion/hydroarylation **(c)**[148] (Scheme 1.B.6).



[140] R. H. F. Manske, M. Kulka, *The Skraup Synthesis of Quinolines. Organic Reactions.* **2011**, *7*, 59–98.
[141] S. E. Denmark, S. Venkatraman, *J. Org. Chem.* **2006**, *71*, 1668–1676.
[142] C.-C. Cheng, S.-J. Yan, *The Friedländer Synthesis of Quinolines. Organic Reactions.* **2005**, *28*, 37–201.
[143] S. A. H. El-Feky, Z. K. Abd El-Samii, N. A. Osman, J. Lashine, M. A. Kamel, H. K. Thabet, *Bioorg. Chem.* **2015**, *58*, 104–116.
[144] R. H. Reitsema, *Chem. Rev.* **1948**, *43*, 43–68.
[145] J. C. Sloop, *J. Phys. Org. Chem.* **2009**, *22*, 110–117.
[146] G. Sundararajan, N. Prabagaran, B. Varghese, *Org. Lett.* **2001**, *3*, 1973–1976.
[147] T. Nemoto, T. Fukuda, Y. Hamada, *Tetrahedron Lett.* **2006**, *47*, 4365–4368.
[148] X.-Y. Liu, P. Ding, J.-S. Huang, C.-M. Che, *Org. Lett.* **2007**, *9*, 2645–2648.

Scheme 1.B.6. Some powerful strategies for the synthesis of quinoline derivatives nowadays.

Regarding the employment of *N*-tosylhydrazones in the synthesis of six membered ring nitrogenates heterocycles, in 2012, our research group reported a straightforward one-pot reaction for the synthesis of isoquinoline derivatives by employing *o*-formyl nonaflates **B.100** and α-alkoxy *N*-tosylhydrazones **B.101**.[149] The transformation proceeds via Pd-catalyzed carbene coupling reaction to afford the enol ether **B.102** and a subsequent cyclization process. When *o*-cyano substituted nonaflates were used as substrates, cyano-substituted enol ether intermediates can be generated. Treatment with an organolithium reagent promotes an intramolecular cyclization to provide 1-substituted isoquinolines **B.103**. Thus, the combined strategies serve for the preparation of isoquinolines subtututed at position 1,3 and 4 (Scheme 1.B.7).



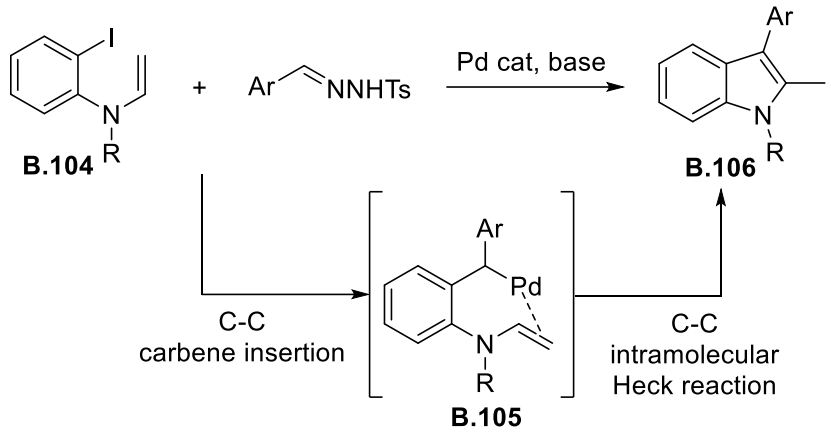
Scheme 1.B.7. Synthesis of isoquinolines developed in our research group using nonaflates and α-alkoxy *N*-tosylhydrazones.

[149] L. Florentino, F. Aznar, C. Valdés, *Org. Lett.* **2012**, *14*, 2323–2325.

1.B.2 Results and discussions

1.B.2.1 Objective and general considerations

In the context of our interest in cascade cyclization reactions based on the employment of aromatic tosylhydrazones and *o*-iodobenzenes featuring a double bond in an appropriate position, we wanted to develop an expansion of the reaction discussed in Chapter 1. Part A. Thus, taking into consideration the high interest of the indole scaffold and the previous experience of our research group in the synthesis of indoles, we decided to apply the same strategy to obtain indole derivatives **B.106** from *o*-iodo-*N*-alkenylanilines **B.104** (Scheme 1.B.8).



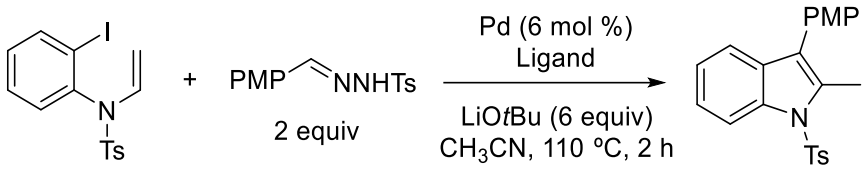
Scheme 1.B.8. Proposed Pd-catalyzed cascade cyclization reaction for the synthesis of indoles.

1.B.2.2 Optimization

We initiated our research using the model reaction between *o*-iodo-*N*-tosyl-*N*-vinylaniline **16a** and the tosylhydrazone of *p*-anisaldehyde **17a**. Firstly, the reaction was attempted employing the standard reaction conditions that had been applied for the cascade reactions that led to indanes and benzofurans, and which employed a Pd(0)/Sphos catalytic system. Quite disappointingly, in this case the cascade reaction did not take place and the iodoaniline **16a** was recovered untouched (Table 1.B.1, entry 1). Thus, an array of different catalytic conditions, involving changes in Pd sources, ligands and bases was examined (Table 1.B.1). Formation of the indole **18a** derived from the expected cascade cyclization reaction was detected by GC/MS only when PPh_3 was

employed as a ligand and in the presence of different Pd sources. Both LiO*t*Bu and LiOH promoted the reaction. However, when LiOH was employed (Table 1.B.1, entry 7), and also when the cascade reaction was carried out in the presence of 5 equivalents of H_2O (Table 1.B.1, entry 6), substantial amounts of the detosylated indole were obtained, due to the base promoted deprotonation in the reaction media. Finally, the slow syringe-pump addition of the tosylhydrazone to the reaction mixture led to an enhancement of the yield (Table 1.B.1, entry 12).

Table 1.B.1. Optimization data for the synthesis of indole **18a**.



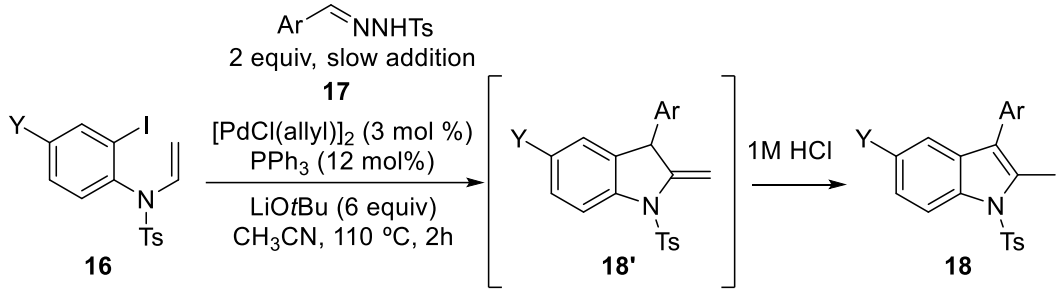
Entry	Pd source	Ligand	Yield[a] (%)
1[b,c]	$Pd_2(dba)_3$	Sphos	0
2[b,c]	$Pd_2(dba)_3$	Xphos	0
3[b,c]	$Pd_2(dba)_3$	P(2-furyl)$_3$	0
4[c]	$PdOAc_2$	PPh_3	20[g]
5[c]	$PdCl_2(MeCN)_2$	PPh_3	20[g]
6[c]	$[PdCl(allyl)]_2$	PPh_3	45[g]
7[d]	$[PdCl(allyl)]_2$	PPh_3	46[g]
8[c]	$[PdCl(allyl)]_2$	P(*o*-Tol)$_3$	0
9[c]	$[PdCl(allyl)]_2$	P(*o*-MeO-C_6H_4)$_3$	0
10	$[PdCl(allyl)]_2$	PPh_3	50
11[e]	$[PdCl(allyl)]_2$	PPh_3	18
12[f]	$[PdCl(allyl)]_2$	PPh_3	60 (53)[h]

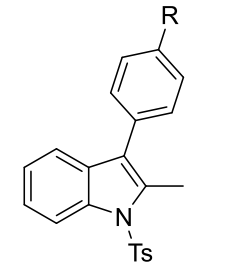
[a] Determined by GC/MS with internal standard. [b] Identical result was obtained employing $PdOAc_2$. [c] Carried out in the presence of 5 equiv. of H_2O. [d] LiOH was used as base. [e] Carried out employing 3 mol % of Pd. [f] Conducted using a syringe pump, slow addition of 17a. [g] Detosylated indole was observed. [h] Isolated yield after flash chromatography.

1.B.2.3 Generalization of the reaction for the synthesis of indoles

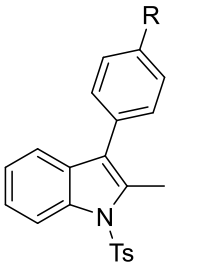
The optimized reaction conditions were then applied to the preparation of a collection of *N*-tosyl-2,3-trisubstituted indoles by varying both coupling partners. It must be noted that in some examples, substantial amounts of the indoline **18'** were detected in the reaction crude together with the indole **18**, leading to a drop in the isolated yield after chromatography. To drive the reactions to the complete formation of the final indole, the reaction mixtures were treated with aqueous 1 M HCl prior to the chromatographic purification (Scheme 1.B.9).

As it is presented in the Scheme 1.B.9, the reaction tolerates the employment of all types of aromatic tosylhydrazones derived from aldehydes. In this way, we have observed that the reaction works efficiently using a wide variety of electron donating (**18a**, **18e**) or electron withdrawing (**18b-c** and **18f-h**) functional groups in *para* and *meta* (**18j** and **18k**) positions. Moreover, the presence of a naphthalene ring is well tolerated (**18i**). In order to expand the generality of the reaction, we decided to carry out the cascade cyclization process bearing substituents on the benzene ring of the *o*-iodoaniline. Thus, the transformation proceeded successfully in the presence of halide (**18l-p**) and trifluoromethyl (**18q**) substituents, giving the indole derivatives with good yield in all cases.

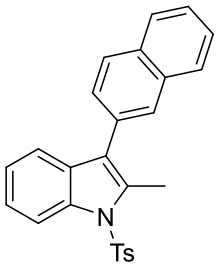




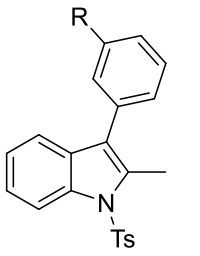
	R	
18a	MeO	53%
18b	F	58%
18c	Cl	84%
18d	H	72%



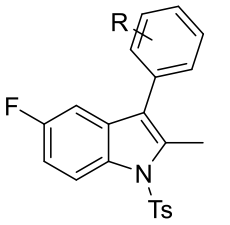
	R	
18e	Me	80%
18f	F_3C	62%
18g	AcO	55%
18h	NC	47%



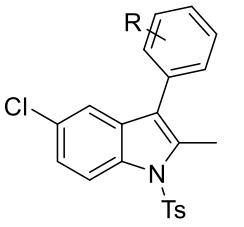
18i 55%



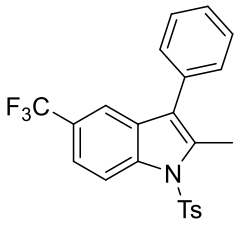
	R	
18j	Cl	66%
18k	NC	53%



	R	
18l	3-Cl	60%
18m	4-Me	58%



	R	
18n	3-Cl	62%
18o	4-Me	50%
18p	H	52%



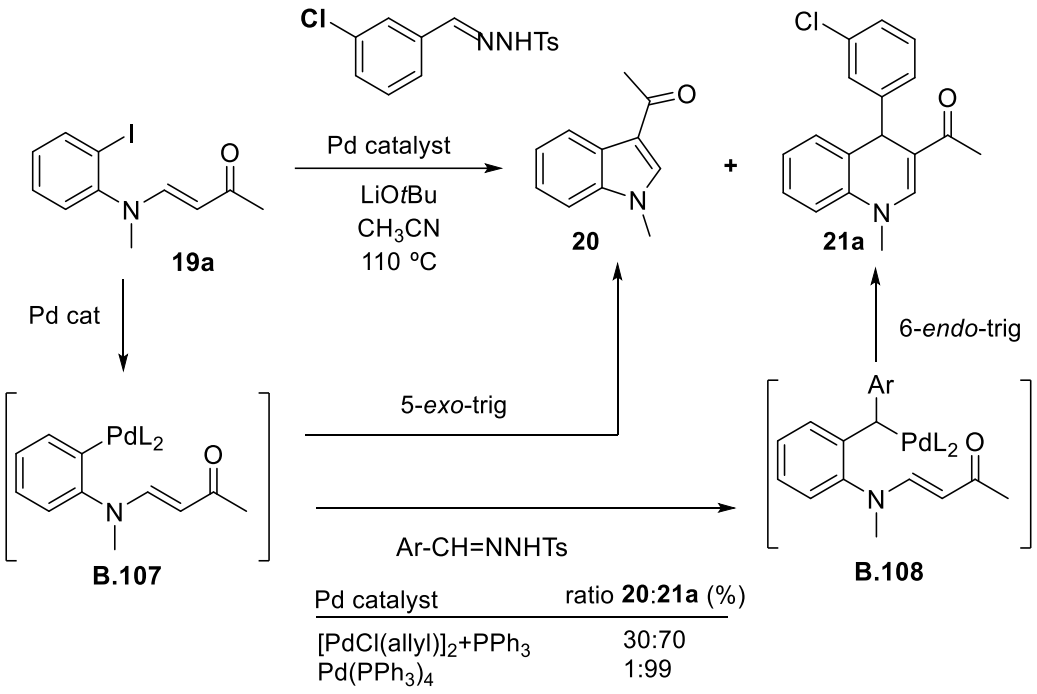
18q 50%

Scheme 1.B.9. Synthesis of indoles **18** by reaction of *o*-iodo-*N*-ethenylanilines **16** with tosylhydrazones **17**.

It is noteworthy that this methodology features a quite unusual [4+1] disconnection in the synthesis of indoles, in which the five-member ring is built by forming two C-C bonds on the hydrazonic carbon in one single step. Thus, it might enable the synthesis of indoles nor easily available through conventional methodologies.

1.B.2.4 Synthesis of dihydroquinolines

Continuing with the study of the scope of the reaction, the cascade process was attempted with the readily available *o*-iodo-*N*-alkenylaniline **19a**. Interestingly, the initial experiments conducted employing **19a** and 3-chlorophenyltosylhydrazone, under the optimized reaction conditions, did not afford the expected trisubstituted indole through a cascade cyclization reaction similar to that described above. In contrast, a mixture of indole **20** and the dihydroquinoline **21a** was detected in the reaction crude. Indole **20** is derived from an intramolecular Heck reaction on **19a** through a 5-*endo*-trig cyclization from arylpalladium complex **B.107**. This type of cyclization, although not very common, has been previously employed in the synthesis of indoles.[150] More surprising was the formation of **21a**, which could be envisioned as a formal 6-*endo*-trig cyclization from the intermediate benzylpalladium complex **B.108** (Scheme 1.B.10).



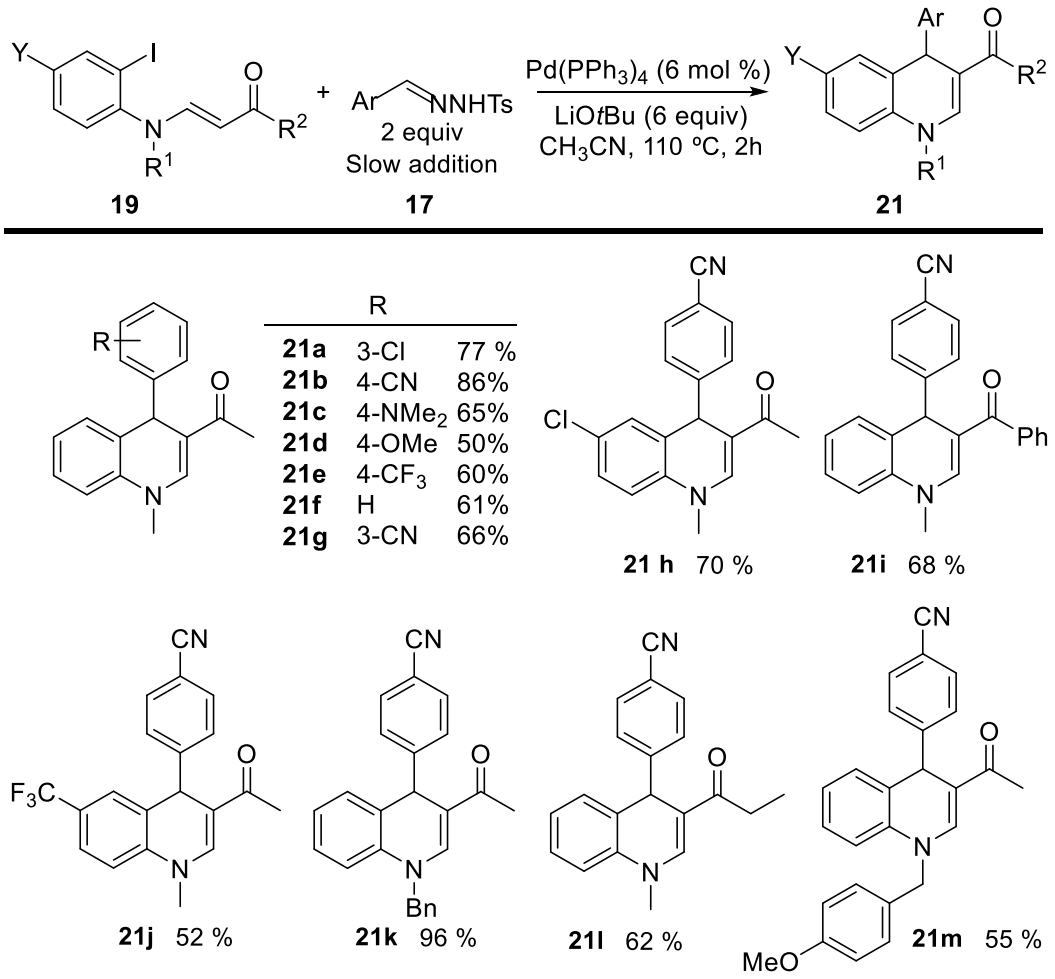
Pd catalyst	ratio **20**:**21a** (%)
$[PdCl(allyl)]_2+PPh_3$	30:70
$Pd(PPh_3)_4$	1:99

Scheme 1.B.10. Pd-catalyzed cyclization reactions of enaminone **19a** with 3-chlorophenyltosylhydrazone.

[150] a) T. Sakamoto, T. Nagano, Y. Kondo, H. Yamanaka, *Synthesis*, **1990**, 215–218; b) C. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1997**, *62*, 2676–2677; c) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Eur. J.* **2005**, *11*, 2276–2283.

In an attempt to avoid the formation of the indole **20** and drive the reaction to the exclusive formation of the dihydroquinoline **21a**, a new optimization study was conducted. Therefore, firstly we decided to carry out the reaction decreasing the temperature below 100 °C, however, the conversion was dramatically reduced and the starting enaminone **19a** was recovered. After some experimentation testing different combinations of Pd sources and ligands, it was found that employing $Pd(PPh_3)_4$ as the catalytic system, with no additional ligand added, the dihydroquinoline **21a** could be obtained in good yield, with almost complete disappearance of the indole **20** (Scheme 1.B.10).

A preliminary study of the scope of the reaction revealed that the cascade cyclization process was suitable for the synthesis of structurally diverse dihydroquinolines **21** with a wide variety of points for diversification. First, the reaction was compatible with aromatic tosylhydrazones featuring a variety of substitutions at the aromatic ring (**21a-g**). Regarding the structure of the enaminone **19**, different kind of substituents can be present at the nitrogen such as benzyl **21k** or 4-methoxybenzyl **21l** groups, at the acyl substituent, which can bear aromatic rings **21i** or alkyl chains **21m**, as well as in the aromatic ring of the starting iodoaniline supporting Cl **21h** or CF_3 **21j** groups (Scheme 1.B.11).

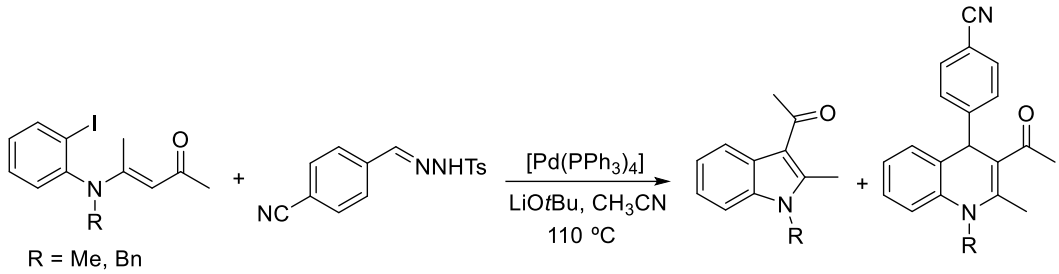


Scheme 1.B.11. Polysubstituted dihydroquinolines **21** prepared by Pd-catalyzed reaction between enaminones **19** and tosylhydrazones **17**.

Considering the simple access to the starting enaminones **19** through a highly efficient modular approach (see the experimental section for details), this methodology offers a very powerful alternative for the generation of structurally diverse dihydroquinolines, valuable heterocycle structures for medicinal chemistry.

Attempts to synthesize different substituted dihydroquinolines employing other *o*-iodoalkenylanilines

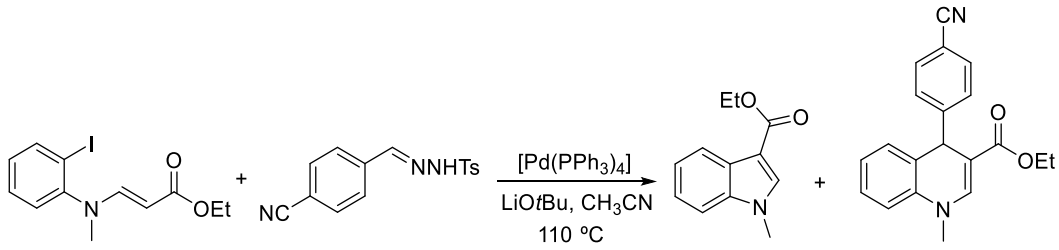
With the goal of obtaining 1,2,3,4-tetrasubstituted dihydroquinolines, we decided to attempt the reaction with the model enaminone **22**. Although the dihydroquinoline **24** was indeed formed, the indole **23** derived from the 5-*endo*-trig cyclization was the major product under all the reaction conditions tested (Scheme 1.B.12).



R	23	:	24
Me	61	:	39
Bn	80	:	20

Scheme 1.B.12. Attempt to synthesis 1,2,3,4-tetresubstituted dihydroquinolines **24**.

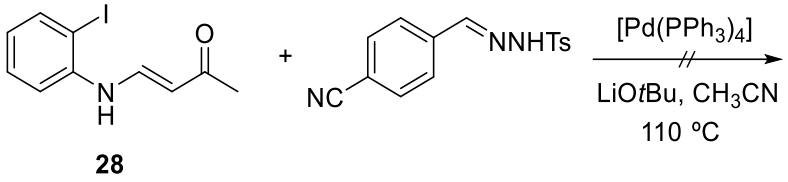
To further explore the structural variability in the enaminone, we prepared the enaminoester **25** so as to afford the corresponding dihydroquinoline derivative **27**. Nevertheless, the transformation also provided a mixture of the indole **26** and the dihydroquinoline **27**, being the indole **26** again the major product under the reaction conditions tested (Scheme 1.B.13).



26	:	27
75	:	25

Scheme 1.B.13. Attempt of carrying out the reaction with the enaminoester **27**.

Finally, we tested the viability of the reaction by using the unprotected enaminone **28**, in the interest of addressing a nitrogen unprotected dihydroquinoline. In this case the transformation did not proceed under the standard conditions and the starting enaminone **28** was recovered (Scheme 1.B.14).



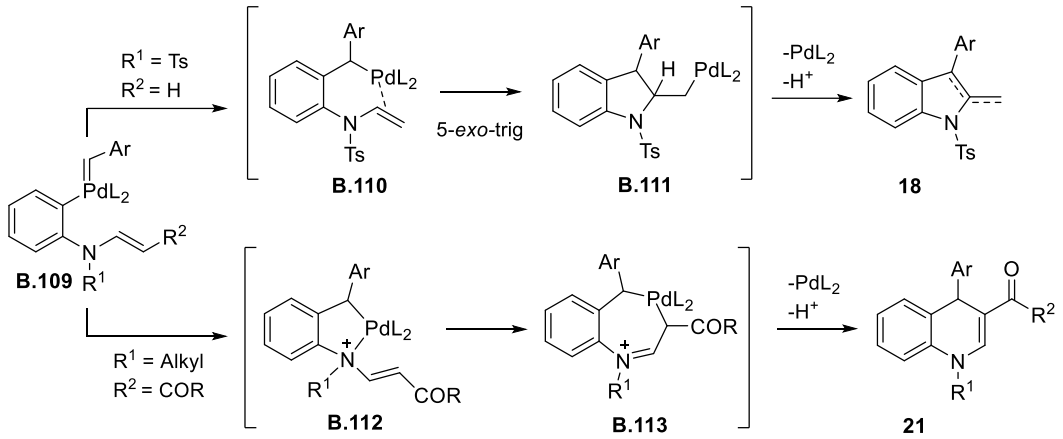
28

Scheme 1.B.14. Attempt of promoting the cascade cyclization process with unprotected enaminone **28**.

1.B.2.5 Mechanistic considerations

The mechanisms proposed for the formation of both the indoles **18** and the dihydroquinolines **21**, are initiated following the typical pathway of Pd-catalyzed cross-coupling reactions based on diazo compounds: oxidative addition and formation of the Pd-carbene **B.109**. Then, the migratory insertion of the carbene ligand would lead to the benzylpalladium intermediate **B.110** and **B.112** respectively. Intermediate **B.110** (R^1 = Ts, R^2 = H) undergoes a 5-*exo*-trig intramolecular carbopalladation, leading to **B.111**, and after the β-hydrogen elimination/aromatization sequence to the corresponding indoles **18** (Scheme 1.B.15). This was certainly the expected pathway, as 5-*exo*-trig Heck type reactions are usually favored compared to the alternative 6-*endo*-trig cyclizations.[114,151] Additionally, this behavior has been previously observed in the reaction for the synthesis of indanes and benzofurans described in Chapter 1. Part A.

[151] a) A. B. Machotta and M.Oestreich, in *The Mizoroki-Heck Reaction*, ed. M. Oestreich, Wiley, **2009**, pp. 179–213; b) T. Muller and S. Brasse, in *The Mizoroki-Heck Reaction*, ed. M. Oestreich, Wiley, **2009**, pp. 215–258.



Scheme 1.B.15. Mechanism proposal for the formation of indoles **18** and dihydroquinolines **21**.

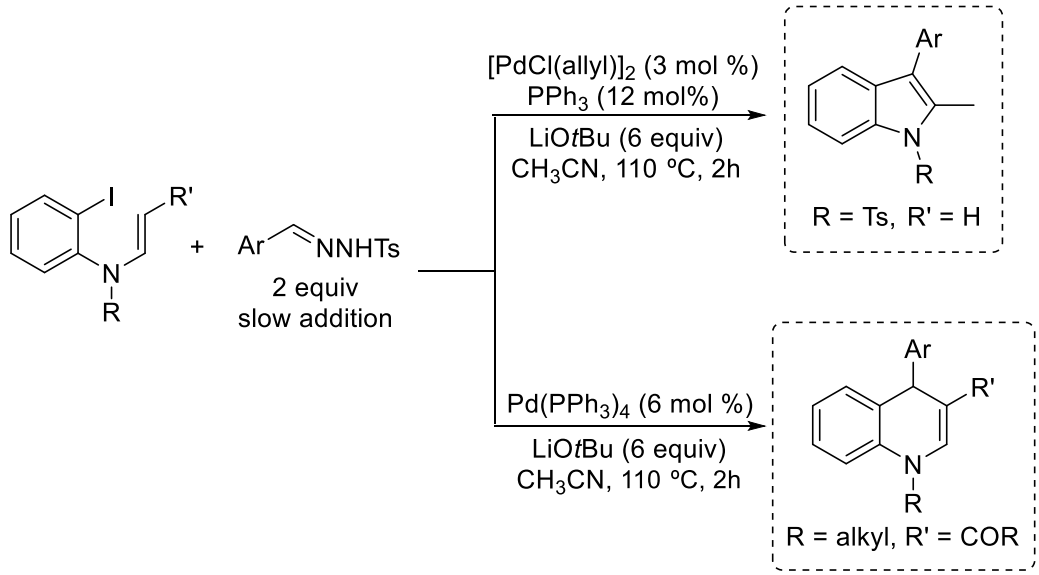
The evolution of the intermediate **B.112** (R^1 = alkyl, R^2 = COR) is quite intriguing because 6-*endo*-trig intramolecular carbopalladations are rather unusual.[114,151] A plausible explanation might involve the participation of the more nucleophilic nitrogen atom of the *N*-alkylated enaminone, which might favour the formation of the transient five-membered ring palladacycle in **B.112** instead of the Pd-alkene complex necessary for the typical carbopalladation reaction. Then, a 1,3-palladatropic rearrangement would lead to intermediate **B.113**, and a reductive elimination followed by tautomerization to the observed dihydroquinoline **21** (Scheme 1.B.15).

1.B.3 Conclusions

Herein, we have shown two different and unprecedented Pd-catalyzed cascade cyclization processes triggered by reaction of *N*-tosylhydrazones with *o*-iodo-*N*-alkenylanilines. First, a new synthesis of 1,2,3-trisubstituted indoles **18** is presented, through a Pd-catalyzed cascade cyclization reaction that involve the migratory insertion of a Pd-carbene followed by a Heck-type 5-*exo*-trig cyclization. Second, a highly versatile synthesis of 1,2,5-trisubstituted dihydroquinolines **21** is described through a similar process, but this time completed by a formal 6-*endo*-trig cyclization. Interestingly, the formation of the different types of heterocycles is determined by the substitution of the *N*-alkenylaniline. It is worth noting that novel [4+1] and [5+1] approaches, respectively, are presented for the synthesis of these benzofused heterocycles, in which two C-C bonds are formed on the same carbon during the cascade process.

Thus, it can be concluded that we have expanded the cascade cyclization strategy developed for the synthesis of indanes and benzofurans (Chapter 1. Part A), with a view to take advances of it in the synthesis of other highly valuable nitrogen-containing heterocycles.

1.B.4 Graphic summary



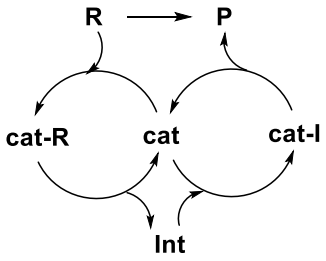
Chapter 2

Synthesis of condensed carbo- and heterocycles *via* Pd-catalyzed auto-tandem cyclization reactions with *N*-tosylhydrazones

2.1. Introduction

2.1.1. Pd-catalyzed auto-tandem cascade reactions with *N*-sulfonylhydrazones

The term auto-tandem catalysis is employed to define those cascade reactions in which the same catalyst promotes various independent transformations with separated catalytic cycles. Consequently, an intermediate formed in the first catalytic step is the substrate of the next catalytic step, and so on (Scheme 2.1).



Scheme 2.1. General representation of a two-step auto-tandem reaction.

Due to the high versatility and robustness of Pd catalysts,[1] many examples of Pd-catalyzed auto-tandem transformations have been developed combining different independent C-C and C-N bond-forming reactions.[152,153] Among the advantages associated to auto-tandem processes can be indicated: catalysis, solvent and time economy, and avoidance of separation and purification of intermediates. Additionally, this methodology allows to engage unstable intermediates, which might be difficult to isolate, in a further transformation.

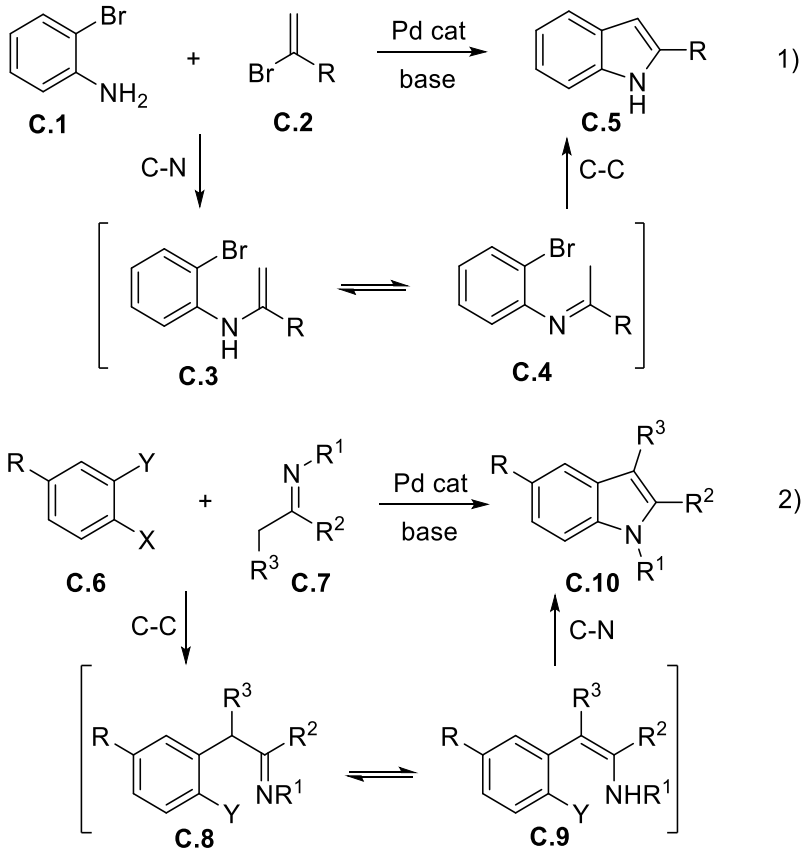
Taking into consideration that Pd-catalyzed cross-couplings involve the participation of a nucleophile and an electrophile, two-main strategies can be applied for the construction of cyclic molecules through auto-tandem catalyzed cascades: 1) Transformations which take place between two molecules featuring one nucleophilic and

[152] For selected examples of C-C/C-N or C-N/C-C Pd-catalyzed auto-tandem processes, see respectively: a) D. A. Candito, M. Lautens, *Angew. Chemie Int. Ed.* **2009**, *48*, 6713–6716; b) L. Ackermann, A. Althammer, *Angew. Chemie Int. Ed.* **2007**, *46*, 1627–1629.

[153] For selected examples of C-C/C-C Pd-catalyzed auto-tandem processes, see: a) T.-P. Liu, C.-H. Xing, Q.-S. Hu, *Angew. Chemie Int. Ed.* **2010**, *49*, 2909–2912; b) S. Ye, J. Liu, J. Wu, *Chem. Commun.* **2012**, *48*, 5028–5030.

one electrophilic center each. 2) Transformations which take place between a molecule featuring two electrophilic centers with a molecule with two electrophilic centers.

In order to illustrate the two different approaches in Pd-catalyzed auto-tandem cyclizations, two reactions for the synthesis of indoles developed by our research group are presented in Scheme 2.2. In equation 1, the construction of the indole **C.5** implied the Pd-catalyzed *N*-alkenylation of an *o*-haloaniline **C.1** with a haloalkene **C.2**, followed by a Pd-catalyzed intramolecular α-arylation of the intermediate imine **C.4**. Thus, two reagents which combine one electrophile and one nucleophile each, are combined.[133a] In equation 2, the formation of the indole **C.10** is performed by reaction of 1,2-dihalobenzene derivatives **C.6** and ketimines **C.7**. In this case, the Pd-catalyzed auto-tandem process occurs via α-arylation of the imine and intramolecular C-N bond-forming reaction on the intermediate enamine **C.9**.[133b,c]

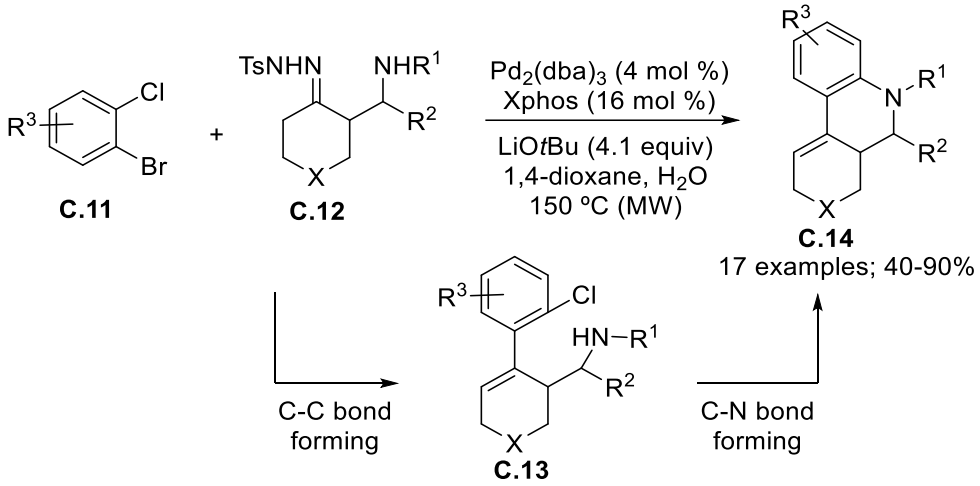


Scheme 2.2. Examples of Pd-catalyzed auto-tandem reactions for the synthesis of indoles.

The Pd-catalyzed cross-coupling with *N*-tosylhydrazones has been also included in various auto-tandem processes. The main advantaces are presented in the following pages. The organization of these transformations will be divided attending to the type of bonds created: C-C/C-N and C-C/C-C.

2.1.1.1 Pd-catalyzed auto-tandem C-C/C-N bond-forming reactions with *N*-tosylhydrazones

In 2011, our research group developed the first Pd-catalyzed auto-tandem reaction with *N*-tosylhydrazones.[154] This transformation was promoted by the employment of *N*-tosylhydrazones derived from β-aminoketones **C.12** (Mannich adducts) and *o*-bromochlorobenzene **C.11** to generate tetrahydroquinolines **C.14**. The sequential C-C/C-N bond formation was achieved *via* C-C cross-coupling reaction of the tosylhydrazone with the 1,2-dihalobenzene, followed by an intramolecular C-N bond-forming reaction on the intermediate **C.13**. Noteworthy, both steps are promoted by the same palladium catalyst. The process could be conducted from the isolated *N*-tosylhydrazone, or directly from the aminoketone forming the tosylhydrazone *in situ* (Scheme 2.3).

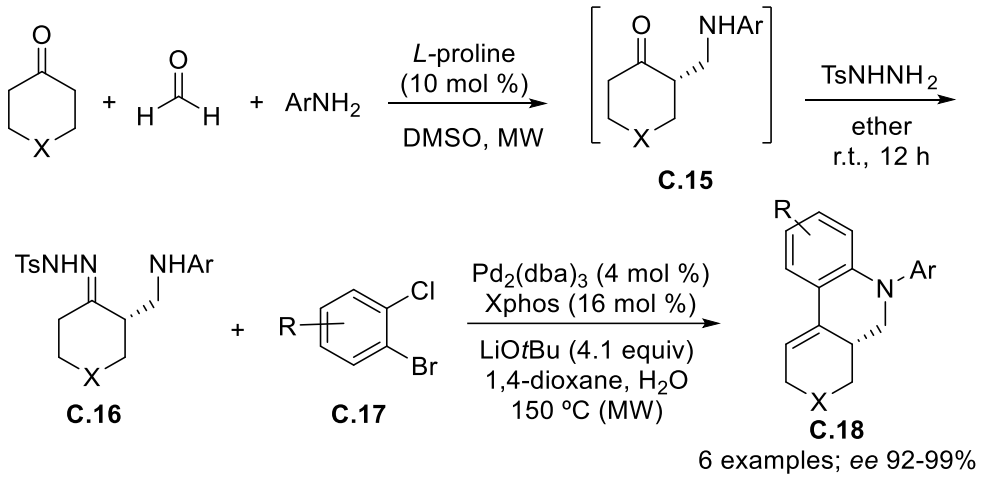


Scheme 2.3. Synthesis of tetrehydroquinolines by Pd-catalyzed C-C/C-N auto-tandem reaction with *N*-tosylhydrazones.

[154] J. Barluenga, N. Quiñones, M.-P. Cabal, F. Aznar, C. Valdés, *Angew. Chemie Int. Ed.* **2011**, *50*, 2350–2353.

It is important to point out that during this auto-tandem process the cross-coupling with the *N*-tosylhydrazone takes place preferentially over the Pd-catalyzed amination reaction.

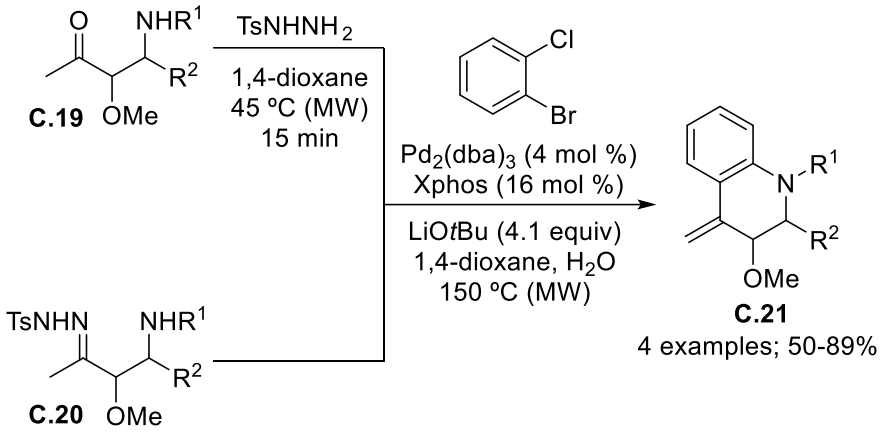
As an additional complement for this reaction, β-aminoketones were prepared in enantiomerically enriched form through an asymmetric organocatalyzed Mannich reaction.[155] Thus, an organocatalysis/Pd catalysis sequence was successfully applied to prepare enantiomerically enriched phenanthridines **C.18**. Remarkably, it was not observed erosion of the enantiomeric purity during the entire sequence that comprises formation of the *N*-tosylhydrazones and Pd-catalyzed cascade (Scheme 2.4).[154]



Scheme 2.4. Synthesis of enantiomerically enrich tetrahydrophenanthridines *via* organocatalysis/Pd catalyzed auto-tandem reaction with tosylhydrazones.

[155] a) I. Ibrahem, J. Casas, A. Córdova, *Angew. Chemie Int. Ed.* **2004**, *43*, 6528–6531; b) B. Rodríguez, C. Bolm, *J. Org. Chem.* **2006**, *71*, 2888–2891.

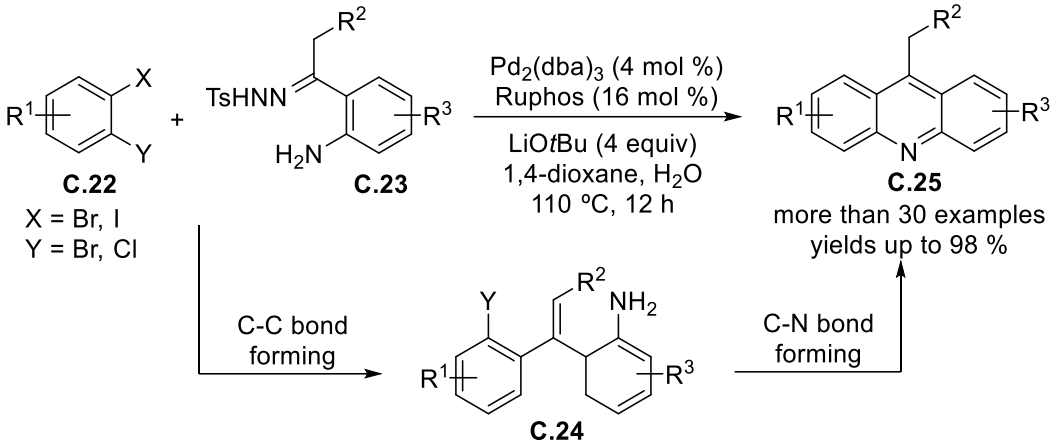
The reaction was also extended to β-aminoketones derived from acyclic ketones **C.19** and **C.20**, providing the corresponding tetrahydroquinoline derivatives **C.21** (Scheme 2.5).[154]



Scheme 2.5. Synthesis of substituted quinoline derivatives employing acyclic β-aminoketones.

This first example of Pd-catalyzed auto-tandem cross-coupling reaction with *N*-tosylhydrazones discovered by our research group served as inspiration for other groups to develop their own approaches based on the same concept. In this manner, in 2012, Wang and co-workers reported a Pd-catalyzed auto-tandem process employing tosylhydrazones derived from *o*-acylanilines **C.23** and *o*-diaholobenzenes **C.22** to synthesize acridines **C.25**.[156] The catalytic system build from $Pd_2(dba)_3$ as source of palladium and the ligand Ruphos promoted the C-C/C-N bond formation through the intermediate **C.24**. In this case, again, the C-C bond-forming reaction with the N-tosylhydrazone occurs preferentially, rather than the aryl amination of the primary amine (Scheme 2.6).

[156] Z. Huang, Y. Yang, Q. Xiao, Y. Zhang, J. Wang, *European J. Org. Chem.* **2012**, 6586–6593.

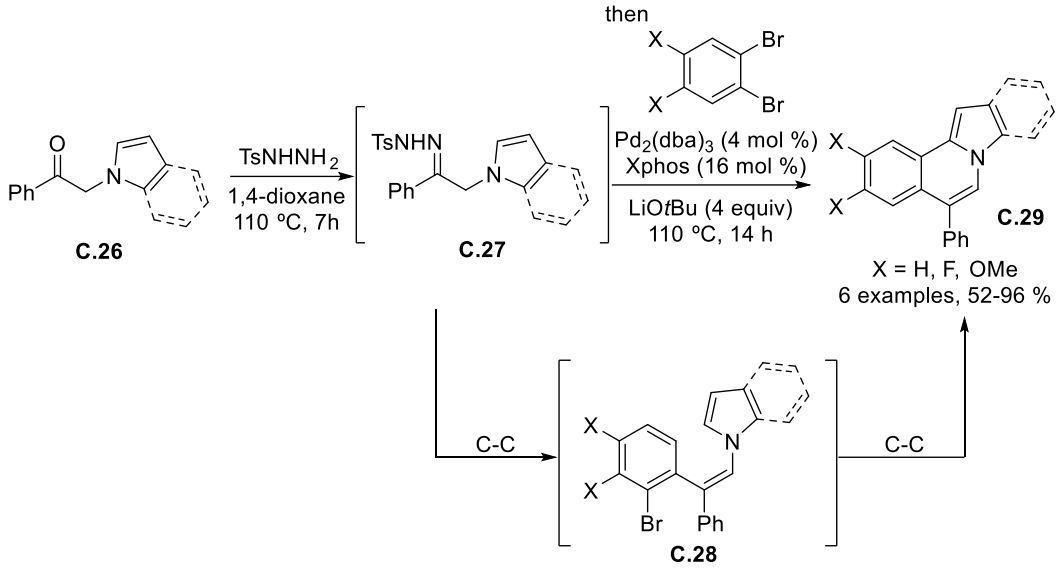


Scheme 2.6. Synthesis of acridines by reaction of *o*-acylaniline tosylhydrazones and *o*-dihalobenzene derivatives.

