Universidad de Oviedo

Departamento de Química Orgánica e Inorgánica

Programa de Doctorado:

"Síntesis y Reactividad Química"

SELECTIVE ORGANIC TRANSFORMATIONS WITH TOSYLHYDRAZONES: REDUCTIVE ALKENYLATIONS AND SYNTHESIS OF POLYSUBSTITUTED PYRAZOLES

María Del Carmen Pérez Aguilar

Tesis Doctoral

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Memoria para optar al grado de Doctor en Química
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RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

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2.- Autor	
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RESUMEN (en español)

En esta memoria se recogen los resultados obtenidos de reacciones de olefinación de compuestos carbonílicos y síntesis de pirazoles polisustituidos empleando tosilhidrazonas y diversos agentes de acoplamiento en ausencia de metal. De esta manera, se ha dividido la memoria en dos partes.

El Capítulo 1 recoge las reacciones entre tosilhidrazonas y ácidos alquenilborónicos en presencia de base para generar diversas olefinas de forma regioselectiva. Dependiendo de los reactivos empleados se puede acceder a diferentes regioisómeros del doble enlace, haciendo de esta reacción un proceso totalmente predecible. Además, se ha podido desarrollar esta metodología de forma *one-pot* directamente desde el carbonilo correspondiente, confiriéndole mayor simplicidad operacional y mayor atractivo desde el punto de vista sintético.

En el Capítulo 2 se describe una síntesis de pirazoles con diferentes patrones de sustitución, moléculas muy atractivas desde el punto de vista farmacéutico y de la química médica. Este Capítulo ha sido dividido en dos partes, en las cuales, se describen el estudio de diferentes familias de estos heterociclos. En la Parte A, se ha descrito la síntesis de pirazoles 1,3,5- y 3,4,5-trisustituidos de forma regioselectiva a través de un proceso en cascada que involucra una cicloadición 1,3-dipolar y un reagrupamiento [1,5]-sigmatrópico. La obtención de una familia u otra va a depender de los sustituyentes que posean ambos reactivos de partida. En la parte B, se amplía este estudio a tosilhidrazonas que poseen un grupo estereogénico en la posición α.. Así, durante el proceso la configuración del grupo se conserva, accediendo a estructuras enantioméricamente enriquecidas de una forma sencilla. Este proceso constituye un ejemplo único, en el cual, la transposición [1,5] transcurre con retención de la configuración. Este Capítulo pone de manifiesto la importancia de las transformaciones que involucran tosilhidrazonas, puesto que dan acceso a estructuras muy difíciles de obtener mediante otras rutas sintéticas

RESUMEN (en Inglés)

In this dissertation, it is summarised the investigation focused on the olefination of carbonyl compounds and the synthesis of polysustituted pyrazoles employing tosylhydrazones and different coupling partner in absence of metal catalyst. In this way, it has been organised in two chapters.

In Chapter 1, the regioselective reaction between tosylhydrazones and alkenylboronic acids in the presence of a base to lead to different olefins is described. Depending on the substitution of starting materials, this methodology allows to access to the different isomers of double bond in a predictable manner. Moreover, this methodology has been developed in one-pot fashion directly from the carbonyl compound, making this process more attractive and operationally simpler from a synthetic point of view.

In Chapter 2, it has been developed a synthesis of pyrazoles with different substitution patterns, very attractive molecules to pharmaceutical industry and medicinal chemistry. This chapter has been divided in two parts. In Part A, it has been described a regioselective synthesis of 1,3,5- and 3,4,5-trisubstituted pyrazoles through a sequence of 1,3-dipolar cycloaddition followed by a [1,5]-sigmatropic rearrangement. Different pyrazoles could be obtained with the adequate selection of starting materials. In Part B, in order to expand the study, tosylhydrazones with a stereogenic group in α position have been employed. It is remarkable that the configuration of the stereogenic center is preserved during the process. This reaction constitutes a unique example in which the [1,5]-sigmatropic rearrangement takes place with retention of the configuration. This Chapter highlights the importance of the transformations of tosylhydrazones, because it is possible to synthesize complex structures in a straightforward manner that otherwise would be difficult to prepare.

SR. PRESIDENTE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN SÍNTESIS Y REACTIVIDAD QUÍMICA

A mi familia, a mis amigos, a "ti"

ABBREVIATIONS AND ACRONYMS

A

Å	ångström
Ac	acetyl
alk	alkyl group
app	apparent
Aq.	aqueous
Ar	aryl group
atm	atmospheres

B

Bn	benzyl group
Boc	*tert*-butyloxycarbonyl
Bu	butyl group
Bz	benzoyl groups

C

^{o}C	degree Celsius
cat	catalyst
Cbz	benzyloxycarbonyl
COSY	Correlation Sprectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
Cyclopent	cyclopentyl

D

dba	dibenzylideneacetone
DBAD	di-tertbutyl azodicarboxylate
DCE	dichloroethane
DCM	dichloromethane
DFT	density functional theory
DHF	2,3-dihydrofuran
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
Dppf	1,1'-bis(diphenylphosphino)ferrocene
Δ	classical heating
δ	chemical shift

E

E	electrophile
EDG	electro-donating group
ee	enantiomeric excess
Ent	enantiomer
equiv	equivalents
Et	ethyl
EWG	electron-withdrawing group

G

g	grams
G_{act}	free Gibbs energy

H

h	hours
HMBC	Heteronuclear Multiple-Bond Correlation Spectroscopy
HOMO	Highest Occupied Molecular Orbital
HPLC	High-Perfomance Liquid Chromatography
HRMS	High-Resolution Mass Spectometry
HSQC	Heteronuclear Single-Quantum Correlation Spectroscopy
Hz	hertz

I

*i*Pr	*iso*-propyl
IR	infrared

K

K	degrees Kelvin
Kcal	kilocalorie

L

L	litre
LA	Lewis acid
LAH	Lithium aliminium hydride
LDA	Lithium diisopropylamide
LUMO	Lowest Unoccupied Molecular Orbital

M

M	metal
Me	Methyl

mg	miligram
MHz	megaherzt
min	minute
mL	mililitre
mmol	milimole
mol	mole
mp	melting point
MS	molecular sieves
MW	microwave

N

n-Bu	*n*-butil
NFSI	*N*-fluorobenzene sulfonimide
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser effect spectroscopy
Nu	nucleophile

P

Ph	phenyl
PMP	*p*-methoxyphenyl
ppm	parts per million
Pr	propyl
PTSA	*para*-toluenesulfonic acid

R

r.t.	room temperature
RCM	Ring Closing Metalhesis
red	reducction
rota	rotamer

S

solv	solvent
Sphos	2-Dicyclohexylphosphino-2’,6’-dimethoxybiphenyl

T

T	Temperature
t	time
TBAB	Tetra-*n*-butylammonium bromide
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl ether

t-Bu	*tert*-butyl
TFE	tetrafluoroethylene
THF	tetrahydrofuran
TMS	Trimethylsilyl group
Tol	tolyl group
TPP	tetraphenylporphyrin
TS	Transition State
Ts	Tosyl group

V

v	volume

X

Xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

TABLE OF CONTENTS

GENERAL INTRODUCTION

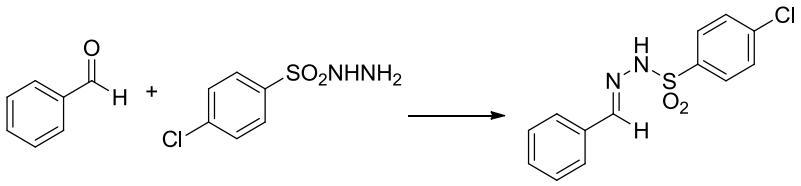
PARTE A: SÍNTESIS REGIOSELECTIVA DE PIRAZOLES A PARTIR DE ALQUINOS Y N-TOSILHIDRAZONAS A TRAVÉS DE UNA SECUENCIA DE CICLOADICIÓN 1,3-DIPOLAR Y UN REAGRUPAMIENTO [1,5]-SIGMATRÓPICO.

GENERAL INTRODUCTION

Sulfonylhydrazones in organic synthesis

N-Sulfonylhydrazones represent a class of stable nitrogen compounds with well known properties. These structures have been employed as synthetic intermediates in a large number of transformations in organic synthesis, mainly in those modifications in which carbonyl compounds are involved. In recent years, sulfonylhydrazones have been extensively used as coupling partner in metal-catalyzed cross-coupling reactions as well as transition metal-free transformations. This renovated interest has been motivated by the ability of sulfonylhydrazones to behave as a safe alternative of diazo compounds and metal carbene precursors, and is clearly illustrated by the large number of publications from several international research groups, that have appeared in last decade.

Although the chemistry of sulfonylhydrazones is enjoying a renaissance since the beginning of this century, it was at the end of nineteenth century, in 1898, when the chemists Curtius and Lorenzen observed that the combination of benzenesulfonyl chloride with hydrazine led to benzenesulfonylhydrazide.[1] The condensation of this species with a carbonyl compound, like benzaldehyde or acetone, gave the corresponding benzenesulphonylhydrazone (Scheme I.1). Next, they could study some properties of these compounds like the acidity of the N-H (pka = 15.8) and their thermal instability.[2]



Scheme I.1. Synthesis of sulfonylhydrazones from benzaldehyde.

Nevertheless, it was not until 1952 when these properties were considered and exploited by Bamford and Stevens.[3] Thus, a useful protocol was described to afford alkenes from tosylhydrazones in a very simple way. In 1967, Shapiro reported a similar reaction using organolithium compounds as base, which involved a vinyllithium intermediate.[4] These processes have become very important transformations and have been broadly employed in organic synthesis.

---

[1] a) R. Escales, *Ber*. **1885**, *58*, 160; b) T. Curtius, *Ber. Dtsch. Chem. Ges*. **1889**, *22*, 2161; c) T. Curtius, F. Lorenzen, *J. Prakt. Chem.* **1898**, *58*, 160.
[2] At high temperatures hydrazones would decompose to lead benzenesulfinic acid and nitrogen.
[3] W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, 4735.
[4] R. H. Shapiro, M. J. Heath, *J. Am. Chem. Soc*. **1967**, *89*, 5734.