2.1.1.2 Pd-catalyzed auto-tandem C-C/C-C bond-forming reactions with *N*-tosylhydrazones

In 2013, our research group described the first Pd-catalyzed C-C/C-C bond forming auto-tandem reaction involving *N*-tosylhydrazones.[157] This novel transformation was based on the one-pot strategy to generate the tosylhydrazones **C.27** *in situ* from α-*N*-indoleacetophenone **C.26**, to later undergo the cascade transformation with 1,2-dribromobenzene. In first place, the Pd-catalyzed arylation of the *N*-tosylhydrazone takes place to give the intermediate **C.28**. Subsequently, and promoted by the same Pd catalyst, the C-H arylation occurs to give the final indolo- or pyrrolo[2,1-a]isoquinolines **C.29** (Scheme 2.7). It is important to note that for the C-H arylation to take place, it is essential that the two substituents that are going to be connected are in a *cis* relationship in the intermediate **C.2**. Interestingly, the required double bond configuration is enforced by the stereodirecting effects exerted by *o*-substituted aromatic ring.[149,158]

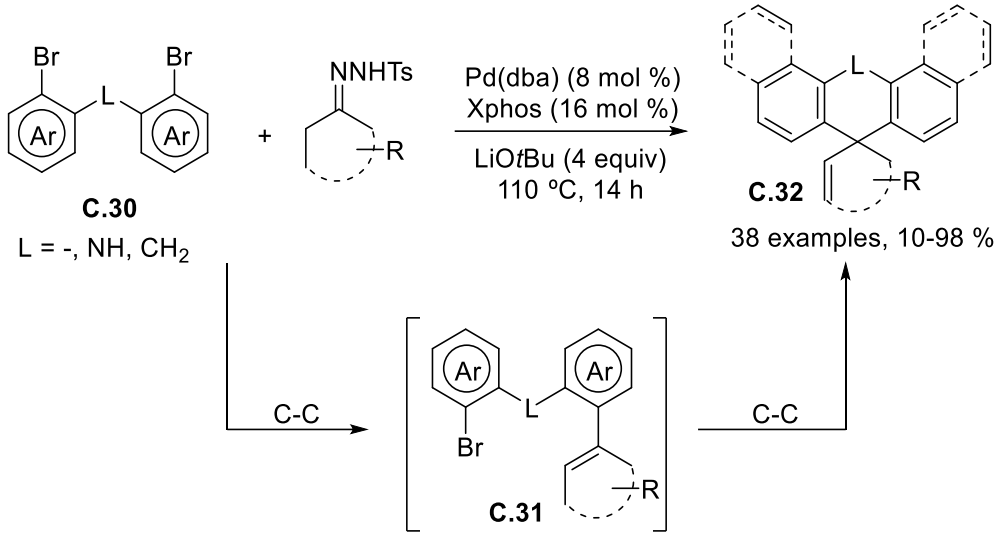
[157] L. Florentino, F. Aznar, C. Valdés, *Chem. Eur. J.* **2013**, *19*, 10506–10510.
[158] J. Barluenga, L. Florentino, F. Aznar, C. Valdés, *Org. Lett.* **2011**, *13*, 510–513.



Scheme 2.7. Synthesis of indolo- and pyrrolo[2,1-a]isoquinolines through C-C/C-C Pd-catalyzed auto-tandem reaction with tosylhydrazones.

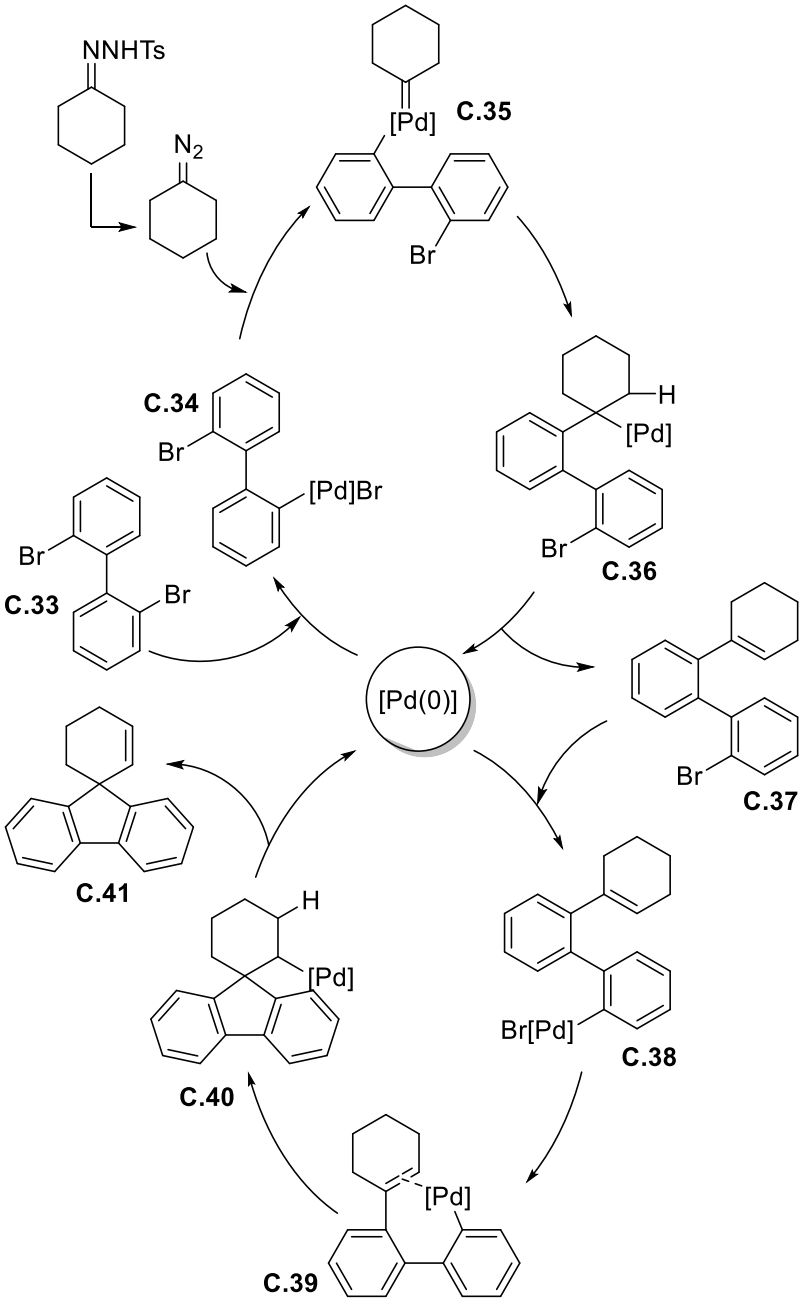
In all the auto-tandem processes introduced so far the reacting functional groups are already present in the starting coupling partners. In this context, in 2014, our research group envisioned a different approach to develop a novel Pd-catalyzed C-C/C-C auto-tandem process involving *N*-tosylhydrazones.[159] Thus, in this transformation, the double bond generated during the Pd-catalyzed cross-coupling reaction between the tosylhydrazone and the aryl halide (**C.31**) would participate in the second Pd-catalyzed process, an intramolecular Heck-type reaction to form carbocyclic compounds. This strategy was initially exploited employing *N*-tosylhydrazones, and 1,2-dibromobiphenyls **C.30**. The transformation was shown remarkably general, allowing the employment of a wide variety of tosylhydrazones and substituted dibrominated scaffolds to generate diverse fluorene derivatives **C.32** (Scheme 2.8).

[159] a) R. Barroso, R. A. Valencia, M.-P. Cabal, C. Valdés, *Org. Lett.* **2014**, *16*, 2264–2267; b) R. Barroso, M.-P. Cabal, R. Badía-Laiño, C. Valdés, *Chem. Eur. J.* **2015**, *21*, 16463–16473.



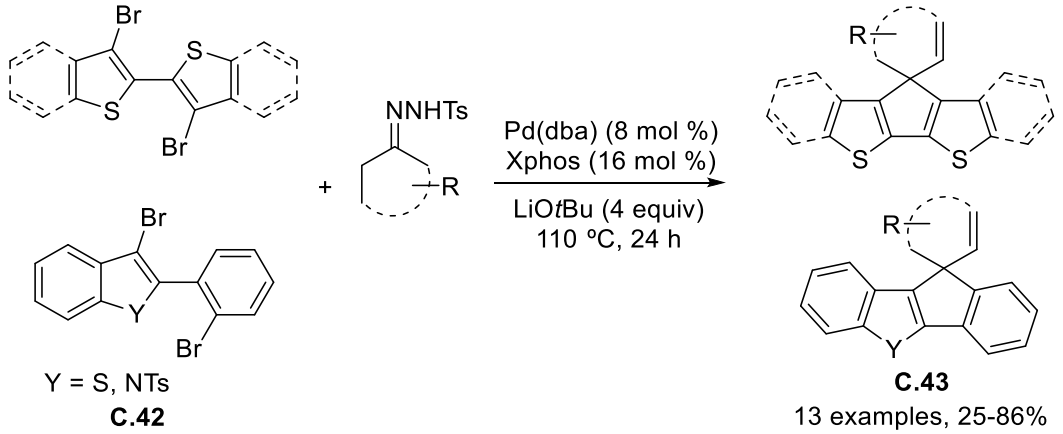
Scheme 2.8. New approach for the synthesis of spirocyclic moleculess through Pd-catalyzed auto-tandem reaction with tosylhydrazones.

A possible explanation for the formation of spirofluorenes can be rationalized considering two independent processes catalyzed by the same Pd species (Scheme 2.9). The first catalytic cycle is based on a typical Pd-catalyzed cross-coupling reaction between tosylhydrazones and aryl halides to provide alkene intermediate **C.37**. In this manner, the oxidative addition of the Pd(0) species to one of the C-Br bonds on the 2,2'-dibromobiphenyl **C.33**, followed by generation of the Pd-carbene intermediate **C.35** allows the migratory insertion to afford the benzylpalladium complex **C.36**. Then, β-hydride elimination takes places to release alkene the intermediate **C.37**. Next, **C.37** enters the second catalytic cycle to provide a 5-*exo*-trig cyclization through an intramolecular Heck reaction, which leads the spirocycle **C.41** after a second β-hydride elimination from the alkylpalladium species **C.40**. Noteworthy, for these auto-tandem processes to be successful, the *N*-tosylhydrazone should feature hydrogen atoms that could be eliminated from both α and β position.



Scheme 2.9. Mechanism proposed for the C-C/C-C Pd-catalyzed auto-tandem synthesis of spirofluorenes.

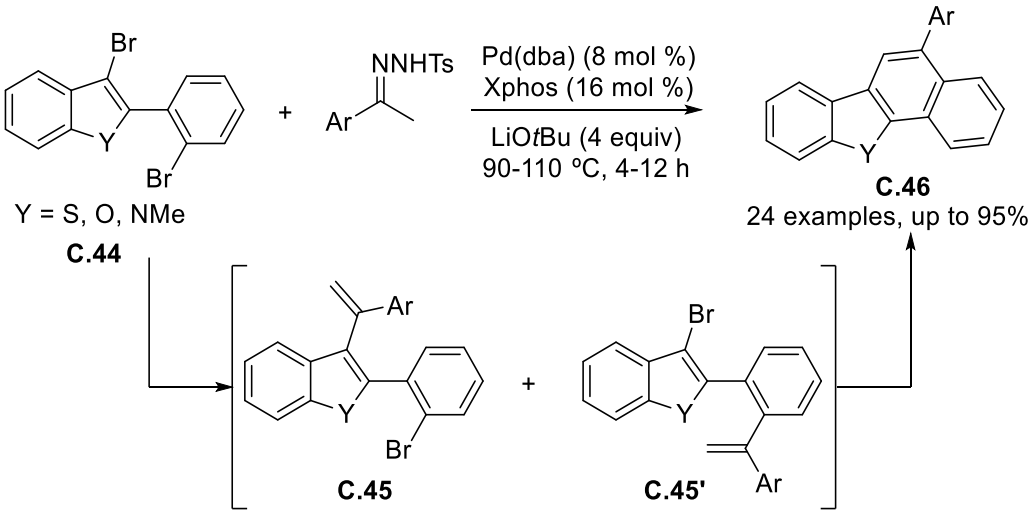
In addition, the robustness of this auto-tandem process was demonstrated with the incorporation of more elaborated heterocyclic scaffolds into the dibrominated starting substrates **C.42**.[159b] Thus, the formation of symmetric and asymmetric spiroheterocylic products **C.43** was achieved including thiophene, benzothiophene or indole heterocycles (Scheme 2.10).



Scheme 2.10. Pd-catalyzed auto-tandem reaction with tosylhydrazones for the synthesis of spiroheterocyclic compounds.

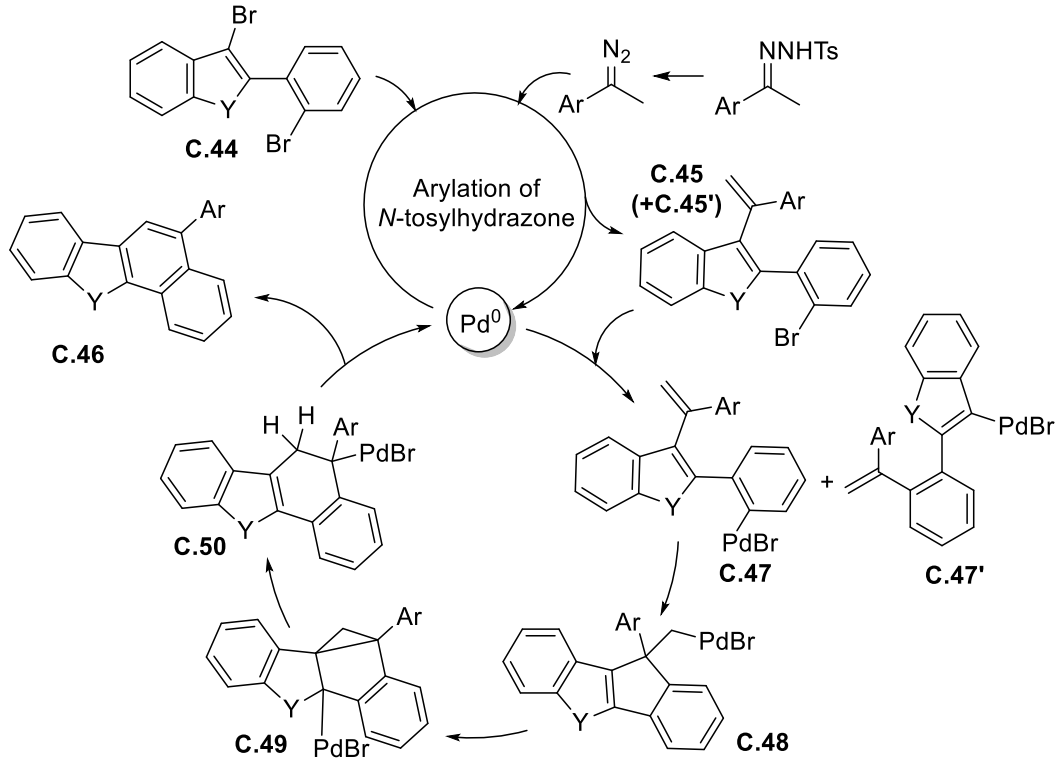
In 2016, Langer and co-workers reported a new Pd-catalyzed C-C/C-C auto-tandem reaction closely related with the previous studies carried out by our research group.[160] In this transformation, non-symmetric dibrominated heterocycles **C.44** and *N*-tosylhydrazones derived from acetophenones were combined to afford naptho-fused heterocycles **C.46**. Attending to the products obtained, it was evident that the mechanism of this reaction was different from that of the reaction discovered by our research group. Interestingly, the two possible intermediates **C.45** and **C.45'** for the coupling with the tosylhydrazones could be detected. Considering that both intermediates give rise to a single regioisomer of the final compound, the possibility of a direct 6-*endo*-trig cyclization for the second step could be excluded (Scheme 2.11).

[160] T. N. Ngo, T. T. Dang, A. Villinger, P. Langer, *Adv. Synth. Catal.* **2016**, *358*, 1328–1336.



Scheme 2.11. Synthesis of naphto-fused heterocycles via Pd-catalyzed auto-tandem reaction with tosylhydrazones.

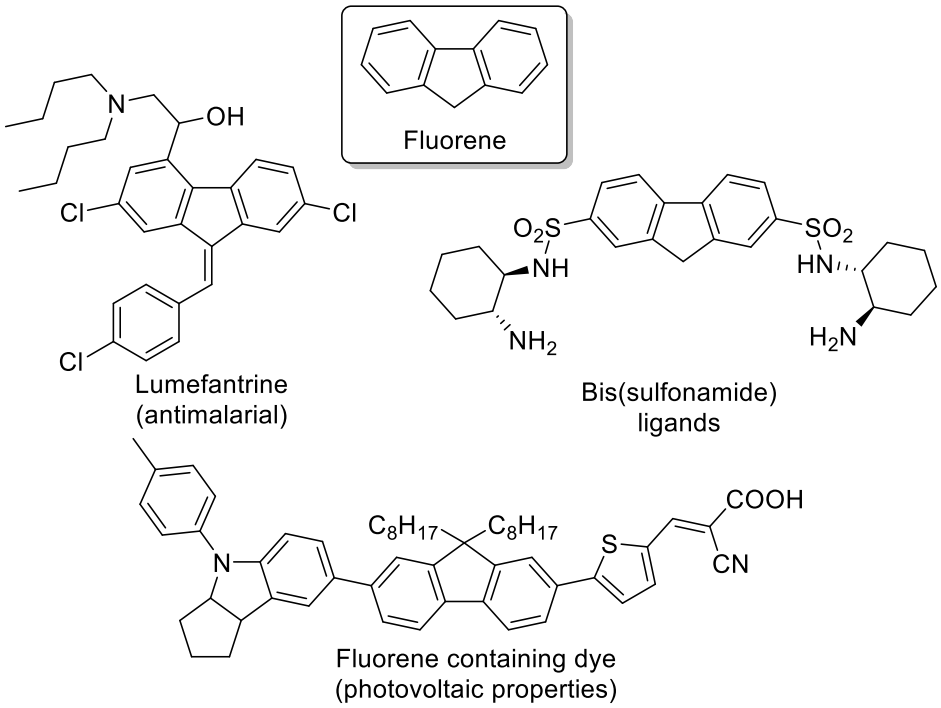
The mechanistic proposal for this peculiar auto-tandem process involves first the typical catalytic cycle of the coupling reaction with tosylhydrazones, in which the two possible intermediates **C.45** and **C.45'** are generated. Then, a second oxidative addition results in the formation of corresponding palladium complex **C.47** and **C.47'**. The intramolecular carbopalladation of **C.47** and **C.47'**, *via* 5-*exo*-trig cyclization provides a single fluorene intermediate **C.48**. As a consequence of the absence of β-hydrogens in **C.5**, this intermediate cannot undergo the β-hydride elimination. Thus, this system evolves through a 3-*exo*-trig cyclization to give cyclopropane intermediate **C.49**. Next, ring opening of the cyclopropane leads to the more stable benzyl palladium complex **C.50**, in which a β-hydride elimination can take place to generate the final naphtho-fused product (Scheme 2.12).



Scheme 2.12. Proposed mechanism for the synthesis of naphtho-fused heterocycles.

2.1.2 Fluorenes

Over recent decades, as a consequence of their utility in photoelectronic or photovoltaic materials, polycyclic aromatic hydrocarbons (PAHs) have become into some of the most important families of compounds in material chemistry.[161] Fluorene is one of the simplest PAH substructures. This hydrocarbon skeleton has been widely employed as structural subunit in biologically active compounds,[162] as well as polymers with electronic properties[163] and ligands in organometallic chemistry (Scheme 2.13).[164]

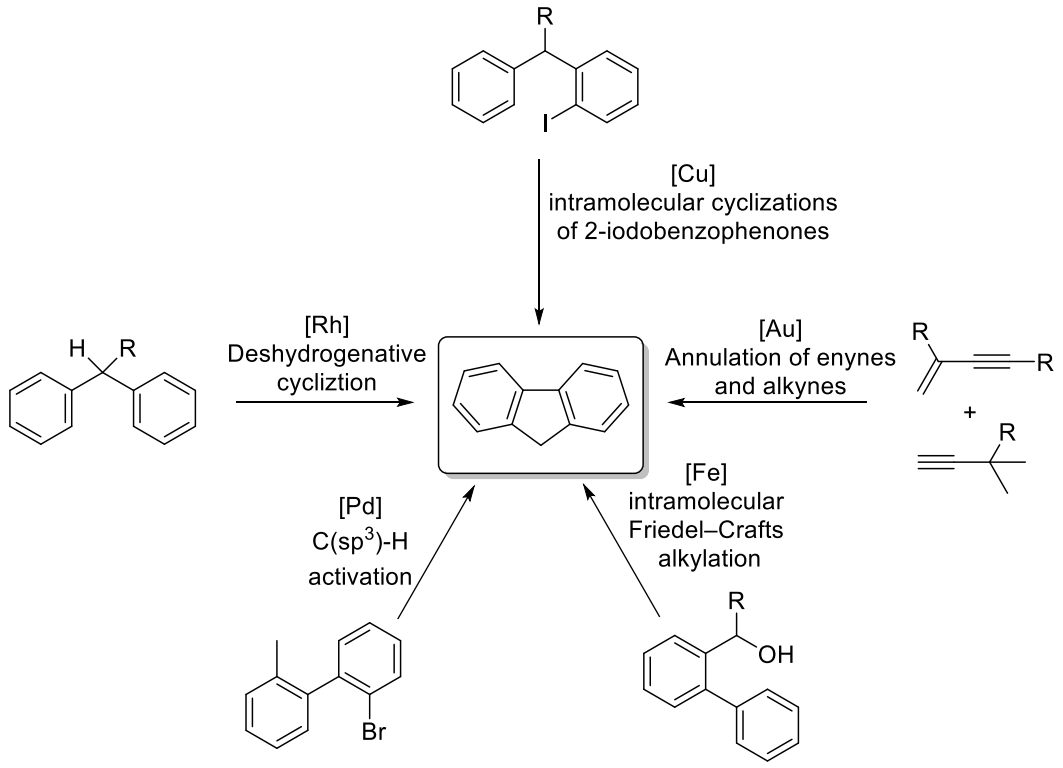


Scheme 2.13. Representative examples of fluorene containing molecules with biological and electronic properties.

[161] a) G. Dennler, M. C. Scharber, C. J. Brabec, *Adv. Mater.* **2009**, *21*, 1323–1338; b) A. E. Javier, S. R. Varshney, R. D. McCullough, *Macromolecules* **2010**, *43*, 3233–3237.
[162] W. Zeng, T. Eric Ballard, A. G. Tkachenko, V. A. Burns, D. L. Feldheim, C. Melander, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5148–5151.
[163] a) O. InganÄs, F. Zhang, M. R. Andersson, *Acc. Chem. Res.* **2009**, *42*, 1731–1739; b) C.-G. Zhen, Z.-K. Chen, Q.-D. Liu, Y.-F. Dai, R. Y. C. Shin, S.-Y. Chang, J. Kieffer, *Adv. Mater.* **2009**, *21*, 2425–2429.
[164] a) L. Zhong, K. Cui, P. Xie, J.-Z. Chen, Z. Ma, *J. Polym. Sci. Part A Polym. Chem.* **2010**, *48*, 1617–1621; b) P. V Ivchenko, I. E. Nifant'ev, V. A. Ezersky, A. V Churakov, *J. Organomet. Chem.* **2011**, *696*, 1931–1934.

Synthesis of fluorenes

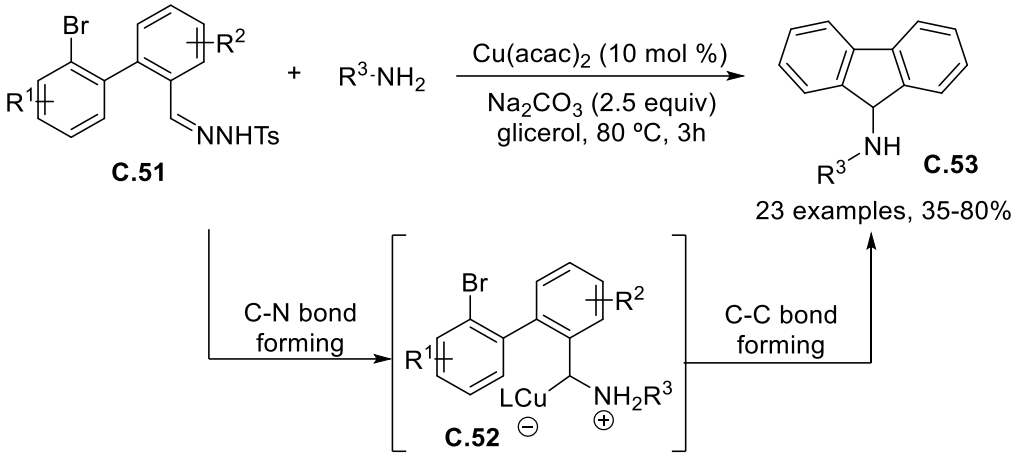
Nowadays, the most powerful methodologies for the synthesis of fluorene scaffolds are based on transition-metal catalyzed reactions. Complexes of palladium, rhodium, gold, copper and iron have resulted the most productive catalyst to provide this important structures (Scheme 2.14).[165] The discovery of these new methods has facilitated the preparation of a wide variety of fluorene derivatives such as fluorenones, fluorene carboxylates, fluorenylamines and fluorenylphosphine oxides. However, considering the topic of this memory, it will be only discussed in detail those methods for the synthesis of fluorene derivatives which employ *N*-tosylhydrazones as principal reagent. The first synthesis of fluorene structures employing *N*-tosylhydrazones has already been discussed: the Pd-catalyzed C-C/C-C auto-tandem transformation described by our research group in 2014, which affords spirofluorene systems (Scheme 2.8).[159]



Scheme 2.14. General metal-catalyzed methods for the synthesis of fluorene scaffold.

[165] A.-H. Zhou, F. Pan, C. Zhu, L.-W. Ye, *Chem. Eur. J.* **2015**, *21*, 10278–10288.

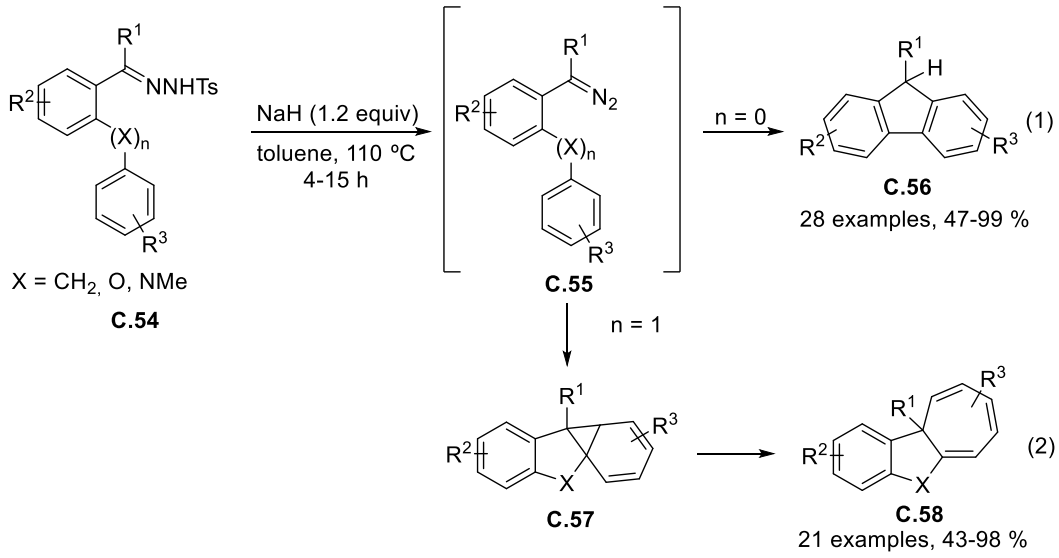
In the same year, Alami and co-workers reported a Cu-catalyzed cross-coupling intramolecular cyclization reaction for the synthesis of 9*H*-fluoren-9-amines derivatives **C.53**.[166] The employment of 2'-bromo-biaryltosylhydrazones **C.51** and primary amines as coupling partners allowed the sequential bond formation C-N/C-C on the carbenic carbon atom. According with the proposed mechanism, after the *in situ* reduction of Cu(II) to Cu(I), a electrophilic Cu-carbene complex is formed on which the nucleophilic addition takes places generating the intermediate **C.52**. Next, this intermediate undergoes oxidative addition with the aryl bromide and reductive elimination to generate the final fluorene **C.53** (Scheme 2.15).



Scheme 2.15. Cu-catalyzed cross-coupling intramolecular reaction for the synthesis of fluorene derivatives.

[166] J. Aziz, G. Frison, M. Gómez, J.-D. Brion, A. Hamze, M. Alami, *ACS Catal.* **2014**, *4*, 4498–4503.

More recently, Wang and co-workers developed a transition-metal-free methodology for the synthesis of fluorenes, based on an intramolecular cyclization reaction employing *N*-tosylhydrazones.[167] Thus, depending on the type of substrate used, a product derived from a formal carbenic insertion on the aromatic C-H bond **C.56** (Scheme 2.16, pathway 1), or the corresponding derivative of an intramolecular Büchner reaction were obtained **C.58** (Scheme 2.16, pathway 2).



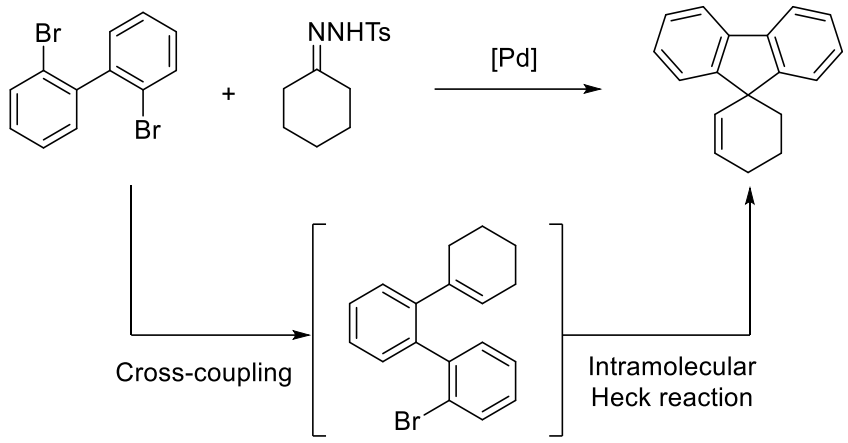
Scheme 2.16. Synthesis of fluorenes and their [6,5,7]benzo-fused analogous through metal-free intramolecular cyclization.

[167] Z. Liu, H. Tan, L. Wang, T. Fu, Y. Xia, Y. Zhang, J. Wang, *Angew. Chemie Int. Ed.* **2015**, *54*, 3056–3060.

2.2 Results and discussions

2.2.1 Objective and general considerations

In the context of our interest in the development of new Pd-catalyzed cascade reactions based on *N*-tosylhydrazones,[168] we wanted to continue taking advantage of the functionality generated during the Pd-catalyzed cross-coupling reaction to undergo auto-tandem cyclizations. The auto-tandem C-C/C-C bond-forming process discovered by our research group in 2014 introduced this concept for the first time (Scheme 2.17).

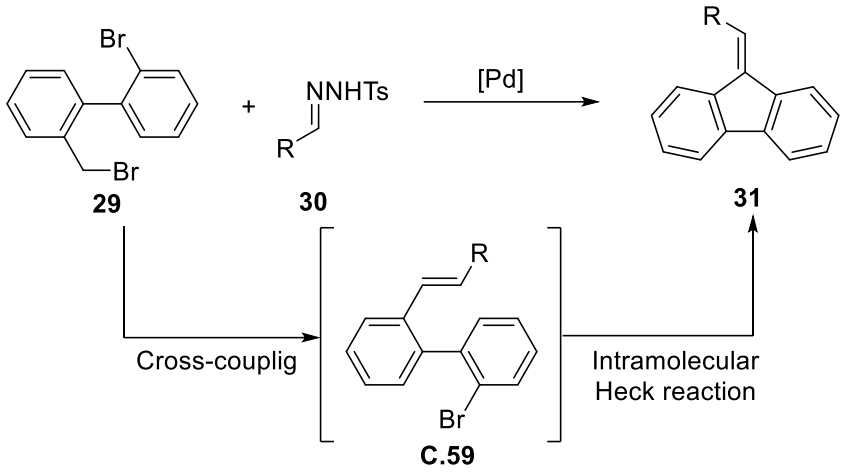


Scheme 2.17. Auto-tandem C-C/C-C bond-forming process developed by our research group.

We envisioned that this approach featured considerable potential for the synthesis of other polycyclic aromatic hydrocarbons upon selection of the proper coupling partners. In this way, we decided to explore a similar cascade employing dibromobiphenyls **29** which bore a benzyl bromide and an aryl bromide in suitable positions to afford a cascade sequence. The Pd-catalyzed cross-coupling reaction between benzyl bromides and *N*-tosylhydrazones had been widely explored by Wang and co-workers giving excellent results in the preparation of stilbenes.[45] Thus, taking advantage of the higher reactivity of benzyl bromides compared to aryl bromides in the oxidative addition step, we expected the initial formation of the stilbene **C.59** by reaction with the *N*-tosylhydrazone **30**. Then, **C.59** could suffer a 5-*exo*-trig intramolecular Heck reaction,

[168] a) M. Paraja, M. Carmen Perez-Aguilar, C. Valdes, *Chem. Commun.* **2015**, *51*, 16241–16243; b) M. Paraja, C. Valdes, *Chem. Commun.* **2016**, *52*, 6312–6315.

which would provide the final 9-fluorenylidene **31**. If this approach were successful, it would represent a novel and convergent route to an important class of fluorenyl derivatives. Moreover, it would consist of a rare example of the formation of a C-C single bond and a C=C double bond on the same carbon atom in a single reaction (Scheme 2.18).



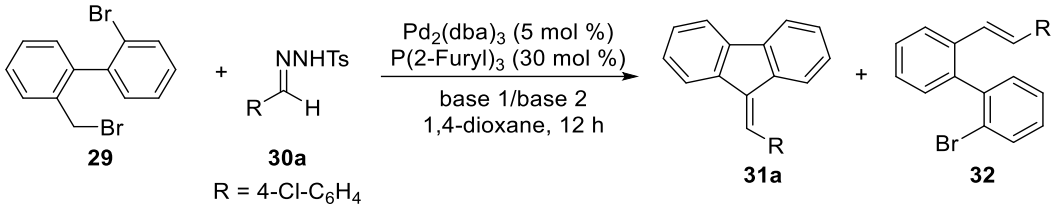
Scheme 2.18. Proposed new auto-tandem cyclization for the synthesis of fluorenes.

2.2.2 Optimization

We initiated our study with the reaction between 2-bromo-2'-(bromomethyl)-1,1'-byphenyl **29** and the *N*-tosylhydrazone of 4-chlorobenzaldehyde **30a**. In an initial experiment, we chose a set of catalytic conditions similar to those described by Wang for the Pd-catalyzed cross-coupling between *N*-tosylhydrazones and benzyl bromides,[45] which should be the first step of the auto-tandem process: $Pd_2(dba)_3$ (5mol %)/P(2-Furyl)$_3$ (20 mol %), in toluene at 80 °C, but employing 6 equiv of LiO*t*Bu as base, as an additional load of base would be necessary for the second step of the cascade process. Under this conditions, the cross coupling proceeded with excellent conversion leading to stilbene **32**, but formation of the desired benzylidenefluorene **31a** was not detected (Table 2.1, entry 1). Nevertheless, formation of **31a** occurred to a considerable extent when the reactions were conducted under reflux of 1,4-dioxane or CH_3CN (Table 2.1, entries 2-4). In particular, the reaction in 1,4-dioxane provided a 1:1 mixture of **31a** and **32** (Table 2.1, entry 3). After some experimentation, it was found that the employment of a combination of two bases, LiO*t*Bu (3 equiv) and an alkaline carbonate (3 equiv), led to an increment on the formation of **31a** (Table 2.1, entry 5, 7-9). The presence of both bases in the reaction had a beneficial effect on the conversion, as the reaction carried out only with the

participation of K_2CO_3 led again to the exclusive formation of stilbene **32**. It was determined that the combination LiO*t*Bu (3 equiv)/Cs_2CO_3 (3 equiv) afforded the best **31a**:**32** ratio. Finally, running the reaction in a sealed tube with a bath temperature of 120°C brought a complete conversion into the fluorene **31a** with an isolated yield of 79% (Table 2.1, entry 10).

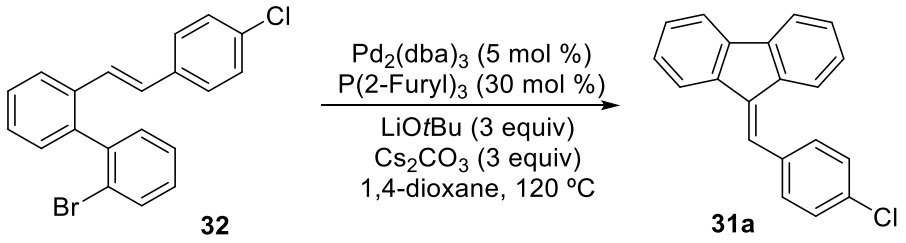
Table 2.1. Selected optimization experiments for the C-C/C-C Pd-catalyzed auto-tandem reaction.



Entry	base 1/base 2 (6 equiv)	T (°C)[b]	31a/32[c]
1	LiO*t*Bu/-	80	0:1[d]
2	LiO*t*Bu/-	100	1:4[e]
3	LiO*t*Bu/-	100	1:1
4	LiO*t*Bu/-	100	2:3[f]
5[a]	LiO*t*Bu/K_2CO_3	100	2:1
6	K_2CO_3/-	100	0:1
7[a]	LiO*t*Bu/Na_2CO_3	100	1:4
8[a]	LiO*t*Bu/Li_2CO_3	100	7:3
9[a]	LiO*t*Bu/Cs_2CO_3	100	4:1
10[a]	LiO*t*Bu/Cs_2CO_3	120	1:0 (79%)[g]

[a] Base 1 (3 equiv)/base 2 (3 equiv). [b] Temperature of the bath in the sealed tube reaction. [c] Calculated by GC/MS. [d] Carried out in toluene as solvent. [e] $Pd_2(dba)_3$ (3 mol %) was used. [f] Carried out in CH_3CN as solvent. [g] Isolated yield of **31a** after flash chromatography.

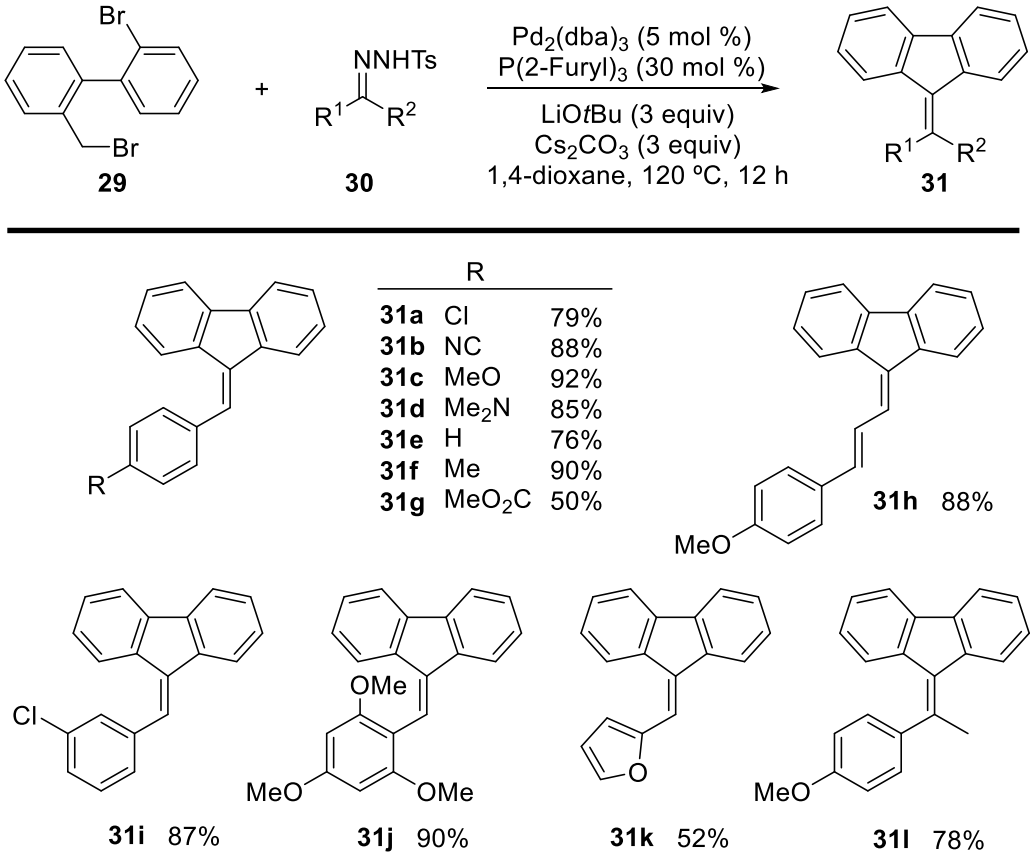
In a separate experiment, stilbene **32** was subjected to the same reaction conditions of entry 10, giving rise to **31a** with complete conversion, indicating that **32** is indeed an intermediate in the catalyzed auto-tandem cascade (Scheme 2.19).



Scheme 2.19. Demonstration of the participation of **32** as intermediate in the auto-tandem cyclization.

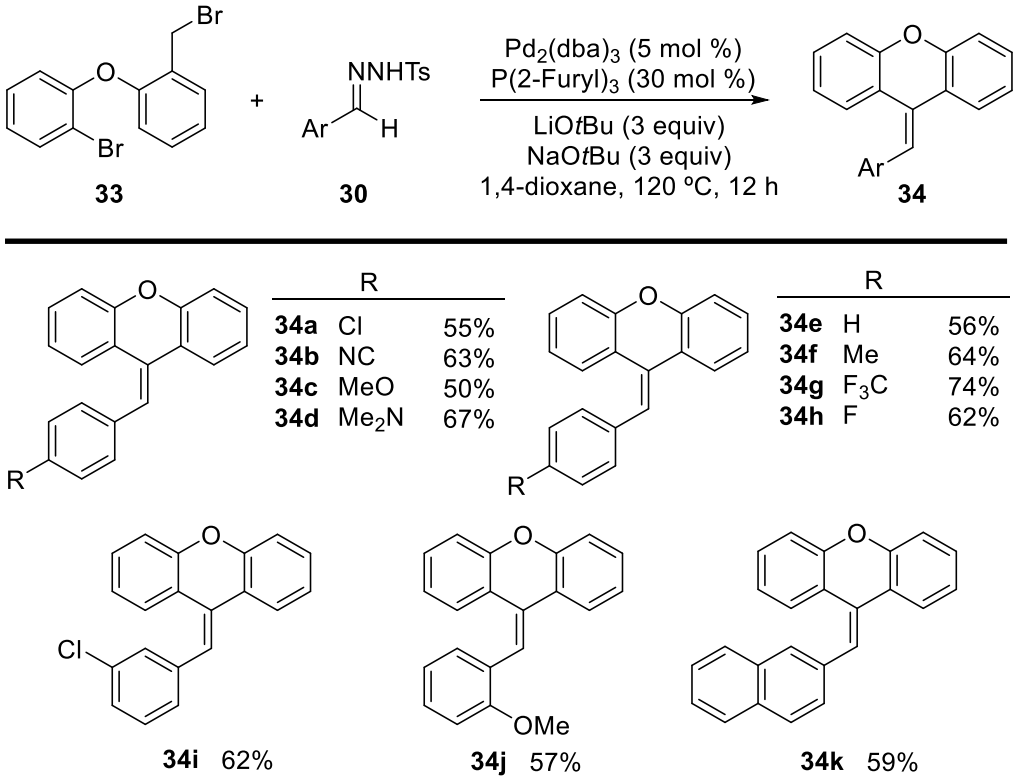
2.2.3 Generalization

The optimized reaction conditions were applied to the coupling of dibromide **29** with a set of different *N*-tosylhydrazones **30** to establish the scope of the reaction (Scheme 2.20). Thus, a wide number of fluorenes **31** were obtained with excellent to moderate yields through the reactions with N-tosylhydrazones derived from aromatic aldehydes bearing both electron-donating (**31c**, **31d** and **31j**) or electron-withdrawing (**31b** and **31g**) functional groups, as well as heterocycles **31k**. Moreover, *ortho*-substitution is also tolerated, as represented by the highly sterically hindered **31j**. The *N*-tosylhydrazone of *trans*-*p*-methoxycinnamaldehyde provided the 2-propenyl-1-ylidene-9*H*-fluorene **31h** in excellent yield. Finally, the reaction was also attempted with the *N*-tosylhydrazone derived from 4-methoxyacetophenone, leading to the fluorene featuring a tetrasubstituted double bond **31l**.



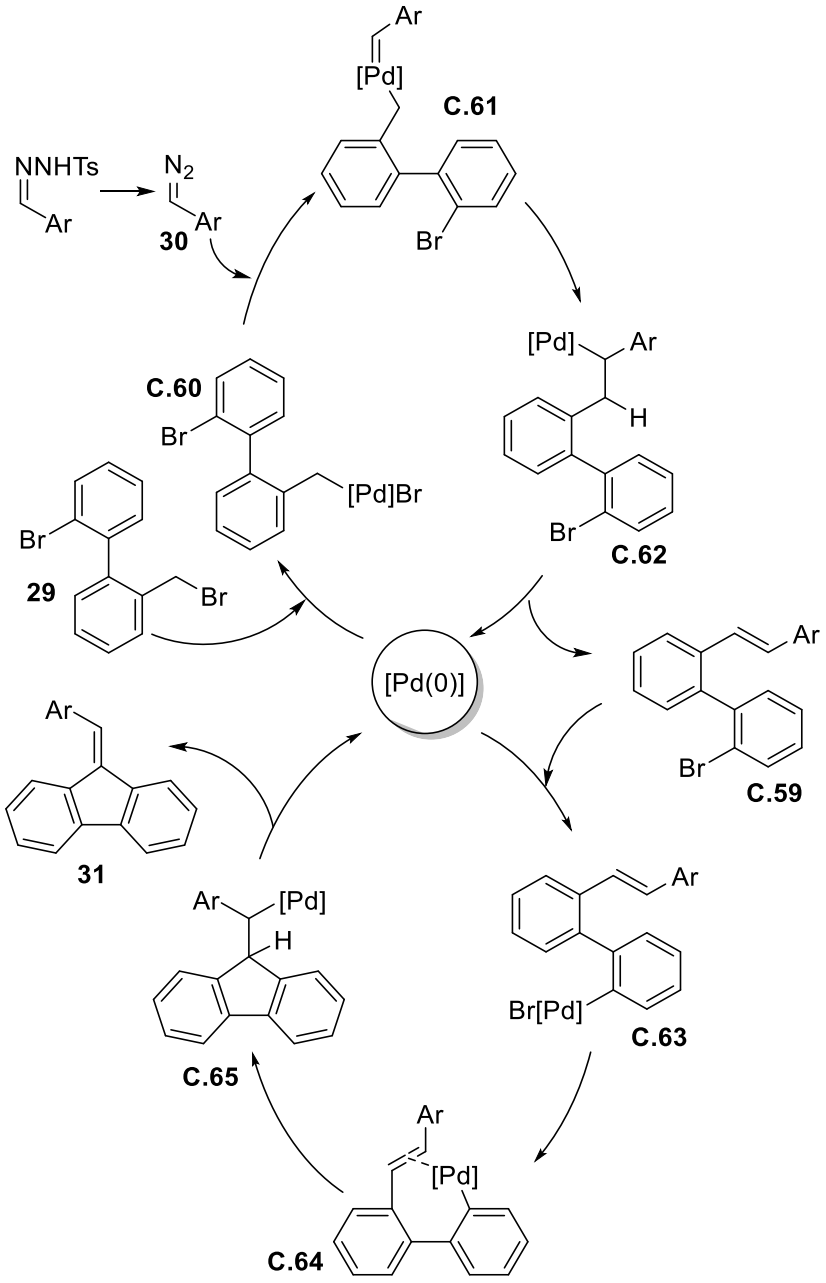
Scheme 2.20. Pd-catalyzed reaction of dibromide **29** with *N*-tosylhydrazones **30** for the synthesis of 9-methylene-9*H*-fluorenes **31**.

Next, the cascade reaction was applied to diphenyl ether **33**, which should provide xanthenes **34**, after the cross-coupling/6-*exo*-trig Heck cyclization. However, under the optimized experimental conditions described above, the reaction furnished the intermediate stilbene in which the cross-coupling reaction with the *N*-tosylhydrazone, but not the Heck reaction, had taken place. After some experimentation, we observed that the employment of a mixture of LiO*t*Bu (3 equiv) and NaO*t*Bu (3 equiv) as base combination allowed for the complete transformation into the desired xanthenes **34**. Under these conditions, the reaction showed a scope similar to that for the syntheses of fluorenes **31**, including *N*-tosylhydrazones derived from aromatic aldehydes featuring a variety of functional groups (Scheme 2.21).



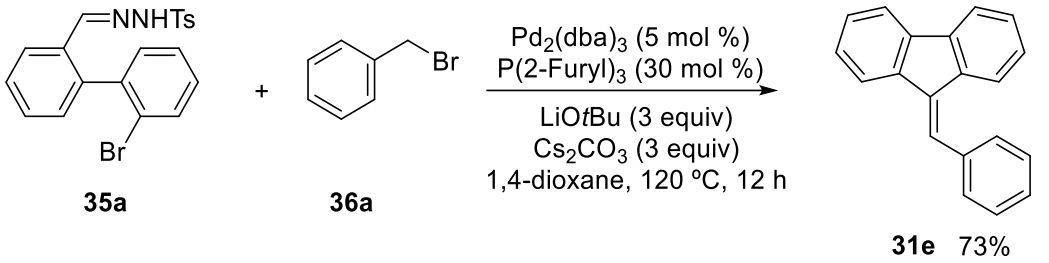
Scheme 2.21. Pd-catalyzed synthesis of 9-benzylidene-9*H*-xantenes **34** by reaction of dibromide **33** with *N*-tosylhydrazones **30**.

The mechanism proposed for the Pd-catalyzed auto-tandem reactions involves two catalytic cycles promoted for the same catalyst. The first catalytic process is based on the Pd-catalyzed cross-coupling between benzyl bromides and tosylhydrazones. In this manner, after the oxidative addition of the dibromide **29** to the Pd(0), the coordination of the diazo compound provides the palladium carbene **C.61**. Then, migratory insertion takes place to give the alkylpalladium species **C.62**, which upon β-hydride elimination generates the stilbene intermediate **C.59**. At this point, stilbene **C.59** enters in the second catalytic cycle through the oxidative addition of the C(Ar)-Br to the Pd(0) catalyst. Then 5-*exo*-trig carbopalladation, followed by another β-hydrogen elimination leads to the final fluorene **31** (Scheme 2.22).



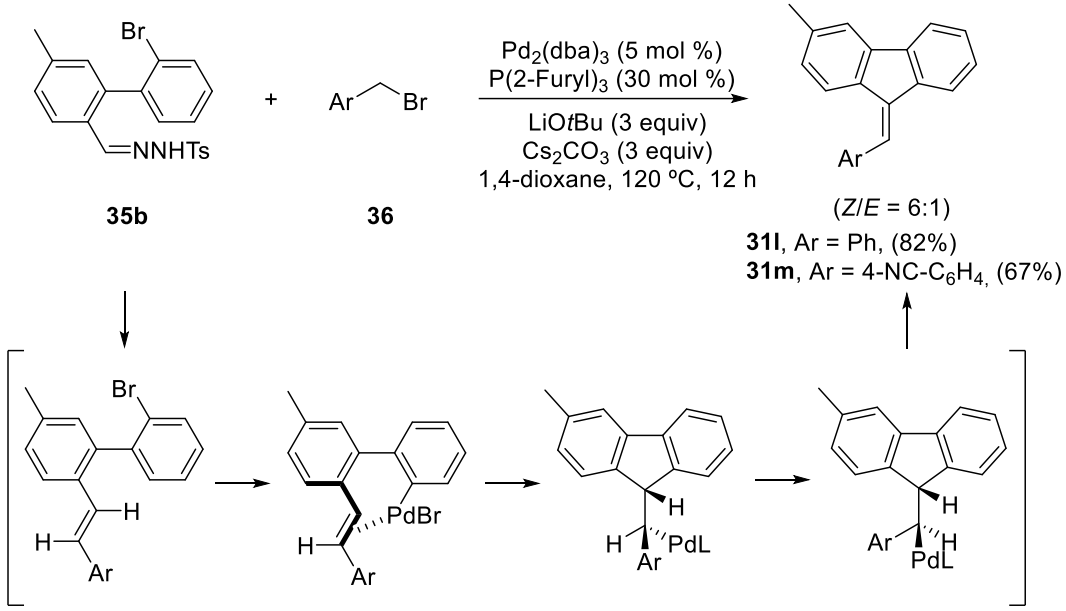
Scheme 2.22. Mechanistic proposal for the Pd-catalyzed auto-tandem cyclization employing *N*-tosylhydrazone

Interestingly, the same intermediate stilbene **C.59** could be reached by exchanging the positions of the reactive functional groups. Indeed, when the reaction of *N*-tosylhydrazone **35a** and the benzyl bromide **36a** was conducted under the conditions described in Scheme 2.18, the 9-methylene-9*H*-fluorene **31e** was obtained in nearly identical yield compared to the original reaction employing dibromide **29** and the *N*-tosylhydrazone of benzaldehyde (Scheme 2.23).



Scheme 2.23. Synthesis of 9-methylene-9*H*-fluorene **31e** through the same reaction from different starting materials.

The possibility of synthesizing the same products through the same type of reaction but from different starting materials is very interesting, since it may enable access to a wide variety of structures depending on the availability of the coupling partners. In particular, *N*-tosylhydrazones **35** featuring additional substitution on the aromatic rings are readily available and have been previously employed by Alami et al. in the Cu-catalyzed synthesis of 9*H*-fluorene-9-amines (Scheme 2.15).[166] Thus, we turned our attention to *N*-tosylhydrazone **35b** as a platform to check the stereoselectivity of the cascade reaction. As presented in the Scheme 2.24, the reaction between **35b** and benzyl bromide **36** provided the nonsymmetrically substituted 9-methylene-9*H*-fluorenes **31l** and **31m** as a 6:1 mixture of *Z*/*E*-diastereoisimers.

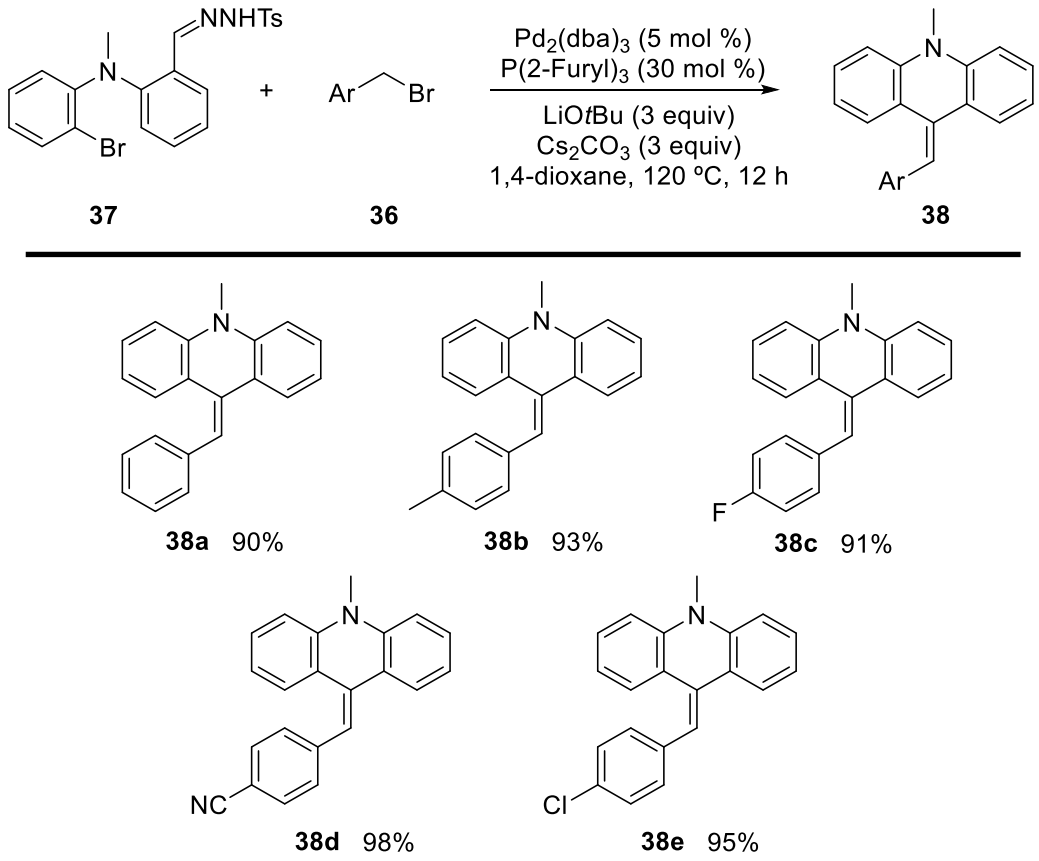


Scheme 2.24. Stereoselective synthesis of nonsymmetrically substituted 9-methylene-9*H*-fluorenes **31**.

The major isomer corresponds to the one expected considering a *syn*-carbopalladation followed by a *syn*-β-hydrogen elimination (stereochemistry was confirmed by 2D-NMR experiments). It must be noted that 9-methylene-9*H*-fluorenes **31** have been reported to undergo slow *Z*/*E* isomerization upon heating in the presence of Pd catalysts;[169] thus, the presence of a minor amount of the *E* isomer can be explained considering partial isomerization under the reaction conditions (Scheme 2.24).

[169] a) N. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2008**, *130*, 5636–5637; b) N. Chernyak, V. Gevorgyan, *Adv. Synth. Catal.* **2009**, *351*, 1101–1114.

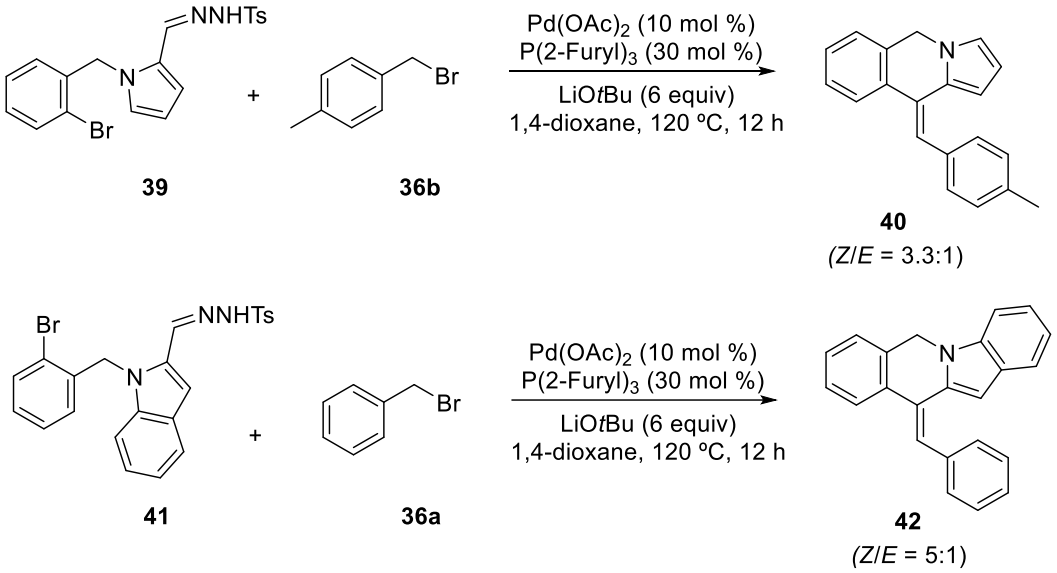
This approach was then applied for the preparation of 9-benzylidene-9,10-dihydroacridines **38** from easily available *N*,*N*-diarylaniline **37** and benzyl bromides **36**. The reaction conditions established for the synthesis of 9-methylene-9*H*-fluorenes **31**, involving the LiO*t*Bu/Cs_2CO_3 combination, were most appropiate for these transformations. Again, the examples selected include benzyl bromides bearing either electron-donating or electron-withdrawing functional groups, and led to the generation of this important class of condensed heterocycles[170] in nearly quantitative yields (Scheme 2.25).



Scheme 2.25. Synthesis of 9-methylene-9,10-dihydroacreidines **38** by reaction of benzyl bromides 36 with *N*-tosylhydrazone **37**.

[170] L. F. M. L. Ciscato, F. H. Bartoloni, D. Weiss, R. Beckert, W. J. Baader, *J. Org. Chem.* **2010**, *75*, 6574–6580.

Finally, to further illustrate the versatility of the auto-tandem process, we chose the heterocyclic *N*-tosylhydrazones **39** and **41** as substrates for the C-C/C=C cascade reaction with benzyl bromides, which would lead to pyrroloisoquinoline and indoloisoquinoline derivatives, respectively. In these cases the employment of $Pd(OAc)_2$ as Pd source provided better results. Additionally, the participation of two different bases did not result in any reaction improvement. In this manner, dihydropyrrolo[1,2-*b*]isoquinoline **40** and dihydroindolo[1,2-*b*]isoquinoline **42** were obtained with moderate stereoselectivity. In both cases, the major isomer corresponded to that expected considering the *syn*-β-hydride elimination on the last step of the cascade process. These results demonstrate the wide versatility of this approach for the preparation of polyaromatic carbo- and heterocyclic structures by combining in the proper way the three reactive elements required for the Pd-catalyzed cascade: the aromatic bromide, the benzyl bromide and the *N*-tosylhydrazone (Scheme 2.26).



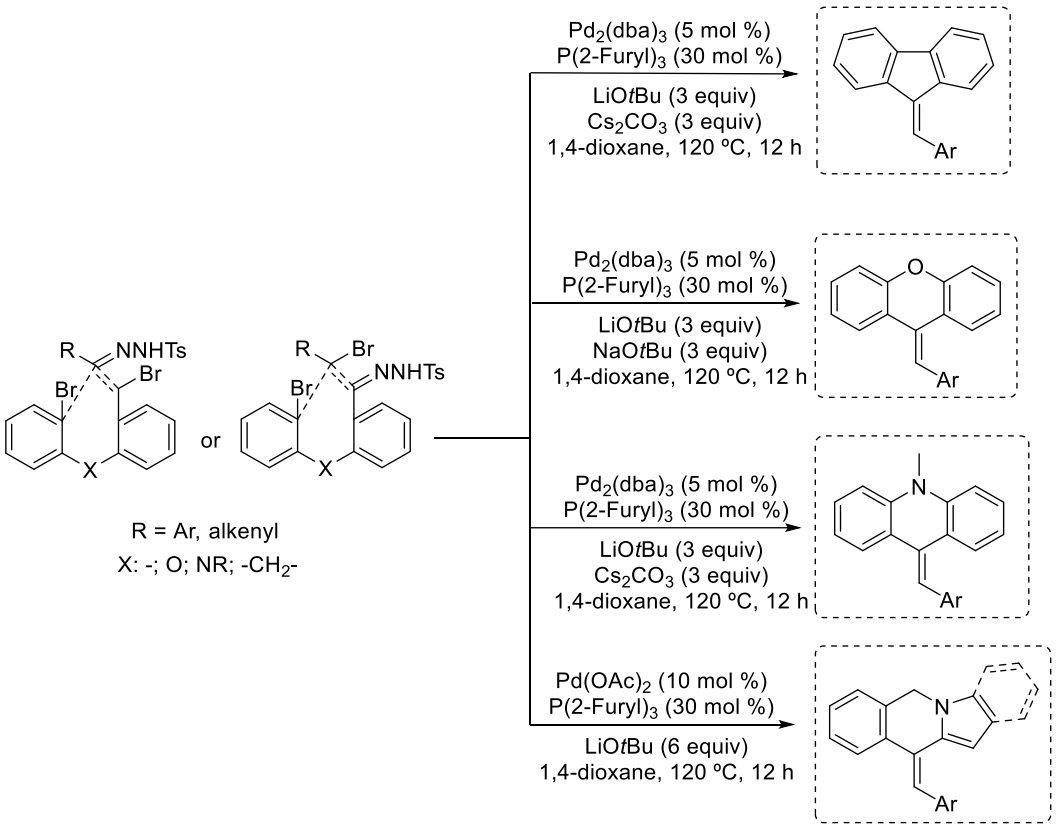
Scheme 2.26. Synthesis of pyrroloisoquinoline **40** and indoloisoquinoline derivatives **42**.

2.3 Conclusions

In this chapter, it has been discovered a new type of Pd-catalyzed auto-tandem cyclization that proceeds by formation of a C-C single bond and a C-C double bond on the same carbon atom. The cascade process includes the cross-coupling reaction between *N*-tosylhydrazones and benzyl bromides followed by an intramolecular Heck reaction. Noteworthy, these are the first examples in which the cross-coupling reaction between *N*-tosylhydrazones and benzyl bromides has been implemented within a cascade process.

The auto-tandem cyclization occurs by reaction of a bifunctional coupling partner with a monofunctionalized system. Interestingly, two different arrangements for the reactive groups are possible, greatly enhancing the synthetic possibilities of the reaction. The versatility has been illustrated with the synthesis of a variety of carbo- and heterocyclic structures employing the same synthetic strategy, including fluorene, xantene, acridine, pyrroloisoquinoline and insoloisoquinoline derivatives.

2.4 Graphic summary



Chapter 3

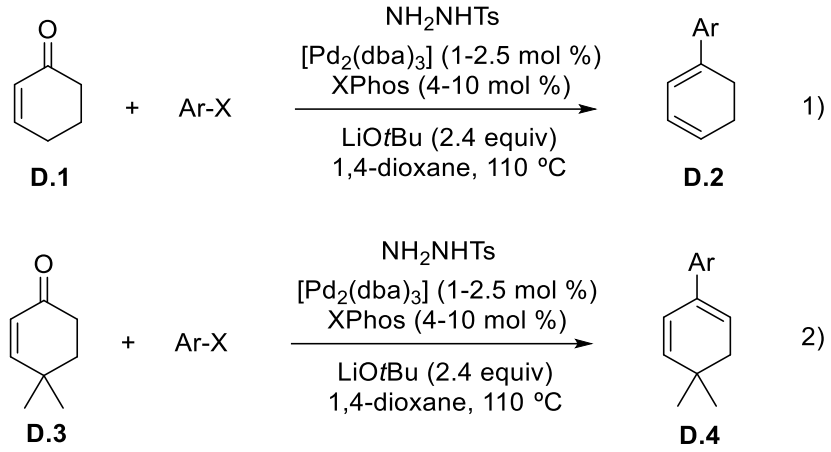
Synthesis of highly substituted polyenes by Pd-catalyzed cross-coupling of sterically encumbered alkenyl bromides and *N*-tosylhydrazones

3.1 Introduction

3.1.1 Synthesis of conjugated dienes by Pd-catalyzed cross-coupling with tosylhydrazones

As it has been shown in the previous sections, the development of the Pd-catalyzed cross-coupling reaction with *N*-tosylhydrazones has been highly fructiferous in different areas. Herein, it will be introduced those Pd-catalyzed cross-couplings with sulfonylhydrazones in which conjugated dienes are obtained as products.

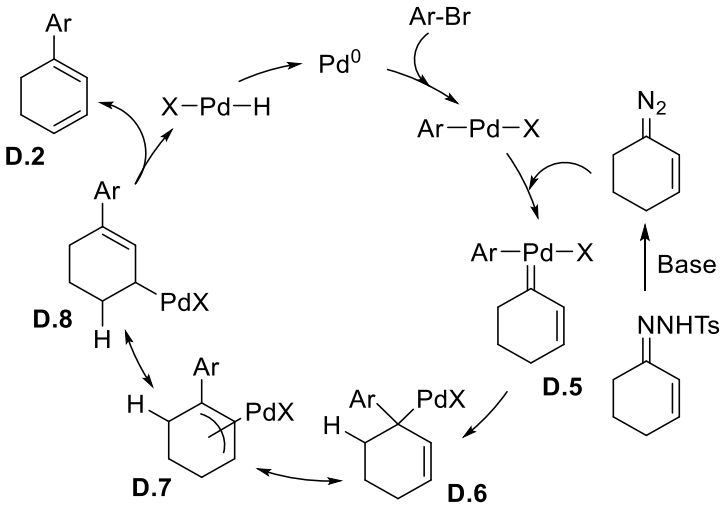
In 2010, our research group studied the synthesis of conjugated dienes employing α,β-unsaturated carbonyls and aryl bromides under the typical one-pot reaciontion conditions. Quite surprinsingly, when the starting ketone features a hydrogen atom at the ϒ position **D.1**, the reaction led to the unexpected linear conjugated dienes **D.2** (Scheme 3.1, equation 1). However, with ketones without ϒ-hydrogens **D.3**, the cross-conjugated dienes **D.4** were obtained through a typical β-hydrogen elimination (Scheme 3.1, equation 2).[171]



Scheme 3.1. Synthesis of conjugated dienes through Pd-catalyzed cross-coupling reaction with *N*-tosylhydrazones.

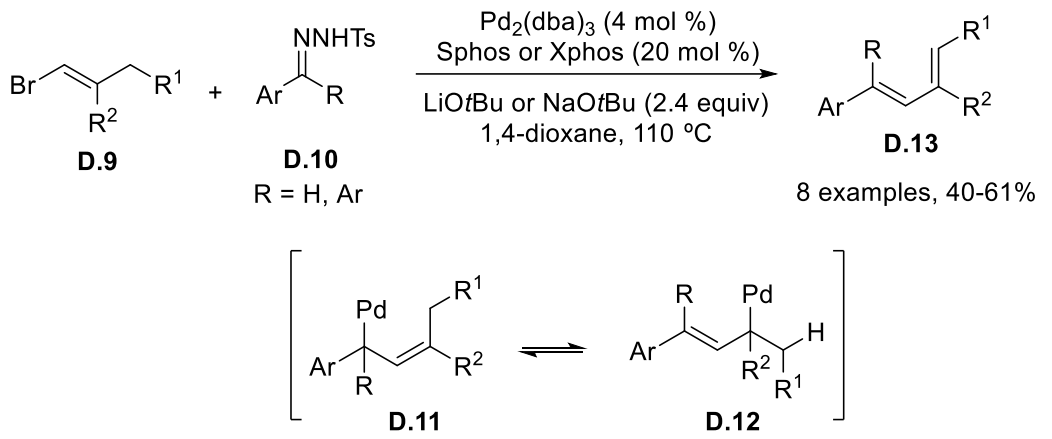
[171] J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Adv. Synth. Catal.* **2010**, *352*, 3235–3240.

The formation of the linear conjugated systems was rationalized in terms of a formal δ-hydride elimination. The initially formed σ-allyl palladium complex **D.6** can evolve through the η^3-allylpalladium intermediate **D.7** to a new σ-allyl palladium complex **D.8**, which can then undergo β-hydride elimination to give the final conjugated diene **D.2** (Scheme 3.2).



Scheme 3.2. Mechanistic proposal for the synthesis of linear conjugated dienes.

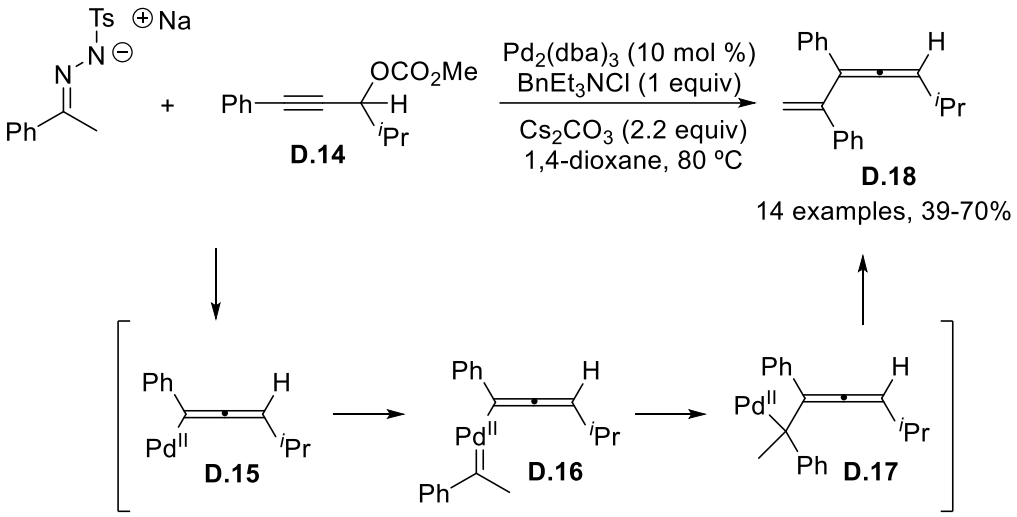
In the same seminal publication, it was shown the employment of alkenyl halides as electrophiles in the Pd-catalyzed cross-coupling reaction with *N*-tosylhydrazones.[171] Thus, the reaction between alkenyl bromides **D.9** and tosylhydrazones derived from non-enolizable carbonyl compounds **D.10** proceeded through a formal δ-hydride elimination giving the conjugated dienes **D.13**, although only in moderate yields. A possible explanation for this unusual transformation implies that the allyl palladium intermediate **D.11** evolves through a [1,3]-palladatropic rearrangement to form the palladium complex **D.12**. Then, a β-hydride elimination would provide the conjugated diene (Scheme 3.3).



Scheme 3.3. Synthesis of conjugated dienes through Pd-catalyzed cross-coupling reaction between alkenyl halides and *N*-tosylhydrazones.

Noteworthy, these are the only example of the synthesis of conjugated dienes by coupling of *N*-tosylhydrazones and alkenyl halides. Nevertheless, some other limited examples have been uncovered of the synthesis of conjugated dienes by cross-coupling with sulfonylhydrazones.

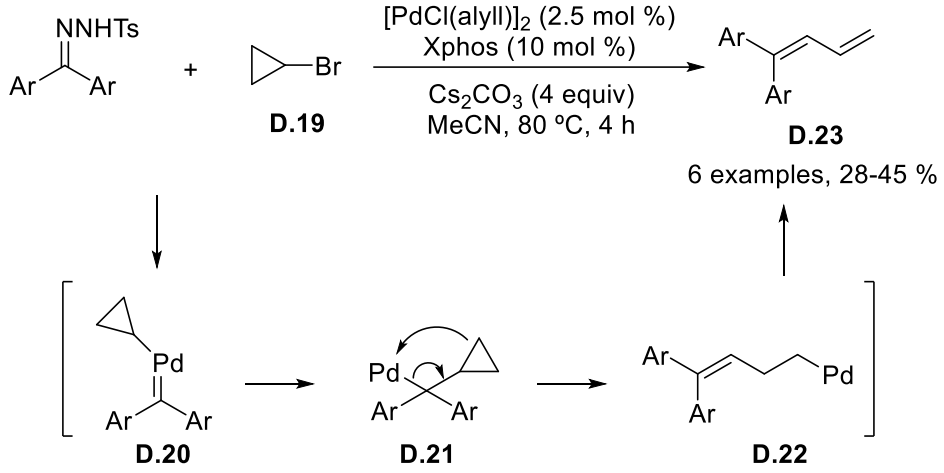
In 2011, Liang and co-workers presented an interesting Pd-catalyzed cross-coupling reaction between propargylic carbonates **D.14** and tosylhydrazone salts.[172] This reaction promoted by Pd_2dba_3 as catalyst and $BnEt_3NCl$ as PTC afforded multisubstituted vinylallenes **D.18** with moderate yields. The proposed mechanism of this transformation is based on the generation of the allenylpalladium complex **D.15** by reaction of the propargyl carbonate with the Pd(0) catalyst. Next, the incorporation of the sulfonylhydrazone gives rise to the allenylpalladium carbene **D.16**, which undergoes a migratory insertion to give the allylpalladium species **D.17**. Finally a β-hydride elimination takes place to release the 1,3,4-triene **D.18** (Scheme 3.4).



Scheme 3.4. Migratory insertion of allenyl group for the synthesis of multisubstituted vinylallenes.

[172] Z.-S. Chen, X.-H. Duan, L.-Y. Wu, S. Ali, K.-G. Ji, P.-X. Zhou, X.-Y. Liu, Y.-M. Liang, *Chem. Eur. J.* **2011**, *17*, 6918–6921.

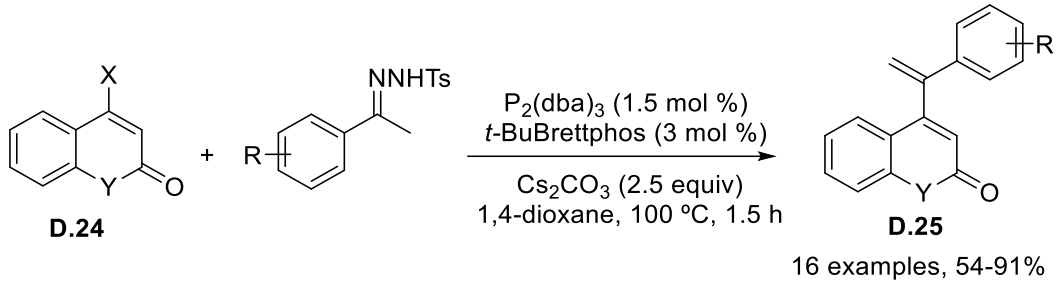
In 2012, cyclopropyl bromides **D.19** were incorporated as electrophiles in the Pd-catalyzed cross-coupling reaction with *N*-tosylhydrazones by Wang and co-workers.[173] The employment of this new type of electrophile enabled the access to 1,3-dienes **D.23** *via* migratory insertion of the cyclopropyl group to generate the cyclopropylmethyl palladium intermediate **D.21**. This species evolves through ring-opening rearrangement to provide the alkyl palladium complex **D.22**, which undergoes a β-hydride elimination to form the final diene **D.23** (Scheme 3.5).



Scheme 3.5. Synthesis of 1,4-dienes by employment of cyclopropyl bromides in Pd-catalyzed cross-coupling with *N*-tosylhydrazones.

[173] L. Zhou, F. Ye, Y. Zhang, J. Wang, *Org. Lett.* **2012**, *14*, 922–925.

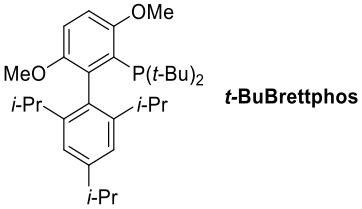
Very recently, Chikhalia and co-workers reported the Pd-catalyzed cross-coupling reaction between *N*-tosylhydrazones derived from ketones and benzofused heterocyclic alkenyl tosylates and mesylates **D.24**.[174] The employment of these less activated alkenyl electrophiles provided a new synthetic pathway to obtain 1,3-dienes **D.25**. Noteworthy, it was found that the use of the sterically hindered ligand *t*-BuBrettphos[175] was crucial for the appropriate operation of the reaction (Scheme 3.6).



Scheme 3.6. Pd-catalyzed cross-coupling reaction between alkenyl tosylates or mesylates and *N*-tosylhydrazones.

[174] P. K. Patel, J. P. Dalvadi, K. H. Chikhalia, *RSC Adv.* **2014**, *4*, 55354–55361.

[175] 2-(Di-*tert*-butylphosphino)-2',4',6'- triisopropyl-3,6-dimethoxy-1,1'-biphenyl (*t*-BuBrettphos)



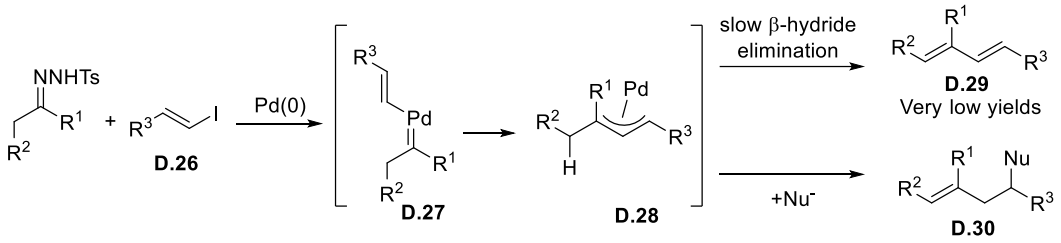
***t*-BuBrettphos**

3.2 Results and discussions

3.2.1 Objective and general considerations

As it has been shown in the previous introduction, the application of the Pd-catalyzed cross-coupling reaction with *N*-tosylhydrazones involving alkenyl halides for the synthesis of dienes remains almost unexplored. As previously shown, our research group reported several years ago some limited examples on the couplings of certain alkenyl halides with arylaldehyde tosylhydrazones, which led to 1,3-dienes through a non-conventional catalytic cycle that involved a formal δ-hydride elimination (Scheme 3.3).[171]

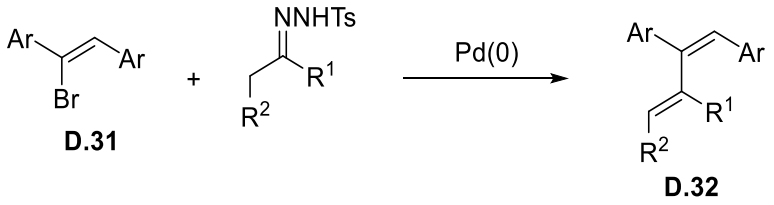
On the other hand, Van Vranken, in the context of the study of the elegant cascade carbenylative amination of alkenyl iodides showed that the η^3-allylpalladium intermediates **D.28** generated upon migratory insertion of the carbene ligand on the palladium-alkenyl bond on intermediate **D.27**, do not undergo fast β-hydride elimination. Instead, nucleophilic attack at the less hindered site of the η^3-allylpalladium complex **D.28** takes place, giving rise to the product of the cascade reaction **D.30**. However, in the absence of an external nucleophile, the catalytic cycle is slowed down and uncatalyzed decomposition of the *N*-tosylhydrazones is observed, leading to very low yields of the coupling products **D.29** (Scheme 3.7).[176]



Scheme 3.7. Possible reaction pathways of three-component cascade processes between *N*-tosylhydrazones and alkenyl iodides.

[176] I. D. U. A. Premachandra, T. A. Nguyen, C. Shen, E. S. Gutman, D. L. Van Vranken, *Org. Lett.* **2015**, *17*, 5464–5467.

In this context, we decided to explore the cross-couplings of *N*-tosylhydrazones with sterically encumbered alkenyl halides. Taking into consideration these precedents and the work by Chikhalia described above,[174] we reasoned that a sterically congested environment around the metal might unstabilize the η^3-allylpalladium complex and favour the β-hydride elimination. Thus, we envisioned that choosing highly substituted alkenyl halides **D.31**, the appropriate sterically congested environment could be provided enabling the synthesis of polysubstituted 1,3-dienes **D.32** (Scheme 3.8).

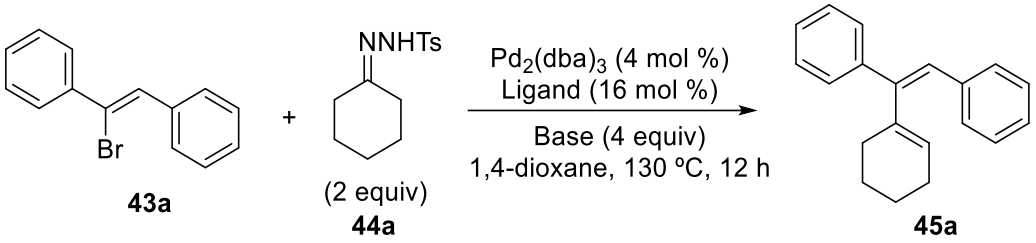


Scheme 3.8. Reaction proposal for the coupling of alkenyl halides and *N*-tosylhydrazones.

3.2.2 Optimization

Thus, we initiated our study with the reaction between (*Z*)(1-bromoethene-1,2-diyl)dibenzene **43a** and cyclohexanone tosylhydrazone **44a**. Several reaction conditions and catalytic systems were examined (Table 3.1) to discover that the diene **45a** could be best obtained employing a combination of $Pd_2(dba)_3$ (4 mol %) and Xphos (16 mol %) with Li*O*t*Bu as the base in 1,4-dioxane as solvent at 130 °C in a sealed tube (Table 3.1, entry 3). Lower catalyst loading (Table 3.1, entry 7) led to the recovery of substantial amounts of the starting bromide while almost no reaction product was obtained at lower temperature (Table 3.1, entry 9). It was also observed that P(2-furyl)$_3$ and PPh_3 promoted the reaction with acceptable yields respectively (Table 3.1, entries 1 and 2). Otherwise, the employment of P(*o*-Tol)$_3$, BINAP or Xantphos as ligands lead to the complete recovery of the starting bromoalkene (Table 3.1, entries 4-6). Other bases were tested instead of Li*O*t*Bu, with considerable decrease in the reaction yield (Table 3.1, entries 10 and 11).

Table 3.1. Optimization of the reaction conditions for the cross-coupling between bromoalkene **43a** and *N*-tosylhydrazone **44a**.

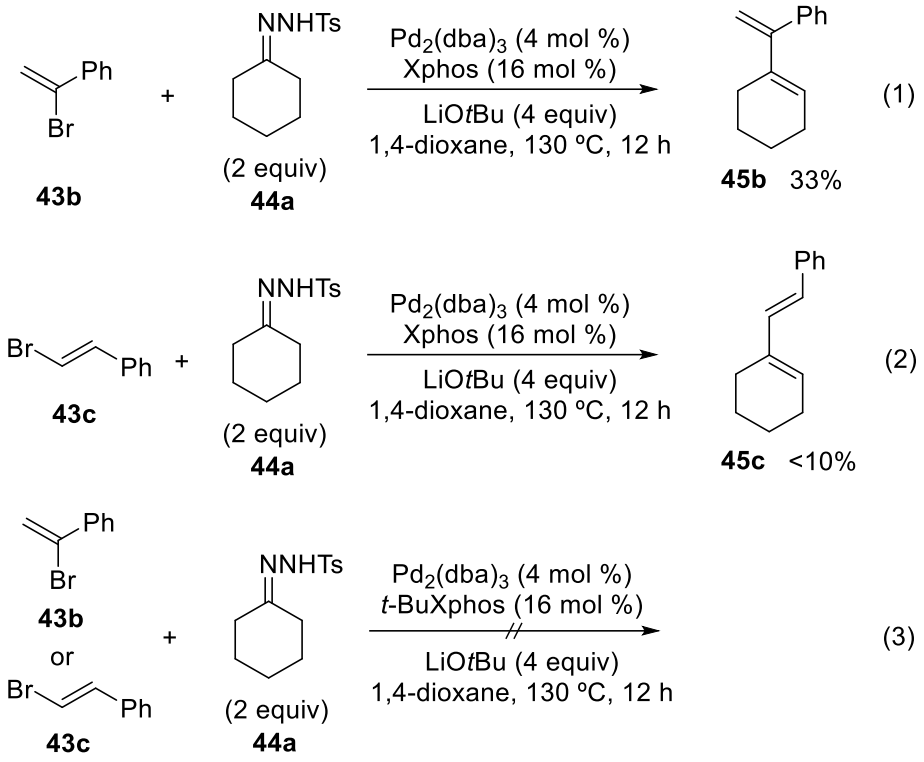


43a **44a** **45a**

Entry	Base	Ligand	Yield (%)[a]
1	LiO*t*Bu	P(2-furyl)$_3$[b]	50
2	LiO*t*Bu	PPh$_3$[b]	70
3	LiO*t*Bu	Xphos	79
4	LiO*t*Bu	P(*o*-Tol)$_3$[b]	0
5	LiO*t*Bu	BINAP	0
6	LiO*t*Bu	Xantphos	0
7[c]	LiO*t*Bu	Xphos	35
8[d]	LiO*t*Bu	Xphos	46
9[e]	LiO*t*Bu	Xphos	<10
10	Cs_2CO_3	Xphos	<10
11	K_2CO_3	Xphos	36

[a] Isolated yields after flash chromatography. [b] A 3:1 Ligand/Pd ratio was used. [c] $Pd_2(dba)_3$ (2 mol %) and Xphos (8 mol %). [d] *N*-tosylhydrazone **44a** (1.2 equiv) and LiO*t*Bu (3.2 equiv). [e] carried out at 110 °C.

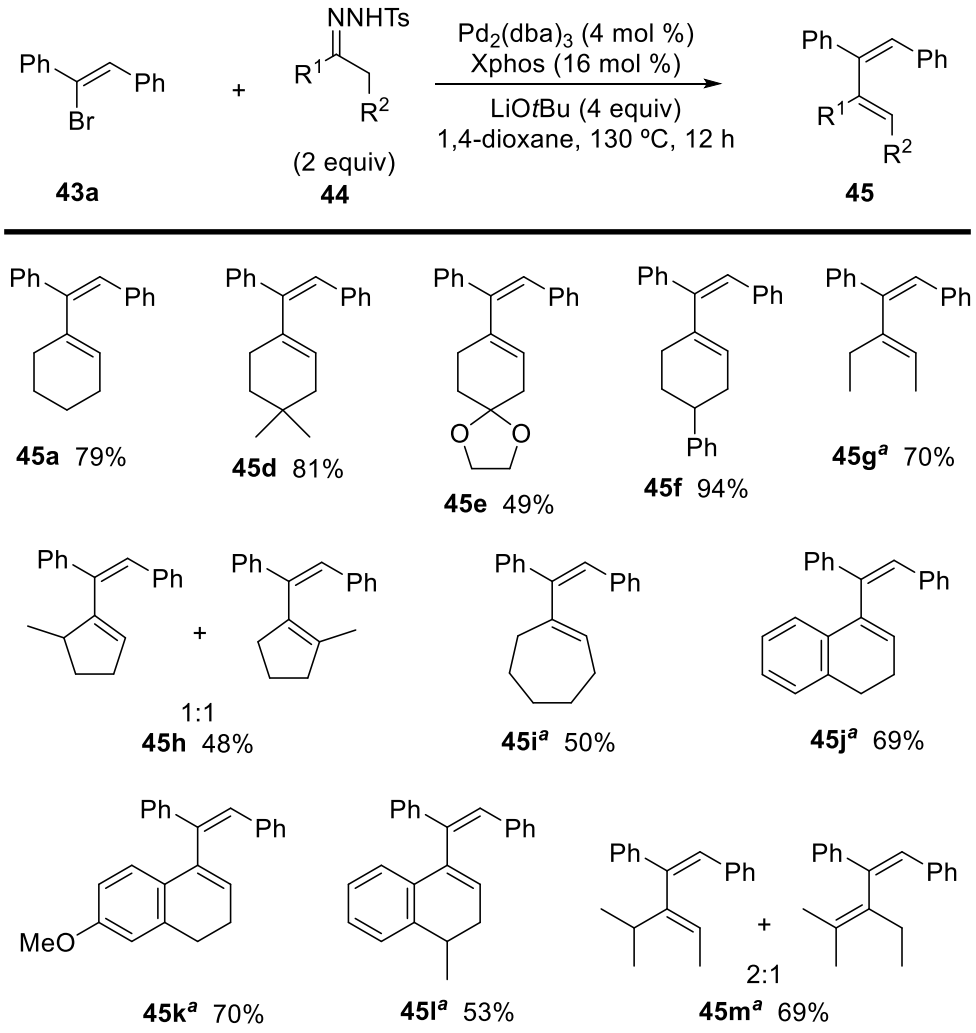
In contrast with these results, when the same reaction was conducted employing α-bromostyrene **43b**, the expected diene **45b** was obtained in a quite poor 33% isolated yield (Scheme 3.9, equation 1). Moreover, in the reaction with β-bromostyrene **43c** that features the lowest steric hindrance of the examples examined, although the expected diene could be detected by GC/MS of the reaction crude, very low isolated yield was finally obtained (Scheme 3.9, equation 2). This observation tend to indicate that the coupling reaction is favoured in dienes that generate steric congestion around the metal. With this idea, we decided to examine the coupling of **43b** and **43c** with bulkier ligands. Unfortunately, the employment *t*-BuXphos did not provide the expected coupling products (Scheme 3.9, equation 3).



Scheme 3.9. Tests to determine the importance of the sterically encumbered environment in the alkenyl bromide.

3.2.3 Generalization

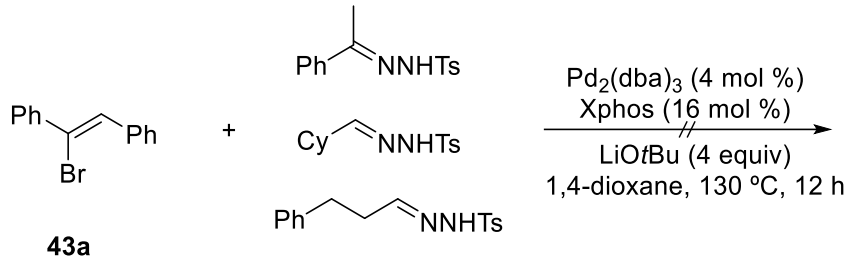
The optimized reaction conditions were applied to the coupling of alkenyl bromide **43a** with a set of different *N*-tosylhydrazones **44** to establish the scope of the reaction (Scheme 3.10). Thus, the substituted 1,3-dienes **45** were obtained with excellent to moderate yields for the reactions with cyclic *N*-tosylhydrazones derived from cyclohexanones (**45a-f**), cyclopentatone (**3h**), cycloheptanone (**3i**) and tetralones (**3j-l**). Also the *N*-tosylhydrazone of 3-pentanone provided the coupling product in excellent yield (**45g**). Moreover, the employment of unsymmetrically substituted *N*-tosylhydrazones led to a mixture of regioisomers derived from a non-selective β-hydride elimination step (**45h**, **45m**).



[a] N-tosylhydrazone 2 (1.2 rquiv) and LiO*t*Bu (3.2 equiv)

Scheme 3.10. 1,3-Dienes prepared by Pd-catalyzed cross-coupling between alkenyl bromide **43a** and different tosylhydrazones **44**.

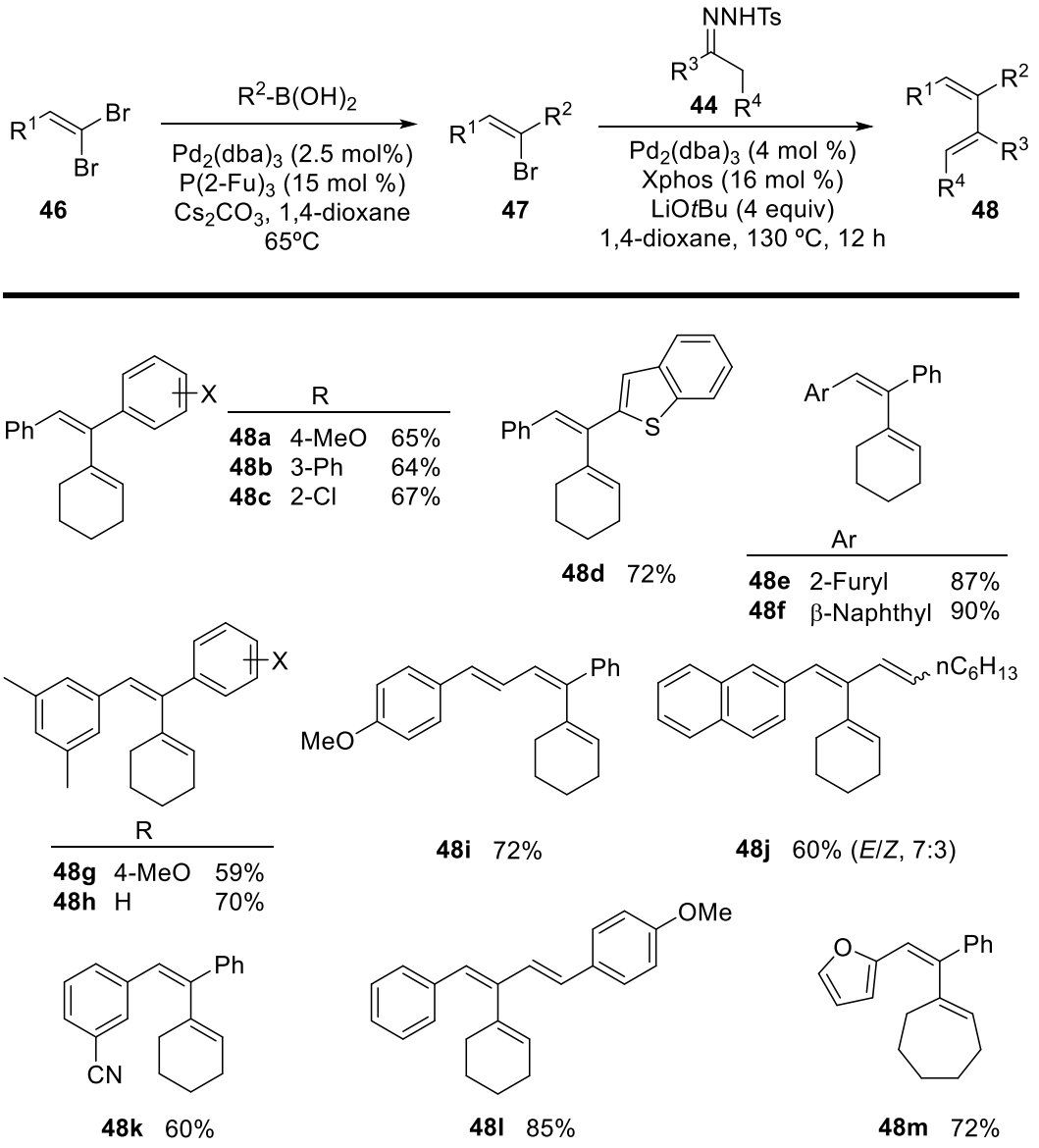
Tosylhydrazones derived from acetophenone or aliphatic aldehydes failed to provide the expected dienes in a synthetically useful yield, although small amounts of the dienes, together with several unidentified products were detected by GC/MS (Scheme 3.11).



Scheme 3.11. No reaction product observed with tosylhydrazones derived from acetophenone and aliphatic aldehydes.