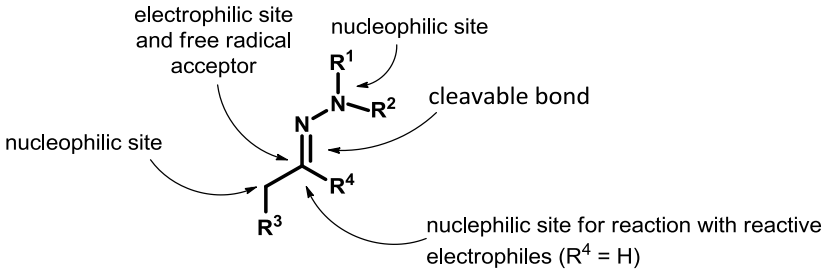
Particularly, the chemistry described by Aggarwal[5] about the use of tosylhydrazone salts as precursors of diazocompounds, is based on these reactions. These intermediates have been applied to different transition metal-catalyzed transformations, such as asymmetric epoxidations, aziridinations, cyclopropanations and C-H activations. Moreover, the discovery of a new cross-coupling reaction by our group has promoted and renewed the interest for these compounds.[6, 7]

This thesis is focused in transformations based on tosylhydrazones that do not require a metal catalyst. The methodologies presented are employed to form C-C and C-N bonds between tosylhydrazones and different available coupling partners. For this reason, this General Introduction describes the main aspects related with the chemistry of sulfonylhydrazones.

I.1. General reactivity of hydrazones.

Hydrazones are versatile moieties with distinct reactivity sites, which confer them different properties. Looking at the structure, the carbon atom of the hydrazone group has both electrophilic and nucleophilic character. On one hand, the carbon atom is predisposed to nucleophilic addition of organometallic compounds. On the other hand, this same carbon of aldehyde derived hydrazones could be attacked by electrophiles.[8] Moreover, the C=N bond is susceptible to hydrolysis, restoring the carbonyl functionality, and also to oxidative and reductive cleavage. Finally, the N-N bond could produce primary amines through a reductive reaction. Additionally, hydrazones can participate not only in polar reactions, but also in free radical, pericyclic processes as well as in organometallic catalytic reactions.[9] For these reasons, the hydrazone moiety is a very versatile and attractive functionality in organic chemistry. The observed reactivity is summarized in Scheme I.2.

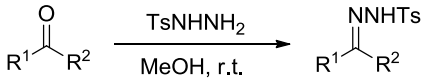
[5] J. R. Fulton, V. K. Aggarwal, J. de Vicente, *Eur. J. Org. Chem.* **2005**, 1479.
[6] J. Barluenga, C. Valdés, *Angew. Chem. Int. Ed*. **2011**, *50*, 7486.
[7] Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560.
[8] R. Brehne, D. Enders, R. Fernández, J. M. Lassaletta, *Eur. J. Org. Chem*. **2007**, 5629.
[9] S. Kim, J.-Y. Yoon, *Sci. Synth*. **2004**, *27*, 671.



Scheme I.2. Typical reactivity sites of hydrazones.

I.2. Fundamental transformations of sulfonylhydrazones.

One particular class of hydrazones with distinct reactivity are sulfonylhydrazones. The ability of these species to lose the sulfonyl group under different conditions has converted tosylhydrazones into very useful and versatile intermediates in organic synthesis. Moreover, due to their very easy preparation form carbonyl compounds (Scheme I.3),[10] the employment of tosylhydrazones have became a powerful tool for the modification of aldehydes and ketones.



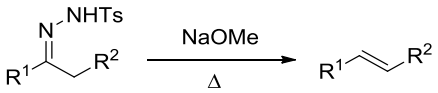
Scheme I.3. Synthesis of tosylhydrazones from the corresponding carbonyl compounds.

I.2.1.The Bamford-Stevens reaction.

The first synthetically useful transformation of tosylhydrazones dates back to 1952, and is known as the Bamford-Steven reaction. The reaction consists in the base catalyzed decomposition of arylsulfonylhydrazones from aldehydes and ketones in order to synthesize alkenes (Scheme I.4).[3,11]

[10] 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.

[11] Some modifications, improvements and mechanism studies: a) J. W. Powell, M. C. Whiting, *Tetrahedron*, **1959**, *7*, 305; b) S. Winstein, S. Smith, D. Darwish, *J. Am. Chem. Soc*. **1959**, *81*, 5511; c) L. Friedman, H. Shechter, *J. Am. Chem. Soc.* **1959**, *81*, 5512; d) L. Friedman, H. Shechter, *J. Am. Chem. Soc.* **1960**, *82*, 1002; e) L. Friedman, H. Shechter, *J. Am. Chem. Soc.* **1961**, *83*, 3159; f) L. Friedman, H. Shechter, *J. Am. Chem. Soc.* **1965**, *87*, 935.



Scheme I.4. General Bamford-Stevens reaction.

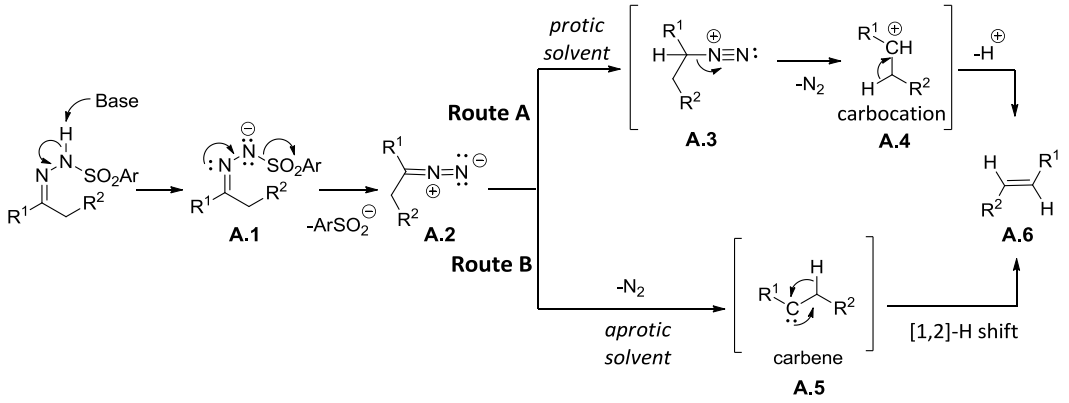
The mechanism has been broadly studied and depends on the media where the reaction is carried out.[12] For this reason, the effect of the solvent is something that should be taken into account. The proposed mechanism is described below in Scheme I.5.

The process begins with the deprotonation of the hydrazone by a strong base, generally metal alkoxides, generating the hydrazone salt **A.1**. Next, the sulfinate ion is lost forming the corresponding diazo compound **A.2**. Depending on the structure of the diazo compound, the solvent and the reaction conditions, the diazo compound can evolve through different pathways. Therefore, when the reaction conditions are mild and protic media is used, a few of these diazo compounds could be isolated. Nevertheless, most of these compounds undergo thermal decomposition leading to alkenes. According to what was said before, the reaction conditions employed are crucial in this step:

- In protic media (*Route A*), the diazo compound can be protonated to form a diazonium ion **A.3**, resulting in the formation of a carbocation **A.4** upon loss of nitrogen. This intermediate **A.4** undergoes a 1,2 hydrogen shift leading to the corresponding alkene **A.6.**

- In aprotic media (*Route B*), the loss of nitrogen generates a very unstable carbene intermediate **A.5** which gives also the same alkene **A.6** after 1,2-hydride migration.

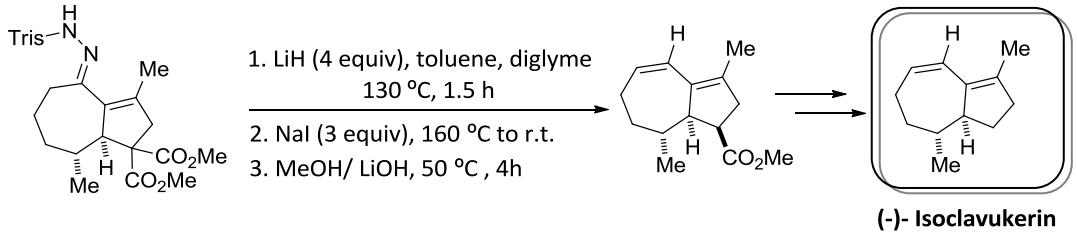
[12] H. W. Davies, M. Schwarz, *J. Org. Chem.* **1965**, *30*, 1242.



Scheme I.5. Bamford-Stevens mechanism.

Synthetic applications:

The Bamford Stevens reaction is a very useful transformation that has been widely applied in preparation of alkenes from carbonyl compounds as well as in total synthesis.[13] For example, during total synthesis of (-)-Isoclavukerin A, reported by professor Trost, the introduction of the diene moiety was accomplished by the use of this methodology (Scheme I.6).



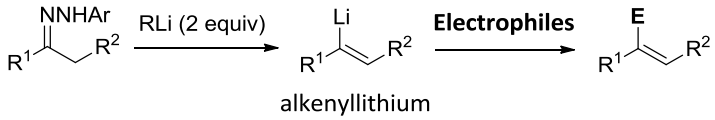
Scheme I.6. Total synthesis of (-)- Isoclavukerin.

I.2.2. The Shapiro reaction.

The second fundamental reaction of tosylhydrazones is the Shapiro reaction discovered in 1967.[4] Although this transformation is also used to obtain alkenes from carbonyl compounds, the mechanism and the reaction conditions are totally different from the Bamford-Stevens reaction discussed above. This time, the reaction is carried out with two equivalents of an organolithium compound and at low temperature

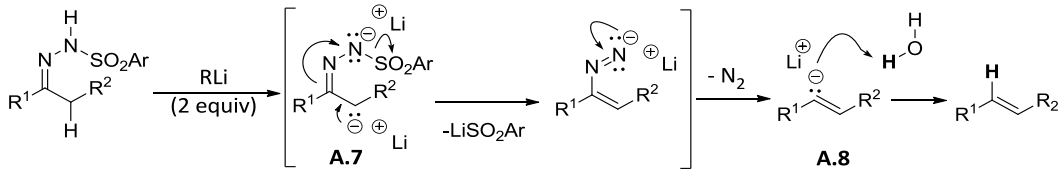
[13] L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Burlington, **2005,** pag 37.