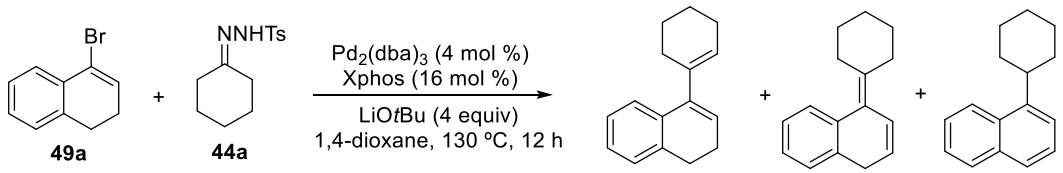
Next, we decided to apply the coupling reaction to different trisubstituted bromoalkenes. Stereodefined trisubstituted bromoalkenes **47** can be efficiently prepared by the stereoselective cross-coupling of 1,1-dibromoolefins **46** with boronic acids (Scheme 3.12).[177] Following the Suzuki coupling, a set of trisubstituted bromoalkenes **47** was prepared, and the cross coupling reactions with *N*-tosylhydrazones **44** were examined. The results presented in Scheme 3.13 show that the scope of the reaction is very broad allowing for the preparation of a diversity of sterically encumbered dienes **48**, and also the synthesis of linear-conjugated (**48i**) and cross-conjugated (**48j** and **48l**) trienes. The reaction proceeded successfully employing different functional groups in one (**48a-c** and **48k**) or both phenyl rings (**48g-h**). It was also observed that the reaction generated the expected dienes when other aromatic (**48f**) or heteraromatic (**48d-e**) rings where used instead benzene. The reaction was also compatible with the *N*-tosylhydrazone of cycloheptanone, which led to the corresponding diene **48m**.

[177] W.Shen, *Synlett,* **2000**, 737–739.



Scheme 3.12. Structurally diverse and stereodefined dienes **48** prepared by sequential Pd-catalyzed Suzuki and *N*-tosylhydrazone cross-coupling.

The reactions presented in Scheme 3.11 and 3.12 were restricted to the employment of (*Z*)-alkenyl bromides. To continue the study of the scope of the cross-coupling, we tested the reaction with bromides **49**, as representatives of trisubstituted (*E*)-alkenyl bromides. Bromides **49** could be efficiently prepared also from the corresponding *N*-tosylhydrazones following a procedure recently reported by Prabhu et al.[178] However, the reaction of **49a** with *N*-tosylhydrazone **44a** proceeded sluggishly, leading to a mixture of various isomeric coupling products differing in the position of the double bonds, that could not be speared (Scheme 3.13).



Scheme 3.13. First approach for the cross-coupling between (*E*)-alkenyl bromides and *N*-tosylhydraones.

Gratifyingly, when the coupling reaction was conducted with the tetralone derived *N*-tosylhydrazones **44h-j**, the expected 3,3',4,4'-tetrahydro-1,1'-binaphthalenes **50** were obtained in good yields. (Scheme 3.15). It is worth noting the synthetic interest of dienes **50** that have been previously used as precursors of substituted binaphthyls, as well as dienes in [4+2] cycloadditions, oriented to the preparation of polyclyclic aromatic hydrocarbons, phtalocyanines and helicenes with applications in materials chemistry,[179] and even in graphene functionalization.[180] Noteworthy, the methods available for their synthesis are based on the dimerization of the corresponding tetralone, and thus, restricted to symmetric systems. However, our methodology enables the selective synthesis of the non-symmetrically substituted systems in a straightforward manner from two different tetralones through their tosylhydrazones (Scheme 3.14).

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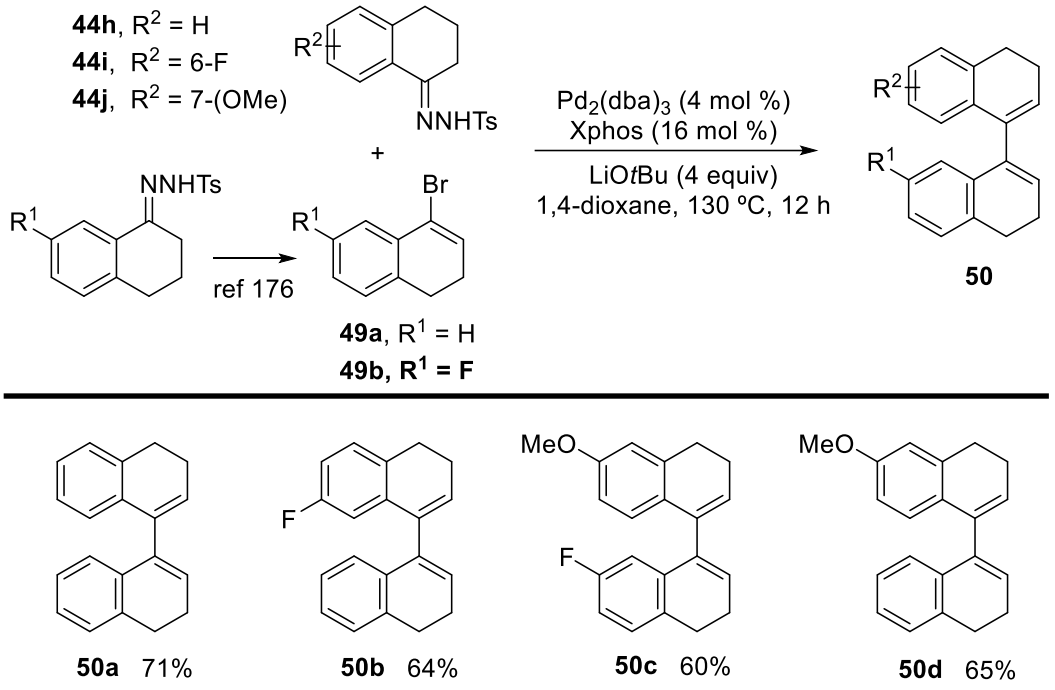
[178] D. P. Ojha, K. R. Prabhu, *Org. Lett.* **2015**, *17*, 18–21.

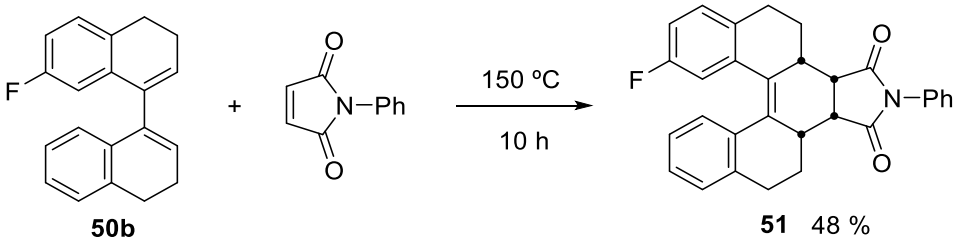
[179] a) L. Minuti, A. Taticchi, A. Marrocchi, E. Gacs-Baitz, *Tetrahedron* **1997**, *53*, 6873–6878; b) T. Sooksimuang, B. K. Mandal, *J. Org. Chem.* **2003**, *68*, 652–655; c) B. K. Mandal, T. Sooksimuang, C.-H. Lee, R. Wang, *J. Porphyrins Phthalocyanines*, **2006**, *10*, 140–146; d) J.-D. Chen, H.-Y. Lu, C.-F. Chen, *Chem. Eur. J.* **2010**, *16*, 11843–11846; e) Y. Shen, H.-Y. Lu, C.-F. Chen, *Angew. Chemie Int. Ed.* **2014**, *53*, 4648–4651; f) X.-J. Li, M. Li, H.-Y. Lu, C.-F. Chen, *Org. Biomol. Chem.* **2015**, *13*, 7628–7632; g) K. Sbargoud, M. Mamada, J. Marrot, S. Tokito, A. Yassar, M. Frigoli, *Chem. Sci.* **2015**, *6*, 3402–3409.

[180] J. Li, M. Li, L.-L. Zhou, S.-Y. Lang, H.-Y. Lu, D. Wang, C.-F. Chen, L.-J. Wan, *J. Am. Chem. Soc.* **2016**, *138*, 7448–7451.



Scheme 3.14. Synthesis of 3,3',4,4'-tetrahydro-1,1'-binaphthalenes **50** by reaction of (*E*)-alkenyl bromides with *N*-tosylhydrazones derived from tetralone.

As an example of the usefulness of these dienes, reaction of **50b** with *N*-phenylmaileimide led to the unprecedented non-symmetrically substituted pentahelicene precursor **51** (Scheme 3.15).



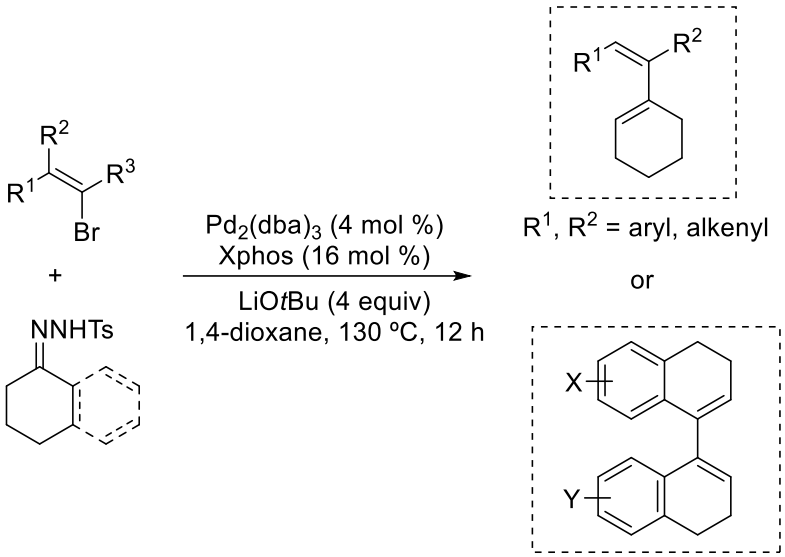
Scheme 3.15. Application of binaphtalenes **50b** in the synthesis of the non-symmetric pentahelicene precursor **51**.

3.3 Conclusions

In this Chapter 3, it has been described the Pd-catalyzed cross-coupling of alkenyl bromides and *N*-tosylhydrazones as an efficient method for the preparation of a wide structural variety of conjugated dienes and polyenes. These results contribute to highlight the versatility of the already well developed Pd-catalyzed cross-coupling with *N*-sulfonylhydrazones by the incorporation of sterically congested alkenyl bromides as coupling partners. Moreover, the methodology presented allows the straightforward preparation of these class of poorly described polyenic systems.

As a demonstration of the synthetic usefulness of the reaction, new 3,3',4,4'-tetrahydro-1,1'-binaphtalenes were synthesized. Moreover, their utility in the preparation of complex polycyclic molecules through [4+2] cycloadditions was also shown.

3.4 Graphic summary



Conclusiones Generales

Como se ha mostrado en la presente Memoria, el desarrollo de nuevas reacciones de acoplamiento cruzado catalizadas por paladio con *N*-tosilhidrazonas sigue hoy en día suscitando un gran interés. En los últimos años, un amplio número de variables han sido incorporadas en la reacción original presentada por nuestro grupo de investigación en 2007. De entre todos los avances surgidos en este campo, cabe destacar especialmente la implementación de las reacciones en cascada.

En el Capítulo 1, se describe una nueva reacción de ciclación en cascada en la que se combina la reaccion de inserción de un carbeno de paladio generado a partir de una *N*-tosilhidrazona, con una reacción de Heck intramolecular para permitir una ciclación 5-*exo*-trig. En la Parte A de este capitulo, se utiliza esta novedosa transformación para sintetizar una amplia variedad de indanos, benzofuranos e indanonas. Por otro lado, en el Parte B se muestra la expansión de esta reacción para la preparación de heterociclos nitrogenados como son los índoles. Además, se observó que este proceso de ciclación en cascada podía promover ciclaciones 6-*endo*-trig empleando enaminonas en lugar de enaminas en el halogenuro inicial, para dar lugar a derivados de quinolina. De manera general es importante destacar que durante el transcurso de esta reacción son generados dos nuevos enlaces C-C sobre el mismo átomo de carbono hidrazónico.

En el Capítulo 2 se presenta una nueva reacción de ciclación auto-tandem que tiene lugar mediante el empleo de 2-bromo-2'-bromometilbifenilos. De este modo, una primera reacción de acoplamiento entre una tosilhidrazona y el bromuro bencílico proporciona un intermedio que incorpora la olefina resultante del acoplamiento. Seguidamente, una reacción de Heck intramolecular con el doble enlace generado en la reacción de acoplamiento, permite la ciclación final para dar lugar a fluorenos, xantenos, acridinas y a sistemas heterocíclicos benzofusionados. En este caso, es importante destacar que durante la reacción se generan dos enlace C-C/C=C en una única etapa sintética y en el mismo átomo hidrazónico.

Por último, en el Capítulo 3 se ha estudiado la reacción de acoplamiento cruzado catalizada por paladio entre *N*-tosilhidrazonas y halogenuros de alquenilo para generar dienos conjugados. Durante este estudio, se establecio como elemente clave para dar lugar a la β-eliminación de hidrogeno y por consiguiente a los productos finales, el empleo de halogenuros de alquenilo con entronos altamente congestionados. Esta nueva reaccion permitio la síntesis de dienes conjugados altamente funcionalizados de entre los que destacan los tetrahidrobinaftalenos, que permitieron la preparación de un precursor de pentaheliceno sustituido asimétricamente.

Experimental Section

E.1 General considerations

E.1.1 Reactions

Unless otherwise indicates, the Pd-catalyzed principal reactions of the different chapters were carried out under nitrogen atmosphere in carousel tubes or microwave glass vials. Carousel tubes were placed in a RR98030 12 place Carousel Reaction Station™ from Radleys Discovery Technologies, equipped with gas tight threaded caps with a valve, cooling reflux head system, and digital temperature controller. Microwave glass vials were sealed with their caps with septums and heated in a PEG bath on a stirring hot plate equipped with a temperature controller. The glassware was dried, evacuated and purged before its use.

E.1.2 Solvents

The solvents employed in the reactions under inert atmosphere were dried and distilled before their use according with the standard techniques[181] or through columns filled with active alumina, Innovative Technology, Pure Solv, model PS-400-7 (adapted system for toluene, acetonitrile, dimethylformamide, dichloromethane, hexane and tetrahydrofuran). The only exception was 1,4-dioxane, which was dried with sodium as dehydrating agent and distilled under nitrogen atmosphere.

E.1.3 Reagents

Commercial reagents such as Pd_2dba_3, ligands, aryl or benzyl halides, alcohols, anilines, boronic acids, carbonyl compounds and tosylhydrazide were purchased with the highest degree of accessible purity, and employed without previous purification. *N*-Tosylhydrazones were prepared from the corresponding carbonyl compounds and through previously described methodologies.[182]

[181] D.D. Perrin, W. L. F. Armarego, D. R. Perrin*, Purification of Laboratory Chemicals*, 2nd Ed, Pergamon Press, **1980**.

[182] V. K. Aggarwal, E. Alonso, I. Bae, G. Hynd, K. M. Lydon, M. J. Palmer, M. Patel, M. Porcelloni, J. Richardson, R. A. Stenson, J. R. Studley, J.-L. Vasse, C. L. Winn, *J. Am. Chem. Soc.* **2003**, *125*, 10926–10940.

Due to their hygroscopic character, commercial bases were purchased with the highest degree of accessible purity, dried under vacuum and stored in a flask purged with nitrogen.

E.1.4 Separation and purification

The purifications by flash chromatography were made employing silica gel 60 (230-400 mesh) as stationary phase. Thin layer chromatography (TLC) was carried out using silica gel 60 plates with F_{254} indicator on aluminum support. The development of TLCs was made through exposition to ultraviolet light (λ = 254) or by employment of staining solutions based on potassium permanganate or cerium (IV) and heating.

E.1.5 Analytical and instrumental techniques

- Gas chromatography-mass spectrometry (GC-MS)

Reactions were monitored employing a gas chromatograph coupled to a mass detector Shimadzu Corporation GCMS-QP2010 with auto-injector AOC-20i.

- Nuclear magnetic resonance spectroscopy (NMR)

The NMR spectra were recorded using the spectrometers Bruker AV-300, Bruker AV-400 and Bruker AV-600. The value of chemical shift (δ) are represented in parts per million (ppm), using tetramethylsilane as internal standard for ^{1}H and the residual solvent signals as standard for ^{13}C. The coupling constants (J) are given in Hertz (Hz). The abbreviations used to indicate the multiplicity of the signals of H^{1}-NMR are: s = singlet, bs = broad singlet, d = doublet, dd = double doublet, t = triplet, dt = double triplet, q = quatriplet p = quintuplet and m = multiplet or unresolved.

- Mass spectrometry (HRMS)

Experiments of high resolution mass spectrometry (HRMS) were carried out with the Finnigan-Mat 95 (University of Oviedo) and VG Autospec M (University of Burgos) spectrometers employing electro ionization (EI) or electrospray ionization (ESI) as ionization methods, and a time-of-flight (TOF) mass analyzer.

- Melting points

Melting points were measured in a Gallenkamp apparatus using open capillary tubes, and they are uncorrected.

E.2 Chapter 1. Part A: Synthesis of indanes and benzofurans

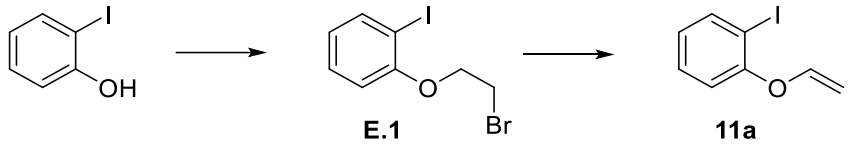
E.2.1 Synthesis of starting materials

- General procedure for the synthesis of **1** and **5**

1-Allyl-2-bromobenzene **1**[183] and 1-allyl-2-iodobenzene **5**[184] were synthesized following the processes described in the literature.

- General procedure for the synthesis of **11a** and **11b**

1-Iodo-2-(vinyloxy)benzene (**11a**)



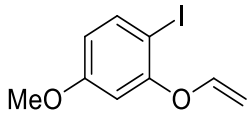
To a solution of 2-iodophenol (4.5 mmol) and 1,2-dibromoethane (4.25 g, 22.5 mmol) in acetone (50 mL) was added K_2CO_3 (1.25 g, 9 mmol). The resulting mixture was stirred at room temperature for 14 h and then at reflux for 6 h. The reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by a silica gel column chromatography using hexane as eluent to give **E.1** (805 mg, 2.5 mmol, 55% yield) as a colorless solid.

To a solution of **E.1** (805 mg, 2.5 mmol) in DMSO (20 mL) was added KO*t*Bu (287 mg, 2.5 mmol). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water, and extracted with AcOEt. The organic layers were washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography using hexane as eluent to give **11a** (409 mg, 1.66 mmol, 78% yield) as a yellow oil. NMR data were consistent with those reported in the literature.[185]

[183] J. Knight, P. J. Parsons, *J. Chem. Soc. Perkin Trans. 1*, **1989**, 979–984.
[184] S. García-Rubín, C. González-Rodríguez, C. García-Yebra, J. A. Varela, M. A. Esteruelas, C. Saá, *Angew. Chem. Int. Ed.* **2014**, *53*, 1841–1844.
[185] H. Bhandal, V. F. Patel, G. Pattenden, J. J. Russell, *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2691

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.34 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.87 (td, *J* = 7.6, 1.4 Hz, 1H), 6.61 (dd, *J* = 13.8, 6.1 Hz, 1H), 4.80 (dd, *J* = 13.7, 1.9 Hz, 1H), 4.54 (dd, *J* = 6.1, 1.9 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.79 (C), 148.07 (CH), 139.72 (CH), 129.58 (CH), 125.14 (CH), 117.31 (CH), 95.91 (CH), 87.43 (C). EI HRMS: calcd. For C_8H_7IO: 245.9542, found: 245.9541

1-Iodo-4-methoxy-2-(vinyloxy)benzene (**11b**)



11b

The title compound was prepared as a colorless oil in 82% isolated yield from 2-Iodo-5-methoxyphenol according to the procedure for **11a**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.7 Hz, 1H), 6.70 – 6.51 (m, 2H), 6.46 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.80 (dd, *J* = 13.7, 1.9 Hz, 1H), 4.53 (dd, *J* = 6.1, 1.9 Hz, 1H), 4.53 (dd, *J* = 6.1, 1.9 Hz, 1H), 3.79 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (C), 156. 7 (C) 148.0 (CH), 139.6 (CH), 111.0 (CH), 104.3 (CH), 96.4 (CH_2), 75.9 (C-I), 55.7 (CH_3). EI HRMS: calcd. For $C_9H_9IO_2$: 275.9647, found: 275.9650

- General procedure for the synthesis of **14**

Iodochalcone **14** was prepared as previously described in the literature.[186]

E.2.2 General procedure and characterization data for indanes 3

Method A: employing 1-allyl-2-bromobenzene **1**

A carousel reaction tube was charged under nitrogen atmosphere with the corresponding *N*-tosylhydrazone (1.1 equiv), 1-allyl-2-bromobenzene **1** (0.16 mmol), tris(dibenzylideneacetone)dipalladium(0) (3 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Sphos) (12 mol %), lithium *tert*-butoxide (5 equiv), H_2O (5 equiv) and 1,4-dioxane (2 mL). The reaction mixture was stirred at 90 °C for 6 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash

[186] A. Minatti, X. Zheng, S. L. Buchwald, *J. Org. Chem*. **2007**, *72*, 9253–9258.

chromatography on silica gel using hexane or a mixture of hexane / ethyl acetate as eluent.

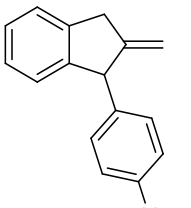
Method B: employing 1-allyl-2-iodobenzene **5**

A carousel reaction tube was charged under nitrogen atmosphere with the corresponding *N*-tosylhydrazone (2 equiv), 1-allyl-2-iodobenzene **5** (0.16 mmol), tris(dibenzylideneacetone)dipalladium(0) (3 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Sphos) (12 mol %), lithium *tert*-butoxide (6 equiv), H_2O (5 equiv) and acetonitrile (1.8 mL). The reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane or a mixture of hexane / ethyl acetate as eluent.

N,N-Dimethyl-4-(2-methylene-2,3-dihydro-1*H*-inden-1-yl)aniline (**3a**)

Following the general method A, from 1-allyl-2-bromobenzene **1** (0.16 mmol) and 4-(dimethylamino)benzaldehyde tosylhydrazone (46 mg, 0.18 mmol) were obtained 31.8 mg of **3a** (76 % isolated yield) as a yellow oil. R_f 0.18 (30:1 hexane : AcOEt).

Following the general method B, from 1-allyl-2-iodobenzene **5** (0.16 mmol) and 4-(dimethylamino)benzaldehyde tosylhydrazone (106.6 mg, 0.33 mmol) were obtained 40 mg of **3a** (96 % isolated yield) as a yellow oil. R_f 0.18 (30:1 hexane : AcOEt).



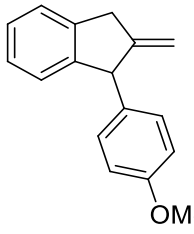
3a

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.33 (d, *J* = 6.7 Hz, 1H), 7.28 – 7.14 (m, 2H), 7.10 – 6.97 (m, 3H), 6.81 – 6.68 (m, 2H), 5.18 (q, *J* = 2.0 Hz, 1H), 4.88 (m, 2H), 3.84 (s broad, 2H), 2.96 (s, 6H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2) δ 155.5 (C), 150.1 (C), 147.3 (C), 142.2 (C), 133.1 (C), 129.6 (CH), 127.3, 127.2 (CH), 125.6 (CH), 124.8 (CH), 113.2 (CH), 109.3 (CH_2), 56.0 (CH), 41.1 (CH_3), 39.4 (CH_2) ppm. EI HRMS: calcd. For $C_{18}H_{19}N$: 249.1517, found: 249.1513

1-(4-Methoxyphenyl)-2-methylene-2,3-dihydro-1*H*-indene (**3b**)

Following the general method A, from 1-allyl-2-bromobenzene **1** (0.16 mmol) and *p*-anisaldehyde tosylhydrazone (56.2 mg, 0.18 mmol) were obtained 16 mg of **3b** (40 % isolated yield) as a colourless oil. R_f 0.27 (30:1 hexane : AcOEt).

Following the general method B, from 1-allyl-2-iodobenzene **5** (0.16 mmol) and *p*-anisaldehyde tosylhydrazone (102.2 mg, 0.33 mmol) were obtained 38 mg of **3b** (96 % isolated yield) as a colourless oil. R_f 0.27 (30:1 hexane : AcOEt).



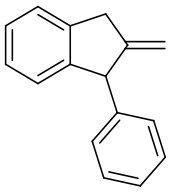
3b

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.34 (d, *J* = 7.0 Hz, 1H), 7.25 (t, *J* = 7.0 Hz, 1H), 7.19 (t, *J* = 7.0 Hz, 1H), 7.16 – 7.07 (m, 2H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.96 – 6.84 (m, 2H),5.21 (q, *J* = 2.2 Hz, 1H), 4.93 (s broad, 1H), 4.87 (q, *J* = 2.2 Hz, 1H), 3.86 (s broad, 2H), 3.82 (s, 3H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.3 (C), 154.6 (C), 146.3 (C), 141.6 (C), 136.8 (C), 129.5 (CH), 126.9 (CH), 126.7 (CH), 125.0 (CH), 124.3 (CH), 113.7 (CH), 109.1 (CH_2), 55.4 (CH), 55.2 (CH_3), 38.80 (CH_2) ppm. EI HRMS: calcd. For $C_{17}H_{16}O$: 236.1201, found: 236.1201

2-Methylene-1-phenyl-2,3-dihydro-1*H*-indene (**3c**)

Following the general method A, from 1-allyl-2-bromobenzene **1** (0.16 mmol) and benzaldehyde tosylhydrazone (50.6 mg, 0.18 mmol) were obtained 19.3 mg of **3c** (56 % isolated yield) as a colourless oil. R_f 0.25 (hexane).

Following the general method B, from 1-allyl-2-iodobenzene **5** (0.16 mmol) and benzaldehyde tosylhydrazone (92.1 mg, 0.33 mmol) were obtained 26.5 mg of **3c** (77 % isolated yield) as a colorless oil. R_f 0.25 (hexane). Spectroscopic data were consistent with those reported in the literature.[187]



3c

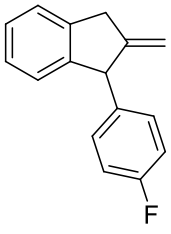
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.18 (m, 8H), 7.03 (d, *J* = 7.3 Hz, 1H), 5.21 (q, *J* = 2.3 Hz, 1H), 4.96 (s broad, 1H), 4.88 (q, *J* = 2.3 Hz, 1H), 3.87 (s broad, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 154. (C), 145.7 (C), 144.5 (C), 141.7 (C), 128.7 (CH), 128.5 (CH), 127.0 (CH), 126.8 (CH), 126.5 (CH), 125.3 (CH), 124.3 (CH), 109.7 (CH_2), 56.3 (CH), 39.0 (CH_2) ppm. EI MS: 206 (M^+).

[187] L. Ackermann, S. I. Kozhushkov, D. S. Yufit, *Chem. Eur. J.* 2012, **18**, 12068–12077.

1-(4-Fluorophenyl)-2-methylene-2,3-dihydro-1*H*-indene (**3d**)

Following the general method A, from 1-allyl-2-bromobenzene **1** (0.16 mmol) and 4-fluorobenzaldehyde tosylhydrazone (54 mg, 0.18 mmol) were obtained 17.6 mg of **3d** (47 % isolated yield) as a colourless oil. R_f 0.32 (hexane).

Following the general method B, from 1-allyl-2-iodobenzene **5** (0.16 mmol) and 4-fluorobenzaldehyde tosylhydrazone (98.2 mg, 0.33 mmol) were obtained 30.1 mg of **3d** (80 % isolated yield) as a colourless oil. R_f 0.32 (hexane).



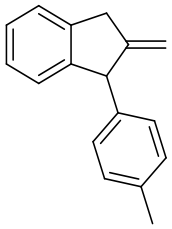
3d

^{1}H NMR (401 MHz, CD_2Cl_2) δ 7.34 (d, *J* = 7.2 Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.21 – 7.13 (m, 3H), 7.04 (td, *J* = 8.8, 3.0 Hz, 2H), 6.98 (d, *J* = 7.2 Hz, 1H), 5.21 (s broad, 1H), 4.96 (s broad, 1H), 4.85 (s broad, 1H), 3.85 (s, 2H) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2) δ 161.6 (d, *J* = 243.5 Hz, C-F), 154.2 (C), 145.8 (C), 141.7 (C), 140.5 (d, *J* = 3.2 Hz, C), 130.1 (CH, d, *J* = 7.8 Hz), 127.1 (CH), 126.8 (CH), 124.9 (CH), 124.4 (CH), 115.1 (CH, d, *J* = 21.2 Hz),109.5 (CH_2), 55.4 (CH), 38.8 (CH_2) ppm. EI HRMS: calcd. For $C_{16}H_{13}F$: 224.1001, found: 224.1008

2-Methylene-1-(*p*-tolyl)-2,3-dihydro-1*H*-indene (**3e**)

Following the general method A, from 1-allyl-2-bromobenzene **1** (0.16 mmol) and *p*-tolualdehyde tosylhydrazone (53 mg, 0.18 mmol) were obtained 12.9 mg of **3e** (35 % isolated yield) as a yellow oil. R_f 0.25 (hexane).

Following the general method B, from 1-allyl-2-iodobenzene **5** (0.16 mmol) and *p*-tolualdehyde tosylhydrazone (96.8 mg, 0.33 mmol) were obtained 33.2 mg of **3e** (90 % isolated yield) as a yellow oil. R_f 0.25 (hexane).



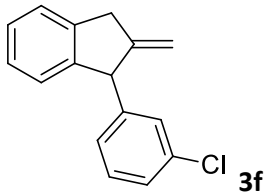
3e

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.30 (d, *J* = 6.7 Hz, 1H), 7.25 – 7.10 (m, 5H), 7.03 (d, *J* = 7.9 Hz, 2H) , 6.96 (d, *J* = 7.3 Hz, 1H), 5.16 (s, broad 1H), 4.90-4.84 (m, 2H), 3.83 (s broad, 2H), 2.33 (s, 3H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2) δ 155.0 (C), 146.8 (C), 142.3 (C), 136.6 (C), 129.7 (CH), 120.0 (CH), 127.5 (CH), 127.3 (CH), 125.6 (CH), 124.9 (CH), 109.8 (CH_2), 56.4 (CH), 39.4 (CH_2), 21.3 (CH_3) ppm. EI HRMS: calcd. For $C_{17}H_{16}$: 220.1252, found: 220.1261

1-(3-Chlorophenyl)-2-methylene-2,3-dihydro-1*H*-indene (**3f**)

Following the general method A, from 1-allyl-2-bromobenzene **1** (0.16 mmol) and 3-chlorobenzaldehyde tosylhydrazone (56.8 mg, 0.18 mmol) were obtained 9.3 mg of **3f** (23 % isolated yield) as a colourless oil. R_f 0.33 (hexane).

Following the general method B, from 1-allyl-2-iodobenzene **5** (0.16 mmol) and 3-chlorobenzaldehyde tosylhydrazone (103.7 mg, 0.33 mmol) were obtained 33 mg of **3f** (82 % isolated yield) as a colourless oil. R_f 0.33 (hexane).

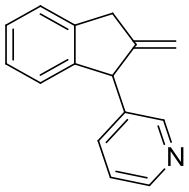


3f

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.31 (d, *J* = 7.5 Hz, 1H), 7.29 – 7.11 (m, 5H), 7.10 – 7.04 (m, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 5.21 (q, *J* = 2.2 Hz, 1H), 4.92 (s broad, 1H), 4.86 (q, *J* = 2.2 Hz, 1H), 3.83 (s broad) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2) δ 154.1 (C), 147.5 (C), 145.8 (C), 142.3 (C), 134.7 (C), 130.3 (CH), 129.1 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 127.1 (CH), 125.6 (CH), 125.0 (CH), 110.5 (CH_2), 56.4 (CH), 39.4 (CH_2) ppm. EI HRMS: calcd. For $C_{16}H_{13}Cl$: 240.0706, found: 240.0716

3-(2-Methylene-2,3-dihydro-1*H*-inden-1-yl)pyridine (**3g**)

Following the general method A, from 1-allyl-2-bromobenzene **1** (0.16 mmol) and 3-pyridinecarboxaldehyde tosylhydrazone (50.6 mg, 0.18 mmol) were obtained 30.2 mg of **3g** (87 % isolated yield) as a yellow oil. R_f 0.31(hexane).

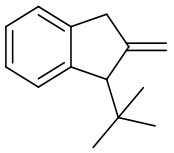


3g

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s broad, 2H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.35-7.15 (m, 4H), 6.94 (d, *J* = 7.4 Hz, 1H), 5.22 (s, 1H), 4.94 (s, 1H), 4.82 (s, 1H), 3.85 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (C), 150.1 (CH), 148.0 (CH), 144.9 (C), 141.8 (C), 140.1 (C), 136.3 (CH), 127.5 (CH), 127.2 (CH), 125.1 (CH), 124.6 (CH), 123.8 (CH), 110.6 (CH_2), 53.6 (CH), 39.0 (CH_2) ppm. EI HRMS: calcd. For $C_{16}H_{13}Cl$: 207.1048, found: 207.1050

1-(*tert*-Butyl)-2-methylene-2,3-dihydro-1*H*-indene (**3h**)

Following the general method B, from 1-allyl-2-iodobenzene **5** (0.16 mmol) and trimethylacetaldehyde tosylhydrazone (85.4 mg, 0.33 mmol) were obtained 15 mg of **3h** (48 % isolated yield) as a colourless oil. R_f 0.57 (hexane).

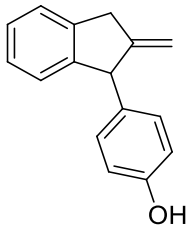


3h

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.27-7.13 (m, 4H), 5.16 (m, 1H), 5.01 (m, 1H), 3.70 (d, *J* = 19.5 Hz, 1H), 3.38 (d, *J* = 19.5 Hz, 1H), 3.32 (s, 1H), 0.93 (s, 9H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2) δ 152.1 (C), 144.9 (C), 143.8 (C), 127.11 (CHx2), 126.0 (CH), 124.6 (CH), 110.8 (CH_2), 61.8 (CH), 40.8 (CH_2), 35.7 (C), 27.7 (CH_3) ppm. EI HRMS: calcd. For $C_{16}H_{13}Cl$: 186.1409, found: 207.1412

4-(2-Methylene-2,3-dihydro-1*H*-inden-1-yl)phenol (**3i**)

Following the general method B, from 1-allyl-2-iodobenzene **5** (0.16 mmol) and 4-acetoxybenzaldehyde tosylhydrazone (111.6 mg, 0.33 mmol) were obtained 23.5 mg of **3i** (63 % isolated yield) as a brown oil. R_f 0.27 (5:1 hexane : AcOEt).

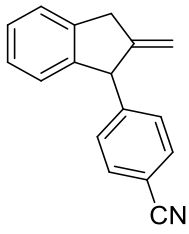


3i

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.33 (d, *J* = 7.2 Hz, 1H), 7.26-7.16 (m, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.20 (m, 1H), 5.13 (broad, 1H), 4.90 (broad, 1H), 4.90-4.86 (m, 1H), 3.84 (s broad 2H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2) δ 155.1 (C), 154.9 (C), 146.8 (C), 142.2 (C), 137.4 (C), 130.3 (CH), 127.5 (CH), 127.3 (CH), 125.5 (CH), 124.8 (CH), 115.7 (CH), 109.7 (CH_2), 56.0 (CH), 39.4 (CH_2) ppm. EI HRMS: calcd. For $C_{16}H_{14}O$: 222.1045, found: 222.1039

4-(2-Methylene-2,3-dihydro-1*H*-inden-1-yl)benzonitrile (**3j**)

Following the general method B, from 1-allyl-2-iodobenzene **5** (0.16 mmol) and 4-acetoxybenzaldehyde tosylhydrazone (100 mg, 0.33 mmol) were obtained 19.2 mg of **3j** (50 % isolated yield) as a colourless oil. R_f 0.30 (15:1 hexane : AcOEt).

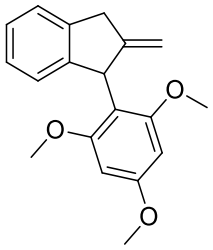


3j

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.60 (d, *J* = 8.3 Hz, 1H), 7.36 – 7.21 (m, 1H), 7.16 (t, *J* = 6.9 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 5.22 (q, *J* = 2.3 Hz, 1H), 4.82 (q, *J* = 2.3 Hz, 1H), 3.84 (s, 1H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2) δ 153.8 (C), 150.7 (C), 145.3 (C), 142.4 (C), 132.9 (CH), 129.9 (CH), 128.0 (CH), 127.5 (CH), 125.5 (CH), 125.1 (CH), 119.5 (C), 110.9 (CH_2), 56.7 (CH), 39.4 (CH_2). EI HRMS: calcd. For $C_{16}H_{14}O$: 231.1048, found: 231.1046

2-Methylene-1-(2,4,6-trimethoxyphenyl)-2,3-dihydro-1*H*-indene (**3k**)

Following the general method B, from 1-allyl-2-iodobenzene **5** (0.16 mmol) and 2,4,6-trimethoxybenzaldehyde tosylhydrazone (122 mg, 0.33 mmol) were obtained 35 mg of **3k** (71 % isolated yield) as a colourless oil. R_f 0.31 (15:1 hexane: AcOEt).



3k

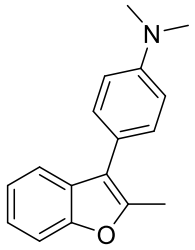
^{1}H NMR (300 MHz, C_6D_6) δ 7.20 – 7.00 (m, 4H), 6.12 (broad, 2H), 5.96 (s broad, 1H), 5.12 (s broad, 2H), 3.96 (d, *J* = 20.2 Hz, 1H), 3.82 (d, *J* = 20.2 Hz, 1H), 3.38 (s, 1H), 3.4-2.9 (broad, 6H) ppm. ^{13}C NMR (75 MHz, C_6D_6) δ 160.6 (C), 159.8 (C), 154.8 (C), 147.7 (C), 142.0 (C), 126.7 (CH), 126.3 (CH), 124.2 (CH), 124.0 (CH), 114.8 (s), 106.1 (CH_2), 92.1 (broad CH) 55.5 (CH_3), 54.9 (CH_3), 45.8 (CH), 39.7 (CH_2) ppm. EI HRMS: calcd. For $C_{16}H_{14}O$: 296.1412, found: 296.1413

E.2.3 General procedure and characterization data for benzofurans 13

A carousel reaction tube was charged under nitrogen atmosphere with the corresponding 1-iodo-2-(vinyloxy)benzene (**11a**) or 1-iodo-4-methoxy-2-(vinyloxy)benzene (**11b**) (0.16 mmol), tris(dibenzylideneacetone)dipalladium(0) (3 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Sphos) (12 mol %), lithium *tert*-butoxide (6 equiv), H_2O (5 equiv) and acetonitrile (1.8 mL). The *N*-tosylhydrazone (2 equiv) is added via syringe pump over a period of 1 h. The reaction mixture was stirred at 85 °C for 1 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane or a mixture of hexane / ethyl acetate as eluent.

N,N-Dimethyl-4-(2-methylbenzofuran-3-yl)aniline (**13a**)

Following the general method, from 1-iodo-2-(vinyloxy)benzene **11a** (0.16 mmol) and 4-(dimethylamino)benzaldehyde tosylhydrazone (104.1 mg, 0.32 mmol) were obtained 20.3 mg of **13a** (50 % isolated yield) as a yellow oil. R_f 0.21 (20:1 hexane : AcOEt).

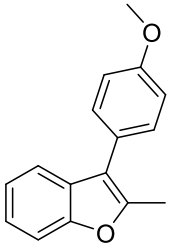


13a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 1H), 7.50-7.40 (m, 3H), 7.32-7.20 (m, 2H), 6.90 (d, 2H, ^3J = 8.8 Hz), 3.05 (s, 6H), 2.57 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0 (C), 150.5 (C), 149.5 (C), 129.7 (CH), 129.3 (C), 123.3 (CH), 122.4 (CH), 120.7 (C), 119.5 (CH), 116.8 (C), 112.8 (CH), 110.6 (CH), 40.6 (CH_3), 12.9 (CH_3) ppm. EI HRMS: calcd. For $C_{17}H_{17}NO$: 251.1310, found: 251.1311

3-(4-Methoxyphenyl)-2-methylbenzofuran (**13b**)

Following the general method, from 1-iodo-2-(vinyloxy)benzene **11a** (0.16 mmol) and *p*-anisaldehyde tosylhydrazone (99.8 mg, 0.32 mmol) were obtained 30 mg of **13b** (77 % isolated yield) as a colourless oil. R_f 0.24 (30:1 hexane : AcOEt).

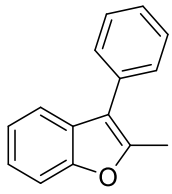


13b

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.53 (d, 1H, ^3J = 6.7 Hz), 7.44 (m, 3H) 7.24 (m, 2H), 7.04 (d, 2H, ^3J = 8.3 Hz), 3.86 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 159.3 (C), 154.5 (C), 151.6 (C), 130.5 (CH), 129.5 (C), 125.5 (C), 124.0 (C), 123.1 (CH), 119.7 (CH), 116.9 (C), 114.7 (CH), 111.1 (CH), 55.9 (CH_3), 13.1 (CH_3). EI HRMS: calcd. For $C_{16}H_{14}O_2$: 238.0994, found: 238.0998

2-Methyl-3-phenylbenzofuran (**13c**)

Following the general method, from 1-iodo-2-(vinyloxy)benzene **11a** (0.16 mmol) and benzaldehyde tosylhydrazone (89.9 mg, 0.32 mmol) were obtained 20.4 mg of **13c** (60 % isolated yield) as a colourless oil. R_f 0.29 (hexane). NMR data were consistent with those reported in the literature.[188]

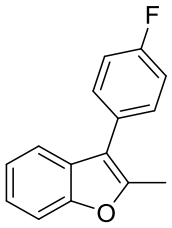


13c

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (m, 1H) 7.70-7.55 (m, 5H), 7.50 (m, 1H), 7.39 (m, 2H), 2.69 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (C), 151.4 (C), 133.0 (C), 129.1 (CH), 128.9 (CH), 127.1 (CH), 126.6 (C), 123.7 (CH), 122.7 (CH), 119.5 (CH), 117.0 (C), 110.9 (CH), 13.0 (CH_3) ppm.

3-(4-Fluorophenyl)-2-methylbenzofuran (**13d**)

Following the general method, from 1-iodo-2-(vinyloxy)benzene **11a** (0.16 mmol) and 4-fluorobenzaldehyde tosylhydrazone (95.8 mg, 0.32 mmol) were obtained 21 mg of **13d** (57 % isolated yield) as a colourless oil. R_f 0.31 (hexane).



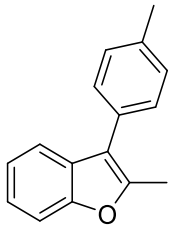
13d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.45 (m, 4H), 7.35-7.15 (m, 4H), 2.55 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (C-F, d,^2J = 246.2 Hz) 154.1 (C), 151.4 (C), 130.6 (CH, d, $^4J_{C\text{-}F}$ = 8.0 Hz), 128.9 (C), 128.8 (C), 123.8 (CH), 122.8 (CH), 119.2 (CH), 116.2 (C), 115.9 (CH, d, $^3J_{C\text{-}F}$= 21.4 Hz), CH, 110.9 (CH), 12.9 (CH_3) ppm. EI HRMS: calcd. For $C_{15}H_{11}FO$: 226.0794, found: 226.0803

[188] D. Kundu, M. Samim, A. Majee, A. Hajra, *Chem. Asian J.* **2011**, *6*, 406–409.

2-Methyl-3-(*p*-tolyl)benzofuran (**13e**)

Following the general method, from 1-iodo-2-(vinyloxy)benzene **11a** (0.16 mmol) and *p*-tolualdehyde tosylhydrazone (94.5 mg, 0.32 mmol) were obtained 21 mg of **13e** (58 % isolated yield) as a colourless oil. R_f 0.32 (hexane).

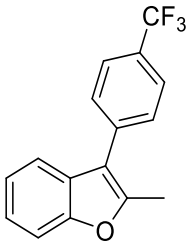


13e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 1H), 7.49 (m, 2H), 7.44 (d, ^3J = 8.0 Hz, 2H), 7.34 (d, ^3J = 8.0 Hz, 2H), 7.27 (m, 2H), 2.57 (s, 3H), 2.46 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (C), 151.2 (C), 136.8 (C), 129.9 (C), 129.6 (CH), 129.0 (C), 128.9 (CH), 123.6 (CH), 122.7 (CH), 119.5 (CH), 116.9 (C), 110.9 (CH), 21.4 (CH_3), 13.0 (CH_3). EI HRMS: calcd. For $C_{16}H_{14}O$: 222.1045, found: 222.1047

2-Methyl-3-(4-(trifluoromethyl)phenyl)benzofuran (**13f**)

Following the general method, from 1-iodo-2-(vinyloxy)benzene **11a** (0.16 mmol) and 4-(trifluoromethyl)benzaldehyde tosylhydrazone (112.2 mg, 0.32 mmol) were obtained 30.7 mg of **13f** (68 % isolated yield) as a colorless oil. R_f 0.28 (hexane).

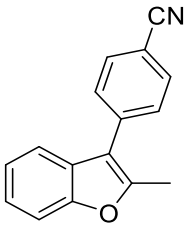


13f

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, 2H, 8.2 H), 7.68-7.65 (m, 2H), 7.61 (dd, 1H, ^3J = 7. 0 Hz, ^4J = 1.5 Hz), 7.54 (dd, 1H, ^3J = 7. 30 Hz, ^4J = 1.5 Hz), 7.40-7.27 (m, 2H), 2.61 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0 (C), 152.1 (C), 136.7 (C), 129.1 (CH), 129.0 (q, C-CF_3, J = 32.5 Hz), 128.2 (C), 125.7 (q, CH, J = 3.5 Hz), 124.0 (CH), 122.9 (CH), 119.0 (CH), 115.9 (C), 111.0 (CH), 12.9 (CH_3) ppm. EI HRMS: calcd. For $C_{16}H_{11}F_3O$: 276.0762, found: 276.0752

4-(2-Methylbenzofuran-3-yl)benzonitrile (**13g**)

Following the general method, from 1-iodo-2-(vinyloxy)benzene **11a** (0.16 mmol) and 4-formylbenzonitrile tosylhydrazone (98.1 mg, 0.32 mmol) were obtained 27.9 mg of **13g** (73 % isolated yield) as a as a white solid. R_f 0.22 (15:1 hexane : AcOEt). m.p = 101.2 - 103.1 °C.

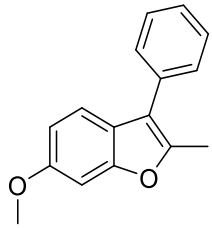


13g

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.79 (m, 2H), 7.66-7.63 (m, 2H), 7.57 (dd, *J* = 7.0, 1.8 Hz, 1H), 7.51 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.36-7.25 (m, 2H), 2.58 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (C), 152.5 (C), 138.0 (C), 132.6 (CH), 129.3 (CH), 127.7 (C), 124.5 (CH), 123.1 (CH), 118.9 (CH), 115.7 (C), 111.1 (CH), 110.5 (C), 13.0 (CH_3) ppm. EI HRMS: calcd. For $C_{16}H_{11}NO$: 233.0841, found: 233.0849

6-Methoxy-2-methyl-3-phenylbenzofuran (**13h**)

Following the general method, from 1-iodo-4-methoxy-2-(vinyloxy)benzene **11b** (0.16 mmol) and benzaldehyde tosylhydrazone (89.9 mg, 0.32 mmol) were obtained 26.5 mg of **13h** (68 % isolated yield) as a colourless oil. R_f 0.19 (50:1 hexane : AcOEt). NMR data were consistent with those reported in the literature.[189]



13h

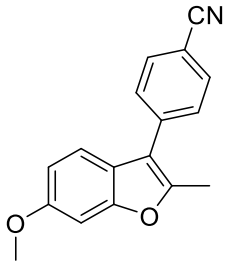
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.41 (m, 5H), 7.40 – 7.32 (m, 1H), 7.01 (d, *J* = 2.2 Hz, 1H) 6.86 (dd, *J* = 8.6, 2.2 Hz, 1H), 3.87 (s, 3H), 2.52 (s, 3H) ppm. ^{13}C NMR (75 MHz,

[189] A. R. Katritzky, Y. Ji, Y. Fang, I. Prakash, *J. Org. Chem.* **2001**, *66*, 5613–5615.

$CDCl_3$) δ 157.5 (C), 154.9 (C), 150.2 (C), 133.0 (C), 128.8 (CH), 128.7 (CH), 126.9 (CH), 122.1 (C), 119.4 (CH), 116.6 (C), 111.1 (CH), 95.8 (CH), 55.8 (CH_3), 12.8 (CH_3) ppm.

4-(6-Methoxy-2-methylbenzofuran-3-yl)benzonitrile (**13i**)

Following the general method, from 1-iodo-4-methoxy-2-(vinyloxy)benzene **11b** (0.16 mmol) and 4-formylbenzonitrile tosylhydrazone (98.1 mg, 0.32 mmol) were obtained 22.8 mg of **13i** (53 % isolated yield) as a as a white solid. R_f 0.22 (10:1 hexane : AcOEt). m.p = 128.9 - 130.5 °C.

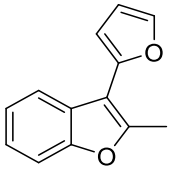


13i

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.89 (dd, *J* = 8.6, 2.2 Hz, 1H) 3.87 (s, 3H), 2.53 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9 (C), 155.0 (C), 151.3 (C), 138.2 (C), 132.6 (CH), 129.2 (CH), 121.0 (C), 119.1 (CH), 119.0 (C), 115.5 (C), 111.7 (CH), 110.7 (C), 96.0 (CH), 55.8 (CH_3), 13.0 (CH_3) ppm. EI HRMS: calcd. For $C_{16}H_{14}O$: 263.0946, found: 263.0944

3-(Furan-2-yl)-2-methylbenzofuran (**13j**)

Following the general method, from 1-iodo-2-(vinyloxy)benzene **11a** (0.16 mmol) and furfural tosylhydrazone (86.7 mg, 0.32 mmol) were obtained 13 mg of **13j** (40 % isolated yield) as a colourless oil. R_f 0.40 (hexane).



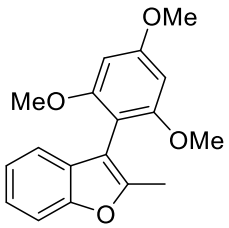
13j

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.80 (m, 1H), 7.55 (s broad, 1H), 7.33-7.25 (m, 2H), 6.59-6.53 (m, 2H), 2.69 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9 (C), 151.8 (C), 148.2 (C), 141.3 (CH), 126.8 (C), 123.8 (CH), 122.9 (CH), 120.2 (CH), 111.1 (CH), 110.6 (CH),

108.2 (C), 106.2 (CH), 13.8 (CH_3) ppm. EI HRMS: calcd. For $C_{16}H_{14}O$: 198.0681, found: 198.0683

2-Methyl-3-(2,4,6-trimethoxyphenyl)benzofuran (**13k**)

Following the general method, from 1-iodo-2-(vinyloxy)benzene **11a** (0.16 mmol) and 2,4,6-trimethoxybenzaldehyde tosylhydrazone (119.5 mg, 0.32 mmol) were obtained 28.9 mg of **13k** (59 % isolated yield) as a yellow oil. R_f 0.12 (15:1 hexane : AcOEt).

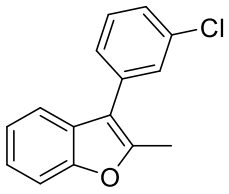


13k

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 1H), 7.20-7.05 (m, 3H), 6.27 (s, 2H), 3.90 (s, 3H), 3.75 (s, 6H), 2.31 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (C), 159.3 (C), 154.2 (C), 153.2 (C), 130.1 (C), 122.7 (CH), 122.0 (CH), 120.5 (CH), 110.7 (CH), 108.7 (C), 102.2 (C), 90.9 (CH), 55.9 (CH_3), 55.5 (CH_3), 13.5 (CH_3) ppm. EI HRMS: calcd. For $C_{18}H_{18}O_4$: 298.1205, found: 298.1207

3-(3-Chlorophenyl)-2-methylbenzofuran (**13l**)

Following the general method, from 1-iodo-2-(vinyloxy)benzene **11a** (0.16 mmol) and 3-chlorobenzaldehyde tosylhydrazone (101.2 mg, 0.32 mmol) were obtained 22.5 mg of **13l** (57 % isolated yield) as a colourless oil. R_f 0.34 (hexane).



13l

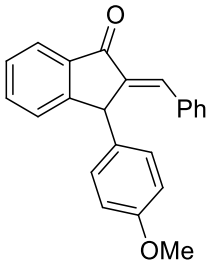
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.22 (M, 8H), 2.57 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0 (C), 151.8 (C), 134.7 (C), 134.6 (C), 130.0 (CH), 128.9 (CH), 128.3 (C), 127.1 (CH), 123.8 (CH), 122.8 (CH), 119.1 (CH), 115.8 (C), 110.9 (CH), 12.9 (CH_3) ppm. EI HRMS: calcd. For $C_{15}H_{11}ClO$: 242.0498, found: 242.0500

E.2.4 General procedure and characterization data for benzylideneindenones 15

A carousel reaction tube was charged under nitrogen atmosphere with the corresponding *N*-tosylhydrazone (2 equiv), (*E*)-1-(2-iodophenyl)-3-phenylprop-2-en-1-one **14** (0.17 mmol), tris(dibenzylideneacetone)dipalladium(0) (3 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (Sphos) (12 mol %), K_2CO_3 (6 equiv), H_2O (5 equiv) and 1,4-dioxane (2 mL). The reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the reaction crude was dissolved in methylene chloride and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane or a mixture of hexane/ethyl acetate as eluent.

(*E*)-2-Benzylidene-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one (**15a**)

Following the general method, from iodoketone **14** (0.17 mmol) and *p*-anisaldehyde tosylhydrazone (103.4 mg, 0.34 mmol) were obtained 38.8 mg of **15a** (70 % isolated yield) as a as a brown solid as a 5.8: 1 mixture of *E/Z* isomers. R_f 0.15 (10:1, hexane: AcOEt).

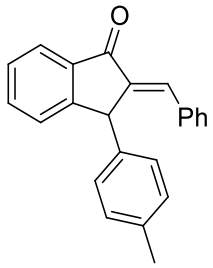


15a

Spectroscopic data of major isomer *E*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.7 Hz, 1H), 7.79 (s, 1H), 7.56, 7.56-7.51(m, 3H), 7.44-7.37 (m, 2H), 7.30-7.27 (m, 3H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.37 (s, 1H), 3.70 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7 (C), 159.1 (C), 155.4 (C), 139.5 (C), 136.6 (C), 135.5 (CH), 135.4 (CH), 134.7 (C), 134.1 (C), 132.0 (CH), 130.2 (CH), 129.2 (CH), 128.9 (CH), 128.4 (CH), 126.5 (CH), 124.4 (CH), 114.7 (CH), 55.6 (CH_3), 48.4 (CH) ppm. EI HRMS: calcd. For $C_{23}H_{18}O_2$: 326.1307, found: 326.1312

(*E*)-2-Benzylidene-3-(*p*-tolyl)-2,3-dihydro-1*H*-inden-1-one (**15b**)

Following the general method, from iodoketone **14** (0.17 mmol) and *p*-tolualdehyde tosylhydrazone (98 mg, 0.34 mmol) were obtained 34 mg of **15b** (65 % isolated yield) as a as a brown solid as a 14: 1 mixture of *E/Z* isomers. R_f = 0.12 (20:1 hexane: AcOEt).



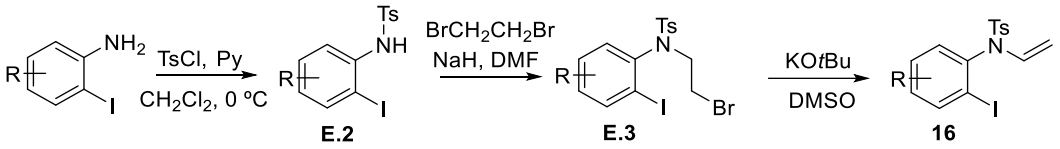
15b

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.88 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 1.9 Hz, 1H), 7.55-7.53 (m, 3H), 7.40-7.38 (m, 3H), 7.29-7.28 (m, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 5.38 (s, 1H), 2.24 (s, 3H) ppm. ^{13}C NMR (151 MHz, CD_2Cl_2) δ 194.7 (C), 155.3 (C), 139.4 (C), 139.1 (C), 137.2 (C), 136.6 (C), 135.5 (CH), 135.4 (CH), 134.7 (C), 132.0 (CH), 130.1 (CH), 128.9 (CH), 128.4 (CH), 128.0 (CH), 126.5 CH), 124.5 (CH), 48.8 (CH), 21.3 (CH_3) ppm. EI HRMS: calcd. For $C_{16}H_{14}O$: 310.1358, found: 310.1367

E.3 Chapter 1. Part B: Synthesis of indoles and 1,4-dihydroquinolines

E.3.1 Synthesis of starting materials

- General procedure and characterization data for enamides **16**



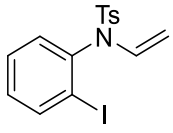
A Schlenk was charged under nitrogen atmosphere with the corresponding 2-iodoaniline (4.6 mmol) and CH_2Cl_2 (15 mL). The solution was stirred at 0 °C, then *p*-toluenesulfonyl chloride (5.0 mmol) and pyridine (137 mmol) were added. The reaction mixture was stirred at room temperature and monitored by TLC. When the starting material was consumed *N*,*N*-dimethylendiamine (0.91 mmol) was added and the reaction mixture was allowed stir during 2 hours. The resulting mixture was washed with 1M HCl aqueous solution and extracted with CH_2Cl_2. After removal solvents, *N*-tosylamide **E.2** was obtained as a white solid which was used in the next step without further purification.

A 1 M solution of NaH in DMF (6.4 mL) under nitrogen was stirred at 0 °C. A 0.5 M solution of **E.2** in DMF (6.4 mL) was poured slowly onto the first solution. The reaction was stirred at room temperature during 1 hour and then 1,2-dibromoethane (4.81 mmol) was added. The reaction mixture was maintained at 80 °C during 1.5 hours. The resulting mixture was quenched with a saturated aqueous solution of NH_4Cl, and extracted with AcOEt. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue of the reaction **E.3** was directly used in the next step of the synthesis without further purification.

To a solution of the residue from the previous step (3.0 mmol) in DMSO (15 mL) was added KO*t*Bu (4.0 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water, and extracted with AcOEt. The organic layers were washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of hexane / ethyl acetate as eluent to give **16** as a solid. The solid was recrystallized using a mixture methanol / dichloromethane 98:2 giving a crystalline material.

N-(2-Iodophenyl)-4-methyl-*N*-vinylbenzenesulfonamide (**16a**)

The title compound **16a** was prepared as yellow crystals in 45 % isolated yield (888 mg) from 2-iodoaniline, according to the general procedure for **16**. R_f 0.22 (10:1 hexane : AcOEt). m.p = 92.4 – 94.0 °C. Spectroscopic data were consistent with those reported in the literature.[190]

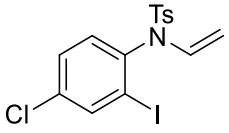


16a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 9.0 Hz, 3H), 7.23 – 7.01 (m, 2H), 6.78 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.33 (dd, *J* = 8.8, 1.3 Hz, 1H), 3.68 (dd, *J* = 15.5, 1.2 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3 (C), 140.9 (CH), 138.5 (C), 136.3 (C), 133.1 (CH), 130.6 (CH), 130.6 (CH), 129.8 (CH), 129.2 (CH), 127.7 (CH), 102.03 (C), 94.78 (CH_2), 21.69 (CH_3). EI HRMS: calcd. For $[C_{15}H_{14}INO_2S+H]^+$: 399.9853, found: 399.9849

N-(4-Chloro-2-iodophenyl)-4-methyl-*N*-vinylbenzenesulfonamide (**16b**)

The title compound **16b** was prepared as yellow crystals in 37 % isolated yield (695 mg) from 4-chloro-2-iodoaniline, according to the general procedure for **16**. R_f 0.24 (10:1 hexane : AcOEt). m.p = 167.7 – 169.3 °C



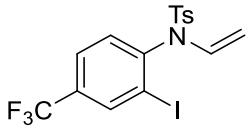
16b

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.25 (m, 3H), 7.13 (dd, *J* = 15.4, 8.8 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.35 (dd, *J* = 8.8, 1.4 Hz, 1H), 3.70 (dd, *J* = 15.5, 1.4 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4 (C), 140.3 (CH), 137.3 (C), 136.0 (C), 135.6 (C), 132.9 (CH), 131.1 (CH), 129.8 (CH), 129.4 (CH), 127.7 (CH), 102.3 (C), 94.8 (CH_2), 21.6 (CH_3). EI HRMS: calcd. For $[C_{15}H_{13}ClINO_2S+H]^+$: 433.9474, found: 433.9473

[190] H. Liu, J. Wei, Z. Qiao, Y. Fu, X. Jiang, *Chem. Eur. J.* **2014**, *20*, 8308–8313.

N-(2-Iodo-4-(trifluoromethyl)phenyl)-4-methyl-*N*-vinylbenzenesulfonamide (**16c**)

The title compound **16c** was prepared as yellow crystals in 40 % isolated yield (701 mg) from 4-trifluoromethyl-2-iodoaniline, according to the general procedure for **16**. R_f 0.15 (15:1 hexane : AcOEt). m.p = 112.7 – 113.9 °C

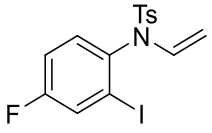


16c

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 1.9 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.59 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.14 (dd, *J* = 15.5, 8.8 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 4.38 (dd, *J* = 8.8, 1.5 Hz, 1H), 3.67 (dd, *J* = 15.4, 1.5 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6 (C), 137.9 (q, C-CF_3, J = 34.5 Hz), 135.9 (C), 132.7 (CH), 130.9 (CH), 129.9 (CH), 127.7 (C), 127.7 (CH), 126.2 (CH), 126.1 (CH), 116.5 (C), 102.1 (C), 95.2 (CH_2), 21.6 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.82. EI HRMS: calcd. For $[C_{16}H_{13}F_3INO_2S+H]^+$: 467.9738, found: 467.9754

N-(4-Fluoro-2-iodophenyl)-4-methyl-*N*-vinylbenzenesulfonamide (**16d**)

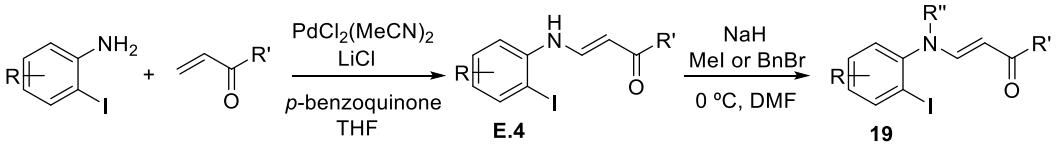
The title compound **16d** was prepared as yellow crystals in 40 % isolated yield (701 mg) from 4-fluoro-2-iodoaniline, according to the general procedure for **16**. R_f 0.21 (10:1 hexane : AcOEt). m.p = 161.6 – 162.3 °C



16d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.8, 2.9 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.15 (dd, *J* = 15.4, 8.8 Hz, 1H), 7.04 (ddd, *J* = 8.8, 7.6, 2.9 Hz, 1H), 6.75 (dd, *J* = 8.8, 5.4 Hz, 1H), 4.35 (dd, *J* = 8.8, 1.3 Hz, 1H), 3.69 (dd, *J* = 15.4, 1.3 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (C-F, d, ^2J = 254.9 Hz), 144.4 (C), 136.0 (C), 134.7 (C, d, $^5J_{C-F}$= 3.6 Hz) 133.1 (CH), 131.3 (CH, d, $^4J_{C-F}$= 8.8 Hz), 129.8 (CH), 127.8 (CH, d, $^3J_{C-F}$= 24.4 Hz), 127.72 (CH), 116.3 (CH, d, $^3J_{C-F}$= 22.3 Hz), 102.16 (C, d, $^4J_{C-F}$= 8.8 Hz), 94.7 (CH_2), 21.6 (CH_3). EI HRMS: calcd. For $[C_{15}H_{13}FINO_2S+H]^+$: 417.9770, found: 417.9768

- General procedure and characterization data of starting enaminones **19**



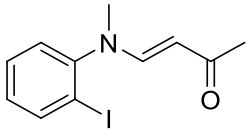
Methyl vinyl ketone and ethyl vinyl ketone are commercially available from Aldrich Chemical Co. Phenyl vinyl ketone was synthesized following the process described in the literature.[191]

Intermediate iodoenaminones **E.4** was prepared according to the method previously described in the literature.[192]

To a solution of **E.4** (2.32 mmol) in anhydrous DMF (12 mL) under nitrogen was added NaH (5.82 mmol) slowly at 0 °C. The mixture was stirring at room temperature for 2 hours before methyl iodide, benzyl bromide or 4-methoxybenzyl bromide (5.82 mmol) were added dropwise to the mixture. The reaction progress was monitored using TLC. After the consumption of starting material, the reaction mixture was washed with water and extracted with ethyl acetate. The organic layers were combined and dried with Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of hexane / ethyl acetate as eluent to give **19**.

(*E*)-4-((2-Iodophenyl)(methyl)amino)but-3-en-2-one (**19a**)

The title compound **19a** was prepared as yellow oil in 41 % isolated yield (286 mg) from 2-iodoaniline and methyl vinyl ketone, according to the general procedure for **19**. R_f 0.31 (1:2 hexane : AcOEt).



19a

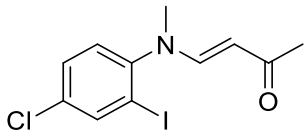
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 13.0 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.20 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 5.36 (bs, 1H), 3.19 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1 (C), 151.1 (CH), 149.5 (C, broad signal

[191] S. Chanthamath, S. Takaki, K. Shibatomi, S. Iwasa, *Angew. Chemie Int. Ed.* **2013**, *52*, 5818–5821.
[192] T. Sakamoto, T. Nagano, Y. Kondo, H. Yamanaka, *Synthesis.* **1990**, 215–218.

due to the presence of rotamers), 140.3 (CH), 129.7 (CH), 129.3 (CH), 127.9 (CH), 100.6 (CH), 96.3 (C), 38.6 (CH_3, broad signal due to the presence of rotamers), 27.8 (CH_3). EI HRMS: calcd. For $[C_{11}H_{12}INO+H]^+$: 302.0031, found: 302.0036

(*E*)-4-((4-Chloro-2-iodophenyl)(methyl)amino)but-3-en-2-one (**19b**)

According to the general procedure, for the corresponding iodoenaminone intermediate **E.4** (0.58 mmol) was obtained 59 mg of **19b** (30 % isolated yield) as a colourless oil. R_f 0.35 (1:2 hexane : AcOEt).

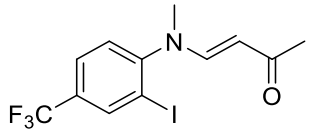


19b

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.45 (d, *J* = 12.6 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 5.33 (bs, 1H), 3.17 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0 (C), 150.6 (CH), 147.0 (C, broad signal due to the presence of rotamers), 139.6 (CH), 134.0 (C), 129.9 (CH), 128.4 (CH), 101.0 (CH), 96.7 (C), 38.7 (CH_3, broad signal due to the presence of rotamers), 28.0 (CH_3). EI HRMS: calcd. For $[C_{11}H_{11}ClINO+H]^+$: 335.9637, found: 335.9646

(*E*)-4-((2-Iodo-4-(trifluoromethyl)phenyl)(methyl)amino)but-3-en-2-one (**19c**)

According to the general procedure, for the corresponding iodoenaminone intermediate **E.4** (0.25 mmol) was obtained 19 mg of **19c** (20 % isolated yield) as a yellow oil. R_f 0.35 (1:2 hexane : AcOEt).

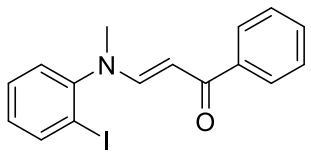


19c

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 13.1 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 5.30 (bs, 1H), 3.24 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2 (C), 152.0 (C, broad signal due to the presence of rotamers), 150.1 (CH), 137.5 (CH), 128.0 (CH), 126.8 (CH), 108.6 (C), 101.7 (CH), 95.9 (C), 39.0 (CH_3), 28.0 (CH_3). EI HRMS: calcd. For $[C_{12}H_{11}F_3INO+H]^+$: 369.9910, found: 369.9910

(*E*)-3-((2-Iodophenyl)(methyl)amino)-1-phenylprop-2-en-1-one (**19d**)

According to the general procedure, for the corresponding iodoenaminone intermediate **E.4** (1.12 mmol) was obtained 204 mg of **19d** (50 % isolated yield) as a yellow oil. R_f 0.33 (2:1 hexane : AcOEt).

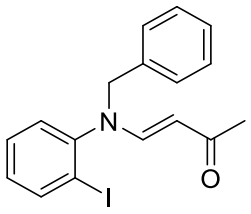


19d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (bs, 4H), 7.43 (bs, 4H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.06 (bs, 1H), 6.08 (bs, 1H), 3.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4 (C), 152.7 (CH), 149.4 (C broad signal due to the presence of rotamers), 140.3 (C), 140.0 (CH), 131.2 (CH), 129.7 (CH), 129.5 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 96.2 (C), 95.7 (CH), 39.0 (CH_3). EI HRMS: calcd. For $[C_{16}H_{14}INO+H]^+$: 364.0189, found: 364.0192

(*E*)-4-(Benzyl(2-iodophenyl)amino)but-3-en-2-one (**19e**)

According to the general procedure, for the corresponding iodoenaminone intermediate **E.4** (0.27 mmol) was obtained 49 mg of **19e** (48 % isolated yield) as a brown oil. R_f 0.14 (2:1 hexane : AcOEt).

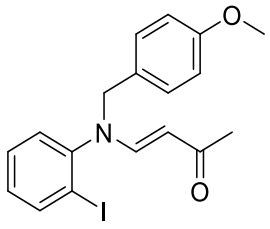


19e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.70 (bs, 1H), 7.36 – 7.28 (m, 4H), 7.27 – 7.21 (m, 2H), 7.03 (td, *J* = 7.8, 1.5 Hz, 1H), 6.92 (bs, 1H), 4.70 (bs, 3H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2 (C), 150.8 (CH), 140.5 (CH), 140.0 (C, broad signal due to the presence of rotamers), 135.5 (C), 129.6 (CH), 129.4 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 100.9 (CH), 97.4 (C), 60.0 (CH_2, broad signal due to the presence of rotamers), 28.1 (CH_3). EI HRMS: calcd. For $[C_{17}H_{16}INO+H]^+$: 378.0351, found: 378.0349

(*E*)-4-((2-Iodophenyl)(4-methoxybenzyl)amino)but-3-en-2-one (**19f**)

According to the general procedure, for the corresponding iodoenaminone intermediate **E.4** (0.80 mmol) was obtained 147 mg of **19f** (45 % isolated yield) as a yellow oil. R_f 0.09 (2:1 hexane : AcOEt).

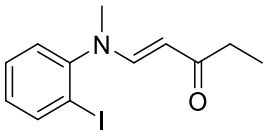


19f

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 – 7.86 (m, 2H), 7.67 (bs, 1H), 7.32 – 7.21 (m, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.01 (td, *J* = 7.5, 1.5 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 3H), 4.62 (bs, 2H), 3.78 (s, 3H), 2.90 (d, *J* = 21.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1 (C), 162.5 (CH), 159.3 (C), 150.7 (CH), 140.4 (CH), 129.8 (CH), 129.6 (CH), 129.4 (CH), 127.4 (C), 114.0 (CH), 110.3 (CH, broad signal due to the presence of rotamers), 100.7 (C), 97.5 (C), 60.3 (CH_2, broad signal due to the presence of rotamers), 55.2 (CH_3), 36.4 (CH_3). EI HRMS: calcd. For $[C_{18}H_{18}INO_2+H]^+$: 408.0451, found: 408.0455

(*E*)-1-((2-Iodophenyl)(methyl)amino)pent-1-en-3-one (**19g**)

According to the general procedure, for the corresponding iodoenaminone intermediate **E.4** (1.32 mmol) was obtained 121 mg of **19g** (29 % isolated yield) as a yellow oil. R_f 0.12 (2:1 hexane : AcOEt).



19g

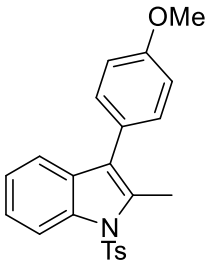
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 13.2 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 5.31 (bs, 1H), 3.15 (bs, 3H), 2.39 (bs, 2H), 1.08 (bs, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3 (C), 150.3 (CH), 147.4 (C, broad signal due to the presence of rotamers), 140.2 (CH), 129.7 (CH), 129.2 (CH), 127.9 (CH), 99.2 (CH), 96.4 (C), 38.6 (CH_3, broad signal due to the presence of rotamers), 34.2 (CH_2), 9.4 (CH_3). EI HRMS: calcd. For $[C_{12}H_{14}INO+H]^+$: 316.0185, found: 316.0192

E.3.2 General procedure and characterization data for indoles 18

A carousel reaction tube was charged under nitrogen atmosphere with the corresponding iodoenamine **16** (0.05 mmol), allylpalladium(II) chloride dimer (3 mol %), triphenylphosphine (PPh_3) (12 mol %), lithium tert-butoxide (6 equiv), and acetonitrile (1 mL). The *N*-tosylhydrazone (2 equiv) is diluted in 2 mL of acetonitrile and then added via syringe pump over a period of 2 h. The reaction mixture was stirred at 110 °C during the slow addiction. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure. The reaction crude was diluted in 3 mL of THF and then 0.5 mL of 1 M HCl (aqueous solution) were added. The reaction mixture was extracted with ethyl acetate and washed with water. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using a mixture of hexane / ethyl acetate as eluent.

3-(4-Methoxyphenyl)-2-methyl-1-tosyl-1*H*-indole (**18a**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and *p*-anisaldehyde tosylhydrazone (30.4 mg, 0.1 mmol) were obtained 10.4 mg of **18a** (53 % isolated yield) as a yellow oil. R_f 0.12 (20:1 hexane : AcOEt). Spectroscopic data were consistent with those reported in the literature.[193]



18a

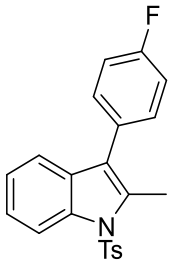
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.27 – 7.19 (m, 4H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 2.59 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8 (C), 144.6 (C), 136.4 (C), 136.2 (C), 132.8 (C), 131.1 (CH), 130.2 (C), 129.8 (CH), 126.4 (CH), 125.2 (C), 124.1 (CH),

[193] C. Zhu, S. Ma, *Org. Lett.* **2013**, *15*, 2782–2785.

123.4 (CH), 122.2 (C), 119.1 (CH), 114.5 (CH), 114.0 (CH), 55.3 (CH_3), 21.5 (CH_3), 13.5 (CH_3). EI HRMS: calcd. For $[C_{23}H_{21}NO_3S+H]^+$: 392.1314, found: 392.1314

3-(4-Fluorophenyl)-2-methyl-1-tosyl-1*H*-indole (**18b**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and 4-fluorobenzaldehyde tosylhydrazone (29.2 mg, 0.1 mmol) were obtained 11 mg of **18b** (58 % isolated yield) as a colourless oil. R_f 0.15 (20:1 hexane : AcOEt).

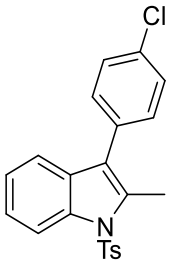


18b

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.30 (m, 4H), 7.26 (d, *J* = 7.9 Hz, 3H), 7.17 (t, *J* = 8.6 Hz, 2H), 2.59 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (C-F, d, ^2J = 246.7 Hz), 144.8 (C), 136.3 (C), 136.1 (C), 133.1 (C), 131.6 (CH, d, $^4J_{C\text{-}F}$= 8.1 Hz), 129.9 (CH), 129.8 (C), 128.9 (C, d, $^5J_{C\text{-}F}$= 3.2 Hz), 126.4 (CH), 124.3 (CH), 123.5 (CH), 121.5 (C), 118.9 (CH), 115.5 (CH, d, $^3J_{C\text{-}F}$= 21.3 Hz), 114.5 (CH), 21.5 (CH_3), 13.4 (CH_3). EI HRMS: calcd. For $[C_{22}H_{18}FNO_2S+H]^+$: 380.1116, found: 380.1115

3-(4-Chlorophenyl)-2-methyl-1-tosyl-1*H*-indole (**18c**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and 4-chlorobenzaldehyde tosylhydrazone (30.8 mg, 0.1 mmol) were obtained 16 mg of **18c** (84 % isolated yield) as a colourless oil. R_f 0.15 (20:1 hexane : AcOEt).

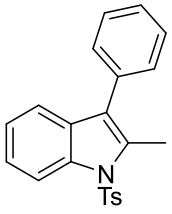


18c

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.37 (t, *J* = 7.0 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 3H), 2.59 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8 (C), 136.3 (C), 136.2 (C), 133.2 (C), 131.5 (C), 131.3 (CH), 129.9 (CH), 129.5 (C), 128.8 (CH), 126.4 (CH), 124.9 (C), 124.4 (CH), 123.6 (CH), 121.3 (C), 118.9 (CH), 114.5 (CH), 21.6 (CH_3), 13.4 (CH_3). EI HRMS: calcd. For $[C_{22}H_{18}ClNO_2S+H]^+$: 396.0818, found: 396.0819

2-Methyl-3-phenyl-1-tosyl-1*H*-indole (**18d**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and benzaldehyde tosylhydrazone (27.4 mg, 0.1 mmol) were obtained 13 mg of **18d** (72 % isolated yield) as a yellow oil. R_f 0.16 (20:1 hexane : AcOEt). Spectroscopic data were consistent with those reported in the literature.[194]



18d

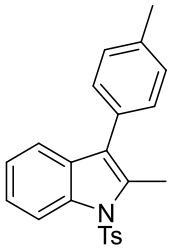
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.49 – 7.41 (m, 3H), 7.41 – 7.35 (m, 3H), 7.32 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 2.62

[194] S. W. Youn, T. Y. Ko, M. J. Jang, S. S. Jang, *Adv. Synth. Catal.* **2015**, *357*, 227–234.

(s, 3H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9 (C), 136.5 (C), 136.4 (C), 133.3 (C), 133.2 (C), 130.2 (CH), 130.1 (C), 130.0 (CH), 128.7 (CH), 127.4 (CH), 126.6 (CH), 124.4 (CH), 123.6 (CH), 122.7 (C), 119.3 (CH), 114.7 (CH), 21.7 (CH_3), 13.7 (CH_3). EI HRMS: calcd. For $[C_{22}H_{19}NO_2S+H]^+$: 362.1211, found: 362.1209

2-Methyl-3-(*p*-tolyl)-1-tosyl-1*H*-indole (**18e**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and *p*-tolualdehyde tosylhydrazone (28.8 mg, 0.1 mmol) were obtained 15 mg of **18e** (80 % isolated yield) as a yellow oil. R_f 0.16 (20:1 hexane : AcOEt).

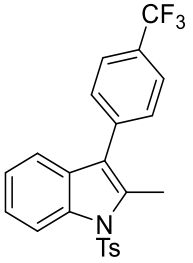


18e

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.29 – 7.22 (m, 6H), 2.61 (s, 3H), 2.43 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6 (C), 137.0 (C), 136.4 (C), 136.2 (C), 132.9 (C), 130.1 (C), 130.0 (C), 129.8 (2xCH), 129.27 (CH), 126.4 (CH), 124.1 (CH), 123.4 (CH), 122.4 (C), 119.2 (CH), 114.5 (CH), 21.5 (CH_3), 21.2 (CH_3), 13.5 (CH_3). EI HRMS: calcd. For $[C_{23}H_{21}NO_2S+H]^+$: 376.1365, found: 376.1365

2-Methyl-1-tosyl-3-(4-(trifluoromethyl)phenyl)-1*H*-indole (**18f**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and 4-(trifluoromethyl)benzaldehyde tosylhydrazone (34.2 mg, 0.1 mmol) were obtained 13 mg of **18f** (62 % isolated yield) as a yellow oil. R_f 0.23 (25:1 hexane : AcOEt).

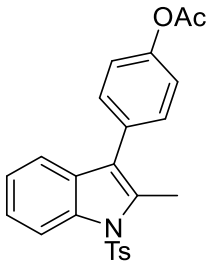


18f

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.2 Hz, 1H), 7.75 (t, *J* = 8.4 Hz, 4H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.30 (m, 2H), 7.27 (d, *J* = 7.0 Hz, 3H), 2.62 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0 (C), 137.1 (C), 137.1 (C), 136.3 (C), 136.3 (C), 133.7 (C), 130.4 (CH), 130.0 (CH), 129.3 (C), 126.5 (CH), 125.6 (q, CH-CF_3, *J* = 3.7 Hz), 124.6 (CH), 123.8 (CH), 121.2 (C), 118.9 (CH), 114.6 (CH), 21.6 (CH_3), 13.5 (CH_3). EI HRMS: calcd. For $[C_{23}H_{18}F_3NO_2S+H]^+$: 430.1084, found: 430.1083

4-(2-Methyl-1-tosyl-1*H*-indol-3-yl)phenyl acetate (**18g**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and 4-(trifluoromethyl)benzaldehyde tosylhydrazone (33.2 mg, 0.1 mmol) were obtained 11 mg of **18g** (55 % isolated yield) as a brown oil. R_f 0.22 (5:1 hexane : AcOEt).



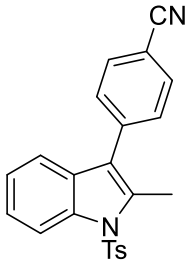
18g

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 2H), 7.56 – 7.38 (m, 4H), 7.38 – 7.31 (m, 3H), 7.29 (d, *J* = 8.3 Hz, 2H), 2.70 (s, 3H), 2.48 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4 (C), 149.8 (C), 144.8 (C), 136.3 (C), 136.2 (C), 133.3 (C), 131.0 (CH), 130.7 (C), 129.9 (CH), 129.8(C), 126.4 (CH), 124.3 (CH), 123.5 (CH), 121.7

(CH), 121.6 (C), 119.0(CH), 114.5 (CH), 21.5 (CH_3), 21.2 (CH_3), 13.5 (CH_3). EI HRMS: calcd. For $[C_{24}H_{21}NO_4S+H]^+$: 420.1263, found: 420.1264

4-(2-Methyl-1-tosyl-1*H*-indol-3-yl)benzonitrile (**18h**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and 4-formylbenzonitrile tosylhydrazone (29.9 mg, 0.1 mmol) were obtained 9 mg of **18h** (47 % isolated yield) as a yellow oil. R_f 0.10 (10:1 hexane : AcOEt).

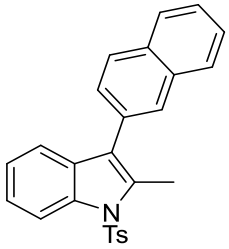


18h

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 – 8.26 (m, 1H), 7.79 – 7.73 (m, 4H), 7.53 – 7.46 (m, 2H), 7.41 – 7.33 (m, 2H), 7.31 – 7.28 (m, 1H), 7.27 – 7.24 (m, 2H), 2.61 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6 (C), 138.8 (C), 136.7 (C), 136.7 (C), 134.4 (C), 132.9 (CH), 131.2 (CH), 130.5 (CH), 129.3 (C), 127.0 (CH), 125.2 (CH), 124.3 (CH), 121.2 (C), 119.3 (C), 119.1 (CH), 115.1 (CH), 111.5 (C), 22.1 (CH_3), 14.0 (CH_3). EI HRMS: calcd. For $[C_{23}H_{18}N_2O_2S+H]^+$: 387.1164, found: 387.1168

2-Methyl-3-(naphthalen-2-yl)-1-tosyl-1*H*-indole (**18i**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and 2-naphthaldehyde tosylhydrazone (32.4 mg, 0.1 mmol) were obtained 11 mg of **18i** (55 % isolated yield) as a colourless oil. R_f 0.19 (20:1 hexane : AcOEt).

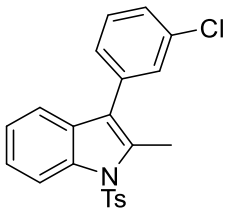


18i

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.4 Hz, 1H), 7.97 – 7.82 (m, 4H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.57 – 7.44 (m, 4H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.30 – 7.22 (m, 3H), 2.67 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7 (C), 136.4 (C), 136.3 (C), 133.4 (C), 133.4 (C), 132.5 (C), 130.6 (C), 130.0 (C), 129.9 (CH), 128.9 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 126.4 (CH), 126.3 (CH), 126.1 (CH), 124.3 (CH), 123.5 (CH), 122.4 (C), 119.2 (CH), 114.5(CH), 21.6 (CH3), 13.6 (CH3). EI HRMS: calcd. For $[C_{26}H_{21}NO_2S+H]^+$: 412.1354, found: 412.1365

3-(3-Chlorophenyl)-2-methyl-1-tosyl-1*H*-indole (**18j**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and 3-chlorobenzaldehyde tosylhydrazone (30.9 mg, 0.1 mmol) were obtained 13 mg of **18j** (66 % isolated yield) as a colourless oil. R_f 0.18 (20:1 hexane : AcOEt).



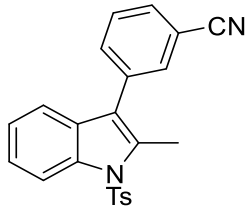
18j

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.46 – 7.31 (m, 5H), 7.30 – 7.22 (m, 4H), 2.61 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9 (C), 136.2 (C), 136.2 (C), 135.0 (C), 134.4 (C), 133.5 (C), 130.0 (CH), 129.9 (CH), 129.8 (CH), 129.4 (C), 128.2 (CH), 127.4 (CH), 126.4 (CH), 124.4 (CH), 123.6 (CH), 121.2 (C), 118.9

(CH), 114.5 (CH), 21.6 (CH_3), 13.5 (CH_3). EI HRMS: calcd. For $[C_{22}H_{18}ClNO_2S+H]^+$: 396.0819, found: 396.0819

3-(2-Methyl-1-tosyl-1*H*-indol-3-yl)benzonitrile (**18k**)

Following the general method, from iodoenamine **16a** (0.05 mmol) and 3-formylbenzonitrile tosylhydrazone (29.9 mg, 0.1 mmol) were obtained 10 mg of **18k** (53 % isolated yield) as a colourless oil. R_f 0.16 (10:1 hexane : AcOEt).

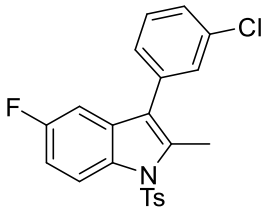


18k

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.80 – 7.62 (m, 4H), 7.52 – 7.40 (m, 2H), 7.40 – 7.31 (m, 3H), 2.68 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0 (C), 136.1 (C), 136.1 (C), 134.7 (C), 134.4 (CH), 133.8 (C), 133.5 (CH), 130.8 (CH), 130.0 (CH), 129.5 (CH), 129.0(C), 126.4 (CH), 124.7 (CH), 123.8 (CH), 120.2 (C), 118.6 (C), 118.5 (CH), 114.6 (CH), 112.9 (C), 21.6 (CH_3), 13.4 (CH_3). EI HRMS: calcd. For $[C_{23}H_{18}N_2O_2S+H]^+$: 387.1159, found: 387.1161

3-(3-Chlorophenyl)-5-fluoro-2-methyl-1-tosyl-1*H*-indole (**18l**)

Following the general method, from iodoenamine **16d** (0.05 mmol) and 3-chlorobenzaldehyde tosylhydrazone (30.8 mg, 0.1 mmol) were obtained 12 mg of **18l** (60 % isolated yield) as a colourless oil. R_f 0.23 (20:1 hexane : AcOEt).



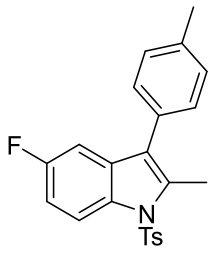
18l

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (ddd, *J* = 8.5, 4.6, 1.2 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.37 (m, 2H), 7.32 (td, *J* = 1.8, 0.7 Hz, 1H), 7.29 – 7.28 (m, 1H), 7.27 – 7.26 (m, 1H), 7.25 – 7.20 (dt, J = 6.9, 1.8 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 2.59 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.98 (C-F, d, ^2J = 240.6 Hz), 145.1 (C), 136.0 (C), 135.2 (C),

134.5 (C), 134.5 (C), 132.4 (C, d, $^{5}J_{C\text{-}F}$= 1.1 Hz), 130.6 (C, d, $^{4}J_{C\text{-}F}$= 9.4 Hz), 130.0 (CH), 129.9 (CH), 129.8 (CH), 128.0 (CH), 127.7 (CH), 126.4 (CH), 121.1 (C, d, $^{5}J_{C\text{-}F}$= 3.8 Hz), 115.68 (CH, d, $^{4}J_{C\text{-}F}$= 8.8 Hz), 112.17 (CH, d, $^{3}J_{C\text{-}F}$= 24.8 Hz), 104.64 (CH, d, $^{3}J_{C\text{-}F}$= 24.7 Hz), 21.6 (CH_3), 13.6 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -119.35. EI HRMS: calcd. For $[C_{22}H_{17}ClFNO_2S+H]^+$: 414.0711, found: 414.0713

5-Fluoro-2-methyl-3-(*p*-tolyl)-1-tosyl-1*H*-indole (**18m**)

Following the general method, from iodoenamine **16d** (0.05 mmol) and *p*-tolualdehyde tosylhydrazone (28.8 mg, 0.1 mmol) were obtained 11 mg of **18m** (58 % isolated yield) as a colourless oil. R_f 0.20 (20:1 hexane : AcOEt).

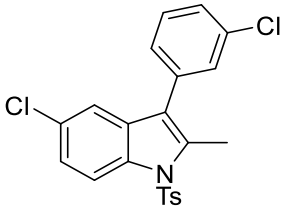


18m

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.9, 4.5 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.20 (m, 6H), 7.06 (dq, *J* = 8.5, 2.6 Hz, 2H), 2.59 (s, 3H), 2.43 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.93 (C-F, d, ^{2}J = 240.1 Hz), 144.9 (C), 137.3 (C), 136.1 (C), 134.7 (C), 132.4 (C), 131.28 (C, d, $^{4}J_{C\text{-}F}$= 9.5 Hz), 129.9 (CH), 129.7 (CH), 129.5 (C), 129.4 (CH), 126.3 (CH), 122.4 (C, d, $^{5}J_{C\text{-}F}$= 4.0 Hz), 115.5 (CH, d, $^{4}J_{C\text{-}F}$= 9.0 Hz), 111.8 (CH, d, $^{3}J_{C\text{-}F}$= 25.0 Hz), 104.9 (CH, d, $^{3}J_{C\text{-}F}$= 24.8 Hz), 21.6 (CH_3), 21.2 (CH_3), 13.6 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -119.84. EI HRMS: calcd. For $[C_{23}H_{20}FNO_2S+H]^+$: 394.1272, found: 394.1271

5-Chloro-3-(3-chlorophenyl)-2-methyl-1-tosyl-1*H*-indole (**18n**)

Following the general method, from iodoenamine **16b** (0.05 mmol) and 3-chlorobenzaldehyde tosylhydrazone (30.8 mg, 0.1 mmol) were obtained 13 mg of **18n** (62 % isolated yield) as a colourless oil. R_f 0.24 (20:1 hexane : AcOEt).

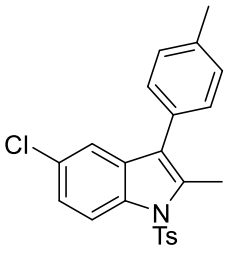


18n

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.9 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.34 (d, *J* = 2.1 Hz, 1H), 7.32 – 7.28 (m, 3H), 7.28 – 7.26 (m, 1H), 7.22 (dt, *J* = 6.9, 1.8 Hz, 1H), 2.58 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2 (C), 135.9 (C), 134.9 (C), 134.5 (C), 134.5 (C), 134.3 (C), 130.7 (C), 130.0 (CH), 130.0 (CH), 129.8 (CH), 129.5 (C), 128.1 (CH), 127.8 (CH), 126.4 (CH), 124.5 (CH), 120.6 (C), 118.5 (CH), 115.6 (CH), 21.6 (CH_3), 13.5 (CH_3). EI HRMS: calcd. For $[C_{22}H_{17}Cl_2NO_2S]^+$: 429.0351, found: 429.0351

5-Chloro-2-methyl-3-(*p*-tolyl)-1-tosyl-1*H*-indole (**18o**)

Following the general method, from iodoenamine **16b** (0.05 mmol) and *p*-tolualdehyde tosylhydrazone (28.8 mg, 0.1 mmol) were obtained 10 mg of **18o** (50 % isolated yield) as a colourless oil. R_f 0.17 (20:1 hexane : AcOEt).

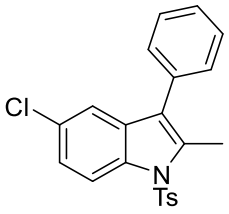


18o

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 2.2 Hz, 1H), 7.31 – 7.29 (m, 1H), 7.28 – 7.26 (m, 2H), 7.26 – 7.20 (m, 4H), 2.58 (s, 3H), 2.43 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0 (C), 137.3 (C), 136.1 (C), 134.5 (C), 134.4 (C), 131.4 (C), 130.0 (CH), 129.7 (CH), 129.4 (CH), 129.3 (C), 129.3 (C), 126.4 (CH), 124.2 (CH), 121.9 (C), 118.8 (CH), 115.5 (CH), 21.6 (CH_3), 21.2 (CH_3), 13.5 (CH_3). EI HRMS: calcd. For $[C_{23}H_{20}ClNO_2S+H]^+$: 410.0969, found: 410.0976

5-Chloro-2-methyl-3-phenyl-1-tosyl-1*H*-indole (**18p**)

Following the general method, from iodoenamine **16b** (0.05 mmol) and benzaldehyde tosylhydrazone (27.4 mg, 0.1 mmol) were obtained 10 mg of **18p** (52 % isolated yield) as a colourless oil. R_f 0.18 (20:1 hexane : AcOEt).

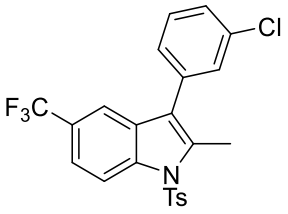


18p

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.41 (m, 3H), 7.41 – 7.30 (m, 5H), 7.28 – 7.24 (m, 1H), 2.60 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0 (C), 136.0 (C), 135.1 (C), 134.6 (C), 132.4 (C), 131.2 (C), 130.0 (CH), 129.9 (CH), 129.4 (C), 128.7 (CH), 127.6 (CH), 126.4 (CH), 124.3 (CH), 121.9 (C), 118.8 (CH), 115.5 (CH), 21.6 (CH_3), 13.5 (CH_3). EI HRMS: calcd. For $[C_{22}H_{18}ClNO_2S+H]^+$: 396.0816, found: 396.0819

3-(3-Chlorophenyl)-2-methyl-1-tosyl-5-(trifluoromethyl)-1*H*-indole (**18q**)

Following the general method, from iodoenamine **16c** (0.05 mmol) and 3-chlorobenzaldehyde tosylhydrazone (30.8 mg, 0.1 mmol) were obtained 11 mg of **18q** (50 % isolated yield) as a colourless oil. R_f 0.21 (20:1 hexane : AcOEt).



18q

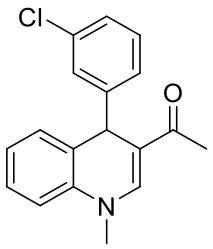
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.65 – 7.55 (m, 2H), 7.46 – 7.38 (m, 2H), 7.36 – 7.28 (m, 3H), 7.24 (dt, *J* = 6.9, 1.8 Hz, 1H), 2.61 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4 (C), 137.6 (C), 135.9 (C), 135.4 (C), 134.6 (C), 134.1 (C), 130.1 (CH), 130.1 (CH), 129.9 (CH), 129.2 (C), 128.2 (CH), 127.9 (CH), 126.5(CH), 126.2 (C), 121.1 (q, CH-CF_3, *J* = 3.7 Hz), 121.0 (C), 116.3 (q, CH-CF_3, *J* = 4.1 Hz), 114.7 (CH), 21.6 (CH_3), 13.4 (CH_3). EI HRMS: calcd. For $[C_{23}H_{17}ClF_3NO_2S+H]^+$: 464.0689, found: 464.0693

E.3.3 General procedure and characterization data for 1,4-dihydroquinolines 21

A carousel reaction tube was charged under nitrogen atmosphere with the corresponding iodoenaminone **19**, tetrakis(triphenylphosphine)palladium(0) (6 mol %), lithium tert-butoxide (6 equiv), and acetonitrile (1 mL). The *N*-tosylhydrazone (2 equiv) is diluted in 2 mL of acetonitrile and then added via syringe pump over a period of 2 h. The reaction mixture was stirred at 110 °C during the slow addiction. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane or a mixture of hexane / ethyl acetate as eluent.

1-(4-(3-Chlorophenyl)-1-methyl-1,4-dihydroquinolin-3-yl)ethan-1-one (**21a**)

Following the general method, from iodoenaminone **19a** (0.07 mmol) and 3-chlorobenzaldehyde tosylhydrazone (47.1 mg, 0.15 mmol) were obtained 17 mg of **21a** (77 % isolated yield) as a yellow oil. R_f 0.15 (2:1 hexane : AcOEt).