(Scheme I.7). A very reactive alkenyllithium compound is generated *in situ* when this kind of bases is employed.[14] The generated intermediate could react with different electrophiles leading to useful products as vinylsilanes, nitro olefins, vinyl sulfides and functionalized acrylic acid derivatives. [15] Thus, this reaction provides a method to convert ketones into functionalized olefinic compounds in a simple way.



Scheme I.7. The Shapiro reaction

Regarding the mechanism (Scheme I.8), two equivalents of base are needed. The first one is used to deprotonate the tosylhydrazone by abstraction of the more acidic proton. The second one would abstract the proton at the α-carbon position giving a dianion **A.7** that then proceeds with loss of the tosylate group and nitrogen. As a result, a vinyl lithium species **A.8** is formed, which could be subsequently hydrolyzed or trapped with a variety of electrophiles. In this way, depending on the electrophile, different alkenylcompounds could be obtained.



Scheme I.8. Proposed Shapiro reaction mechanism.

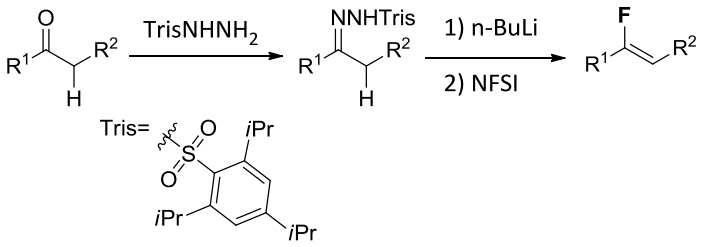
The advantage of the Shapiro over Bamford-Stevens reaction is that the resulting dianion does not tend to rearrange, which can occur with intermediate carbenes and carbenium ions. In addition, the process is predictable because the less highly substituted alkene is predominantly formed.

The proposed mechanism has been extensively studied. Therefore, to understand the regioselectivity of the reaction, a theoretical study has been recently carried out.[16]

[14] a) J. E. Stemke, F. T. Bond, *Tetrahedron* **1975**, *16*, 1815; b) A. R. Chamberlin, J. E. Stemke, F. T. Bond, *J. Org. Chem.* **1978**, *43*, 147.
[15] R. M. Adlington, A. G. M. Barret, *Acc. Chem. Res*. **1983**, *16*, 55.
[16] I. Tunes-Ardoiz, R. Losantos, D. Sampedro, *RSC Adv.*, **2015**, *5*, 37292.

In a subsequent modification, a catalytic version of the reaction was developed in which the stoichiometric amount of base could be replaced by catalytic lithium amides.[17]

The synthetic utility and the importance of the Shapiro reaction has been demonstrated by the large number of publications in which this transformation has been applied since its discovery. For instance, this methodology was recently used for the preparation of fluorinated alkenes from carbonyl compounds (Scheme I.9).[18]

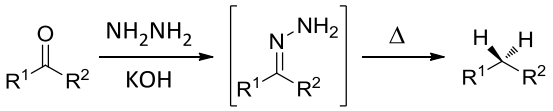


Scheme I.9. "Shapiro-based" electrophilic fluorination.

I.2.3. Reduction of hydrazones.

I.2.3.1. The Wolff-Kishner reaction.

Wolff-Kishner represents a general method to convert aldehydes and ketones to the corresponding alkane by reaction with base and heat.[19] The general mechanism proposed for this reduction is the condensation of the hydrazine with the carbonyl group to generate the hydrazone *in situ*. This hydrazone undergoes decomposition at high temperatures to lead the hydrocarbon (Scheme I.10).



Scheme I.10. The Wolff-Kishner reduction.

Several numbers of modifications have been reported in order to carry out the reaction under milder conditions and adapt them to the specific substrate.[20] However, a

[17] K. Maruoka, M. Oishi, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 2289.
[18] M.-H. Yang, S. S Matikonda, R. A. Atlman, *Org. Lett*. **2013**, *15*, 3894.
[19] N. Kishner*, J. Russ. Chem. Soc*. **1911**, *43,* 582.
[20] a) M. F. Grundon; H. B. Henbest; M. D. Scott*, J. Am. Chem. Soc.* **1945**, *67*, 2061; b) M. Huan, *J. Am. Chem. Soc.* **1946**, *68*, 2487; c) D. J. Cram, M. R. V. Sahyun, *J. Am. Chem. Soc*. **1962**, *84*, 1734; d) M. F. Grundon; H. B.

limitation of the Wolff–Kishner reduction is that it requires highly basic conditions and is unsuitable for base-sensitive substrates with functional groups like ester, amide, halogens and nitro.

As result of the broad study of this interesting and useful method, some side reactions have been reported in the literature:

- Formation of azines.[21]
- Reduction of ketone substrates to alcohols.[22]
- The *Kishner-Leonard elimination*[23] that consists on the synthesis of alkenes through elimination of a heteroatom, which is located in alfa position from a carbonyl group.
- The rearrangement of α,β-epoxy ketones to give allylic alcohols, which is known as the *Wharton reaction*.[24]
- Finally, rearrangement of strained rings adjacent to the carbonyl group, for instance *Eschenmoser-Tanabe fragmentation*.[25]

I.2.3.2. *N*-Tosylhydrazones reduction with hydride species.[26]

The reduction of sulfonylhydrazones follows a different pathway, due to the tendency of these systems to lose sulfinate. Thus, tosylhydrazones could be also reduced into alkanes by treatment with a hydride base. This sulfonylhydrazone transformation, commonly known as *Caglioti reaction*,[27] constitutes an alternative to the Wolff-Kishner reaction for the deoxygenation of carbonyl compounds.

The first reducing agent employed was sodium borohydride, but the side products generated and the low selectivity encouraged the search for other hydride sources. In this way, other metal hydrides like sodium cyanoborohydride[28] or catechol borane[29]

Henbest; M. D. Scott*, J. Chem. Soc.* **1963**, 1855; e) L. Caglioti, M. Magi, *Tetrahedron*, **1963**, *19*, 2061; f) M. E. Furrow, A. G. Myers, *J. Am. Chem. Soc*. **2004**, *126*, 5436.

[21] D. J. Cram, M. R. V. Knox, *J. Am. Chem. Soc*. **1962**, *84*, 1734.

[22] F. Eisenlohr, R. Polenske, *Ber*. **1924**, *57*, 1639.

[23] a) N. J. Leonard, S. Gelfand, *J. Am. Chem. Soc.* **1955**, *77*, 3269; b) N. J. Leonard, S. Gelfand, *J. Am. Chem. Soc.* **1955**, *77*, 3272.

[24] a) P. S. Wharton, D. H. Bohlen, *J. Org. Chem.* **1961**, *26*, 3615; b) L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Burlington, **2005**, pag. 482.

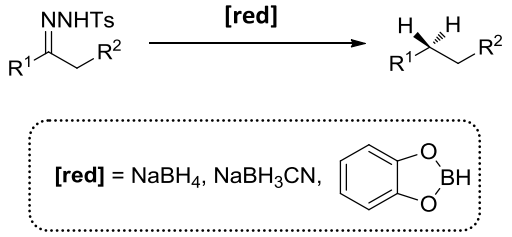
[25] L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Burlington, **2005**, pag. 156.

[26] Barry M. Trost, *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*, **1991**, vol. 8, pag, 327

[27] L. Caglioti, *Tetrahedron*, **1966**, *22*, 487.

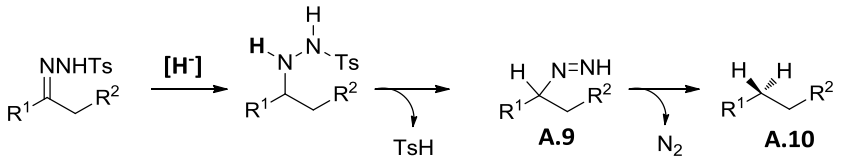
[28] R. O. Hutchins, B. E. Maryanoff, C. A. Milewski, *J. Am. Chem. Soc.* **1971**, *93*, 1793.

have been employed on account of their very high reducing ability towards most functional groups. These processes present highly selective conversion in presence of most functionalities (Scheme I.11). Furthermore, Hesse and co-workers made use of the nucleophilic agent $CuBH_4(PPh_3)_2$ as reductant in the synthesis an oxolactone.[30]



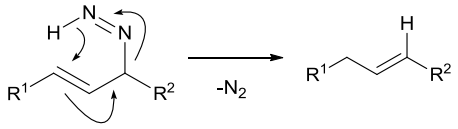
Scheme I.11. Reduction of tosylhydrazones using different hydride species.

The mechanism involves the reduction of the C=N double bond of the tosylhydrazone followed by elimination of *p*-toluenesulfinic acid. Subsequent decomposition of the diimide intermediate **A.9** lead to the alkane **A.10** (Scheme I.12).[31]



Scheme I.12. Reduction mechanism with a hydride reagent.

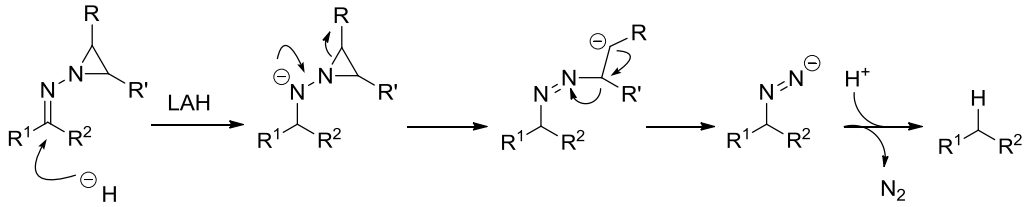
Moreover, this kind of reductants have been also used to reduce α,β-unsaturated carbonyl tosylhydrazones into the corresponding alkenes with migration of double bond (Scheme I.13),[27] which is commonly known as "*alkene walk*", or to obtain allenes from α,β-alkynic ketones.[32]



Scheme I.13. Intermediate species involved in the "*alkene walk*".