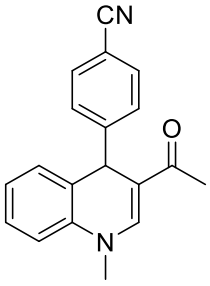


21a

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.24 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.18 – 7.12 (m, 4H), 7.09 (dt, *J* = 7.3, 1.9 Hz, 1H), 7.04 (td, *J* = 7.5, 1.2 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 5.33 (s, 1H), 3.47 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.5 (C), 149.5 (C), 143.7 (CH), 137.4 (C), 134.1 (C), 130.4 (CH), 129.5 (CH), 127.5 (CH), 127.4 (CH), 126.4 (C), 126.3 (CH), 125.7 (CH), 124.1 (CH), 113.4 (C), 112.9 (CH), 41.2 (CH), 39.5 (CH_3), 24.6 (CH_3). EI HRMS: calcd. For $[C_{18}H_{16}ClNO+H]^+$: 298.0982, found: 298.0993

4-(3-Acetyl-1-methyl-1,4-dihydroquinolin-4-yl)benzonitrile (**21b**)

Following the general method, from iodoenaminone **19a** (0.05 mmol) and 4-formylbenzonitrile tosylhydrazone (29.8 mg, 0.1 mmol) were obtained 12 mg of **21b** (86 % isolated yield) as a yellow oil. R_f 0.20 (1:1 hexane : AcOEt).

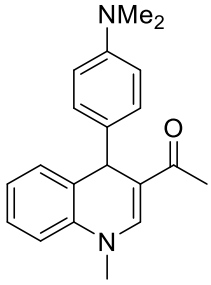


21b

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.40 (s, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.26 (ddd, *J* = 8.6, 7.4, 1.6 Hz, 1H), 7.12 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.05 (td, *J* = 7.4, 1.1 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 5.41 (s, 1H), 3.49 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.4 (C), 152.6 (C), 143.9 (CH), 137.5 (C), 132.2 (CH), 130.5 (CH), 128.3 (CH), 127.8 (CH), 125.7 (C), 124.3 (CH), 119.1 (C), 113.1 (C), 113.0 (CH), 109.7 (C), 41.6 (CH), 39.5 (CH_3), 24.4 (CH_3). To confirm the structure of the expected product 2D NMR experiments were performed. EI HRMS: calcd. For $[C_{19}H_{16}N_2O+H]^+$: 289.1334, found: 289.1335

1-(4-(4-(Dimethylamino)phenyl)-1-methyl-1,4-dihydroquinolin-3-yl)ethan-1-one (**21c**)

Following the general method, from iodoenaminone **19a** (0.05 mmol) and 4-(dimethylamino)benzaldehyde tosylhydrazone (35.5 mg, 0.11 mmol) were obtained 11 mg of **21c** (65 % isolated yield) as a red oil. R_f 0.14 (1:1 hexane : AcOEt).



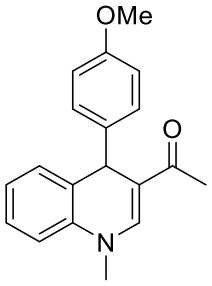
21c

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.19 (td, *J* = 7.2, 1.7 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 7.01 (td, *J* = 7.5, 1.1 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 8.7 Hz, 2H),

5.24 (s, 1H), 3.43 (s, 3H), 2.87 (s, 6H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1 (C), 149.0 (C), 143.0 (CH), 137.6 (C), 136.3 (C), 130.4 (CH), 127.9 (CH), 127.9 (C), 126.8 (CH), 123.9 (CH), 114.3 (C), 112.6 (CH), 112.4 (CH), 40.6 (CH_3), 40.3 (CH), 39.3 (CH_3), 24.9 (CH_3). EI HRMS: calcd. For $[C_{20}H_{22}N_2O+H]^+$: 307.1806, found: 307.1804

1-(4-(4-Methoxyphenyl)-1-methyl-1,4-dihydroquinolin-3-yl)ethan-1-one (**21d**)

Following the general method, from iodoenaminone **19a** (0.08 mmol) and *p*-anisaldehyde tosylhydrazone (50.5 mg, 0.16 mmol) were obtained 12 mg of **21d** (50 % isolated yield) as a yellow oil. R_f 0.10 (2:1 hexane : AcOEt).

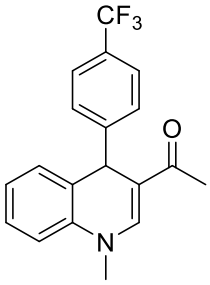


21d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.25 – 7.15 (m, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.02 (td, *J* = 7.4, 1.2 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 2H), 5.29 (s, 1H), 3.73 (s, 3H), 3.45 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9 (C), 157.8 (C), 143.2 (CH), 140.2 (C), 137.5 (C), 130.4 (CH), 128.3 (CH), 127.5 (C), 127.0 (CH), 124.0 (CH), 114.2 (C), 113.6 (CH), 112.6 (CH), 55.1 (CH_3), 40.5 (CH), 39.4 (CH_3), 24.7 (CH_3). EI HRMS: calcd. For $[C_{19}H_{19}NO_2+H]^+$: 294.1487, found: 294.1488

1-(1-Methyl-4-(4-(trifluoromethyl)phenyl)-1,4-dihydroquinolin-3-yl)ethan-1-one (**21e**)

Following the general method, from iodoenaminone **19a** (0.05 mmol) and 4-(trifluoromethyl)benzaldehyde tosylhydrazone (31.8 mg, 0.09 mmol) were obtained 9 mg of **21e** (60 % isolated yield) as a yellow oil. R_f 0.34 (1:1 hexane : AcOEt).

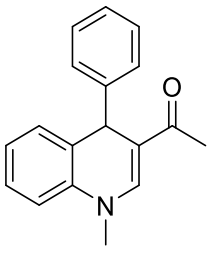


21e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 2H), 7.40 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.21 (m, 1H), 7.15 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.05 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 5.41 (s, 1H), 3.48 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5 (C), 151.3 (C), 143.7 (CH), 137.5 (C), 130.4 (CH), 128.4 (C), 127.7 (CH), 127.5 (CH), 126.2 (C), 125.3 (q, CH-CF_3, *J* = 3.7 Hz), 124.2 (CH), 113.5 (C), 112.9 (CH), 41.3 (CH), 39.5 (CH_3), 24.5 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.35. EI HRMS: calcd. For $[C_{19}H_{16}F_3NO+H]^+$: 332.1253, found: 332.1256

1-(1-Methyl-4-phenyl-1,4-dihydroquinolin-3-yl)ethan-1-one (**21f**)

Following the general method, from iodoenaminone **19a** (0.07 mmol) and benzaldehyde tosylhydrazone (37.8 mg, 0.14 mmol) were obtained 11 mg of **21f** (61 % isolated yield) as a yellow oil. R_f 0.35 (1:1 hexane : AcOEt).



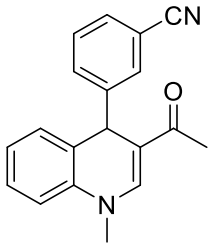
21f

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.24 – 7.17 (m, 6H), 7.14 – 7.07 (m, 1H), 7.02 (td, *J* = 7.6, 1.1 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 5.34 (s, 1H), 3.45 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8 (C), 147.6 (C), 143.4 (CH), 137.6 (C), 130.4 (CH), 128.3

(CH), 127.3 (CH), 127.2 (C), 127.1 (CH), 126.0 (CH), 124.0 (CH), 114.0 (C), 112.6 (CH), 41.4 (CH), 39.4 (CH_3), 24.7 (CH_3). EI HRMS: calcd. For $[C_{18}H_{17}NO+H]^+$: 264.1384, found: 264.1382

3-(3-Acetyl-1-methyl-1,4-dihydroquinolin-4-yl)benzonitrile (**21g**)

Following the general method, from iodoenaminone **19a** (0.04 mmol) and 3-formylbenzonitrile tosylhydrazone (25.8 mg, 0.08 mmol) were obtained 8 mg of **21g** (66 % isolated yield) as a yellow oil. R_f 0.20 (1:1 hexane : AcOEt).

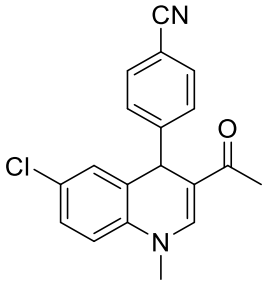


21g

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.42 – 7.38 (m, 3H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.12 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.06 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.38 (s, 1H), 3.49 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4 (C), 148.8 (C), 143.9 (CH), 137.4 (C), 132.1 (CH), 131.3 (CH), 130.4 (CH), 129.7 (CH), 128.9 (CH), 127.7 (CH), 125.8 (C), 124.3 (CH), 119.2 (C), 113.2 (C), 113.0 (CH), 112.2 (C), 41.0 (CH), 39.6 (CH_3), 24.4 (CH_3). EI HRMS: calcd. For $[C_{19}H_{16}N_2O+H]^+$: 289.1336, found: 289.1335

4-(3-Acetyl-6-chloro-1-methyl-1,4-dihydroquinolin-4-yl)benzonitrile (**21h**)

Following the general method, from iodoenaminone **19b** (0.07 mmol) and 4-formylbenzonitrile tosylhydrazone (44.7 mg, 0.14 mmol) were obtained 16 mg of **21h** (70 % isolated yield) as a yellow oil. R_f 0.12 (1:1 hexane : AcOEt).

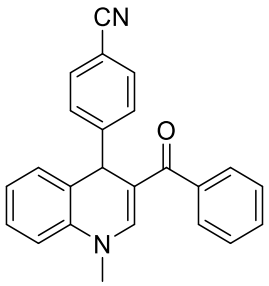


21h

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.37 (s, 1H), 7.31 – 7.27 (m, 2H), 7.20 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 5.33 (s, 1H), 3.46 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3 (C), 151.9 (C), 143.5 (CH), 136.2 (C), 132.3 (CH), 130.2 (CH), 129.2 (C), 128.3 (CH), 127.7 (CH), 127.4 (C), 118.9 (C), 114.3 (CH), 113.1 (C), 110.1 (C), 41.5 (CH), 39.6 (CH_3), 24.5 (CH_3). EI HRMS: calcd. For $[C_{19}H_{15}ClN_2O+H]^+$: 323.0943, found: 323.0945

4-(3-Benzoyl-1-methyl-1,4-dihydroquinolin-4-yl)benzonitrile (**21i**)

Following the general method, from iodoenaminone **19d** (0.06 mmol) and 4-formylbenzonitrile tosylhydrazone (37.9 mg, 0.12 mmol) were obtained 15 mg of **21i** (68 % isolated yield) as a yellow oil. R_f 0.16 (3:1 hexane : AcOEt).



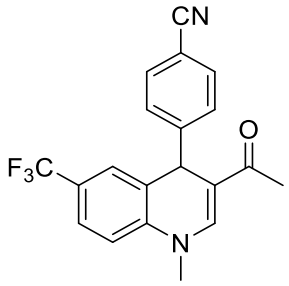
21i

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.50 – 7.45 (m, 3H), 7.44 – 7.38 (m, 4H), 7.29 – 7.24 (m, 1H), 7.19 – 7.14 (m, 2H), 7.08 (td, *J* = 7.4, 1.2 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 5.60 (s, 1H), 3.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2 (C), 152.5 (C), 147.4

(CH), 139.7 (C), 137.3 (C), 132.3 (CH), 130.6 (CH), 130.3 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 127.9 (CH), 125.7 (C), 124.6 (CH), 119.1 (C), 113.1 (CH), 112.3 (C), 109.8 (C), 41.9 (CH), 39.6 (CH_3). EI HRMS: calcd. For $[C_{24}H_{18}N_2O+H]^+$: 351.1497, found: 351.1491

4-(3-Acetyl-1-methyl-6-(trifluoromethyl)-1,4-dihydroquinolin-4-yl)benzonitrile (**21j**)

Following the general method, from iodoenaminone **19c** (0.05 mmol) and 4-formylbenzonitrile tosylhydrazone (29.2 mg, 0.1 mmol) were obtained 9 mg of **21j** (68 % isolated yield) as a yellow oil. R_f 0.10 (1:1 hexane : AcOEt).

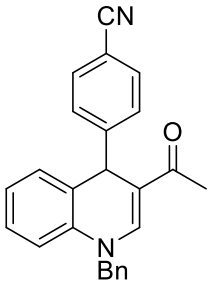


21j

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.47 (m, 3H), 7.38 (s, 1H), 7.35 (bs, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 1H), 5.41 (s, 1H), 3.51 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4 (C), 151.5 (C), 143.3 (CH), 140.3 (C), 132.4 (CH), 128.2 (CH), 127.44 (q, CH-CF_3, *J* = 3.6 Hz), 126.0 (C), 125.0 (q, CH-CF_3, *J* = 3.6 Hz), 124.9 (C), 118.8 (C), 114.1 (C), 113.0 (CH), 110.3 (C), 41.4 (CH), 39.6 (CH_3), 24.6 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.00. EI HRMS: calcd. For $[C_{20}H_{15}F_3N_2O+H]^+$: 357.1206, found: 357.1209

4-(3-Acetyl-1-benzyl-1,4-dihydroquinolin-4-yl)benzonitrile (**21k**)

Following the general method, from iodoenaminone **19e** (0.06 mmol) and 4-formylbenzonitrile tosylhydrazone (37.9 mg, 0.12 mmol) were obtained 22 mg of **21k** (96 % isolated yield) as a yellow oil. R_f 0.11 (2:1 hexane : AcOEt).

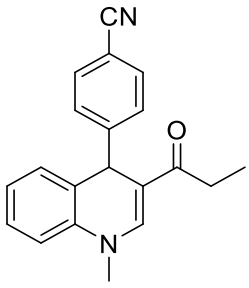


21k

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 3H), 7.44 – 7.37 (m, 3H), 7.36 – 7.27 (m, 4H), 7.16 – 7.08 (m, 2H), 6.99 (t, *J* = 6.8 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 5.46 (s, 1H), 5.08 (d, *J* = 16.6 Hz, 1H), 4.96 (d, *J* = 16.7 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7 (C), 152.4 (C), 143.6 (CH), 136.7 (C), 135.7 (C), 132.2 (CH), 130.6 (CH), 129.1 (CH), 128.4 (CH), 128.1 (CH), 127.7 (CH), 126.3 (CH), 125.8 (C), 124.4 (CH), 119.1 (C), 114.1 (CH), 113.6 (C), 109.8 (C), 55.3 (CH_2), 41.5 (CH), 24.5 (CH_3). EI HRMS: calcd. For $[C_{25}H_{20}N_2O+H]^+$: 365.1641, found: 365.1648

4-(1-Methyl-3-propionyl-1,4-dihydroquinolin-4-yl)benzonitrile (**21l**)

Following the general method, from iodoenaminone **19g** (0.08 mmol) and 4-formylbenzonitrile tosylhydrazone (49.4 mg, 0.16 mmol) were obtained 15 mg of **21l** (62 % isolated yield) as a yellow oil. R_f 0.17 (2:1 hexane : AcOEt).



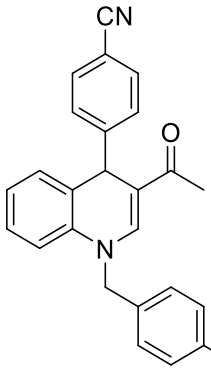
6l

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.43 (s, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.21 (m, 1H), 7.11 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.04 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.99 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.39 (s, 1H), 3.47 (s, 3H), 2.69 – 2.45 (m, 2H), 1.09 (t, *J* = 7.4 Hz,

3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6 (C), 152.7 (C), 142.9 (CH), 137.5 (C), 132.2 (CH), 130.4 (CH), 128.2 (CH), 127.7 (CH), 125.7 (C), 124.2 (CH), 119.1 (C), 112.9 (CH), 112.3 (C), 109.7 (C), 41.7 (CH), 39.5 (CH_3), 29.3 (CH_2), 9.2 (CH_3). EI HRMS: calcd. For $[C_{20}H_{18}N_2O+H]^+$: 303.1483, found: 303.1478

4-(3-Acetyl-1-(4-methoxybenzyl)-1,4-dihydroquinolin-4-yl)benzonitrile (**21m**)

Following the general method, from iodoenaminone **19f** (0.05 mmol) and 4-formylbenzonitrile tosylhydrazone (30.8 mg, 0.10 mmol) were obtained 12 mg of **21m** (60 % isolated yield) as a yellow oil. R_f 0.10 (2:1 hexane : AcOEt).



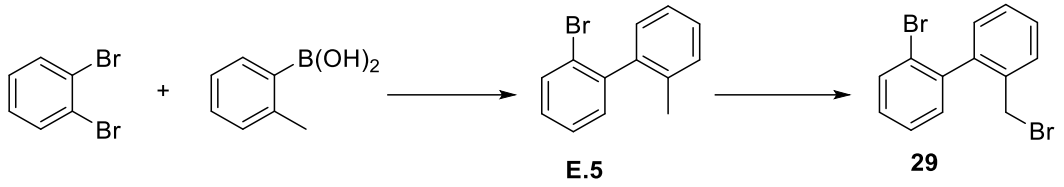
21m

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 3H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.17 – 7.09 (m, 2H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.97 – 6.90 (m, 3H), 5.45 (s, 1H), 5.02 (d, *J* = 16.2 Hz, 1H), 4.88 (d, *J* = 16.4 Hz, 1H), 3.84 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6 (C), 159.4 (C), 152.4 (C), 143.4 (CH), 136.7 (C), 132.2 (CH), 130.6 (CH), 128.4 (CH), 127.7 (CH), 127.7 (CH), 127.5 (C), 125.9 (C), 124.3 (CH), 119.1 (C), 114.5 (CH), 114.1 (CH), 113.5 (C), 109.8 (C), 55.3 (CH_3), 54.9 (CH_2), 41.5 (CH), 24.5 (CH_3). EI HRMS: calcd. For $[C_{26}H_{22}N_2O_2+H]^+$: 395.1758, found: 395.1754

E.4 Chapter 2: Synthesis of condensed carbo- and heterocycles *via* Pd-catalyzed auto-tandem cyclizations

E.4.1 Synthesis of starting materials

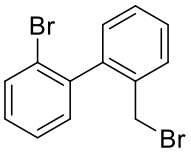
- Synthesis of 2-Bromo-2'-(bromomethyl)-1,1'-biphenyl (**29**)



E.5 **29**

2-Bromo-2'-methyl-1,1'-biphenyl **E.5** was synthesized following the processes described in the literature from 1,2-dibromobenzene and *o*-tolylboronic acid.[195]

A flask was charged with 2-bromo-2'-methyl-1,1'-biphenyl **E.5** (4.32 mmol), *N*-bromosuccinimide (0.95 equiv, 4.1 mmol), benzoyl peroxide (5 mg per mmol, 21.6 mg) and CCl_4 (21.6 mL). The reaction mixture was refluxed at 80 °C for about 40 h and then cooled to rt, filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexane as eluent R_f 0.21 (hexane). Dibromide **29** was prepared as a colourless oil in 56 % isolated yield (788 mg). Spectroscopic data were consistent with those reported in the literature.[196]

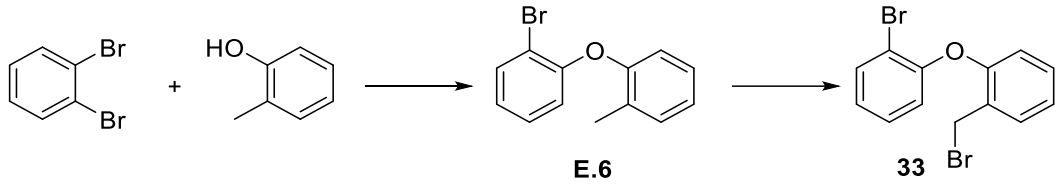


29

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.36 (m, 4H), 7.37 – 7.27 (m, 1H), 7.21 (d, *J* = 6.6 Hz, 1H), 4.48 (d, *J* = 10.2 Hz, 1H), 4.26 (d, *J* = 10.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0 (C), 140.5 (C), 135.5 (C), 132.6 (CH), 131.3 (CH), 130.4 (CH), 130.3 (CH), 129.4 (CH), 128.7 (CH), 128.4 (CH), 127.2 (CH), 123.6 (C), 31.7 (CH_2).

[195] C.-G. Dong, T.-P. Liu, Q.-S Hu, *Synlett.* **2009**, 1081-1086.
[196] L. J. Altman, T. R. Erdman, *J. Org. Chem.* **1970**, *35*, 3237–3239.

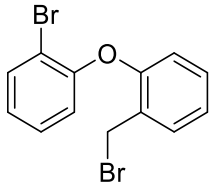
- Synthesis of 1-bromo-2-(2-(bromomethyl)phenoxy)benzene (**33**)



E.6 **33**

A Schlenk under nitrogen atmosphere was charged with 1,2-dibromobenzene (4 mmol), *o*-cresol (1.5 equiv, 6 mmol), CuI (0.4 mmol,10 mol %), picolinic acid (0.8 mmol, 20 mol%), K_3PO_4 (1.5 equiv, 6 mmol) and DMSO (20 mL). The solution was stirred at 110°C for 24 h. After cooling to room temperature the reaction mixture was diluted with AcOEt (20 mL) and filtered through a short pad of silica gel. The filtrate was treated with a saturated solution of $NaHCO_3$ (20 mL) and extracted with AcOEt (2x40 mL). The combined organic layers were washed with water (5x20 mL) dried over sodium sulfate and concentrated. The resulting residue was purified by flash chromatography on silica gel using hexane as eluent to give **E.6** (340 mg) as a colourless oil with a yield of 32 %.

A flask was charged with 1-bromo-2-(*o*-tolyloxy)benzene **E.6** (1.29 mmol), *N*-bromosuccinimide (0.95 equiv, 1.22 mmol), benzoyl peroxide (5 mg per mmol, 6.5 mg) and CCl_4 (6.5 mL). The reaction mixture was refluxed at 80 °C for about 40 h and then cooled to rt, filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexane as eluent R_f 0.22 (hexane), to afford compound **33** as a colourless oil in 61 % isolated yield (269 mg).



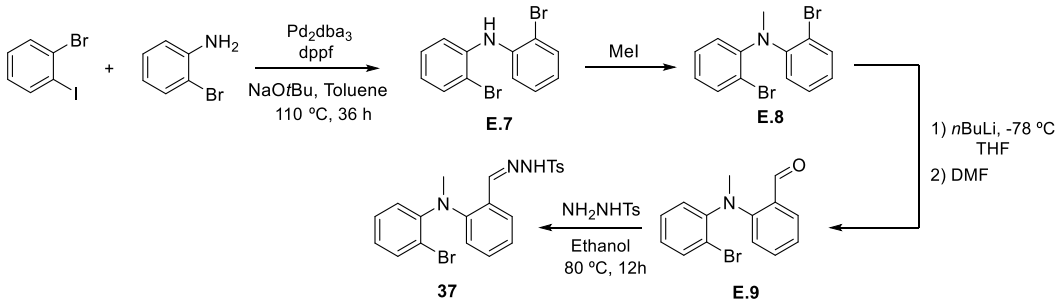
33

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.31 (dt, *J* = 15.3, 7.8 Hz, 2H), 7.18 – 7.05 (m, 3H), 6.75 (d, *J* = 8.1 Hz, 1H), 4.72 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9 (C), 153.2 (C), 133.9 (CH), 131.5 (CH), 130.2 (CH), 128.9 (CH), 128.1 (C), 125.5 (CH), 123.7 (CH), 121.0 (CH), 117.3 (CH), 115.1 (C), 28.1 (CH_2). ESI HRMS: calcd. for $[C_{13}H_{10}Br_2NaO]^+$: 362.8990, found: 362.8989

- Synthesis of *N*-tosylhydrazones **35a** and **35b**

N-Tosylhydrazones **35a** and **35b** were synthesized following the processes described in the literature.[197]

- Synthesis of *N*-tosylhydrazone **37**



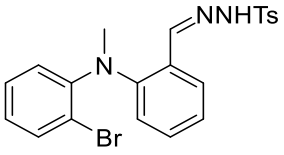
N-(2-Bromophenyl)-*N*-methylaniline **E.8** was prepared following a previously described procedure.[198]

A solution of **E.8** (2.07 mmol, 707 mg) in dry THF (6 mL) at -78 °C was prepared in a Schlenk under nitrogen atmosphere. Then, 0.723 mL of *n*-BuLi (1.6 M in hexane) was added dropwise and the reaction was stirred 1 h at -78 °C. After this time, a solution of DMF (0.197 mL) in THF (1 mL) was poured slowly and the reaction was stirred 1h at -78 °C and 2.5 h at rt. An aqueous solution 1N HCl (10 mL) was added and the reaction was allowed to stir for one additional hour. The reaction mixture was extracted AcOEt (3x15 mL). The combined organic layers were washed with water, dried over sodium sulfate and concentrated. The residue of the reaction was purified by flash chromatography on silica gel using a mixture of hexane/CH_2Cl_2 (2: 1) as eluent (R_f 0.32), to give 2-((2-bromophenyl)(methyl)amino)benzaldehyde **E.9** as a yellow oil (330 mg, 58 %).

In a round bottom flask was introduced aldehyde **E.9** (1.09 mmol, 317 mg), *N*-tosylhydrazide (1.21 mmol) and ethanol (2.4 mL). The reaction mixture was stirred 12 h at 80 °C and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of hexane/ethyl acetate (4: 1) as

[197] J. Aziz, G. Frison, M. Gómez, J.-D. Brion, A. Hamze, M. Alami, *ACS Catal.* **2014**, *4*, 4498–4503.
[198] M. Uchiyama, Y. Matsumoto, S. Nakamura, T. Ohwada, N. Kobayashi, N. Yamashita, A. Matsumiya, T. Sakamoto, *J. Am. Chem. Soc.* **2004**, *126*, 8755–8759.

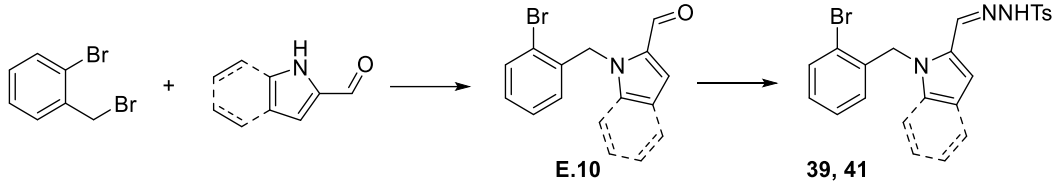
eluent (R_f 0.25) to provide *N*-tosylhydrazone **37** as white solid (400 mg, 80 %). m.p = 87-88 °C



37

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.13 (s, 1H), 7.85 (d, *J* = 6.0 Hz, 2H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.12 (m, 4H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.04 (d, *J* = 2.0 Hz, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0 (C), 149.3 (C), 146.5 (CH), 143.9 (C), 135.3 (C), 134.2 (CH), 130.9 (CH), 129.6 (CH), 128.4 (CH), 127.9 (CH), 127.8 (C), 127.8 (CH), 125.1 (CH), 124.7 (CH), 123.8 (CH), 121.8 (CH), 119.7 (C), 42.8 (CH_3), 21.6 (CH_3).

- Synthesis of *N*-tosylhydrazones 39 and 41



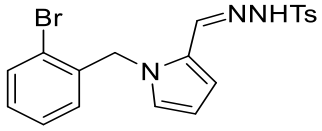
E.10 **39, 41**

A round bottom flask was charged with the corresponding heterocyclic aldehyde (2.1 mmol), 2-bromobenzyl bromide (2.52 mmol), TBAB (0.21 mmol) and CH_2Cl_2 (10 mL). After stirring for two of minutes at rt, an aqueous solution 1.25 M NaOH (1.2 mL) was added dropwise during a period of 30 min at 0 °C. After this time, the mixture was allowed to stir at rt overnight and then, diluted with H_2O and extracted with CH_2Cl_2 (3x 30 mL). The organic layer was washed with 2 M HCl (aq), $NaHCO_3$ (aq) and brine. The residue was dried with sodium sulfate and concentrated under reduced pressure. The crude of the reaction was purified by flash chromatography on silica gel using a mixture of hexane/ ethyl acetate as eluent to give aldehydes **E.10**.

Formation of the *N*-tosyllhydrazones **39** and **41**: In a round bottom flask was introduced carbonyl **E.10** (1.13 mmol), *N*-tosylhydrazide (1.25 mmol) and ethanol (2.5 mL). The reaction mixture was stirred 12 h at 80 °C and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of hexane/ ethyl acetate as eluent to provide hydrazones **39** and **41**.

N'-((1-(2-Bromobenzyl)-1*H*-pyrrol-2-yl)methylene)-4-methylbenzenesulfonohydrazide **39**

The title compound **39** was prepared as brown solid in 78 % isolated yield (384 mg) (overall yield for the two steps) from pyrrole-2-carboxaldehyde. R_f 0.33 (2:1 hexane : AcOEt). m.p = 135 – 136 °C

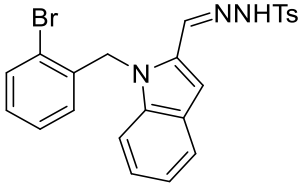


39

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.69 (s, 1H), 7.63 – 7.54 (m, 3H), 7.18 – 7.07 (m, 4H), 6.74 (s, 1H), 6.52 – 6.46 (m, 1H), 6.44 – 6.36 (m, 1H), 6.23 (dd, *J* = 3.9, 2.5 Hz, 1H), 5.52 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7 (C), 142.2 (CH), 137.7 (C), 135.0 (C), 132.5 (CH), 129.5 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 127.7 (2xCH), 126.2 (C), 122.0 (C), 117.6 (CH), 109.6 (CH), 52.4 (CH_2), 21.5 (CH_3).

N'-((1-(2-Bromobenzyl)-1*H*-indol-2-yl)methylene)-4-methylbenzenesulfonohydrazide **41**

The title compound **41** was prepared as white solid in 75 % isolated yield (408 mg) (overall yield for the two steps) from indole-2-carboxaldehyde. R_f 0.36 (2:1 hexane : AcOEt). m.p = 177 – 178 °C



41

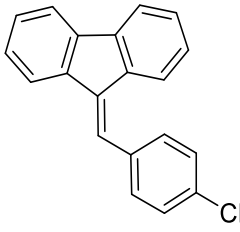
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.00 (s, 1H), 7.92 (s, 1H), 7.70 (dd, *J* = 11.8, 8.0 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.27 – 7.09 (m, 5H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 6.17 (d, *J* = 7.8 Hz, 1H), 5.84 (s, 2H), 5.37 (d, *J* = 1.5 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 144.2 (C), 141.0 (CH), 139.5 (C), 137.1 (C), 134.7 (C), 132.6 (CH), 132.0 (C), 129.6 (CH), 128.4 (CH), 127.5 (CH), 127.5 (CH), 127.3 (C), 126.8 (CH), 124.6 (CH), 121.7 (C), 121.6 (CH), 120.7 (CH), 110.4 (CH), 110.0 (CH), 48.8 (CH_2), 21.2 (CH_3).

E.4.2 General procedure and characterization data for fluorenes 31

The reaction was performed in a 2.5 mL microwave glass vial from Biotage (ref. 355631), which was sealed with their cap with septum and heated in a PEG bath on a stirring hot plate equipped with a temperature controler. The reaction vial was charged under nitrogen atmosphere with the biphenyl bromide **29** (0.1 mmol, 32.3 mg), *N*-tosylhydrazone (1 equiv), tris(dibenzylideneacetone)dipalladium(0) (5 mol %), tri(2-furyl)phosphine (30 mol %), lithium *tert*-butoxide (3 equiv), cesium carbonate (3 equiv) and 1,4-dioxane (2 mL). The vial was sealed and then was stirred at 120 °C for 12 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane or a mixture of hexane/ ethyl acetate.

9-(4-Chlorobenzylidene)-9*H*-fluorene (**31a**)

Following the general method, biphenyl bromide **29** (0.1 mmol) and 4-chlorobenzaldehyde tosylhydrazone (31 mg, 0.1 mmol) were obtained 23 mg of **31a** (79 % isolated yield) as a white solid. R_f 0.22 (hexane). m.p = 147 – 148 °C

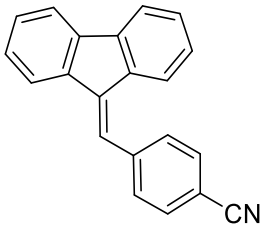


31a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 6.9 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 2jH), 7.62 (s, 1H), 7.58 – 7.50 (m, 3H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.40 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3 (C), 139.2 (C), 139.2 (C), 137.0 (C), 136.2 (C), 135.3 (C), 133.8 (C), 130.6 (CH), 128.7 (2xCH), 128.4 (CH), 127.0 (CH), 126.7 (CH), 125.6 (CH), 124.3 (CH), 120.2 (CH), 119.8 (CH), 119.6 (CH). ESI HRMS: calcd. For $[C_{20}H_{14}Cl]^+$: 289.0778, found: 289.0770

4-((9*H*-Fluoren-9-ylidene)methyl)benzonitrile (**31b**)

Following the general method, biphenyl bromide **29** (0.1 mmol) and 4-formylbenzonitrile tosylhydrazone (30 mg, 0.1 mmol) were obtained 25 mg of **31b** (88 % isolated yield) as a yellow solid. R_f 0.15 (20:1 hexane : AcOEt). Spectroscopic data were consistent with those reported in the literature.[199] m.p = 150 – 151 °C

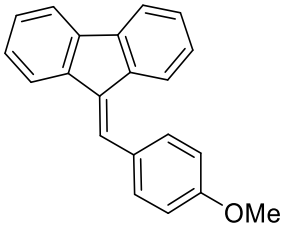


31b

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.67 (m, 7H), 7.60 (s, 1H), 7.46 – 7.31 (m, 4H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9 (C), 141.6 (C), 139.4 (C), 138.9 (C), 138.4 (C), 135.8 (C), 132.3 (CH), 130.0 (CH), 129.3 (CH), 128.9 (CH), 127.2 (CH), 126.9 (CH), 124.3 (CH), 124.2 (CH), 120.4 (CH), 120.0 (CH), 119.7 (CH), 118.8 (C), 111.4 (C). ESI HRMS: calcd. For $[C_{21}H_{14}N]^+$: 280.1120, found: 280.1116

9-(4-Methoxybenzylidene)-9*H*-fluorene (**31c**)

Following the general method, biphenyl bromide **29** (0.1 mmol) and *p*-anisaldehyde tosylhydrazone (33 mg, 0.1 mmol) were obtained 26 mg of **31c** (92 % isolated yield) as a yellow solid. R_f 0.22 (40:1 hexane : AcOEt). Spectroscopic data were consistent with those reported in the literature.[200] m.p = 133 – 134 °C.



31c

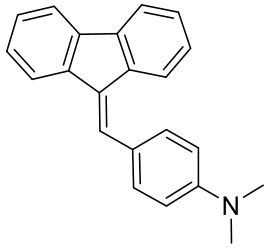
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 6.4 Hz, 1H), 7.78 – 7.72 (m, 3H), 7.68 (s, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.43 – 7.31 (m, 3H), 7.17 – 7.08 (m, 1H), 7.02 (d, *J* = 8.8 Hz,

[199] M. Shimizu, I. Nagao, S.-I. Kiyomoto, T. Hiyama, *Aust. J. Chem.* **2012,** *65*, 1277-1284.
[200] N. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2008,** *130*, 5636-5637.

2H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 (C), 141.1 (C), 139.6 (C), 138.9 (C), 136.6 (C), 135.4 (C), 130.8 (CH), 129.8 (C), 128.3 (CH), 127.9 (CH), 127.3 (CH), 126.9 (CH), 126.6 (CH), 124.1 (CH), 120.0 (CH), 119.7 (CH), 119.5 (CH), 113.9 (CH), 55.3 (CH_3). ESI HRMS: calcd. For $[C_{21}H_{17}O]^+$: 285.1273, found: 285.1280

4-((9*H*-Fluoren-9-ylidene)methyl)-*N*,*N*-dimethylaniline (**31d**)

Following the general method, biphenyl bromide **29** (0.1 mmol) and 4-(dimethylamino)benzaldehyde tosylhydrazone (32 mg, 0.1 mmol) were obtained 25 mg of **31d** (85 % isolated yield) as a yellow solid. R_f 0.31 (20:1 hexane : AcOEt). m.p = 135 - 136 °C.

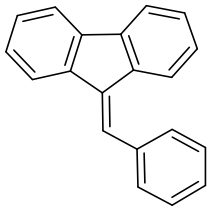


31d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.8 Hz, 1H), 7.83 – 7.74 (m, 3H), 7.68 (s, 1H), 7.60 (d, *J* = 9.0 Hz, 2H), 7.40 – 7.31 (m, 3H), 7.19 – 7.11 (m, 1H), 6.83 (d, *J* = 7.9 Hz, 2H), 3.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1 (C), 140.8 (C), 140.1 (C), 138.5 (C), 136.8 (C), 133.5 (C), 131.1 (CH), 128.5 (CH), 127.8 (CH), 127.3 (CH), 126.7 (CH), 126.4 (CH), 124.3 (C), 123.9 (CH), 119.8 (CH), 119.6 (CH), 119.4 (CH), 111.9 (CH), 40.5 (CH_3). ESI HRMS: calcd. For $[C_{22}H_{20}N]^+$: 298.1590, found: 298.1294

9-Benzylidene-9*H*-fluorene (**31e**)

Following the general method, biphenyl bromide **29** (0.1 mmol) and benzaldehyde tosylhydrazone (27 mg, 0.1 mmol) were obtained 19 mg of **31e** (76 % isolated yield) as a colourless crystals. R_f 0.30 (hexane). Spectroscopic data were consistent with those reported in the literature.[200] m.p = 75 - 76 °C.

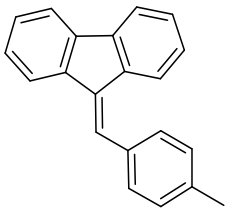


31e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.80 (m, 1H), 7.78 – 7.71 (m, 3H), 7.65 – 7.56 (m, 3H), 7.53 – 7.46 (m, 2H), 7.45 – 7.31 (m, 4H), 7.09 (td, *J* = 7.7, 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2 (C), 139.4 (C), 139.1 (C), 136.8 (C), 136.5 (C), 136.4 (C), 129.2 (CH), 128.5 (2xCH), 128.2 (CH), 128.0 (CH), 127.2 (CH), 126.9 (CH), 126.6 (CH), 124.4 (CH), 120.2 (CH), 119.7 (CH), 119.5 (CH). ESI HRMS: calcd. For $[C_{20}H_{15}]^+$: 255.1168, found: 255.1166

9-(4-Methylbenzylidene)-9*H*-fluorene (**31f**)

Following the general method, biphenyl bromide **29** (0.1 mmol) and *p*-tolualaldehyde tosylhydrazone (29 mg, 0.1 mmol) were obtained 24 mg of **31f** (90 % isolated yield) as a white solid. R_f 0.22 (100:1 hexane : AcOEt). Spectroscopic data were consistent with those reported in the literature.[200] m.p = 108 - 109 °C.

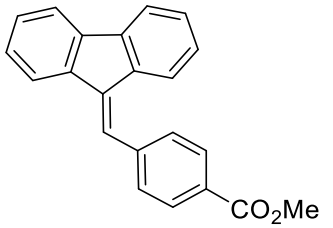


31f

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 1H), 7.74 (d, *J* = 6.7 Hz, 2H), 7.71 – 7.64 (m, 2H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.43 – 7.32 (m, 3H), 7.30 (s, 1H), 7.28 (s, 1H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1 (C), 139.6 (C), 139.0 (C), 138.0 (C), 136.6 (C), 135.9 (C), 133.8 (C), 129.2 (CH), 129.2 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 126.9 (CH), 126.5 (CH), 124.3 (CH), 120.1 (CH), 119.6 (CH), 119.5 (CH), 21.4 (CH_3). ESI HRMS: calcd. For $[C_{21}H_{17}]^+$: 269.1324, found: 269.1326

Methyl-4-((9*H*-fluoren-9-ylidene)methyl)benzoate (**31g**)

Following the general method, biphenyl bromide **29** (0.1 mmol) and methyl 4-formylbenzoate tosylhydrazone (33 mg, 0.1 mmol) were obtained 16 mg of **31g** (50 % isolated yield) as a yellow oil. R_f 0.35 (20:1 hexane : AcOEt). Spectroscopic data were consistent with those reported in the literature.[199]

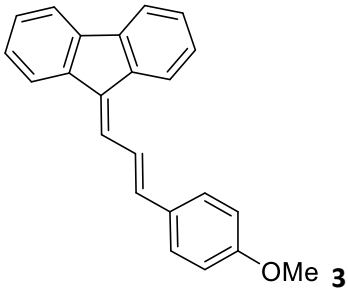


31g

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.13 (m, 2H), 7.80 (d, *J* = 7.1 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.70 (s, 1H), 7.67 (s, 2H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.31 (m, 3H), 7.07 (td, *J* = 7.6, 1.1 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 141.8 (C), 141.4 (C), 139.3 (C), 139.1 (C), 137.7 (C), 136.1 (C), 129.8 (CH), 129.4 (C), 129.3 (CH), 128.9 (CH), 128.6 (CH), 127.1 (CH), 126.7 (CH), 125.6 (CH), 124.4 (CH), 120.3 (CH), 119.8 (CH), 119.6 (CH), 52.2 (CH_3). ESI HRMS: calcd. For $[C_{22}H_{17}O_2]^+$: 313.1223, found: 313.1222

(*E*)-9-(3-(4-Methoxyphenyl)allylidene)-9*H*-fluorene (**31h**)

Following the general method, biphenyl bromide **29** (0.1 mmol) *trans-p*-methoxycinnamaldehyde tosylhydrazone (33 mg, 0.1 mmol) were obtained 27 mg of **31h** (88 % isolated yield) as a yellow solid. R_f 0.24 (20:1 hexane : AcOEt). m.p = 107 – 108 °C



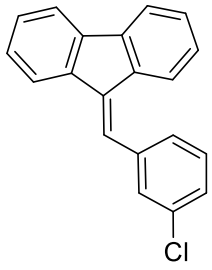
31h

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 – 8.06 (m, 1H), 7.87 (dd, *J* = 15.2, 11.9 Hz, 1H), 7.81 – 7.71 (m, 3H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.37 – 7.31 (m, 3H), 7.03 – 6.94 (m, 3H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1 (C), 140.7 (C), 139.6 (C),

138.7 (C), 138.5 (CH), 137.3 (C), 133.9 (C), 129.8 (C), 128.5 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.8 (CH), 126.8 (CH), 124.9 (CH), 122.8 (CH), 119.9 (CH), 119.9 (CH), 119.6 (CH), 114.3 (CH), 55.3 (CH_3). ESI HRMS: calcd. For $[C_{23}H_{19}O]^+$: 311.1430, found: 311.1434

9-(3-Chlorobenzylidene)-9*H*-fluorene (**31i**)

Following the general method, biphenyl bromide **29** (0.1 mmol) and methyl 3-chlorobenzaldehyde tosylhydrazone (31 mg, 0.1 mmol) were obtained 26 mg of **31i** (87 % isolated yield) as a yellow solid. R_f 0.39 (hexane). m.p = 89 - 90 °C.

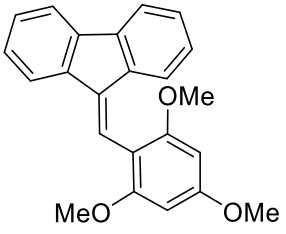


31i

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 6.7 Hz, 2H), 7.61 (s, 1H), 7.59 (s, 1H), 7.53 – 7.47 (m, 2H), 7.45 – 7.32 (m, 5H), 7.14 – 7.06 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4 (C), 139.3 (C), 139.1 (C), 138.7 (C), 137.4 (C), 136.2 (C), 134.4 (C), 129.8 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 127.4 (CH), 127.1 (CH), 126.8 (CH), 125.2 (CH), 124.4 (CH), 120.3 (CH), 119.8 (CH), 119.6 (CH). ESI HRMS: calcd. For $[C_{20}H_{14}Cl]^+$: 289.0778, found: 289. 0780

9-(2,4,6-Trimethoxybenzylidene)-9*H*-fluorene (**31j**)

Following the general method, biphenyl bromide **29** (0.1 mmol) and 2,4,4-trimethoxybenzaldehyde tosylhydrazone (36 mg, 0.1 mmol) were obtained 31 mg of **31j** (90 % isolated yield) as a yellow solid. R_f 0.20 (10:1 hexane : AcOEt). m.p = 195 – 196 °C.

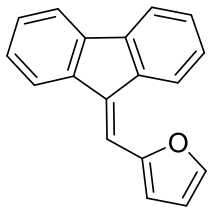


31j

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 1H), 7.75 – 7.69 (m, 2H), 7.46 (s, 1H), 7.37 – 7.32 (m, 2H), 7.32 – 7.26 (m, 2H), 7.12 (ddd, *J* = 8.1, 7.3, 1.2 Hz, 1H), 6.27 (s, 2H), 3.93 (s, 3H), 3.77 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (C), 159.0 (C), 140.5 (C), 139.7 (C), 139.0 (C), 137.7 (C), 136.9 (C), 127.5 (CH), 127.4 (CH), 126.7 (CH), 126.4 (CH), 124.6 (CH), 120.5 (CH), 119.3 (CH), 119.1 (CH), 118.4 (CH), 107.2 (C), 90.5 (CH), 55.6 (CH_3), 55.4 (CH_3). ESI HRMS: calcd. For $[C_{23}H_{21}O_3]^+$: 345.1485, found: 345.1477

2-((9*H*-Fluoren-9-ylidene)methyl)furan (**31k**)

Following the general method, biphenyl bromide **29** (0.1 mmol) and furfural tosylhydrazone (26 mg, 0.1 mmol) were obtained 13 mg of **3g** (52 % isolated yield) as a white solid. R_f 0.32 (40:1 hexane : AcOEt). m.p = 88 - 89 °C.

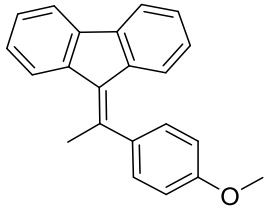


31k

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, *J* = 6.6 Hz, 1H), 7.80 – 7.69 (m, 4H), 7.43 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.35 (s, 1H), 7.31 (s, 1H), 6.80 (d, *J* = 3.3 Hz, 1H), 6.62 (dd, *J* = 3.4, 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1 (C), 143.8 (CH), 141.0 (C), 140.2 (C), 138.9 (C), 136.1 (C), 132.6 (C), 128.4 (CH), 127.8 (CH), 127.1 (CH), 126.8 (CH), 125.6 (CH), 119.8 (CH), 119.5 (CH), 119.5 (CH), 115.5 (CH), 112.6 (CH), 112.4 (CH). ESI HRMS: calcd. For $[C_{18}H_{13}O]^+$: 245.0960, found: 245.0962

9-(1-(4-Methoxyphenyl)ethylidene)-9*H*-fluorene (**31l**)

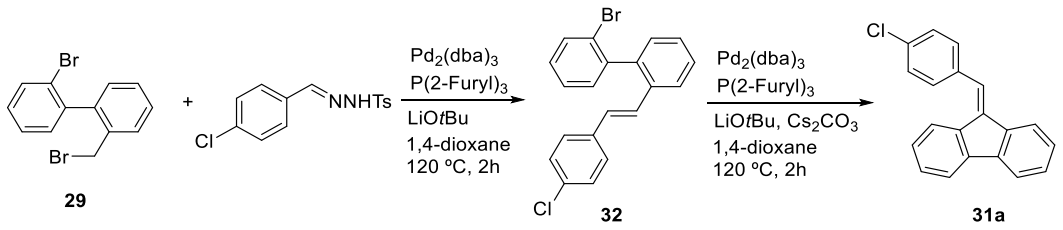
Following the general method, biphenyl bromide **29** (0.1 mmol) 4-methoxyacetophenone tosylhydrazone (32 mg, 0.1 mmol) were obtained 23 mg of **31l** (78 % isolated yield) as a yellow solid. R_f 0.23 (30:1 hexane : AcOEt). m.p = 165 – 166 °C



31l

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 – 8.01 (m, 1H), 7.87 – 7.81 (m, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.20 (m, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.98 – 6.90 (m, 1H), 6.47 (d, *J* = 8.2 Hz, 1H), 3.94 (s, 3H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (C), 142.9 (C), 140.3 (C), 139.5 (C), 139.0 (C), 138.7 (C), 137.6 (C), 133.1 (C), 129.2 (CH), 127.1 (CH), 126.8 (CH), 126.7 (CH), 126.4 (CH), 125.2 (CH), 124.5 (CH), 119.5 (CH), 119.0 (CH), 114.3 (CH), 55.3 (CH_3), 26.1 (CH_3). ESI HRMS: calcd. For $[C_{22}H_{18}ONa]^+$: 321.1249, found: 321.1249

- Synthesis of **31a** through a two steps procedure



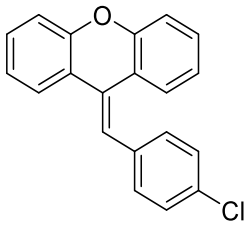
In order to prove that compounds **31** derive from the intramolecular Heck reaction of intermediate **32**, a two steps reaction was conducted. The reaction vial was charged under nitrogen atmosphere with the biphenyl bromide **29** (0.1 mmol, 32.3 mg), 4-formylbenzonitrile-*N*-tosylhydrazone (30 mg, 0.1 mmol), tris(dibenzylideneacetone)dipalladium(0) (5 mol %), tri(2-furyl)phosphine (30 mol %), lithium tert-butoxide (3 equiv), and 1,4-dioxane (2 mL). The vial was sealed and then was stirred at 120 °C for 2 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure. GC/MS analysis of the reaction crude revealed complete conversión, and the exclusive presence of intermediate **32**. The residue was disolved in 1,4-dioxane (2 mL) and placed in a reaction vial under nitrogen atmosphere. To the solution were added tris(dibenzylideneacetone)dipalladium(0) (5 mol %), tri(2-furyl)phosphine (30 mol %), lithium *tert*-butoxide (3 equiv) and Cs_2CO_3 (3 equiv). The vial was sealed and the mixture was stirred at 120 °C for 12 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure. GC/MS analysis of the reaction crude revealed the complete dissapearance of intermediate **32** and the exclusive presence of fluorene **31a**. After column chromatography, 21 mg of **31a** (74 % isolated yield) were obtained.