[29] G. W. Kabalka, D. T. C. Yang, J. D. C. Baker, Jr, *J. Org. Chem.* **1976**, *41*, 574.
[30] B. Milenkow, M. Hesse, *Helv. Chim. Acta*, **1986**, *69*, 1986.
[31] V. P. Miller, D. Y. Yang, T. M. Weigel, O. H. Han, H. W. Liu*, J. Org. Chem.* **1989**, *54*, 4175.
[32] A. Katritzky, O. Meth-Cohn, C. W. Rees, *Comprehensive Organic Functional Group Transformation*, Elservier Academic Press, Oxford, **1995**, pg 962.

Finally, other hydrazones like *N*-azirinylimines, have been explored in order to carry out the reduction under milder conditions using non-acidic media and low temperatures (Scheme I.14).[33]



Scheme I.14. *N*-aziridylimines reduction employing $LiAlH_4$.

I.2.4. Nucleophilic additions to sulfonylhydrazones: C-C bond forming reactions.

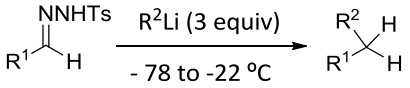
Aldehyde or ketone tosylhydrazones are very convenient synthetic intermediates. These compounds are readily available, stable and frequently crystalline and in consequence, they can be stored indefinitely. However, aldehydes are more reactive and cannot be stored, being susceptible to autoxidation, self-condensation, and hydration. For this reason, hydrazones have been employed as synthetic equivalents of the carbonyl compounds in numerous transformations.

In current practice, C-C sp^3 is not an intuitive disconnection in retrosynthetic analysis because finding straightforward methods to form this kind of linkages is difficult. Below, some methods will be described in which sulfonylhydrazones have been used to generate carbon-carbon sp^3 bonds directly. These strategies are very useful as they represent an alternative to common indirect sequences that consist on the formation of a C-C sp^2 bond followed by hydrogenation. Moreover, at the end of this section, some olefination examples employing tosylhydrazones are described.

I.2.4.1. Aldehyde tosylhydrazones reductive alkylation with organolithium reagents.

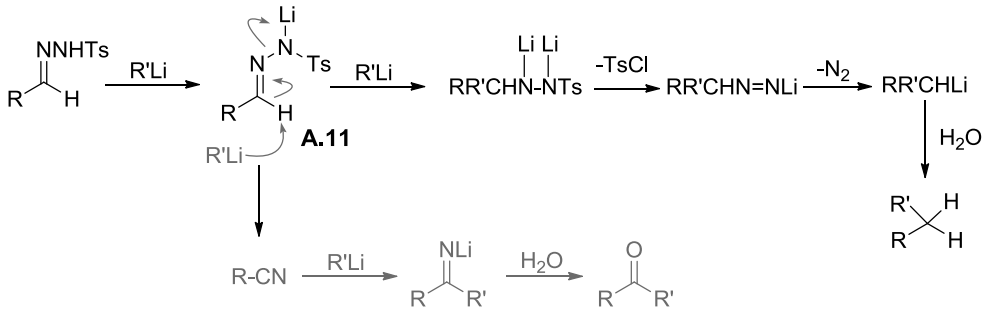
In 1977, Vedejs *co-workers*[34] reported that it was possible to convert aldehydes into the reductive alkylation products via the tosylhydrazones. They observed that alkyllithium reagents could add promptly to the aldehyde tosylhydrazone C=N linkage giving rise to the reductive alkylation products (Scheme I.15).

[33] C. L. Leone, A. R. Chamberlin, *Tetrahedron Lett*. **1991**, *32*, 1691.
[34] E. Vedejs, W. Stole, *Tetrahedron Lett.* **1977**, *18*, 135.



Scheme I.15. Aldehyde tosylhydrazones reductive alkylation with organolithium reagents.

This transformation is very simple however the yields are very low. This is due to competing processes that this reaction possesses. Therefore, the intermediate **A.11** could evolve through two different ways (Scheme I.16): adding other equivalent of organolithium reagent that after the hydrolysis provides the reductive alkylation products, or through the based induced conversion of this monolithiated tosylhydrazone **A.11** into nitrile. In the latter, the nitrile is attacked by the excess of organolithium reagent giving a ketone after the hydrolysis.

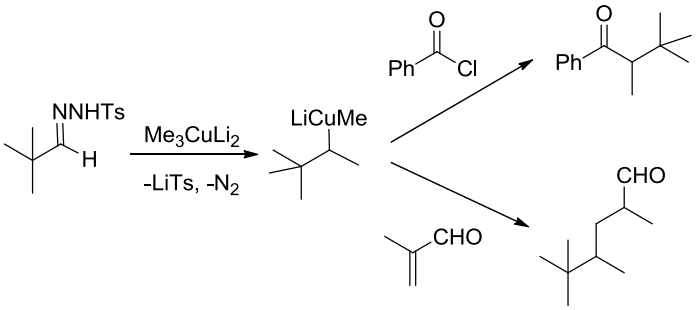


Scheme I.16. Mechanism of different processes that take place in the reductive alkylation of aldehyde tosylhydrazone with organolithium reagents.

I.2.4.2. Aldehyde tosylhydrazones reductive coupling with organocopper reagents.

The studies on the anionic addition were also extended to cuprate reagents.[35] The aldehyde hydrazones are more predisposed to addition than those that proceed from ketones. Particularly, the reactive intermediate carbanion that proceed from aldehyde hydrazones could be trapped by an external electrophiles other than proton. Therefore, the intermediate cuprate generated could be coupled with different partners, such as acid chlorides or other aldehydes, in a one-pot process (Scheme I.17).

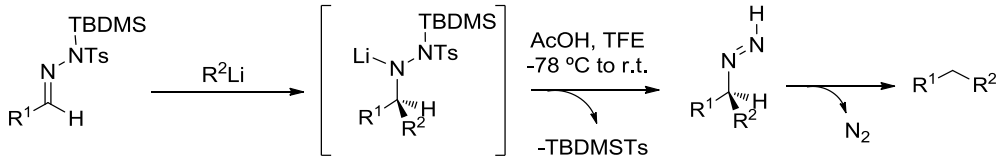
[35] S. H. Bertz, *Tetrahedron Lett.* **1980**, *21*, 3151.



Scheme I.17. Use of organocuprate reagents in *N*-tosylhydrazone reductive coupling.

I.2.4.3. Organometallic additions to *N*-silylated aldehyde tosylhydrazones.

The use of *N*-*tert*butyldimethylsilyl tosylhydrazones as efficient precursors for the creation of carbon-carbon bonds was described by Myers and co-workers.[36,37] These hydrazones allowed that the reaction conditions were mild, consecuently a smooth 1,2 addition of alkyllithium compounds was possible (Scheme I.18).



Scheme I.18. Reductive coupling between *N*-silylated hydrazones and organolithium compounds.

This mechanism to form the C-C single bond directly from *N*-sylilated sulfonylhydrazones and *n*-alkyllithium reagents would start with the 1,2-addition of the alkyllithium compound followed by protonation of the adduct. Next, elimination of *p*-tolunenesulfinic acid, protodesilylation *in situ* to form allylic diazene and finally, loss of dinitrogen would provide the desired alkane. The authors proposed that the final step would proceed through a radical pathway instead of the anionic pathway described in both previous procedures.

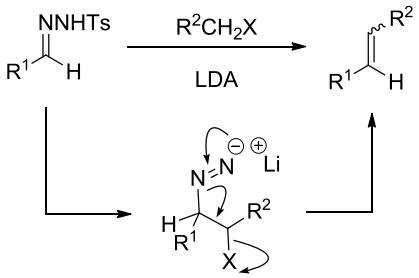
[36] The *N*-*tert*butyldimethylsilyl tosylhydrazones were previously used in the formation of carbon-carbon double bonds. The [1,2]-addition of a vinyllithium compound was enabled by the nitrogen protection with a silyl group. The corresponding olefins were afforded stereoselectively by decomposition of the resulting adducts to lead to an allylic diazene intermediate followed by a [3,3]-sigmatropic rearrangement with loss of dinitrogen. A. G. Myers, P. J. Kukkola, *J. Am. Chem. Soc*. **1990**, *112*, 820.

[37] A. G. Myers, M. Movassaghi, *J. Am. Chem. Soc*. **1998**, *120*, 8891.

The overall reaction is accomplished under mild conditions making this method efficient and compatible with α-chiral aldehydes without epimerization. Moreover, sterically hindered alkyllithiums could be also employed.

I.2.4.4. The use of stabilized organometallic compounds.

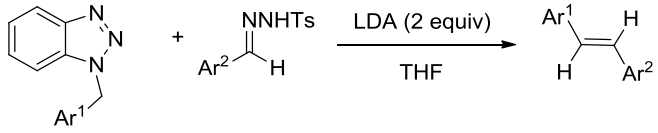
With regard to stabilized organolithium compounds, a simple and inexpensive method was reported by Vedejs and co-workers.[25,38] They showed that arylsulfonylhydrazones of aldehydes react with sterically unhindered α-lithiosulfones or α-lithionitrile to afford olefins. The functional group has two different roles in the mechanism: it is necessary to stabilize the carbanion of the generated salt in the first step and secondly, as a leaving group allowing the formation of final product (Scheme I.19).



Scheme I.19. Alkenes from tosylhydrazones and stabilized carbanions.

This methodology was also developed employing organomagnesium reagents. In this way, some side reactions (as Shapiro fragmentation) could be avoided and the scope of applications could be extended.[39, 40] In addition, the use of benzotriazole-stabilized anions introduced by Katritzky, leads to *E*-stilbenes in a stereospecefic way with predominant *E*-alkene formation (Scheme I.20).[41] The benzotriazole moiety plays a double role both as anion stabilizing and leaving group.

[38] E. Vedejs, J. M. Dolphin, W. T. Stolle, *J. Am. Chem. Soc.* **1979**, *101*, 249.
[39] A. Kurek-Tyrlik, S. Marczak, K. Michalak, J. Wicha, A. Zarechi, *J. Org. Chem.* **2001**, *66*, 6994.
[40] J. Wicha, A. Zarecki*, J. Org. Chem*. **2004**, *69*, 5810.
[41] A. R. Katritzky, D. O. Tymoshenko, S. A. Belyakov, *J. Org. Chem*. **1999**, *64*, 3332.



Scheme I.20. Synthesis of *E*-stilbenes from *N*-tosylhydrazones and benzotriazole-stabilized carbanions.

Both methods described above could be envisioned as a good alternative to the classical Julia olefination.[42]

I.3. *N*-Tosylhydrazones and diazo compounds.

Along this chapter, some reactivity of sulfonylhydrazones and processes in which they are involved have been examined. However, one of the most important aspects of the sulfonylhydrazones are their employment as starting materials to generate diazo compounds *in situ*.[5] This is possible through the Bamford-Stevens reaction, that concerns a diazo compound intermediate. Even though their inherent risk, diazo compounds are used in a large number of synthetic procedures. For this reason, a lot of methods to synthesize them have been reported and deeply studied. Within them, it is noteworthy the use of tosylhydrazones as a safe and simple alternative. Hence, in this section, some general aspects about diazo compounds will be treated. Additionally, an overview of *N*-tosylhydrazones as diazo compound precursors, and their use in some relevant reactions will be presented.

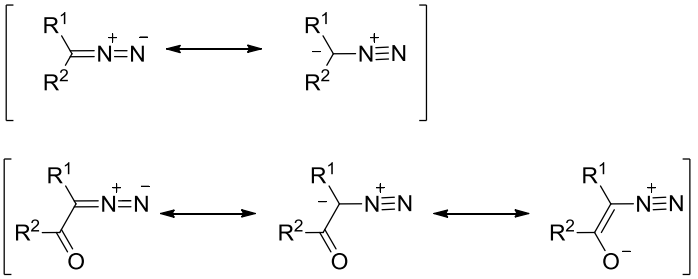
I.3.1. Diazo compounds and their reactivity.

Diazo compounds exhibit high synthetic versatility, spreading to organic and inorganic chemistry and have been investigated so far since their discovery.[43] Attending to the structure of diazo compounds, it could be noticed that the associated stability is strongly influenced by the nature of the substituents. Thus, stabilized diazo compounds, such as α-diazoketones and α-diazoesters are considered to be much safer and stable

[42] L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Burlington, **2005**, pag. 230.

[43] a) H. Zollinger, *Diazo Chemistry I and II*, VCM Weinheim, **1994**; b) M. Regitz, G. Maas, *Diazo Compounds; Properties and Synthesis, Academic Press*, Orlando, **1986**; c) H. Zollinger, *Diazo Chemistry II: Aliphatic, Inorganic and Organometallic Compounds*, VCH Verlagsgesellschaft, Weinheim, Germany, **1995**; d) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo compounds,* Wiley, New York, **1998**; e) D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stupple, *Chem. Soc. Rev*. **2001**, *30*, 50.

than diazomethane or other unfunctionalized diazo compounds. Indeed, this is due to the resonance stabilization of the negative charge by the functional group (Scheme I.21).[44] Despite some of them still are unsteady and their use is limited, the chemistry of stabilized diazo compounds is currently extreme rich. However, it is out of the scope of this revision.



Scheme I.21. Main resonance structures of diazo compounds and stabilized diazo compounds.

In any case, the use of these species imply an inherent risk due to the toxicity, instability and their tendency to explode. In consequence, diazo compounds must be handled carefully in the laboratory due to the inherent reactivity:

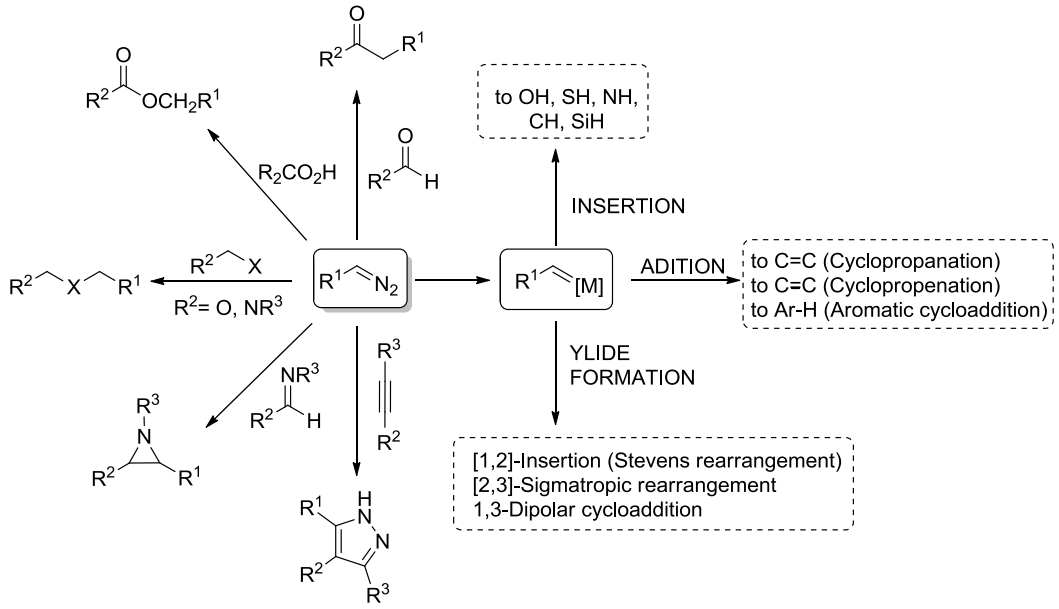
1. Diazo compounds have a high nitrogen content that make them explosive substances. For this reason, they cannot be stored in a large quantity.

2. The temperature that is required in different reactions, involves certain risks associated with both, their explosive nature and their toxicity.

Despite of their instability and toxicity mentioned above, diazo compounds are highly reactive reagents commonly used in a large numbers of transformations. They are able to react with different transition metal to generate metal carbene complexes, that can participate in a variety of catalytic processes. These processes are summarized on the right part of the Scheme I.22. For instance, they could react leading to a carbene insertion in C-H,[45] O-H, S-H, N-H[46] and Si-H bonds that constitutes an important area in actual organic chemistry or cyclopropanation reactions, a well-studied metal-catalyzed transformation.[47] On the left side of the scheme, it is shown the direct reactions between diazo compounds and organic substrates, such as addition to suitable

[44] a) T. Ye, A. McKervey, *Chem. Rev.* **1994**, *94*, 1091; b) Z. Zhang, J. Wang, *Tetrahedron*, **2008**, *64*, 6577.
[45] a) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861; b) M. P. Doyle, R. Duffi, M. Ratnikov, L. Zhou, *Chem. Rev*. **2010**, *110*, 704; c) D. Zhao, J. Hokim, L. Stegemann, C. A. Strassert, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *15*, 4508.
[46] E. C. Lee, G. C. Fu*, J. Am. Chem. Soc.* **2007**, *129*, 12066.
[47] a) M. P. Doyle, *Chem. Rev*. **1986**, *86*, 919; b) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911.

electrophiles,[47b] aziridination[48] and Wittig reactions.[49] A selection of the most useful processes is summarized in Scheme I.22.



Scheme I.22. Summary of typical transformations of diazo compounds.

Nevertheless, the applicability of these compounds has been considerably limited and the scope of the reactions is restricted by their scarce availability. Therefore, safer and reliable routes have been consequently pursued, wherein the reactive species would be generated *in situ* or employing a carbene equivalent.

Particularly, alternative protocols that provide new routes to access to non-stabilized diazo compounds[42b,50] have been described. The use of phenyliodonium ylides,[51] *N*-aziridinylimines,[52] amino ester hydrochloride or the generation of diazoalkanes through oxidation of silylated hydrazone derivatives by using difluoroiodobenzene[53] are the examples recovered in literature. Furthermore, other protocols, such as the use of acyl triazenes, which undergo thermal or base catalyzed

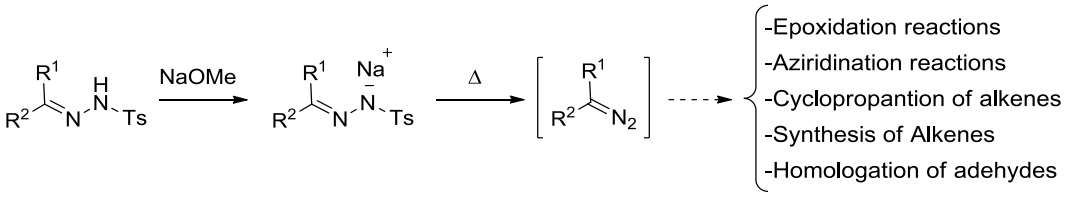
[48] L. Degenaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *144*, 7881.
[49] X. L. Sun, J. C. Zhang, Y. Jang, *Pure Appl. Chem.* **2010**, *82*, 625.
[50] M. I. Javed, M. Brewer, *Org. Lett*. **2007**, *9*, 1789.
[51] P. Muller, *Acc. Chem. Res*. **2004**, *37*,243.
[52] a) R. K. Muller, R. Joos, D. Felix, J. Schreiber, C. Wintner, A. Eschenmoser, *Org. Synth. Coll. Vol.* **1988**, *56*, 56; b) J. A. May, B. M. Stoltz, *J. Am. Chem. Soc.* **2002**, *124*, 12426.
[53] a) M. E. Furrow, A. G. Myers, *J. Am. Chem. Soc.* **2004**, *126*, 12222 ; b) J. R. Denton, D. Sukumaran, H. M. L. Davies, *Org. Lett.* **2007**, *9*, 2625.

fragmentation, allow the *in situ* generation of diazo compound.[54] However, most of these methods present limitations and restrictions which could not be avoided. In this context, the use of tosylhydrazones as versatile diazo compound precursors has emerged during last decade. Indeed, throughout this method, it is possible to access to non-stabilized diazo compound structures that otherwise would be very difficult to obtain. This class of transformations will be discussed in detail in next section.