E.4.3 General procedure and characterization data for xanthenes 34

A reaction vial was charged under nitrogen atmosphere with 1-bromo-2-(2-(bromomethyl)phenoxy)benzene **33** (0.1 mmol, 34 mg), *N*-tosylhydrazone (1 equiv), tris(dibenzylideneacetone)dipalladium(0) (5 mol %), tri(2-furyl)phosphine (30 mol %), lithium *tert*-butoxide (3 equiv), sodium *tert*-butoxide (3 equiv) and 1,4-dioxane (2 mL). The vial was sealed and then was stirred at 120 °C for 12 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane or a mixture of hexane/ ethyl acetate.

9-(4-Chlorobenzylidene)-9*H*-xanthene (**34a**)

Following the general method, employing dibromide **33** (0.1 mmol) and 4-chlorobenzaldehyde tosylhydrazone (31 mg, 0.1 mmol) were obtained 14 mg of **34a** (55 % isolated yield) as a yellow solid. R_f 0.23 (hexane). m.p = 131 – 132 °C

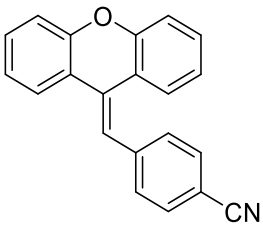


34a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.29 (m, 5H), 7.29 – 7.24 (m, 2H), 7.23 – 7.17 (m, 3H), 6.91 – 6.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (C), 151.4 (C), 136.4 (C), 132.5 (C), 129.9 (CH), 129.3 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 127.5 (C), 124.5 (C), 123.8 (CH), 123.1 (CH), 122.4 (CH), 120.9 (CH), 120.8 (C), 117.3 (CH), 116.9 (CH). ESI HRMS: calcd. For $[C_{20}H_{14}ClO]^+$: 305.0727, found: 305.0732

4-((9*H*-Xanthen-9-ylidene)methyl)benzonitrile (**34b**)

Following the general method, employing dibromide **33** (0.1 mmol) and 4-formylbenzonitrile tosylhydrazone (30 mg, 0.1 mmol) were obtained 18 mg of **34b** (63 % isolated yield) as a yellow solid. R_f 0.22 (30:1 hexane : AcOEt). m.p = 172 – 173 °C.

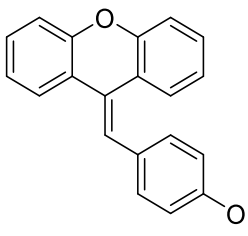


34b

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.41 – 7.34 (m, 1H), 7.31 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.26 – 7.19 (m, 4H), 6.93 – 6.83 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (C), 151.4 (C), 143.1 (C), 132.1 (CH), 130.0 (CH), 129.5 (C), 129.3 (2xCH), 128.3 (CH), 124.0 (C), 124.0 (CH), 123.1 (CH), 122.5 (CH), 120.1 (C), 119.8 (CH), 119.0 (C), 117.5 (CH), 117.0 (CH), 110.1 (C). ESI HRMS: calcd. For $[C_{21}H_{14}NO]^+$: 296.1069, found: 296.1073

9-(4-Methoxybenzylidene)-9*H*-xanthene (**34c**)

Following the general method, employing dibromide **33** (0.1 mmol) and *p*-anisaldehyde tosylhydrazone (30 mg, 0.1 mmol) were obtained 15 mg of **34c** (50 % isolated yield) as a white solid. R_f 0.24 (30:1 hexane : AcOEt). Spectroscopic data were consistent with those reported in the literature.[201] m.p = 103 – 104 °C.



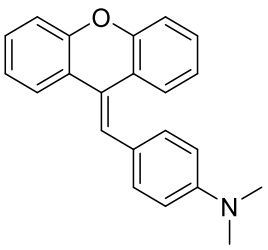
34c

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.39 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.30 – 7.18 (m, 1H), 7.24 – 7.12 (m, 3H), 6.91 (s, 1H), 6.91 – 6.79 (m, 3H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6 (C), 153.0 (C), 151.5 (C), 130.0 (C), 129.8 (CH), 128.9 (CH), 128.4 (CH), 128.3 (CH), 125.8 (C), 125.1 (C), 123.7 (CH), 123.0 (CH), 122.3 (CH), 122.2 (CH), 121.5 (C), 117.1 (CH), 116.8 (CH), 113.8 (CH), 55.2 (CH_3). ESI HRMS: calcd. For $[C_{21}H_{17}O_2]^+$: 301.1223, found: 301.1220

[201] E. Dimitrijevic, M. Cusimano, M. S. Taylor, *Org. Biomol. Chem.* **2014,** *12*, 1391-1394.

4-((9*H*-Xanthen-9-ylidene)methyl)-*N*,*N*-dimethylaniline (**34d**)

Following the general method, employing dibromide **33** (0.1 mmol) and 4-(dimethylamino)benzaldehyde tosylhydrazone (32 mg, 0.1 mmol) were obtained 21 mg of **34d** (67 % isolated yield) as a yellow crystals. R_f 0.19 (30:1 hexane : AcOEt). m.p = 121 – 122 °C.

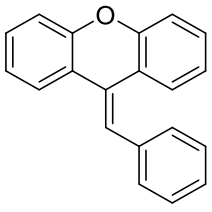


34d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.55 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.20 (m, 2H), 7.20 – 7.13 (m, 3H), 6.93 – 6.84 (m, 2H), 6.69 (d, *J* = 8.2 Hz, 2H), 3.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1 (C), 151.6 (C), 149.2 (C), 129.6 (CH, C), 128.6 (CH), 128.3 (CH), 128.0 (CH), 125.7 (C), 124.3 (C), 123.7 (CH), 123.2 (CH), 122.9 (CH), 122.2 (CH), 122.1 (C), 117.0 (CH), 116.7 (CH), 112.3 (CH), 40.6 (CH_3). ESI HRMS: calcd. For $[C_{22}H_{20}NO]^+$: 314.1539, found: 314.1540

9-Benzylidene-9*H*-xanthene (**34e**)

Following the general method, employing dibromide **33** (0.1 mmol) and benzaldehyde tosylhydrazone (27 mg, 0.1 mmol) were obtained 15 mg of **34e** (56 % isolated yield) as a yellow solid. R_f 0.31 (hexane). m.p = 116 – 117 °C.



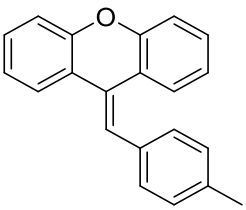
34e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.9 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 3H), 7.32 (d, *J* = 7.5 Hz, 3H), 7.27 (d, *J* = 7.4 Hz, 2H), 7.25 – 7.18 (m, 3H), 6.98 (s, 1H), 6.84 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (C), 151.5 (C), 137.9 (C), 129.1 (CH), 128.6 (2xCH), 128.5 (CH), 128.4 (CH), 126.9 (CH), 126.8 (C), 124.8 (C), 123.7 (CH), 123.2 (CH), 122.4 (CH),

122.3 (CH), 121.2 (C), 117.1 (CH), 116.8 (CH). ESI HRMS: calcd. For $[C_{20}H_{15}O]^+$: 271.1117, found: 271.1117

9-(4-Methylbenzylidene)-9*H*-xanthene (**34f**)

Following the general method, employing dibromide **33** (0.1 mmol) and *p*-tolualaldehyde tosylhydrazone (29 mg, 0.1 mmol) were obtained 18 mg of **34f** (64 % isolated yield) as a yellow crystals. R_f 0.23 (hexane). m.p = 106 – 107 °C.

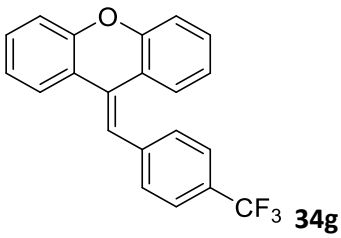


34f

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.38 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.35 – 7.26 (m, 3H), 7.24 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.22 – 7.16 (m, 3H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.94 (s, 1H), 6.85 (ddd, *J* = 8.3, 6.9, 1.5 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (C), 151.5 (C), 136.6 (C), 134.8 (C), 129.1 (CH), 129.0 (CH), 128.5 (CH), 128.5 (2xCH), 126.3 (C), 125.0 (C), 123.7 (CH), 123.1 (CH), 122.6 (CH), 122.2 (CH), 121.4 (C), 117.1 (CH), 116.8 (CH), 21.3 (CH_3). ESI HRMS: calcd. For $[C_{21}H_{17}O]^+$: 285.1273, found: 285.1275.

9-(4-(Trifluoromethyl)benzylidene)-9*H*-xanthene (**34g**)

Following the general method, employing dibromide **33** (0.1 mmol) and 4-(trifluoromethyl)benzaldehyde tosylhydrazone (34 mg, 0.1 mmol) were obtained 25 mg of **34g** (74 % isolated yield) as a yellow oil. R_f 0.35 (hexane).



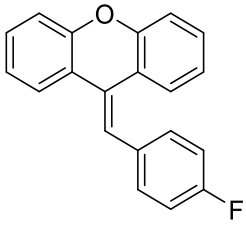
34g

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.40 – 7.32 (m, 1H), 7.28 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.27 – 7.19 (m, 4H), 6.91 (s, 1H), 6.87 (ddd, *J* = 8.1, 7.0, 1.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (C), 151.4 (C),

141.8 (C), 141.8 (C), 129.6 (CH), 129.0 (CH), 128.9 (C, CH), 128.6 (C), 128.4 (CH), 125.3 (q, CH-CF_3, *J* = 3.9 Hz), 124.3 (C), 123.9 (CH), 123.1 (CH), 122.5 (CH), 120.5 (CH), 117.4 (CH), 117.0 (CH). ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.43. ESI HRMS: calcd. For $[C_{21}H_{14}F_3O]^+$: 339.0991, found: 339.0983

9-(4-Fluorobenzylidene)-9*H*-xanthene (**34h**)

Following the general method, employing dibromide **33** (0.1 mmol) and 4-fluorobenzaldehyde tosylhydrazone (29 mg, 0.1 mmol) were obtained 18 mg of **34h** (62 % isolated yield) as a colourless oil. R_f 0.33 (hexane).

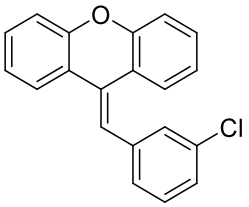


34h

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.32 – 7.24 (m, 3H), 7.23 – 7.17 (m, 3H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.90 (s, 1H), 6.86 (ddd, *J* = 7.8, 7.2, 1.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (C-F, d, ^2J = 246.9 Hz), 152.9 (C), 151.5 (C), 133.8 (C, d, $^5J_{C\text{-}F}$= 3.5 Hz), 130.2 (CH, d, $^4J_{C\text{-}F}$= 7.9 Hz), 129.2 (CH), 128.7 (CH), 128.4 (CH), 127.1 (C), 124.6 (C), 123.8 (CH), 123.1 (CH), 122.3 (CH), 121.3 (CH), 121.0 (C), 117.0 (CH, d, $^3J_{C\text{-}F}$= 26.7 Hz), 115.5 (CH), 115.3 (CH). ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.90. ESI HRMS: calcd. For $[C_{20}H_{14}FO]^+$: 289.1023, found: 289.1022

9-(3-Chlorobenzylidene)-9*H*-xanthene (**34i**)

Following the general method, employing dibromide **33** (0.1 mmol) and 3-chlorobenzaldehyde tosylhydrazone (31 mg, 0.1 mmol) were obtained 19 mg of **34i** (62 % isolated yield) as a yellow solid. R_f 0.39 (hexane). m.p = 127 – 128 °C.

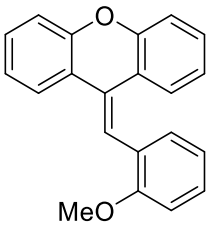


34i

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.37 (m, 1H), 7.34 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.30 (dd, *J* = 4.3, 2.7 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.25 – 7.21 (m, 4H), 7.21 (s, 1H), 7.20 – 7.16 (m, 1H), 6.91 – 6.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9 (C), 151.4 (C), 139.9 (C), 134.2 (C), 129.6 (CH), 129.5 (CH), 128.9 (CH), 128.6 (CH), 128.45 (CH) 128.0 (C), 126.9 (CH), 126.7 (CH), 124.3 (C), 123.8 (CH), 123.2 (CH), 122.4 (CH), 120.6 (C), 120.6 (CH), 117.3 (CH), 116.9 (CH). ESI HRMS: calcd. For $[C_{20}H_{13}ClO]^+$: 305.0727, found: 305.0732

9-(2-Methoxybenzylidene)-9*H*-xanthene (**34j**)

Following the general method, employing dibromide **33** (0.1 mmol) and *o*-anisaldehyde tosylhydrazone (30 mg, 0.1 mmol) were obtained 18 mg of **34j** (57 % isolated yield) as a yellow oil. R_f 0.18 (40:1 hexane : AcOEt).



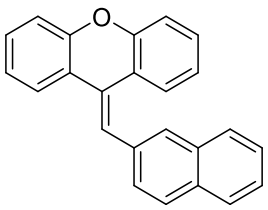
34j

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.26 – 7.15 (m, 4H), 7.01 (s, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.84 (q, *J* = 8.1 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3 (C), 152.7 (C), 151.4 (C), 129.6 (C), 129.6 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 126.6 (CH), 125.0 (C), 123.6 (CH), 123.5 (CH), 122.2 (CH), 121.62 (C) 120.3

(CH), 118.4 (CH), 117.9 (C), 116.9 (CH), 116.7 (CH), 110.7 (CH), 55.4 (CH_3). ESI HRMS: calcd. For $[C_{21}H_{17}O_2]^+$: 301.1223, found: 301.1214

9-(Naphthalen-2-ylmethylene)-9*H*-xanthene (**34k**)

Following the general method, employing dibromide **33** (0.1 mmol) and 2-naphthaldehyde tosylhydrazone (32 mg, 0.1 mmol) were obtained 19 mg of **34k** (59 % isolated yield) as a yellow oil. R_f 0.18 (hexane).



34k

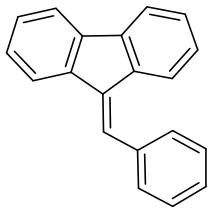
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.78 (m, 4H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.39 – 7.31 (m, 2H), 7.27 – 7.19 (m, 4H), 7.13 (s, 1H), 6.79 (ddd, *J* = 8.2, 6.7, 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0 (C), 151.5 (C), 135.4 (C), 133.6 (C), 132.4 (C), 129.2 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.6 (2xCH), 127.5 (CH), 127.1 (C), 126.8 (CH), 126.0 (CH), 125.8 (CH), 124.8 (C), 123.8 (CH), 123.1 (CH), 122.3 (CH), 122.2 (CH), 121.3 (C), 117.1 (CH), 116.9 (CH). ESI HRMS: calcd. For $[C_{24}H_{17}O]^+$: 321.1273, found: 321.1264

E.4.4 General procedure and characterization data for fluorenes 31e, 31l and 31m obtained using biphenyl *N*-tosylhydrazones 35

A reaction vial was charged under nitrogen atmosphere with the *N*-tosylhydrazone **35** (0.1 mmol), the corresponding benzyl bromide (1 equiv), tris(dibenzylideneacetone)dipalladium(0) (5 mol %), tri(2-furyl)phosphine (30 mol %), lithium *tert*-butoxide (3 equiv), cesium carbonate (3 equiv) and 1,4-dioxane (2 mL). The vial was sealed and then was stirred at 120 °C for 12 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane or a mixture of hexane/ ethyl acetate.

9-Benzylidene-9*H*-fluorene (**31e**)

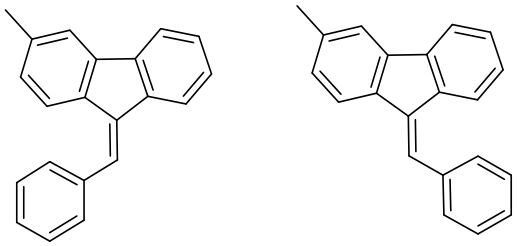
Following the general method, *N*-tosylhydrazone **35a** (0.1 mmol) and benzyl bromide (17 mg, 0.1 mmol) were obtained 18 mg of **31e** (73 % isolated yield) as colourless crystals. R_f 0.30 (hexane). Spectroscopic data were consistent with those previously reported. m.p = 75 - 76 °C



31e

9-Benzylidene-3-methyl-9*H*-fluorene (**31l**)

Following the general method, *N*-tosylhydrazone **35b** (0.1 mmol) and benzyl bromide (17 mg, 0.1 mmol) were obtained 22 mg of **31l** (82 % isolated yield) as a yellow oil. Rf 0.24 (hexane). Spectroscopic data were consistent with those reported in the literature.[202]



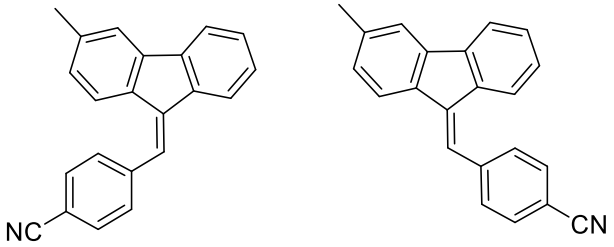
(*Z*)-31l 6 : 1 **(*E*)-31l**

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.56 (s, 1H), 7.51 – 7.47 (m, 3H), 7.44 – 7.39 (m, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.5 (C), 139.9 (C), 139.2 (C), 138.6 (C), 137.0 (C), 136.3 (C), 133.9 (C), 129.3 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 126.8 (CH), 126.2 (CH), 124.1 (CH), 120.3 (CH), 120.2 (CH), 119.4 (CH), 21.7 (CH_3). To confirm the identity of the major diastereoisomer 2D NMR experiments were performed. ESI HRMS: calcd. For $[C_{21}H_{17}]^+$: 269.1324, found: 269.1322

[202] R. C. Larock, Q. Tian, *J. Org. Chem.* **2001**, *66*, 7372–7379.

4-((3-Methyl-9*H*-fluoren-9-ylidene)methyl)benzonitrile (**31m**)

Following the general method, N-tosylhydrazone **35b** (0.1 mmol) and 4-(bromomethyl)benzonitrile (20 mg, 0.1 mmol) were obtained 20 mg of **31m** (67 % isolated yield) as a white solid. R_f 0.34 (20:1 hexane : AcOEt). m.p = 119 - 120 °C.



(*Z*)-31m 6 : 1 **(*E*)-31m**

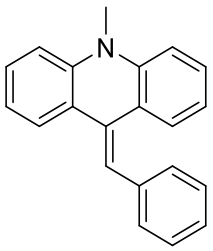
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 3H), 7.72 – 7.67 (m, 3H), 7.54 (s, 1H), 7.51 (s, 1H), 7.41 (td, *J* = 7.4, 1.2 Hz, 1H), 7.36 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0 (C), 141.9 (C), 139.6 (C), 139.4 (C), 139.3 (C), 138.4 (C), 133.2 (C), 132.2 (CH), 130.0 (CH), 128.8 (CH), 127.7 (CH), 127.1 (CH), 124.0 (CH), 123.3 (CH), 120.7 (CH), 120.4 (CH), 119.6 (CH), 118.8 (C), 111.3 (C), 21.7 (CH_3). ESI HRMS: calcd. For $[C_{22}H_{16}N]^+$: 294.1277, found: 294.1272

E.4.5 General procedure and characterization data for acridines 38

A reaction vial was charged under nitrogen atmosphere with the *N*-tosylhydrazone **37** (0.1 mmol), the corresponding benzyl bromide (1 equiv), tris(dibenzylideneacetone)dipalladium(0) (5 mol %), tri(2-furyl)phosphine (30 mol %), lithium *tert*-butoxide (3 equiv), cesium carbonate (3 equiv) and 1,4-dioxane (2 mL). The vial was sealed and then was stirred at 120 °C for 12 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by filtration with silica gel using a mixture of hexane/ ethyl acetate (1:1).

9-Benzylidene-10-methyl-9,10-dihydroacridine (**38a**)

Following the general method, with *N*-tosylhydrazone **37** (0.1 mmol) and benzyl bromide (17 mg, 0.1 mmol) were obtained 26 mg of **38a** (90 % isolated yield) as a yellow oil. Spectroscopic data were consistent with those reported in the literature.[170]

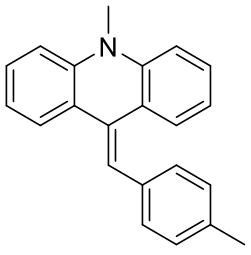


38a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.37 – 7.30 (m, 4H), 7.27 – 7.16 (m, 4H), 7.12 – 7.07 (m, 1H), 7.07 – 7.01 (m, 2H), 6.76 (ddd, *J* = 7.8, 7.3, 1.1 Hz, 1H), 6.71 (s, 1H), 3.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0 (C), 141.2 (C), 138.4 (C), 131.6 (C), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 126.6 (C), 126.2 (CH), 123.5 (CH), 122.5 (CH), 122.1 (C), 121.2 (CH), 119.9 (CH), 113.1 (CH), 112.3 (CH), 33.5 (CH_3). ESI HRMS: calcd. For $[C_{21}H_{18}N]^+$: 284.1433, found: 284.1428

10-Methyl-9-(4-methylbenzylidene)-9,10-dihydroacridine (**38b**)

Following the general method, with *N*-tosylhydrazone **37** (0.1 mmol) and 4-methylbenzyl bromide (19 mg, 0.1 mmol) were obtained 28 mg of **38b** (93 % isolated yield) as a yellow oil. Spectroscopic data were consistent with those reported in the literature.[170]



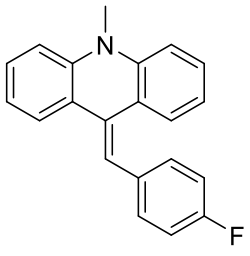
38b

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.35 – 7.24 (m, 5H), 7.08 (d, *J* = 7.6 Hz, 3H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.70 (s, 1H), 3.52 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0 (C), 141.3 (C), 135.9 (C), 135.3 (C), 131.0 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 126.9

(C), 123.4 (CH), 122.7 (CH), 122.3 (C), 121.2 (CH), 119.9 (CH), 113.1 (CH), 112.3 (CH), 33.5 (CH_3), 21.2 (CH_3). ESI HRMS: calcd. For $[C_{22}H_{20}N]^+$: 298.1590, found: 298.1595

9-(4-Fluorobenzylidene)-10-methyl-9,10-dihydroacridine (**38c**)

Following the general method, with *N*-tosylhydrazone **37** (0.1 mmol) and 4-fluorobenzyl bromide (19 mg, 0.1 mmol) were obtained 27 mg of **38c** (91 % isolated yield) as a yellow oil.

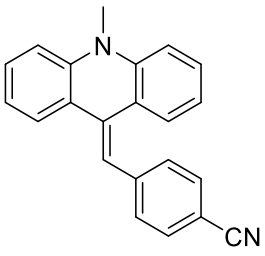


38c

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.35 – 7.25 (m, 6H), 7.09 (td, *J* = 7.4, 1.1 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.95 (t, *J* = 8.8 Hz, 2H), 6.78 (td, *J* = 7.5, 1.1 Hz, 1H), 6.65 (s, 1H), 3.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (C-F, d, ^2J = 245.7 Hz), 143.0 (C), 141.2 (C), 134.3 (C, d, $^5J_{C\text{-}F}$= 3.5 Hz)i, 131.7 (C), 130.0 (CH, d, $^4J_{C\text{-}F}$= 7.5 Hz), 128.6 (CH), 128.5 (CH), 128.0 (CH), 126.5 (C), 123.4 (CH), 121.8 (C), 121.3 (CH), 121.2 (CH), 119.9 (CH), 115.1 (CH, d, $^3J_{C\text{-}F}$= 21.3 Hz), 113.2 (CH), 112.4 (CH), 33.5 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.84. ESI HRMS: calcd. For $[C_{21}H_{17}FN]^+$: 302.1339, found: 302.1339

4-((10-Methylacridin-9(10*H*)-ylidene)methyl)benzonitrile (**38d**)

Following the general method, with *N*-tosylhydrazone **37** (0.1 mmol) and 4-(bromomethyl)benzonitrile (20 mg, 0.1 mmol) were obtained 30 mg of **38d** (98 % isolated yield) as a orange oil. Spectroscopic data were consistent with those reported in the literature.[170]

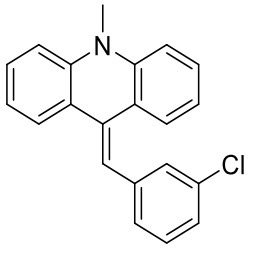


38d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.30 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.16 – 7.11 (m, 2H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.84 – 6.76 (m, 1H), 6.62 (s, 1H), 3.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8 (C), 142.7 (C), 140.7 (C), 134.4 (C), 131.9 (CH), 129.3 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 125.7 (C), 123.4 (CH), 121.4 (CH), 120.8 (C), 120.2 (CH), 119.7 (CH), 119.3 (C), 113.6 (CH), 112.6 (CH), 109.0 (C), 33.7 (CH_3). ESI HRMS: calcd. For $[C_{22}H_{17}N_2]^+$: 309.1386, found: 309.1381

9-(3-Chlorobenzylidene)-10-methyl-9,10-dihydroacridine (**38e**)

Following the general method, with *N*-tosylhydrazone **37** (0.1 mmol) and 4-chlorobenzyl bromide (21 mg, 0.1 mmol) were obtained 30 mg of **38e** (95 % isolated yield) as a brown oil.



38e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.36 – 7.27 (m, 4H), 7.22 – 7.14 (m, 3H), 7.12 – 7.07 (m, 2H), 7.05 (d, *J* = 9.3 Hz, 1H), 6.83 – 6.76 (m, 1H), 6.61 (s, 1H), 3.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8 (C), 141.0 (C), 140.5 (C), 134.0 (C), 132.8

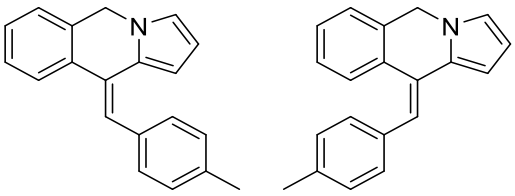
(C), 129.3 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 126.6 (CH), 126.2 (CH), 126.1 (C), 123.5 (CH), 121.4 (C), 121.3 (CH), 120.6 (CH), 120.0 (CH), 113.3 (CH), 112.4 (CH), 33.6 (CH_3). ESI HRMS: calcd. For $[C_{21}H_{17}ClN]^+$: 318.1044, found: 318.1045

E.4.6 General procedure and characterization data for heterocyclic systems 40 and 42

A reaction vial was charged under nitrogen atmosphere with the *N*-tosylhydrazones **39** or **41** (0.1 mmol), the corresponding benzyl bromide (1 equiv), palladium(II) acetate (10 mol %), tri(2-furyl)phosphine (30 mol %), lithium *tert*-butoxide (4 equiv) and 1,4-dioxane (2 mL). The vial was sealed and then stirred at 120 °C for 12 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane or a mixture of hexane/ ethyl acetate.

10-(4-Methylbenzylidene)-5,10-dihydropyrrolo[1,2-b]isoquinoline (**40**)

Following the general method, biphenyl hydrazone **39** (0.1 mmol) and 4-methylbenzyl bromide (19 mg, 0.1 mmol) were obtained 14 mg of **40** (52 % isolated yield) as a yellow oil. R_f 0.33 (20:1 hexane : AcOEt).

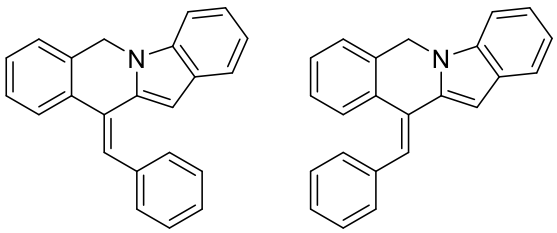


(Z)-40 3.3 : 1 **(*E*)-40**

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.91 (d, *J* = 7.1 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.42 – 7.37 (m, 1H), 7.36 – 7.32 (m, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.06 (s, 1H), 6.78 (dd, *J* = 2.5, 1.6 Hz, 1H), 6.08 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.99 (dd, *J* = 3.8, 1.6 Hz, 1H), 5.18 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 136.8 (C), 135.3 (C), 134.8 (C), 131.2 (C), 128.9 (CH), 128.7 (C), 128.6 (CH), 127.5 (CH), 127.0 (CH) 126.4 (C), 126.0 (CH), 123.6 (CH), 122.2 (CH), 119.4 (CH), 108.5 (CH), 108.3 (CH), 48.2 (CH_2), 20.9 (CH_3). ESI HRMS: calcd. For $[C_{20}H_{18}N]^+$: 272.1433, found: 272.1433

11-Benzylidene-6,11-dihydroindolo[1,2-b]isoquinoline (**42**)

Following the general method, biphenyl hydrazone **41** (0.1 mmol) and benzyl bromide (17 mg, 0.1 mmol) were obtained 17 mg of **42** (54 % isolated yield) as a yellow oil. R_f 0.18 (50:1 hexane : AcOEt).



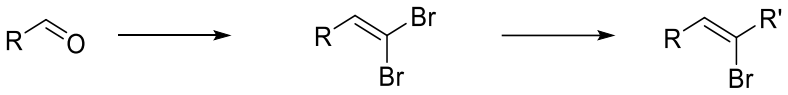
(Z)-42 5 : 1 **(E)-42**

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.01 – 7.93 (m, 1H), 7.61 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.58 (dt, *J* = 1.4, 0.8 Hz, 1H), 7.48 – 7.40 (m, 7H), 7.37 (s, 2H), 7.27 – 7.19 (m, 1H), 7.13 – 7.04 (m, 1H), 6.28 (s, 1H), 5.35 (s, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 138.0 (C), 135.3 (C), 134.2 (C), 132.9 (C), 131.1 (C), 128.7 (CH), 128.4 (CH), 128.0 (C), 127.7 (CH), 127.5 (CH), 127.3 (CH), 127.1 (C), 126.7 (CH), 126.4 (CH), 123.7 (CH), 121.6 (CH), 120.5 (CH), 119.8 (CH), 108.8 (CH), 101.0 (CH), 44.9 (CH_2). ESI HRMS: calcd. For $[C_{23}H_{18}N]^+$: 308.1433, found: 308.1430

E.5 Chapter 3: Synthesis of highly substituted polyenes

E.5.1 Synthesis of starting materials

- General procedure and characterization data for alkenyl bromides **43a** and **47**



46 **43a, 47**

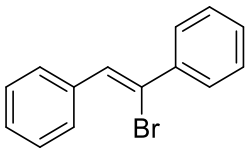
A Schlenk was charged under nitrogen atmosphere with the corresponding aldehyde (3 mmol), tetrabromomethane (4.5 mmol), and dry CH_2Cl_2 (5.2 mL). The solution was stirred at 0 °C and then a solution of PPh_3 (9 mmol) in dry CH_2Cl_2 (4.2 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min, and then at room temperature for another 10 min. The resulting red suspension was diluted with ice-cold hexane and filtered through celite/silica. The filtration cake was washed two times with ice-cold hexane. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using a mixture of hexane/ethyl acetate as eluent affording the dibromoalkene **46**.

The resulting dibromoalkene **46** (0.85 mmol), the corresponding boronic acid (1.05 eq, 0.89 mmol), Pd_2dba_3 (0.02 mmol, 2.5 mol %), tri(2-furyl)phosphine (0.12 mmol, 15 mol%) and 1,4-dioxane (3.4 mL) were placed in a sealed tube. Then a 1M aqueous solution of Cs_2CO_3 (0.6 mL) was poured to the reaction mixture. The reaction was stirred at 65 °C during 24 hours. After this time, the resulting mixture was diluted with H_2O, and extracted with AcOEt. The combined organic layers were dried over sodium sulfate and concentrated. The residue of the reaction was purified by flash chromatography on silica gel using a mixture of hexane/ethyl acetate as eluent to give provide the alkenyl bromides.

Employing this procedure were prepared the following alkenyl bromides:

(*Z*)-(1-Bromoethene-1,2-diyl)dibenzene (**43a**)

The title compound **43a** was prepared as brown oil in 54 % isolated yield (119 mg) from benzaldehyde and phenylboronic acid. R_f 0.27 (hexane). Spectroscopic data were consistent with those reported in the literature.[203]

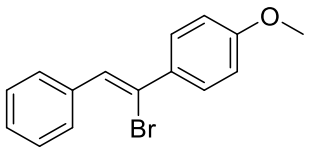


43a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.6 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.61 – 7.43 (m, 6H), 7.37 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1 (C), 136.4 (C), 130.1 (CH), 129.4 (CH), 128.9 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 124.2 (C).

(*Z*)-1-(1-Bromo-2-phenylvinyl)-4-methoxybenzene (**47a**)

The title compound **47a** was prepared as brown oil in 60 % isolated yield (148 mg) from benzaldehyde and (4-methoxyphenyl)boronic acid. R_f 0.36 (20:1 hexane : AcOEt). Spectroscopic data were consistent with those reported in the literature.[204]



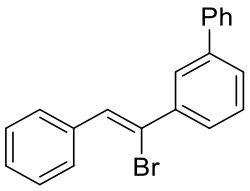
47a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.3 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.47 – 7.39 (m, 2H), 7.39 – 7.31 (m, 1H), 7.17 (s, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0 (C), 136.5 (C), 133.5 (C), 129.1 (CH), 129.1 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 123.9 (C), 113.6 (CH), 55.4 (CH_3). ESI HRMS: calcd. For $[C_{15}H_{14}BrO]^+$: 289.0222, found: 289.0222

[203] L. He, M. Schulz-Senft, B. Thiedemann, J. Linshoeft, J. P. Gates, A. Staubitz, *Euro. J. Org. Chem.* **2015**, *11*, 2498–2502.
[204] G. Chelucci, *Chem. Comm.,* **2014**, *50*, 4069–4072.

(*Z*)-3-(1-Bromo-2-phenylvinyl)-1,1'-biphenyl (**47b**)

The title compound **47b** was prepared as colourless oil in 58 % isolated yield (165 mg) from benzaldehyde and 3-biphenylboronic acid. R_f 0.41 (hexane).

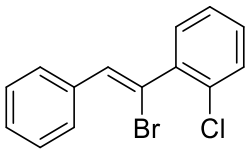


47b

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (t, *J* = 1.9 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.77 – 7.72 (m, 3H), 7.67 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 3H), 7.53 – 7.45 (m, 4H), 7.39 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6 (C), 141.5 (C), 140.7 (C), 136.3 (C), 130.3 (CH), 129.3 (CH), 128.9 (CH), 128.9 (CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 127.7 (CH), 127.3 (CH), 126.8 (CH), 126.8 (CH), 124.0 (C). ESI HRMS: calcd. For $[C_{20}H_{16}Br]^+$: 335.0429, found: 335.0428

(*Z*)-1-(1-Bromo-2-phenylvinyl)-2-chlorobenzene (**47c**)

The title compound **47c** was prepared as colourless oil in 45 % isolated yield (112 mg) from benzaldehyde and (2-chlorophenyl)boronic acid. R_f 0.61 (hexane).

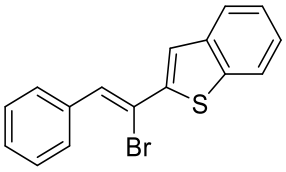


47c

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 6.8 Hz, 2H), 7.51 – 7.44 (m, 3H), 7.44 – 7.35 (m, 2H), 7.35 – 7.29 (m, 2H), 7.01 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7 (C), 135.3 (C), 133.4 (CH), 132.9 (C), 130.9 (CH), 129.9 (CH), 129.7 (CH), 129.0 (CH), 128.4 (CH), 128.2 (CH), 126.8 (CH), 118.5 (C). ESI HRMS: calcd. For $[C_{14}H_{11}BrCl]^+$: 292.9727, found: 292.9727

(*Z*)-2-(1-Bromo-2-phenylvinyl)benzo[*b*]thiophene (**47d**)

The title compound **47d** was prepared as white solid oil in 40 % isolated yield (107 mg) from benzaldehyde and benzo[*b*]thien-2-ylboronic acid. R_f 0.41 (hexane). m.p = 73-75 °C.

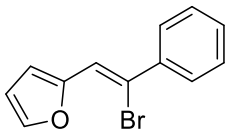


47d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 4H), 7.72 (s, 1H), 7.49 (s, 1H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.44 – 7.38 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1 (C), 139.4 (C), 135.5 (C), 131.6 (C), 130.0 (CH), 129.5 (CH), 128.5 (CH), 128.3 (CH), 125.4 (CH), 125.3 (CH), 124.8 (CH), 124.2 (CH), 122.1 (CH), 115.8 (C). ESI HRMS: calcd. For $[C_{16}H_{12}BrS]^+$: 314.9837, found: 314.9839

(*Z*)-2-(2-Bromo-2-phenylvinyl)furan (**47e**)

The title compound **47e** was prepared as colourless oil in 55 % isolated yield (116 mg) from furfural and phenylboronic acid. R_f 0.39 (hexane).

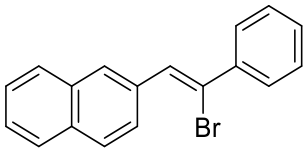


47e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 1.6 Hz, 1H), 7.69 (d, *J* = 1.3 Hz, 1H), 7.54 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.44 – 7.42 (m, 1H), 7.41 – 7.36 (m, 2H), 7.34 (t, *J* = 0.5 Hz, 1H), 7.31 (dt, *J* = 3.5, 0.6 Hz, 1H), 6.58 (ddd, *J* = 3.5, 1.8, 0.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7 (C), 142.3 (CH), 140.1 (C), 128.7 (CH), 128.4 (CH), 127.4 (CH), 121.3 (C), 119.2 (CH), 111.7 (CH), 111.5 (CH). ESI HRMS: calcd. For $[C_{12}H_{10}BrO]^+$: 248.9909, found: 248.9911

(*Z*)-2-(2-bromo-2-phenylvinyl)naphthalene (**47f**)

The title compound **47f** was prepared as white crystals in 58 % isolated yield (123 mg) from 2-naphthaldehyde and phenylboronic acid. R_f 0.29 (hexane). m.p = 78 - 79 °C.

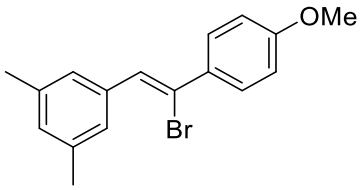


47f

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.94 (bs, 4H), 7.81 (d, *J* = 7.3 Hz, 2H), 7.63 – 7.56 (m, 2H), 7.55 – 7.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1 (C), 133.8 (C), 133.2 (C), 133.0 (C), 130.1 (CH), 128.9 (CH), 128.8 (CH), 128.5 (2xCH), 128.4 (CH), 127.9 8 (CH), 127.7 (CH), 126.9 (CH), 126.5 (CH), 126.3 (CH), 124.5 (C). ESI HRMS: calcd. For $[C_{18}H_{14}Br]^+$: 309.0273, found: 309.0272

(*Z*)-1-(2-Bromo-2-(4-methoxyphenyl)vinyl)-3,5-dimethylbenzene (**47g**)

The title compound **47g** was prepared as brown oil in 64 % isolated yield (173 mg) from 3,5-dimethylbenzaldehyde and (4-methoxyphenyl)boronic acid. R_f 0.26 (40:1 hexane : AcOEt).

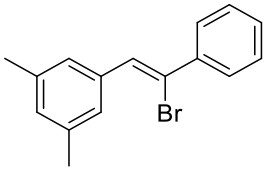


47g

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9 Hz, 2H), 7.35 (s, 2H), 7.12 (s, 1H), 7.00 (s, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 3H), 2.40 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (C), 137.6 (C), 136.4 (C), 133.7 (C), 129.5 (CH), 129.1 (CH), 128.6 (CH), 126.9 (CH), 123.5 (C), 113.6 (CH), 55.4 (CH_3), 21.4 (CH_3). ESI HRMS: calcd. For $[C_{17}H_{18}BrO]^+$: 317.0535, found: 317.0535

(*Z*)-1-(2-Bromo-2-phenylvinyl)-3,5-dimethylbenzene (**47h**)

The title compound **47h** was prepared as brown oil in 55 % isolated yield (134 mg) from 3,5-dimethylbenzaldehyde and phenylboronic acid. R_f 0.42 (hexane).

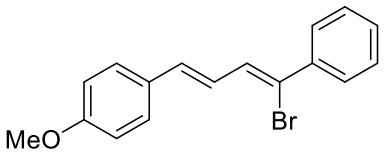


47h

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 2H), 7.47 – 7.34 (m, 5H), 7.22 (s, 1H), 7.03 (s, 1H), 2.41 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1 (C), 137.7 (C), 136.1 (C), 130.2 (CH), 129.8 (CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 127.0 (CH), 123.6 (C), 21.4 (CH_3). ESI HRMS: calcd. For $[C_{16}H_{16}Br]^+$: 287.0429, found: 287.0429

1-((1*E*,3*Z*)-4-Bromo-4-phenylbuta-1,3-dien-1-yl)-4-methoxybenzene (**47i**)

The title compound **47i** was prepared as yellow solid in 52 % isolated yield (139 mg) from *trans-p*-methoxycinnamaldehyde and phenylboronic acid. R_f 0.3 (20:1 hexane : AcOEt). m.p = 120 - 123 °C.

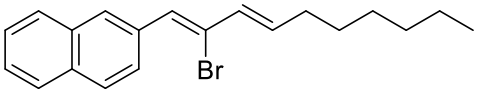


47i

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.44 – 7.31 (m, 3H), 7.19 (ddd, *J* = 15.3, 10.0, 1.1 Hz, 1H), 7.03 (d, *J* = 10.1 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 15.5 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8 (C), 139.5 (C), 136.0 (CH), 129.8 (C), 129.7 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 125.4(CH), 124.5 (C), 114.2 (CH), 55.3 (CH_3). ESI HRMS: calcd. For $[C_{17}H_{16}BrO]^+$: 315.0379, found: 315.0378

2-((1Z,3E)-2-bromodeca-1,3-dien-1-yl)naphthalene (**47j**)

The title compound **47j** was prepared as yellow solid in 34 % isolated yield (99 mg) from 2-naphthaldehyde and *trans*-1-Octen-1-ylboronic acid. R_f 0.43 (hexane). m.p = 45 - 46 °C.

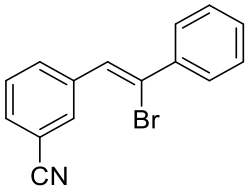


47j

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.93 – 7.83 (m, 4H), 7.58 – 7.49 (m, 2H), 7.06 (s, 1H), 6.43 – 6.28 (m, 2H), 2.41 – 2.22 (m, 2H), 1.65 – 1.49 (m, 2H), 1.49 – 1.34 (m, 5H), 1.07 – 0.91 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3 (CH), 133.5 (C), 133.1 (C), 132.8 (C), 130.5 (CH), 129.6 (CH), 128.9 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.3 (CH), 126.2 (CH), 124.0 (C), 32.4 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 22.7 (CH_2), 14.2 (CH_3). ESI HRMS: calcd. For $[C_{17}H_{16}BrO]^+$: 343.1055, found: 343.1054

(*Z*)-3-(2-Bromo-2-phenylvinyl)benzonitrile (**47k**)

The title compound **47k** was prepared as brown oil in 40 % isolated yield (96 mg) from 3-formylbenzonitrile and phenylboronic acid. R_f 0.18 (20:1 hexane : AcOEt). Spectroscopic data were consistent with those reported in the literature.[205]



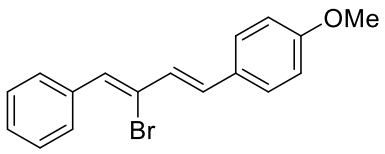
47k

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.73 – 7.60 (m, 3H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 6.3 Hz, 3H), 7.21 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (C), 137.5 (C), 133.5 (CH), 132.6 (CH), 131.2 (CH), 129.4 (CH), 129.1 (CH), 128.5 (CH), 127.8 (CH), 127.5 (CH), 127.0 (C), 118.6 (C), 112.5 (C). ESI HRMS: calcd. For $[C_{15}H_{11}BrN]^+$: 284.0069, found: 284.0070

[205] W. Shen, L. Wang, *J. Org. Chem.*, **1999**, *64*, 8873–8879.

1-((1*E*,3*Z*)-3-Bromo-4-phenylbuta-1,3-dien-1-yl)-4-methoxybenzene (**47l**)

The title compound **47l** was prepared as colourless crystal in 48 % isolated yield (130 mg) from benzaldehyde and *trans*-2-(4-methoxyphenyl)vinylboronic acid. R_f 0.3 (30:1 hexane : AcOEt). m.p = 124 -126 °C.



47l

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.37 – 7.32 (m, 1H), 7.08 (d, *J* = 15.0 Hz, 1H), 7.06 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.84 (dd, *J* = 15.1, 0.9 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7 (C), 135.9 (C), 133.6 (CH), 131.0 (CH), 129.5 (CH), 129.1 (C), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.0 (CH), 123.6 (C), 114.2 (CH), 55.3 (CH_3). ESI HRMS: calcd. For $[C_{17}H_{16}BrO]^+$: 315.0379, found: 315.0384

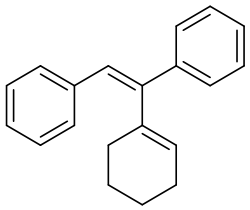
E.5.2 General procedure for the synthesis of dienes 45, 48 and 50

A carousel reaction tube under nitrogen atmosphere was charged with the corresponding alkenyl bromide (0.15 mmol), *N*-tosylhydrazone (1 to 2 equiv.), tris(dibenzylideneacetone)dipalladium(0) (4 mol %), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) (16 mol %), lithium *tert*-butoxide (3-4 equiv for 1-2 equiv of hydrazone respectively), and 1,4-dioxane (2.4 mL). The reaction mixture was stirred at 130 °C for 12 h. After cooling to room temperature, the reaction crude was dissolved in DCM and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using hexane or a mixture of hexane/ethyl acetate.

Employing this general procedure were prepared the following compounds:

(*E*)-(1-(Cyclohex-1-en-1-yl)ethene-1,2-diyl)dibenzene (**45a**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and cyclohexanone tosylhydrazone (51.1 mg, 0.2 mmol) were obtained 19 mg of **45a** (79 % isolated yield) as a colourless oil. *Rf* 0.31 (hexane). Spectroscopic data were consistent with those reported in the literature.[206]

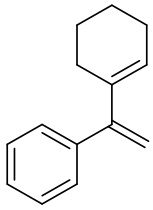


45a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 3H), 7.20 – 7.12 (m, 2H), 7.12 – 7.03 (m, 3H), 6.85 (dd, *J* = 7.8, 1.9 Hz, 2H), 6.64 (s, 1H), 5.52 (t, *J* = 4.1 Hz, 1H), 2.52 – 2.36 (m, 2H), 2.19 – 2.08 (m, 2H), 1.86 – 1.75 (m, 2H), 1.70 – 1.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3 8 (C), 140.2 (C), 138.7 (C), 137.7 (C), 130.1 (CH), 129.9 (CH), 129.3 (CH), 128.3 (CH), 127.7 (CH), 126.8 (CH), 126.0 (CH), 123.8 (CH), 26.3 (CH_2), 26.2 (CH_2), 23.1 (CH_2), 22.2 (CH_2). ESI HRMS: calcd. For $[C_{20}H_{21}]^+$: 261.1637, found: 261.1636

(1-(Cyclohex-1-en-1-yl)vinyl)benzene (**45b**)

Following the general method, from α-bromostyrene (0.15 mmol) and cyclohexanone tosylhydrazone (0.30 mmol) were obtained 9 mg of **45b** (33 % isolated yield) as a colorless oil. *Rf* 0.45 (hexane). Spectroscopic data were consistent with those reported in the literature.[207]



45b

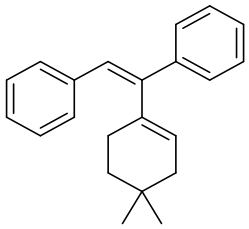
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 5.65 (t, *J* = 4.1 Hz, 1H), 5.22 (d, *J* = 0.9 Hz, 1H), 5.01 (d, *J* = 0.7 Hz, 1H), 2.32 – 2.22 (m, 2H), 2.17 – 2.07 (m, 2H), 1.81 – 1.69

[206] P. De Mayo, G. Wenska, *Chem. Commun*. **1986**, *22*, 1626–1627.
[207] A. Sabarre, J. Love, *Org. Lett.*, **2008**, *10*, 3941–3944.