I.3.2. *In situ* generation of diazo compounds from tosylhydrazones.

The methodology to generate diazo compounds from tosylhydrazones had been known since the seminal work of Bamford and Stevens. However, it had been mostly restricted to the formation of alkenes through the Bamford-Stevens reaction (Section I.2.1) due to their intrinsic unstability. In 2001, Aggarwal and co-workers developed an efficient method to generate diazo compounds *in situ*, and applied it in a variety of interesting transformations. Initially, the protocol involves the deprotonation of the tosylhydrazone with a base to give a tosylhydrazone sodium salt. Then, this salt evolves via thermal decomposition (T ≥ 60 °C) to access to the corresponding diazo compound (

Scheme I.23). In addition, when the deprotonation is carried out at lower temperature, some of these salts can be isolated. The reaction is usually performed in polar solvents, whereas aprotic media is used, a phase transfer catalyst (PTC) is necessary due to the low solubility of the tosylhydrazone salt.



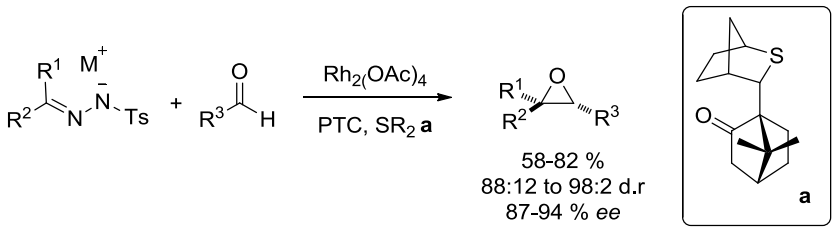
Scheme I.23. Strategy to generate diazo compounds from *N*-tosylhydrazones and its applications.

Finally, the generated diazo compound can be immediately trapped in a subsequent reaction and is compatible with several reaction conditions. This strategy was applied by Aggarwal in a variety of catalytic processes, in which the diazo compound is employed as a precursor of a metal carbene complex. Selected examples of this chemistry will be discussed below.

[54] E. L. Myers, R. T. Raines, *Angew. Chem. Int. Ed.* **2009**, *48*, 2359.

I.3.2.1. *N*-tosylhydrazones as diazo compounds precursor in epoxidation reactions.

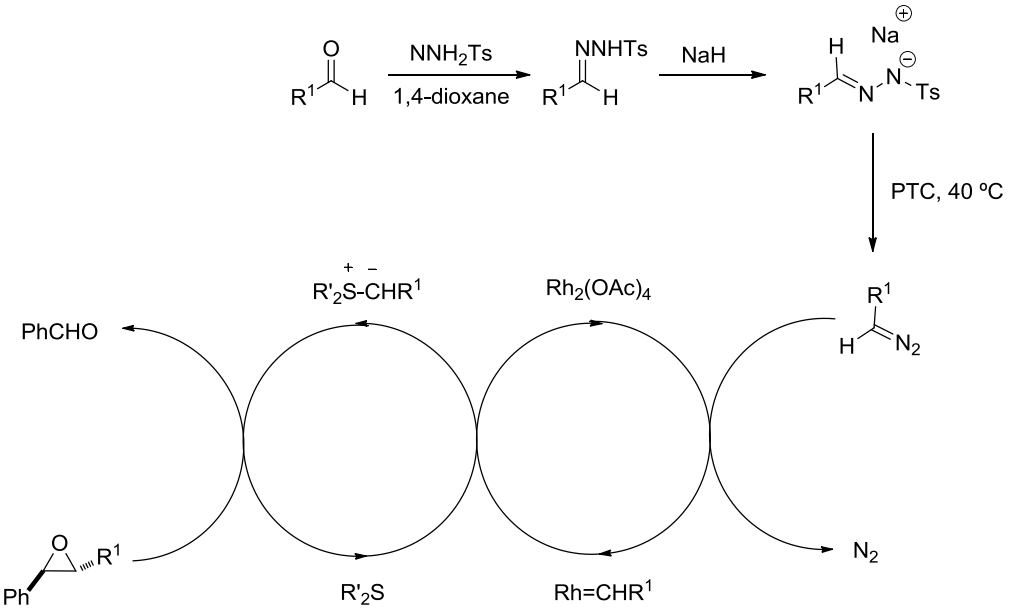
After developing a protocol to generate diazo compounds *in situ* in a manageable way, Aggarwal and co-workers decided to apply it to a large number of useful and typical transformations of diazo compounds. Therefore, they described a general one-pot methodology to synthesize epoxides from the formal coupling of two carbonyl compounds, wherein the tosylhydrazone salt is also generated *in situ* (Scheme I.24).[55] The correct choice of a chiral sulfide and rhodium catalyst provides high diastereoselectivities, high enantioselectivities and excellent yields.



Scheme I.24. *N*-Tosylhydrazones in asymmetric.epoxidation reactions.

To explain the mechanism the authors postulate the catalytic cycle shown in Scheme I.25. The mechanism would begin with decomposition of the tosylhydrazone salt to the diazo compound, followed by the formation of a Rhodium carbenoid by the reaction of the generated diazo compound with the Rhodium catalyst. Then, the carbene ligand would be transferred to the sulfide resulting in a sulfur ylide. Finally, the reaction with the carbonyl compound would give corresponding epoxide.

[55] V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chem. Int. Ed.* **2001**, *40*, 1430.

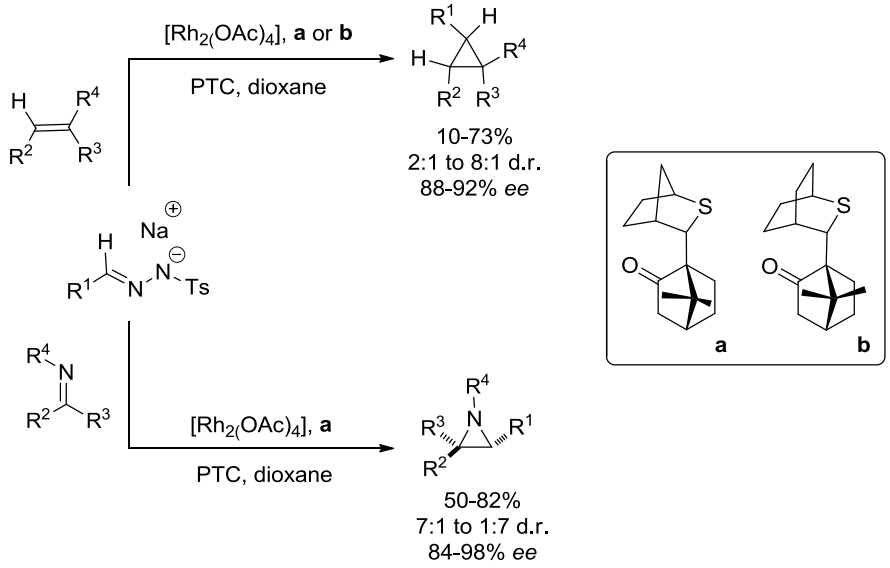


Scheme I.25. Catalytic cycle for the asymmetric synthesis of epoxides through one-pot coupling of a carbonyl compound and the tosylhydrazone salt.

I.3.2.2. *N*-Tosylhydrazones as diazo compounds precursors in aziridination and cyclopropanation reactions.

Next, this strategy was also employed to carry out the asymmetric aziridination of imines and the cyclopropanation[56] of electron deficient alkenes, using again the chiral sulfides previously designed (Scheme I.26).

[56] V. K. Aggarwal, E. Alonso, G. Y. Fang, M. Ferrara, G. Hynd, M. Porcelloni, *Angew. Chem. Int. Ed.* **2001**, *40*, 1433.



Scheme I.26. *N*-Tosylhydrazones in aziridination and cyclopropanation reactions.

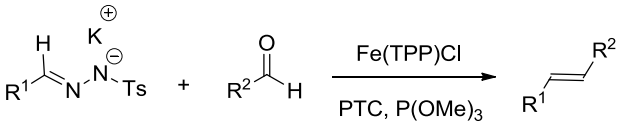
Further studies revealed that the presence of chiral ligands on the metal allowed the asymmetric propanation of alkenes without the need of chiral sulfides.[57]

The Aggarwal's protocol attracted considerable attention, for that reason, other groups, like Che's and Doyle's groups, also developed cyclopropanations employing diazo compounds generated *in situ* from tosylhydrazone salts.[58]

I.3.2.3. *N*-Tosylhydrazones as diazo compounds precursor in Wittig-type transformations.

Diazo compounds are able to generate phosphorus ylides from phosphanes to perform Wittig-type reactions. In this context, Aggarwal and co-workers. described a protocol to synthesize alkenes via Wittig reaction from phosphites, aldehydes and tosylhydrazone salts employing catalytic amounts of Fe(TPP)Cl (Scheme I.27).[59]

[57] V. K. Aggarwal, J. de Vicente, R. V. Bonnert, *Org. Lett.* **2001**, *3*, 2785.
[58] a) M. P. Doyle, M. Yan, *J. Org. Chem.* **2002**, *67*, 602; b) J. L. Zhang, P. W. H. Chan, C. M. Che, *Tetrahedron Lett.* **2003**, *44*, 8733.
[59] V. K. Aggarwal, J. R. Fulton, C. G. Sheldon, J. de Vicente, *J. Am. Chem. Soc*. **2003**, *125*, 6034.

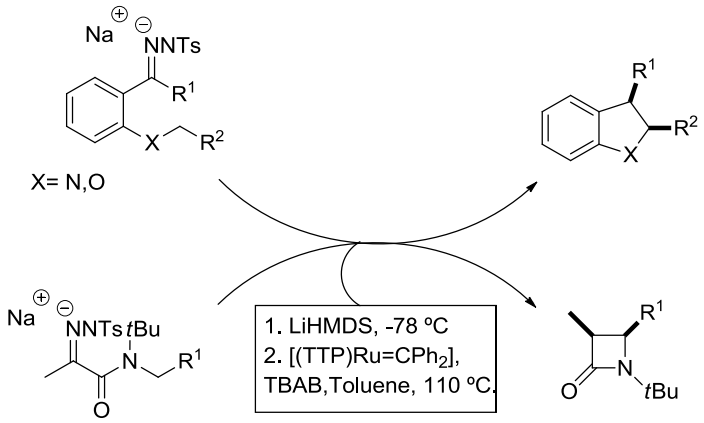


Scheme I.27. *N*-Tosylhydrazones in olefination reactions.

The goal of this work was the discovery of an alternative way to prepare phosphorus ylides by carbene transfer. These new generated ylides permit the improvement in terms of reactivity and selectivity, providing high *trans* selective alkenes in good yields.

I.3.2.4. *N*-Tosylhydrazones as diazo compounds precursor in C-H insertion reaction.

In 2003, Chi Ming Che and co-workers described a ruthenium catalyzed stereoselective intramolecular cyclization of tosylhydrazone salts through C-H insertion to synthesize heterocycles (Scheme I.28).[60] This methodology has been employed to carry out total synthesis of (±)-*epi*-conocarpan.[61]



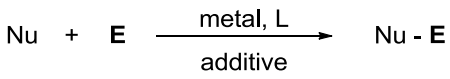
Scheme I.28. *N*-Tosylhydrazones in C-H insertion reaction.

[60] a) W.-H. Cheung, S.-L Zheng, W.-Y. Yu, G.-C. Zhou, C.-M Che, *Org. Lett*. **2003**, *5*, 2535; b) A. R. Reddy, C.-Y. Zhou, Z. Guo, J. Wei, C.-M. Che, *Angew. Chem. Int. Ed.* **2014**, *53*, 14175.
[61] S.-L Zheng, M.-Y Yu, M.-X Xu, C.-M Che, *Tetrahedron Lett.* **2003**, *44*, 1445.

I.4. *N*-Tosylhydrazones in cross-coupling reactions.

Throughout this introduction, some relevant aspects and main reactivity of sulfonylhydrazones have been discussed. Nevertheless, another important role of these useful compounds that has emerged in the recent years, have been their employment as source of diazo compounds in metal-catalyzed cross-coupling reactions as well as metal-free cross-coupling reactions.

Since its discovery in 1960s, cross-coupling reactions have experimented an enormous progress. At the present, they could be regarded as some of the most efficient, reliable, accurate and powerful methods for the formation of C-C and C-heteroatom bonds in organic chemistry. In a broad sense, a transition-metal-catalyzed cross-coupling reaction could be seen as a combination between a nucleophile and an electrophile, in the presence of a metal catalyst leading to the creation of a new bond between them (Scheme I.29).



Scheme I.29. General cross-coupling reactions.

In this field, palladium-catalyzed reactions have become the most important transformations.[62] In fact, Heck, Negishi and Suzuki were awarded the Nobel Prize in Chemistry in 2010 thanks to their fundamental contribution to this topic.

There are a broad number of modifications described in literature. In fact, cross-coupling reactions could be divided in two groups depending on the nucleophilic partner employed:

- The first example of a carbon-carbon bond-forming reaction that followed a Pd(0)/Pd(II) catalytic cycle was discovered by Heck[63] in which the nucleophilic species is a carbon-carbon multiple bond as is shown in Scheme I.30 (*Type **I***).

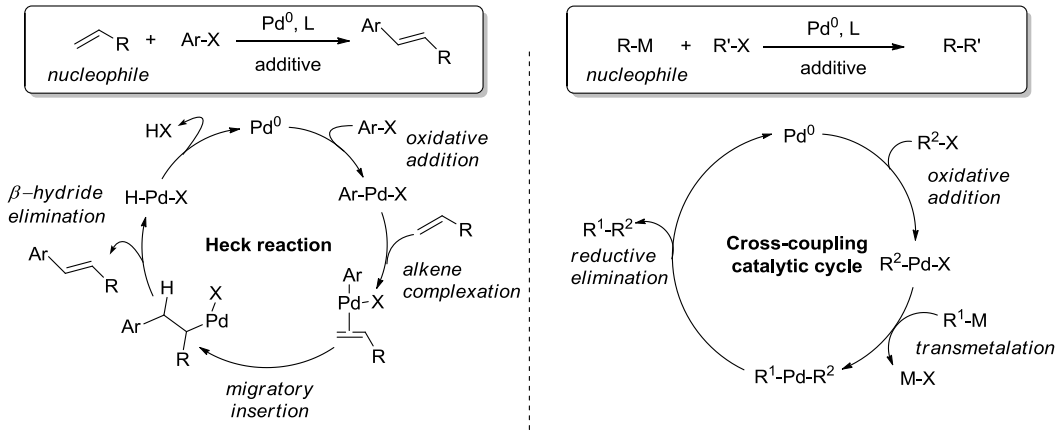
- On the other hand, as it is represented in Scheme I.30, in typical cross-coupling reactions, the nucleophilic partner is an organometallic compound, usually represented by R-M and R-X the electrophilic one (*Type **II***). Depending on the organometallic

[62] a) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley, New York, **2002**; b) A. de Meijere, F. Diederich, *Metal-catalyzed Cross-Coupling Reactions,* Wiley-VCH, Weinheim, **2004**; c) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley Chichester, **2004**; d) C. C. C. Johansson, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062.

[63] a) M. Oestreich, *The Mizoroki-Heck Reaction*, Wiley, Chichester, **2009**; b) S. E. S. Martin, D. A. Watson, *J. Am. Chem. Soc.*, **2013**, *135*, 13330; c) S. J. Sabounchi, M. Ahmadi, T. Azizi, M. Panahimehr, *Synlett*, **2014**, *25*, 336; d) C. Wu, J. Zhou, *J. Am. Chem. Soc.*, **2014**, *136*, 650.

compound, these classical reactions could be classified as Suzuki-Miyaura[64] (M = B), Stille[65] (M = Sn), Negishi[66] (M = Zn, Al, Zr), Kumada-Corriu[67] (M = Mg, Li) or Hiyama[68] (M = Si).

In general aspects, the mechanisms of both reactions are schematically shown below.



Scheme I.30. Palladium-catalyzed cross-coupling reactions and proposed mechanisms.

In the last decade, the discovery of a new class of palladium-catalyzed cross-coupling in which diazo compound is used as nucleophilic coupling partner, has promoted a lot of interest.

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[64] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; c) G. A. Molander, R. Figueroa, *Aldrichim. Acta* **2005**, *38*, 49; d) H. Fu-She, *Chem. Soc. Rev.* **2013**, *42*, 5270.

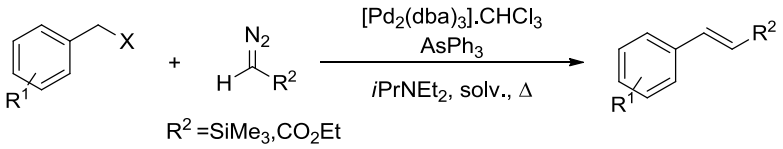
[65] a) J. K. Stille, *Angew. Chem. Int. Ed*. **1986**, *25*, 508; b) J. Hassan, M. Sévignon, C. Gozzi,E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; c) V. Farina, V. Krishnamurthy, W. J. Scott, *The Stille Reactions, Organic Reactions, vol 50*, Wiley Sons; New York, **1997**.

[66] a) O. King, N.Okukado, E. Negishi, *J. Chem. Soc. Chem. Commun.* **1977**, 683; b) N. Okukado, D. E. Van Horn, W. L. Klima, E. Negishi, *Tetrahedron Lett.* **1978**, 1027; c) E. Negishi, N. Okukado, A. O. King, D. E. Van Horn, B. I. Spiegel, *J. Am. Chem. Soc.* **1978**, *100*, 2254; d) E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979; e) E. Negishi, Q. Hu, Z. Huang, M. Qian, G. Wang, *Aldrichim. Acta* **2005**, *38*, 71.

[67] a) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc*. **1972**, *94*, 4374; b) M. Kumada, *Pure Appl. Chem.* **1980**, *52*, 669; c) J. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1999**, *121*, 9889; d) M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *44*, 9364; e) L. Ackermann, R. Born, J. H. Spatz, D. Meyer, *Angew. Chem. Int. Ed.* **2005**, *44*, 7216; f) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, 13, 150.

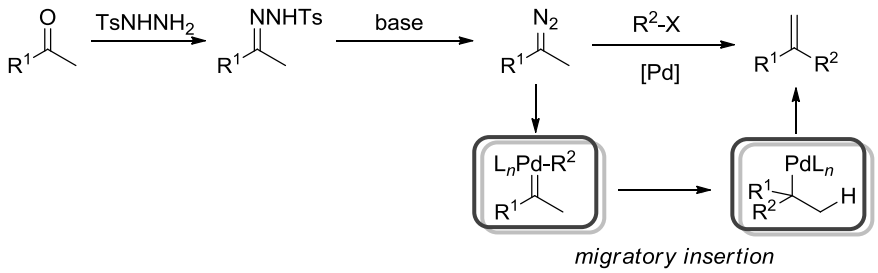
[68] a) T. Hiyama, Y. Hatanaka, *Pure Appl. Chem.* **1994**, *66*, 1471; K. Itami, T. Nokami, J. I. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 5600; c) T. Hiyama, E. Shirakawa, *Top. Curr. Chem.* **2002**, *219*, 61; d) T. Hiyama, J. *Organomet. Chem.* **2002**, *653*, 58; e) S. E. Denmark, R. F. Sweis, *Acc. Chem. Res.* **2002**, *35*, 835; f) S. E. Denmark, M. H. Ober, *Aldrichim. Acta* **2003**, *36*, 75; g) Sore, H. F.; Galloway, W. R. J. D.; Spring, D. R. *Chem. Soc. Rev*. **2012**, *41*, 1845.

The first example of a palladium-catalyzed cross-coupling employing a diazo compound as nucleophilic partner was published by Van Vranken and co-workers.[69] In this work, substituted styrenes were synthesized from trimethylsilyldiazomethane (TMSD) or ethyl diazoacetate (EDA)[70] and benzyl halides in the presence of a Pd(0) catalyst (Scheme I.31). This reaction introduced a migratory insertion of palladium carbene as the key intermediate of a catalytic cycle. Nevertheless, due to the typical limitations associated to diazo compounds, this transformation was not further studied.