(m, 2H), 1.69 – 1.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6 (C), 142.1 (C), 137.0 (C), 129.0 (CH), 128.7 (CH), 127.7 (CH), 126.9 (CH), 110.9 (CH), 26.41 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 22.1 (CH_2). ESI HRMS: calcd. For $[C_{14}H_{17}]^+$: 185.1325, found: 185.1324

(*E*)-(1-(4,4-Dimethylcyclohex-1-en-1-yl)ethene-1,2-diyl)dibenzene (**45d**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and 4,4-dimethylcyclohexanone tosylhydrazone (0.2 mmol) were obtained 22 mg of **45d** (81 % isolated yield) as a colourless oil. Rf 0.26 (hexane).

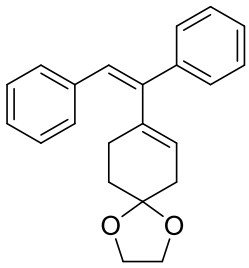


45d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 3H), 7.18 – 7.12 (m, 2H), 7.11 – 7.04 (m, 3H), 6.85 (dd, *J* = 7.9, 1.8 Hz, 2H), 6.64 (s, 1H), 5.43 (t, *J* = 4.3 Hz, 1H), 2.44 (td, *J* = 6.6, 2.1 Hz, 2H), 1.91 (bs, 2H), 1.55 (t, *J* = 6.5 Hz, 2H), 0.97 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0 (C), 140.2 (C), 137.7 (C), 137.4 (C), 130.1 (CH), 129.3 (CH), 128.9 (CH), 128.3 (CH), 127.7 (CH), 126.8 (CH), 126.0 (CH), 124.0 (CH), 40.2 (CH_2), 35.8 (CH_2), 28.5 (C), 28.1 (CH_3), 24.0 (CH_2). ESI HRMS: calcd. For $[C_{22}H_{25}]^+$: 289.1950, found: 289.1951

(*E*)-8-(1,2-Diphenylvinyl)-1,4-dioxaspiro[4.5]dec-7-ene (**45e**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and 1,4-cyclohexanedione monoethylene acetal tosylhydrazone (0.2 mmol) were obtained 16 mg of **45e** (49 % isolated yield) as a yellow oil. Rf 0.22 (10:1 hexane: AcOEt).



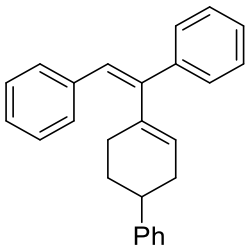
45e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 3H), 7.20 – 7.11 (m, 2H), 7.07 (ddd, *J* = 4.6, 2.0, 0.9 Hz, 3H), 6.89 – 6.79 (m, 2H), 6.67 (s, 1H), 5.38 (d, *J* = 0.6 Hz, 1H), 4.03 (d, *J* =

1.3 Hz, 4H), 2.68 (d, *J* = 1.7 Hz, 2H), 2.42 – 2.34 (m, 2H), 2.00 – 1.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1 (C), 139.8 (C), 138.1 (C), 137.4 (C), 130.1 (CH), 129.3 (CH), 128.4 (CH), 127.7 (CH), 126.9 (CH), 126.4 (CH), 126.2 (CH), 125.0 (CH), 107.9 (C), 64.4 (CH_2), 36.4 (CH_2), 31.2 (CH_2), 25.5 (CH_2). ESI HRMS: calcd. For $[C_{22}H_{23}O_2]^+$: 319.1692, found: 319.1692

(*E*)-4-(1,2-Diphenylvinyl)-1,2,3,6-tetrahydro-1,1'-biphenyl (**45f**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and 4-phenylcyclohexanone tosylhydrazone (0.1 mmol) were obtained 30 mg of **45f** (94 % isolated yield) as a red oil. Rf 0.21 (100:1 hexane : AcOEt).

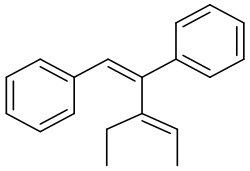


45f

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 6H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 6.2 Hz, 2H), 7.10 (d, *J* = 6.9 Hz, 3H), 6.88 (d, *J* = 6.4 Hz, 2H), 6.69 (s, 1H), 5.61 (s, 1H), 2.96 – 2.83 (m, 1H), 2.65 (d, *J* = 6.0 Hz, 1H), 2.51 – 2.30 (m, 1H), 2.18 (d, *J* = 16.7 Hz, 1H), 1.93 (ddd, *J* = 23.2, 11.7, 5.9 Hz, 1H), 1.40 – 1.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8 (C), 143.7 (C), 140.1 (C), 138.6 (C), 137.5 (C), 130.1 (CH), 129.4 (CH), 129.2 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 126.9 (CH), 126.8 (CH), 126.2 (CH), 126.1 (CH), 124.4 (CH), 39.9 (CH), 34.5 (CH_2), 30.2 (CH_2), 26.9 (CH_2). ESI HRMS: calcd. For $[C_{26}H_{25}]^+$: 337.1950, found: 337.1950

((1*E*,3*E*)-3-Ethylpenta-1,3-diene-1,2-diyl)dibenzene (**45g**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and 3-pentanone tosylhydrazone (0.2 mmol) were obtained 16 mg of **45g** (70 % isolated yield) as a colourless oil. Rf 0.29 (hexane).

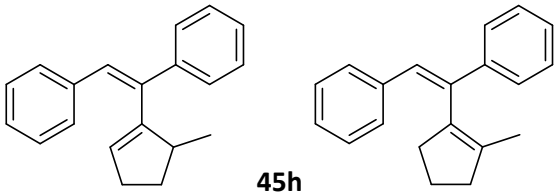


45g

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 3H), 7.18 – 7.12 (m, 2H), 7.13 – 7.03 (m, 3H), 6.88 (dd, *J* = 7.7, 1.9 Hz, 2H), 6.66 (s, 1H), 5.37 (q, *J* = 7.0 Hz, 1H), 2.40 (q, *J* = 7.5 Hz, 2H), 1.74 (d, *J* = 7.0 Hz, 3H), 1.11 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9 (C), 144.1 (C), 140.3 (C), 137.7 (C), 130.0 (CH), 129.4 (CH), 128.3 (CH), 127.7 (CH), 126.8 (CH), 126.0 (CH), 125.6 (CH), 125.0 (CH), 20.8 (CH_2), 14.0 (CH_3), 13.3 (CH_3). ESI HRMS: calcd. For $[C_{19}H_{21}]^+$: 249.1637, found: 249.1632

(*E*)-(1-(5-Methylcyclopent-1-en-1-yl)ethene-1,2-diyl)dibenzene (**45h**) and (*Z*)-(1-(2-Methylcyclopent-1-en-1-yl)ethene-1,2-diyl)dibenzene (**45h'**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and 2-methylcyclopentanone tosylhydrazone (0.2 mmol) were obtained 13 mg of a mixture of isomers **45h** and **45h'** 1.6 : 1 (48 % isolated yield) as a colourless oil. Rf 0.28 (hexane).



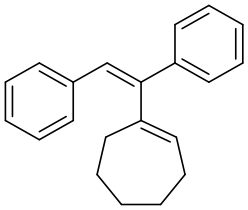
45h **45h'**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 2H), 7.34 (t, *J* = 2.0 Hz, 2H), 7.32 – 7.30 (m, 1H), 7.20 – 7.16 (m, 3H), 7.12 – 7.06 (m, 4H), 6.97 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.90 (dd, *J* = 7.6, 2.0 Hz, 2H). **45h** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (s, 1H), 5.29 (t, *J* = 2.8 Hz, 1H), 3.20 (dd, *J* = 8.6, 6.4 Hz, 1H), 2.56 – 2.40 (m, 4H), 1.24 (d, *J* = 6.9 Hz, 3H). **45h'** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (s, 1H), 2.33 (dt, *J* = 9.0, 2.6 Hz, 1H), 2.27 – 2.12 (m, 2H), 1.84 (p, *J* = 7.5 Hz, 2H), 1.73 – 1.65 (m, 1H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7 (C), 140.5 (C), 140.5 (C), 140.2 (C), 138.6 (C), 137.9 (C), 137.6 (C), 137.3 (C), 137.0 (C), 131.0 (CH), 129.5

(CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 126.8 (CH), 126.8 (CH), 126.5 (CH), 126.3 (CH), 126.1 (CH), 40.4 (CH_2), 38.6 (CH), 36.6 (CH_2), 32.8 (CH_2), 31.0 (CH_2), 21.7 (CH_2), 19.6 (CH_3), 15.6 (CH_3). ESI HRMS: calcd. For $[C_{20}H_{21}]^+$: 261.1637, found: 261.1630

(*E*)-1-(1,2-Diphenylvinyl)cyclohept-1-ene (**45i**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and cycloheptanone tosylhydrazone (0.1 mmol) were obtained 13 mg of **45i** (50 % isolated yield) as a colourless oil. Rf 0.31 (hexane).

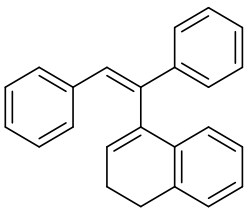


45i

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 3H), 7.20 – 7.02 (m, 5H), 6.90 (dd, *J* = 7.7, 1.8 Hz, 2H), 6.63 (s, 1H), 5.81 (t, *J* = 6.9 Hz, 1H), 2.47 – 2.34 (m, 2H), 2.29 – 2.17 (m, 2H), 1.89 – 1.76 (m, 2H), 1.62 – 1.48 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5 (C), 145.9 (C), 140.1 (C), 137.8 (C), 133.1 (CH), 130.1 (CH), 129.4 (CH), 128.3 (CH), 127.7 (CH), 126.9 (CH), 126.0 (CH), 124.3 (CH), 32.5 (CH_2), 30.4 (CH_2), 28.7 (CH_2), 26.7 (CH_2), 26.6 (CH_2). ESI HRMS: calcd. For $[C_{21}H_{23}]^+$: 275.1794, found: 275.1797

(*Z*)-4-(1,2-Diphenylvinyl)-1,2-dihydronaphthalene (**45j**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and α-tetralone tosylhydrazone (0.1 mmol) were obtained 20 mg of **45j** (69 % isolated yield) as a yellow oil. Rf 0.21 (100:1 hexane: AcOEt).



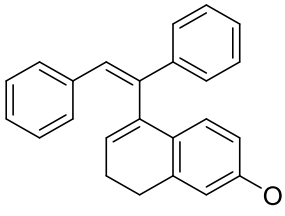
43j

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.35 – 7.29 (m, 2H), 7.27 – 7.22 (m, 3H), 7.20 – 7.16 (m, 5H), 7.15 – 7.09 (m, 3H), 7.08 – 7.05 (m, 1H), 6.83 (s, 1H), 6.21 (t, *J* = 4.7 Hz, 1H), 2.89

– 2.80 (m, 2H), 2.48 – 2.33 (m, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 142.0 (C), 141.9 (C), 139.5 (C), 137.5 (C), 137.0 (C), 134.2 (C), 129.6 (CH), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.1 (CH), 127.8 (CH), 127.3 (CH), 127.1 (CH), 126.6 (CH), 126.5 (CH), 126.0 (CH), 125.6 (CH), 28.2 (CH_2), 23.5 (CH_2). ESI HRMS: calcd. For $[C_{24}H_{21}]^+$: 309.1637, found: 309.1640

(Z)-4-(1,2-Diphenylvinyl)-7-methoxy-1,2-dihydronaphthalene (**45k**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and 6-methoxy-1-tetralone tosylhydrazone (33.1 mg, 0.1 mmol) were obtained 24 mg of **45k** (70 % isolated yield) as a yellow oil. Rf 0.20 (50:1 hexane : AcOEt).

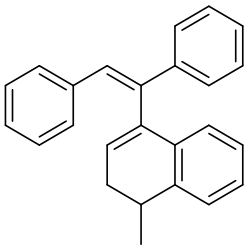


45k

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.35 – 7.30 (m, 2H), 7.28 – 7.23 (m, 3H), 7.21 – 7.16 (m, 3H), 7.14 (d, *J* = 2.9 Hz, 2H), 7.13 – 7.10 (m, 1H), 6.84 (s, 1H), 6.76 (d, *J* = 2.6 Hz, 1H), 6.59 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.10 (t, *J* = 4.7 Hz, 1H), 3.78 (s, 3H), 2.89 – 2.78 (m, 2H), 2.45 – 2.34 (m, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.4 (C), 142.2 (C), 141.5 (C), 139.7 (C), 138.8 (C), 137.6 (C), 129.7 (CH), 129.5 (CH), 128.8 (CH), 128.1 (CH), 127.8 (CH), 127.3 (C), 127.1 (CH), 126.8 (CH), 126.6 (CH), 126.5 (CH), 113.5 (CH), 110.5 (CH), 55.0 (CH_3), 28.8 (CH_2), 23.5 (CH_2). ESI HRMS: calcd. For $[C_{25}H_{23}O]^+$: 339.1743, found: 339.1236

(*Z*)-4-(1,2-Diphenylvinyl)-1-methyl-1,2-dihydronaphthalene (**45l**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and 4-methyl-1-tetralone tosylhydrazone (0.1 mmol) were obtained 17 mg of **45l** (53 % isolated yield) as a yellow oil. Rf 0.22 (100:1 hexane: AcOEt).

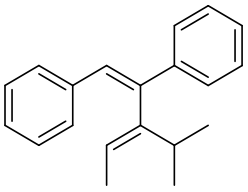


45l

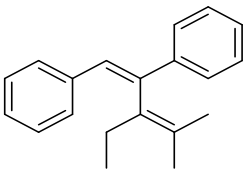
^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.35 – 7.27 (m, 2H), 7.26 – 7.21 (m, 4H), 7.20 – 7.16 (m, 4H), 7.15 – 7.10 (m, 3H), 7.05 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.83 (s, 1H), 6.14 (t, *J* = 4.7 Hz, 1H), 3.04 – 2.90 (m, 1H), 2.58 (ddd, *J* = 16.9, 6.5, 4.2 Hz, 1H), 2.25 (ddd, *J* = 16.9, 7.2, 5.2 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1 (C), 141.7 (C), 141.3 (C), 139.5 (C), 137.5 (C), 133.3 (C), 129.6 (CH), 129.5 (CH), 129.0 (CH), 128.1 (CH), 127.8 (CH), 127.5(CH), 127.1 (CH), 127.0 (CH), 126.6 (CH), 126.0 (CH), 125.9 (CH), 125.8 (CH), 32.2 (CH) , 31.3 (CH2), 19.6 (CH3). ESI HRMS: calcd. For $[C_{25}H_{23}]^+$: 323.1795, found: 323.1794

((1*E*,3*E*)-3-Isopropylpenta-1,3-diene-1,2-diyl)dibenzene (**45m**) and (*Z*)-(3-Ethyl-4-methylpenta-1,3-diene-1,2-diyl)dibenzene (**45m'**)

Following the general method, from vinyl bromide **43a** (0.1 mmol) and 2-methyl-3-pentanone tosylhydrazone (0.1 mmol) were obtained 11 mg of **45m** and **45m'** 2 : 1 (42 % isolated yield) as a colourless oil. Rf 0.5 (hexane).



45m



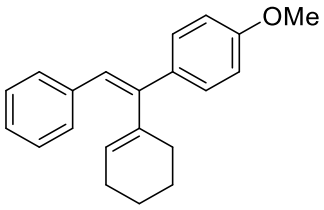
45m'

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 4H), 7.20 – 7.11 (m, 5H), 7.10 – 7.04 (m, 1H). **3m** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 1H), 5.63 – 5.49 (m, 1H), 2.20 – 2.08 (m, 1H), 1.87 (dd, *J* = 6.8, 1.2 Hz, 2H), 0.99 (d, *J* = 6.9 Hz, 6H). **3m'** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (s, 1H), 2.00 (q, *J* = 7.7 Hz, 2H), 1.95 (s, 3H), 1.82 (s, 3H), 0.93 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4 (C), 142.9 (C), 141.0 (C), 140.0 (C), 139.7 (C), 139.3 (C), 137.7

(C), 137.4 (C), 130.0 (C), 129.3 (2xCH), 129.3(CH), 129.1(CH), 128.9 (CH), 128.1 (CH), 128.1 (CH), 127.8 (CH), 127.8 (CH), 127.3 (CH), 127.0 (CH), 126.9 (CH), 126.3 (CH), 126.2 (CH), 118.6 (CH), 32.0 (CH), 23.8 (CH_2), 22.3 (CH_3), 21.8 (CH_3), 19.8 (CH_3), 14.8 (CH_3), 12.9 (CH_3). ESI HRMS: calcd. For $[C_{20}H_{23}]^+$: 263.1794, found: 263.1795

(*E*)-1-(1-(Cyclohex-1-en-1-yl)-2-phenylvinyl)-4-methoxybenzene (**48a**)

Following the general method, from vinyl bromide **47a** (0.09 mmol) and cyclohexanone tosylhydrazone (0.18 mmol) were obtained 17 mg of **48a** (65 % isolated yield) as a yellow oil. Rf 0.12 (50:1 hexane: AcOEt).

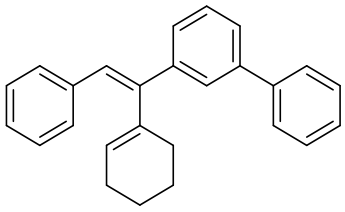


48a

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.13 – 7.00 (m, 5H), 6.94 – 6.87 (m, 4H), 6.62 (s, 1H), 5.53 (t, *J* = 4.2 Hz, 1H), 3.85 (s, 3H), 2.45 – 2.36 (m, 2H), 2.17 – 2.09 (m, 2H), 1.84 – 1.75 (m, 2H), 1.69 – 1.61 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6 (C), 144.0 (C), 139.0 (C), 138.0 (C), 132.2 (C), 131.1 (CH), 129.5 (CH), 129.3 (CH), 127.7 (CH), 125.8 (CH), 123.7 (CH), 113.7 (CH), 55.1 (CH3), 26.3 (CH2), 26.2 (CH2), 23.1 (CH2), 22.3 (CH2). ESI HRMS: calcd. For $[C_{21}H_{23}O]^+$: 291.1743, found: 291.1746

(*E*)-3-(1-(Cyclohex-1-en-1-yl)-2-phenylvinyl)-1,1'-biphenyl (**48b**)

Following the general method, from vinyl bromide **47b** (0.16 mmol) and cyclohexanone tosylhydrazone (0.32 mmol) were obtained 35 mg of **48b** (64 % isolated yield) as a colourless oil. Rf 0.25 (hexane).



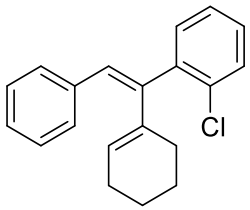
48b

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.59 (m, 3H), 7.50 – 7.42 (m, 5H), 7.41 – 7.37 (m, 1H), 7.19 – 7.14 (m, 1H), 7.14 – 7.09 (m, 2H), 6.95 (dd, *J* = 7.8, 1.8 Hz, 2H), 6.71 (s, 1H),

5.63 (t, *J* = 4.1 Hz, 1H), 2.53 – 2.45 (m, 2H), 2.22 – 2.13 (m, 2H), 1.90 – 1.80 (m, 2H), 1.74 – 1.64 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2 (C), 141.1 (C), 141.0 (C), 140.6 (C), 138.7 (C), 137.7 (C), 130.0 (CH), 129.4 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 127.8 (CH), 127.2 (CH), 127.1 (CH), 126.1 (CH), 125.6 (CH), 124.0 (CH), 26.3 (CH_2), 26.3 (CH_2), 23.1 (CH_2), 22.3 (CH_2). ESI HRMS: calcd. For $[C_{26}H_{25}]^+$: 337.1950, found: 337.1950

(*E*)-1-Chloro-2-(1-(cyclohex-1-en-1-yl)-2-phenylvinyl)benzene (**48c**)

Following the general method, from vinyl bromide **47c** (0.1 mmol) and cyclohexanone tosylhydrazone (0.2 mmol) were obtained 20 mg of **48c** (67 % isolated yield) as a yellow oil. Rf 0.29 (hexane).

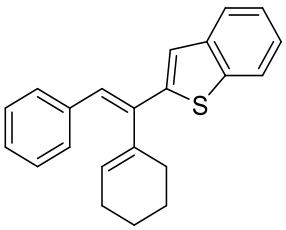


48c

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 1H), 7.34 – 7.21 (m, 2H), 7.15 – 7.06 (m, 4H), 6.86 (dd, *J* = 7.5, 2.0 Hz, 2H), 6.72 (s, 1H), 5.35 (t, *J* = 4.1 Hz, 1H), 2.47 (ddq, *J* = 6.2, 3.9, 2.2 Hz, 2H), 2.12 (bs, 2H), 1.81 (p, *J* = 6.1 Hz, 2H), 1.72 – 1.59 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2 (C), 139.1 (C), 137.3 (C), 137.0 (C), 134.2 (C), 131.8 (CH), 129.6 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 126.9 (CH), 126.4 (CH), 124.8 (CH), 26.2 (CH_2), 26.0 (CH_2), 23.0 (CH_2), 22.2 (CH_2). ESI HRMS: calcd. For $[C_{20}H_{20}Cl]^+$: 295.1248, found: 295.1246

(*E*)-2-(1-(Cyclohex-1-en-1-yl)-2-phenylvinyl)benzo[b]thiophene (**48d**)

Following the general method, from vinyl bromide **47d** (0.14 mmol) and cyclohexanone tosylhydrazone (0.28 mmol) were obtained 32 mg of **48d** (72 % isolated yield) as a colourless oil. Rf 0.30 (hexane).

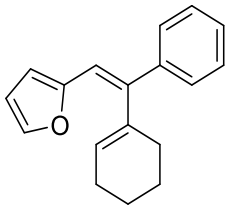


48d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 1H), 7.77 – 7.71 (m, 1H), 7.41 – 7.30 (m, 3H), 7.12 (dd, *J* = 2.1, 1.1 Hz, 4H), 7.09 (d, *J* = 0.8 Hz, 1H), 6.79 (s, 1H), 5.85 (t, *J* = 4.2 Hz, 1H), 2.47 – 2.40 (m, 2H), 2.22 – 2.13 (m, 2H), 1.86 – 1.75 (m, 2H), 1.71 – 1.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7 (C), 140.7 (C), 140.0 (C), 138.3 (C), 137.0 (C), 136.4 (C), 129.8 (CH), 129.3 (CH), 128.0 (CH), 127.2 (CH), 126.7 (CH), 124.3 (CH), 124.0 (CH), 123.8 (CH), 123.4 (CH), 122.3 (CH), 26.5 (CH_2), 26.1 (CH_2), 23.0 (CH_2), 22.1 (CH_2). ESI HRMS: calcd. For $[C_{22}H_{21}S]^+$: 317.1358, found: 317.1359

(*E*)-2-(2-(Cyclohex-1-en-1-yl)-2-phenylvinyl)furan (**48e**)

Following the general method, from vinyl bromide **47e** (0.18 mmol) and cyclohexanone tosylhydrazone (0.36 mmol) were obtained 40 mg of **48e** (87 % isolated yield) as a colourless oil. Rf 0.31 (hexane).



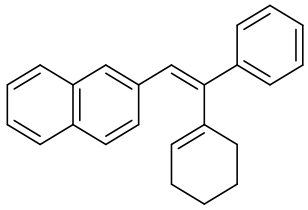
48e

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.35 (m, 3H), 7.25 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.15 (dd, *J* = 8.0, 1.6 Hz, 2H), 6.56 (d, *J* = 0.8 Hz, 1H), 6.14 (ddd, *J* = 3.4, 1.8, 0.8 Hz, 1H), 5.42 (t, *J* = 4.4 Hz, 1H), 4.94 (d, *J* = 3.3 Hz, 1H), 2.48 – 2.39 (m, 2H), 2.17 – 2.06 (m, 2H), 1.85 – 1.74 (m, 2H), 1.69 – 1.58 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6 (C), 142.3 (C), 140.7 (CH), 140.3 (C), 137.8 (C), 130.5 (CH), 129.3 (CH), 128.7 (CH), 127.0 (CH), 112.7 (CH), 111.5 (CH),

107.9 (CH), 26.3 (CH_2), 25.5 (CH_2), 22.9 (CH_2), 22.1 (CH_2). ESI HRMS: calcd. For $[C_{18}H_{19}O]^+$: 251.1430, found: 251.1434

(*E*)-2-(2-(Cyclohex-1-en-1-yl)-2-phenylvinyl)naphthalene (**48f**)

Following the general method, from vinyl bromide **47f** (0.20 mmol) and cyclohexanone tosylhydrazone (0.40 mmol) were obtained 57 mg of **48f** (90 % isolated yield) as a colourless oil. Rf 0.27 (hexane).

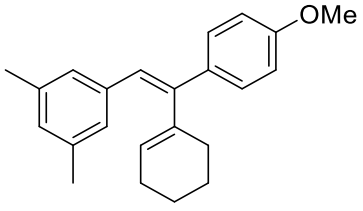


47f

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 1H), 7.65 – 7.56 (m, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.45 – 7.36 (m, 6H), 7.27 – 7.21 (m, 2H), 6.95 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.84 (s, 1H), 5.63 (t, *J* = 4.2 Hz, 1H), 2.58 – 2.47 (m, 2H), 2.23 – 2.15 (m, 2H), 1.92 – 1.81 (m, 2H), 1.76 – 1.65 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.79 (C), 140.2 (C), 138.8 (C), 135.4 (C), 133.2 (C), 131.9 (C), 130.3 (CH), 130.2 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 127.3 (CH), 126.9 (2xCH), 125.7 (CH), 125.5 (CH), 123.9 (CH), 26.4 (CH_2), 26.3 (CH_2), 23.1 (CH_2), 22.3 (CH_2). ESI HRMS: calcd. For $[C_{24}H_{23}]^+$: 311.1794, found: 311.1795

(*E*)-1-(2-(Cyclohex-1-en-1-yl)-2-(4-methoxyphenyl)vinyl)-3,5-dimethylbenzene (**48g**)

Following the general method, from vinyl bromide **47g** (0.15 mmol) and cyclohexanone tosylhydrazone (0.30 mmol) were obtained 28 mg of **48g** (59 % isolated yield) as a yellow oil. Rf 0.38 (40:1 hexane: AcOEt).



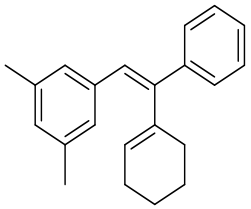
48g

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.70 (s, 1H), 6.54 (s, 1H), 6.48 (s, 2H), 5.54 (t, *J* = 4.2 Hz, 1H), 3.85 (s, 3H), 2.44 – 2.35 (m, 2H), 2.12 (s, 8H), 1.82 – 1.73 (m, 2H), 1.68 – 1.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5 (C),

143.6 (C), 139.0 (C), 137.7 (C), 136.9 (C), 132.5 (C), 131.2 (CH), 129.3 (CH), 127.7 (CH), 127.3 (CH), 124.0 (CH), 113.7 (CH), 55.3 (CH_3), 26.3 (CH_2), 26.2 (CH_2), 23.1 (CH_2), 22.3 (CH_2), 21.2 (CH_3). ESI HRMS: calcd. For $[C_{23}H_{27}O]^+$: 319.2056, found: 319.2056

(*E*)-1-(2-(Cyclohex-1-en-1-yl)-2-phenylvinyl)-3,5-dimethylbenzene (**48h**)

Following the general method, from vinyl bromide **47h** (0.22 mmol) and cyclohexanone tosylhydrazone (0.44 mmol) were obtained 44 mg of **48h** (70 % isolated yield) as a colourless oil. Rf 0.23 (hexane).

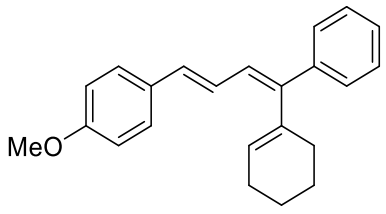


48h

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 3H), 7.17 (dd, *J* = 7.6, 1.9 Hz, 2H), 6.73 (s, 1H), 6.60 (s, 1H), 6.47 (s, 2H), 5.54 (t, *J* = 4.2 Hz, 1H), 2.49 – 2.42 (m, 2H), 2.13 (bs, 8H), 1.87 – 1.77 (m, 2H), 1.72 – 1.61 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0 (C), 140.5 (C), 138.7 (C), 137.5 (C), 136.9 (C), 130.1 (CH), 129.7 (CH), 128.3 (CH), 127.8 (CH), 127.4 (CH), 126.7 (CH), 124.0 (CH), 26.3 (CH_2), 26.2 (CH_2), 23.1 (CH_2), 22.3 (CH_2), 21.2 (CH_3). ESI HRMS: calcd. For $[C_{22}H_{25}]^+$: 289.1950, found: 289.1951

1-((1*E*,3*E*)-4-(Cyclohex-1-en-1-yl)-4-phenylbuta-1,3-dien-1-yl)-4-methoxybenzene (**48i**)

Following the general method, from vinyl bromide **47i** (0.21 mmol) and cyclohexanone tosylhydrazone (0.42 mmol) were obtained 48 mg of **48i** (72 % isolated yield) as an orange oil. Rf 0.24 (50:1 hexane : AcOEt).



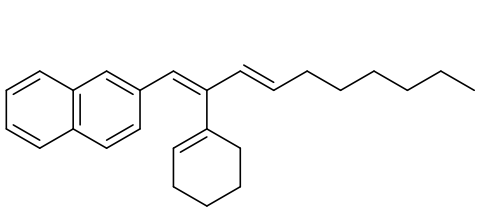
48i

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.44 – 7.34 (m, 3H), 7.23 – 7.14 (m, 4H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 14.8 Hz, 1H), 6.51 (d, *J* = 9.1 Hz, 1H), 6.46 (d, *J* = 14.1 Hz, 1H), 5.42 (t, *J* = 4.3 Hz, 1H), 3.79 (s, 3H), 2.44 – 2.37 (m, 2H), 2.15 – 2.06 (m, 2H), 1.84 – 1.74 (m,

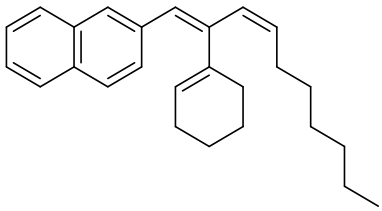
2H), 1.68 – 1.60 (m, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 159.0 (C), 144.4 (C), 139.8 (C), 137.9 (C), 131.3 (CH), 130.5 (C), 130.3 (CH), 129.8 (CH), 127.8 (CH), 127.3 (CH), 126.6 (CH), 125.4 (CH), 124.4 (CH), 113.8 (CH), 55.1 (CH_3), 26.2 (CH_2), 25.9 (CH_2), 23.0 (CH_2), 22.2 (CH_2).). ESI HRMS: calcd. For $[C_{23}H_{25}O]^+$: 317.1899, found: 317.1900

2-((1*Z*,3*E*)-2-(Cyclohex-1-en-1-yl)deca-1,3-dien-1-yl)naphthalene (**48j'**) 2-((1*Z*,3*Z*)-2-(Cyclohex-1-en-1-yl)deca-1,3-dien-1-yl)naphthalene (**48j''**)

Following the general method, from vinyl bromide **47j** (0.15 mmol) and cyclohexanone tosylhydrazone (0.30 mmol) were obtained 31 mg of of a mixture of isomer **48j'** and **48j''** 7 : 3 (60 % isolated yield) as a colourless oil. Rf 0.55 (hexane).



58j'

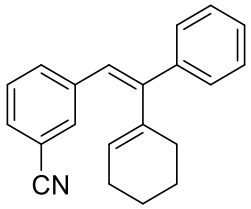


48j''

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.66 (m, 7H), 7.53 – 7.41 (m, 4H), 2.44 – 2.33 (m, 1H), 2.35 – 2.12 (m, 7H), 1.83 – 1.63 (m, 7H), 1.38 – 1.28 (m, 7H). **48j'** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (s, 1H), 6.41 (dq, *J* = 15.8, 1.3 Hz, 1H), 5.90 (tt, *J* = 3.5, 1.4 Hz, 1H), 5.81 (dt, *J* = 15.8, 7.0 Hz, 1H). **48j''** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.16 (dd, *J* = 11.4, 1.6 Hz, 1H), 6.07 (t, *J* = 4.1 Hz, 1H), 5.64 (dt, *J* = 11.4, 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8 (C), 140.4 (C), 139.2 (C), 137.1 (C), 136.3 (CH), 136.2 (C), 135.8 (C), 134.3 (CH), 133.4 (C), 133.3 (C), 132.0 (C), 132.0 (C), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (2xCH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 126.8 (CH), 126.8 (2xCH), 126.5 (CH), 125.9 (CH), 125.7 (CH), 125.5 (CH), 125.4 (CH), 124.6 (CH), 124.1 (CH), 33.1 (CH_2), 31.7 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 28.2 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 25.7 (CH_2), 23.2 (CH_2), 23.1 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 22.3 (CH_2), 14.1 (CH_3), 14.0 (CH_3). ESI HRMS: calcd. For $[C_{26}H_{33}]^+$: 345.2576, found: 345.2576

(*E*)-3-(2-(Cyclohex-1-en-1-yl)-2-phenylvinyl)benzonitrile (**48k**)

Following the general method, from vinyl bromide **47k** (0.16 mmol) and cyclohexanone tosylhydrazone (0.32 mmol) were obtained 27 mg of **48k** (60 % isolated yield) as a yellow oil. Rf 0.30 (20:1 hexane: AcOEt).

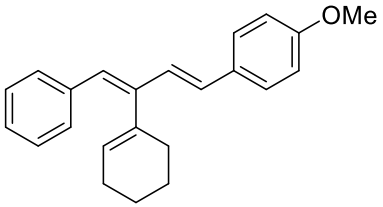


48k

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 3H), 7.32 – 7.28 (m, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.12 – 7.06 (m, 3H), 7.02 (dt, *J* = 7.9, 1.4 Hz, 1H), 6.55 (s, 1H), 5.58 (t, *J* = 4.1 Hz, 1H), 2.45 – 2.36 (m, 2H), 2.24 – 2.03 (m, 2H), 1.87 – 1.73 (m, 2H), 1.71 – 1.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9 (C), 139.1 (C), 139.0 (C), 138.1 (C), 133.3 (CH), 132.7 (CH), 131.8 (CH), 129.8 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 127.4 (CH), 121.4 (CH), 118.9 (C), 111.8 (C), 26.3 (CH_2), 26.1 (CH_2), 22.9 (CH_2), 22.1 (CH_2). ESI HRMS: calcd. For $[C_{21}H_{19}N]^+$: 286.1590, found: 286.1588

1-((1*E*,3*Z*)-3-(Cyclohex-1-en-1-yl)-4-phenylbuta-1,3-dien-1-yl)-4-methoxybenzene (**48l**)

Following the general method, from vinyl bromide **47l** (0.15 mmol) and cyclohexanone tosylhydrazone (0.3 mmol) were obtained 40 mg of **48l** (85 % isolated yield) as a yellow oil. Rf 0.23 (hexane). In this case the product was purified by flash chromatography on aluminium oxide using a gradient hexane to 100 : 1 hexane / ethyl acetate.



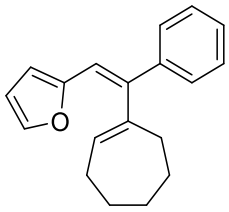
48l

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.40 – 7.34 (m, 6H), 7.31 – 7.23 (m, 1H), 7.02 (dd, *J* = 16.3, 1.1 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 16.2 Hz, 1H), 6.48 (s, 1H), 5.89 – 5.84 (m, 1H), 3.83 (s, 3H), 2.32 – 2.20 (m, 4H), 1.83 – 1.70 (m, 4H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 159.2 (C), 143.7 (C), 139.1 (C), 138.0 (C), 132.4 (CH), 130.4 (C), 129.5 (CH), 128.0 (CH),

127.6 (CH), 126.7 (CH), 126.6 (CH), 126.4 (CH), 123.7 (CH), 113.9 (CH), 55.2 (CH_3), 28.6 (CH_2), 25.6 (CH_2), 23.1 (CH_2), 22.3 (CH_2). ESI HRMS: calcd. For $[C_{23}H_{25}O]^+$: 317.1899, found: 317.1902

(*E*)-2-(2-(Cyclohept-1-en-1-yl)-2-phenylvinyl)furan (**48m**)

Following the general method, from vinyl bromide **47e** (0.15 mmol) and cycloheptanone tosylhydrazone (0.30 mmol) were obtained 29 mg of **48m** (72 % isolated yield) as a colorless oil. Rf 0.32 (hexane).

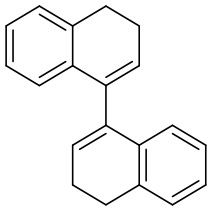


48m

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.34 (m, 3H), 7.25 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.16 (dd, *J* = 8.0, 1.6 Hz, 2H), 6.60 (s, 1H), 6.14 (ddd, *J* = 3.5, 1.8, 0.7 Hz, 1H), 5.63 (t, *J* = 7.0 Hz, 1H), 5.00 (d, *J* = 3.5 Hz, 1H), 2.56 – 2.51 (m, 2H), 2.20 (dd, *J* = 11.2, 7.0 Hz, 2H), 1.87 – 1.75 (m, 2H), 1.64 – 1.55 (m, 2H), 1.54 – 1.44 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6 (C), 146.2 (C), 143.0 (C), 140.7 (CH), 140.5 (C), 134.5 (CH), 129.3 (CH), 128.6 (CH), 127.0 (CH), 113.3 (CH), 111.4 (CH), 107.9 (CH), 32.3 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 26.6 (CH_2), 26.3 (CH_2). ESI HRMS: calcd. For $[C_{19}H_{21}O]^+$: 265.1586, found: 265.1583

3,3',4,4'-Tetrahydro-1,1'-binaphthalene (**50a**)

Following the general method, from vinyl bromide **49a** (0.23 mmol) and α-tetralone tosylhydrazone (0.23 mmol) were obtained 42 mg of **50a** (71 % isolated yield) as white crystals. Rf 0.29 (hexane). m.p = 138 – 139 °C. Spectroscopic data were consistent with those reported in the literature.[208]

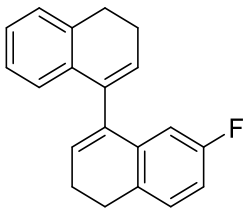


50a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 7.4, 1.0 Hz, 2H), 7.12 (td, *J* = 7.3, 1.5 Hz, 2H), 7.04 (td, *J* = 7.4, 1.6 Hz, 2H), 6.95 (dd, *J* = 7.5, 1.4 Hz, 2H), 6.11 (t, *J* = 4.5 Hz, 2H), 2.93 (t, *J* = 8.0 Hz, 4H), 2.43 (td, *J* = 8.0, 4.5 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3 (C), 135.8 (C), 134.7 (C), 128.0 (CH), 127.3 (CH), 126.7 (CH), 126.36, 125.1 (CH), 28.2 (CH2), 23.3 (CH2). ESI HRMS: calcd. For $[C_{20}H_{19}]^{+}$: 259.1481, found: 259.1482

7-Fluoro-3,3',4,4'-tetrahydro-1,1'-binaphthalene (**50b**)

Following the general method, from vinyl bromide **49a** (0.16 mmol) and 7-fluoro-1-tetralone tosylhydrazone (0.16 mmol) were obtained 28 mg of **50b** (64 % isolated yield) as white crystals. Rf 0.33 (hexane). m.p = 99 – 102 °C.



50b

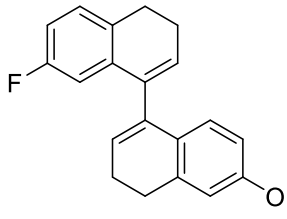
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 1H), 7.17 – 7.10 (m, 2H), 7.05 (td, *J* = 7.4, 1.6 Hz, 1H), 6.91 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.81 (td, *J* = 8.5, 2.8 Hz, 1H), 6.66 (dd, *J* = 10.2, 2.7 Hz, 1H), 6.17 (t, *J* = 4.1 Hz, 1H), 6.11 (t, *J* = 4.5 Hz, 1H), 2.98 – 2.83 (m, 4H), 2.43 (tt, *J* = 8.2, 4.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6 (C-F, d, ^{2}J = 241.8 Hz), 137.8 (C), 137.8 (C), 136.6 (C, d, $^{4}J_{C\text{-}F}$ = 7.6 Hz), 135.9 (C), 134.3 (C), 131.2 (C, d, $^{5}J_{C\text{-}F}$ = 3.1 Hz), 129.2

[208] D. P. Ojha, K. R. Prabhu, *J. Org. Chem.* **2013**, *78*, 12136–12143.

(CH), 128.4 (CH), 128.3 (CH, d, $^{4}J_{C\text{-}F}$ = 8.0 Hz), 127.5 (CH), 126.9 (CH), 126.3 (CH), 124.9 (CH), 113.0 (CH, d, $^{3}J_{C\text{-}F}$ = 21.4 Hz), 112.0 (CH, d, $^{3}J_{C\text{-}F}$ = 22.6 Hz), 28.1 (CH_2), 27.4 (CH_2), 23.4 (CH_2), 23.3 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.75. ESI HRMS: calcd. For $[C_{20}H_{18}F]^+$: 277.1387, found: 277.1387

7'-Fluoro-6-methoxy-3,3',4,4'-tetrahydro-1,1'-binaphthalene (**50c**)

Following the general method, from vinyl bromide **49b** (0.2 mmol) and 6-methoxy-1-tetralone tosylhydrazone (0.2 mmol) were obtained 37 mg of **50c** (60 % isolated yield) as a yellow oil. Rf 0.24 (50:1 hexane : AcOEt).

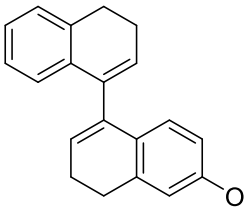


50c

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 8.2, 5.8 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.81 (dd, *J* = 7.6, 2.8 Hz, 2H), 6.70 (dd, *J* = 10.2, 2.8 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.18 (t, *J* = 4.2 Hz, 1H), 6.01 (t, *J* = 4.6 Hz, 1H), 3.81 (s, 3H), 2.99 – 2.83 (m, 4H), 2.49 – 2.39 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (C-F, d, ^{2}J = 242.0 Hz), 158.6 (C), 138.0 (C, d, $^{5}J_{C\text{-}F}$ = 2.2 Hz), 137.7 (C), 137.4 (C), 136.6 (C, d, $^{4}J_{C\text{-}F}$ = 7.8 Hz), 131.30 (C, d, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 129.0 (CH), 128.3 (CH, d, $^{4}J_{C\text{-}F}$ = 8.0 Hz), 127.5 (C), 126.2 (CH), 125.8 (CH), 113.7 (CH), 113.0 (CH, d, $^{3}J_{C\text{-}F}$= 21.4 Hz), 112.0 (CH, d, $^{3}J_{C\text{-}F}$ = 22.6 Hz), 111.0 (CH), 55.2 (CH_3), 28.7 (CH_2), 27.4 (CH_2), 23.4 (CH_2), 23.3 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.67. ESI HRMS: calcd. For $[C_{21}H_{20}FO]^+$: 307.1492, found: 307.1495

6-Methoxy-3,3',4,4'-tetrahydro-1,1'-binaphthalene (**50d**)

Following the general method, from vinyl bromide **49a** (0.25 mmol) and 6-methoxy-1-tetralone tosylhydrazone (0.25 mmol) were obtained 47 mg of **50d** (65 % isolated yield) as a yellow oil. Rf 0.18 (50:1 hexane : AcOEt).

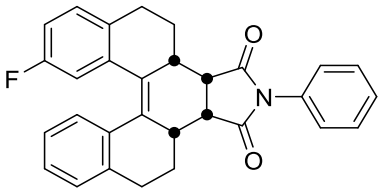


50d

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 6.7 Hz, 1H), 7.12 (td, *J* = 7.2, 1.5 Hz, 1H), 7.04 (td, *J* = 7.5, 1.7 Hz, 1H), 6.95 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 2.6 Hz, 1H), 6.57 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.10 (t, *J* = 4.5 Hz, 1H), 5.98 (t, *J* = 4.5 Hz, 1H), 3.79 (s, 3H), 2.98 – 2.84 (m, 4H), 2.48 – 2.35 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4 (C), 138.5 (C), 137.9 (C), 137.7 (C), 135.8 (C), 134.8 (C), 127.9 (C), 127.8 (CH), 127.3 (CH), 126.7 (CH), 126.4 (CH), 126.3 (CH), 125.4 (CH), 125.2 (CH), 113.6 (CH), 110.8 (CH), 55.1 (CH_3), 28.8 (CH_2), 28.3 (CH_2), 23.3 (CH_2), 23.3 (CH_2). ESI HRMS: calcd. For $[C_{21}H_{21}O]^+$: 289.1586, found: 289.1583

E.5.3 Synthesis and characterization data for Diels-Alder adduct 51

The diene **50b** (63 mg, 0.22 mmol) and *N*-phenylmaleimide (191.4 mg, 1.1 mmol) were heated together at 150 °C for 3 h. The excess *N*-phenylmaleimide was removed by steam distillation and the residue extracted by $CHCl_3$. The combined extracts were washed with water, dried with Na_2SO_4 and evaporated under reduced pressure. The product was purified by flash chromatography on silica gel using a mixture of hexane/ethyl acetate (5:1) to obtain 47 mg of **51** (48 % isolated yield) as a yellow crystals. m.p = 198 – 199 °C



51

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 3H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.18 – 7.07 (m, 3H), 7.02 (dd, *J* = 8.2, 1.6 Hz, 2H), 6.94 – 6.84 (m, 2H), 6.79 (td, *J* = 8.4, 2.7 Hz, 1H), 3.44

(dd, *J* = 4.2, 2.1 Hz, 2H), 3.10 – 2.85 (m, 4H), 2.72 – 2.57 (m, 2H), 2.57 – 2.43 (m, 2H), 2.16 – 1.98 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6 (C), 176.5 (C), 162.6 (C-F, d, ^{2}J = 241.3 Hz), 140.9 (C), 136.4 (C, d, $^{5}J_{C\text{-}F}$ = 2.8 Hz), 135.7 (C, d, $^{4}J_{C\text{-}F}$ = 8.0 Hz), 134.6 (C), 133.4 (C), 132.4 (C, d, $^{5}J_{C\text{-}F}$ = 2.5 Hz), 131.7 (C), 129.6 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.5 (CH), 127.9 (CH), 126.5 (CH), 125.5 (CH), 115.8 (CH, d, $^{3}J_{C\text{-}F}$ = 22.4 Hz), 114.3 (CH, d, $^{3}J_{C\text{-}F}$ = 21.6 Hz), 45.2 (CH), 44.9 (CH), 38.1 (CH), 37.5 (CH), 29.7 (CH_2), 28.9 (CH_2), 25.3 (CH_2), 25.1 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ -117.62. ESI HRMS: calcd. For $[C_{30}H_{25}FNO_2]^+$: 450.1863, found: 450.1862

List of publications

Part of the results collected in this Memory have been published in the following academic articles:

- "The Pd-catalyzed synthesis of benzofused carbo- and heterocycles through carbene migratory insertion/carbopalladation cascades with tosylhydrazones". M. Paraja, M. C. Pérez-Aguilar, C. Valdés, *Chem. Commun*, **2015**. *51*, 16241-16243.
- "Pd-catalyzed cascade reactions between o-iodo-N-alkenylanilines and tosylhydrazones: novel approaches to the synthesis of polysubstituted indoles and 1,4-dihydroquinolines". M. Paraja, C. Valdés, *Chem. Commun*. **2016**, *52*, 6312-6315.
- "Synthesis of Highly Substituted Polyenes by Palladium-Catalyzed Cross–Couplings of Sterically Encumbered Alkenyl Bromides and N-Tosylhydrazones". M. Paraja, R. Barroso, M.P. Cabal, C. Valdés, *Adv. Synth. Cat*. **2017**, *359*, 1058-1062.
- "Pd-Catalyzed Autotandem Reactions with N-Tosylhydrazones. Synthesis of Condensed Carbo- and Heterocycles by Formation of a C−C Single Bond and a C=C Double Bond on the Same Carbon Atom". M. Paraja, C. Valdés, *Org. Lett*. **2017**, *19*, 2034-2037.