Scheme I.31. Palladium-catalyzed cross-coupling reaction with diazo compounds and benzyl halides.

Thus, it was not until 2007 when our research group first introduced the tosylhydrazones as nucleophilic species in couplings reactions.[71] In this way, all the hazards and limitations of diazo compounds were successfully avoided and a new kind of cross-coupling transformation was therefore discovered. Noteworthy, the proposed mechanism for these reactions is different to the catalytic cycles of both Heck and classical cross-coupling reactions. The differential steps involve the formation of palladium carbene complex and a migratory insertion reaction (Scheme I.32).[72]



Scheme I.32. Proposed mechanism for cross-coupling reactions with hydrazones or diazo compounds as nucleophilic partner.

Since the discovery of tosylhydrazones as nucleophilic coupling partner in cross-coupling reactions, the interest generated has been enormous. Indeed, the employment

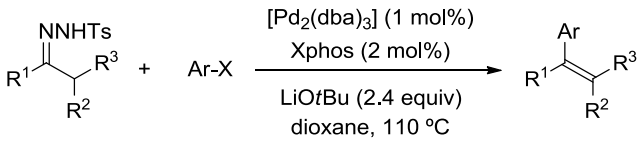
[69] a) D. S. Carter, D. L. Van Vranken, *Tetrahedron Lett.* **1999**, *40*, 1617; b) K. L. Greenman, D. S. Carter, D. L. Van Vranken, *Tetrahedron* **2001**, *57*, 5219.
[70] K. L. Greenman, D. L. Van Vranken, *Tetrahedron* **2005**, *61*, 6438.
[71] J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem. Int. Ed.* **2007**, *46*, 5587.
[72] A. C. Albéniz, P. Espinet, R. Manrique, A. Pérez-Mateo, *Angew. Chem. Int. Ed.* **2002**, *41*, 2363.

of these compounds, particularly in palladium or copper catalyzed-reactions, has suffered considerable development. However, this thesis is focused in transformations that proceed without the need on a metal catalyst. For that reason, only a brief revision of the palladium-catalyzed chemistry developed by our research group will be reflected in next section. Nevertheless, the most important contributions in this field are recovered and indicated in the references below.[73]

I.4.1. Palladium-catalyzed cross-coupling reactions with tosylhydrazones.

I.4.1.1 *N*-Tosylhydrazones and aryl halides.

The employment of tosylhydrazones as nucleophilic coupling partner in palladium-catalyzed cross-couplings, as previously mentioned, was developed by our research group in 2007.[67] These systems react with aryl halides in the presence of LiO*t*Bu as base and catalytic amounts of $Pd_2(dba)_3$ and a ligand (Xphos) to synthesize di- or trisubtituted olefins (Scheme I.33). The transformation is very general and versatile, proceeds with very good yields, with high stereoselectivity and finally, tolerates a broad number of functional groups. Thus, a new alternative with no precedent in literature to generate olefins was discovered.

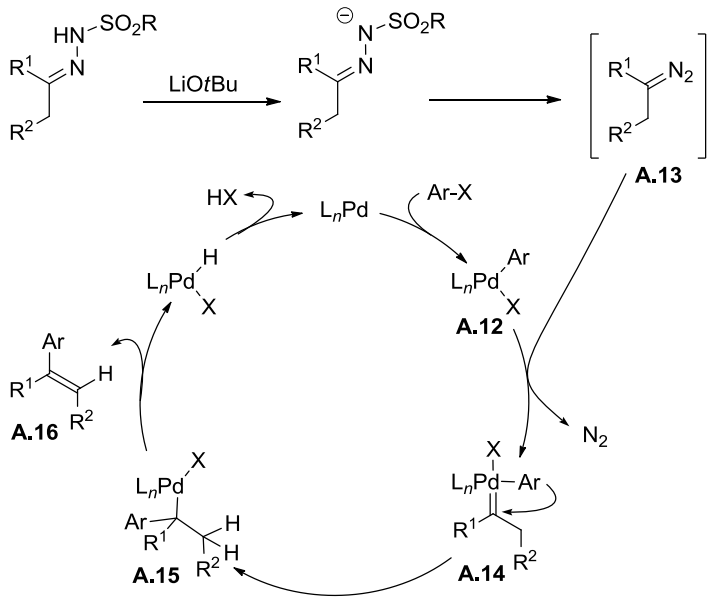


Scheme I.33. Synthesis of di- or trisubstituted olefins.

The proposed mechanism, as noted above (Section I.5), should involve a palladium carbene formation following by a migratory insertion. The catalytic cycle,

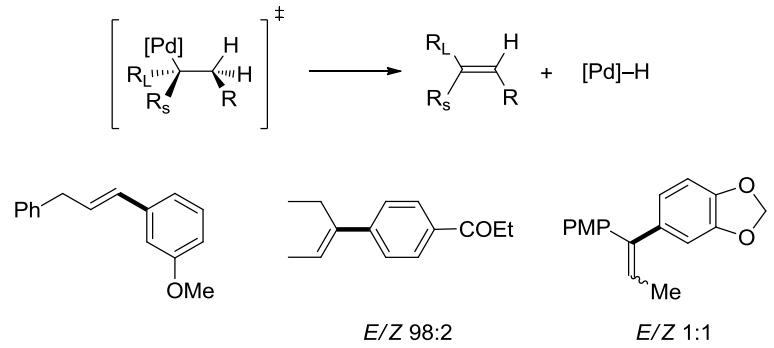
[73] *Review*: a) See references 6 and 7; b) Y. Xia, Y. Zhang, J. Wang, *ACS Catal*. **2013**, *3*, 2586; c) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236; *Palladium*: d) L. Zhou, F. Ye, J. Ma, Y. Zhang, *Angew. Chem. Int. Ed.*, **2011**, *50*, 3510; e) Z.-S. Chen, Z.-H. Duan, L.-Y. Wu, S. Ali, K.-G. Ji, P.-X. Zhou, X.-Y. Liu, Y.-M. Liang, *Chem. Eur. J.* **2011**, *17*, 6918; f) F. Zhou, K. Ding, Q. Cai, *Chem. Eur. J.* **2011**, *17*, 12268; g) H. Chen, L. Huang, W. Fu, X. Liu, H. Jiang, *Chem. Eur. J.* **2012**, *18*, 10497; h) X. Zeng, G. Cheng, J. Shen, X. Cui, *Org. Lett*. **2013**, *15*, 3022; i) R. Barroso, R. A. Valencia, M.-P. Cabal, C. Valdés, *Org. Lett.* **2014**, *16*, 2264; j) Z. Liu, L. Wang, H. Tan, S. Zhou, T. Fu, Y. Xia, Y. Zhang, J. Wang, *Chemm. Commun*. **2014**, *50*, 5061; *Copper*: k) Q. Xiao, Y. Xia, H. Li, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 1114; m) L. Zhou, Y. Shi, Q. Xiao, Y. Liu, F. Ye, Y. Zhang, J. Wang, *Org. Lett*. **2011**, *13*, 968; n) S. Xu, G. Wu, F. Ye, X. Wang, H. Li, X. Zhao, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 4752 and references therein.

shown in Scheme I.34, should start with the oxidative addition of the aryl halide to the palladium catalyst to obtain an arylpalladium complex **A.13**. At the same time, the hydrazone is decomposed by the base to give *in situ* the diazo compound **A.12**. Once formed, this diazo compound would react with **A.13** to generate the palladium carbene complex **A.14**. Next, this intermediate would evolve through a migratory insertion of the carbene ligand in the Pd-C bond to give the aryl palladium complex **A.15**. Finally, a β-hydrogen elimination would provide the final product **A.16** and regenerate the Pd(0) species and in consequence, the catalytic cycle.



Scheme I.34. Proposed mechanism for palladium-catalyzed cross-coupling between tosylhydrazones and aryl halides.

It is noteworthy that *syn* β-hydrogen elimination determines the stereochemistry of the final products. In this way, tosylhydrazones derived from aldehydes led exclusively to *trans*-olefins. However, the stereochemistry of trisubstituted olefins is determined by the size of substituent. In the case of bulky substituents, *trans*-olefins are also provided. Although, when the sizes are similar, a mixture of isomers could be observed (Scheme I.35).



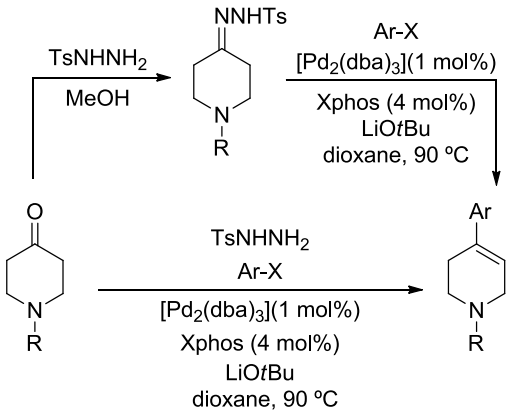
Scheme I.35. *Syn* β-hydrogen elimination determines the stereochemistry of final olefins.

Tosylhydrazones are very accessible from carbonyl compounds. Therefore, this useful and powerful transformation could be seen as direct way to synthesize olefins using aldehydes or ketones as nucleophilic coupling partners.[74] Regarding all the possibilities that this reaction provides, further studies have been carried out by our research group in order to expand the scope of this process to different electrophiles and nucleophiles agents and find new applications.

Synthesis of 4-aryl tetrahydropyridines

Initially, multicomponent process was described to afford di- tri- and tetrasubtituted alkenes (Scheme I.36). In this transformation, the hydrazone is directly generated *in situ* from the corresponding carbonyl compound. These generated olefins provided same results in terms of yields and stereoselectivities than those in which preformed hydrazones are employed. When 4-piperidone is selected as carbonyl compound, the multicomponent transformation allows to access to 4-aryl tetrahydropyridines. These structures are very useful and important for medicinal chemistry.[75,76]

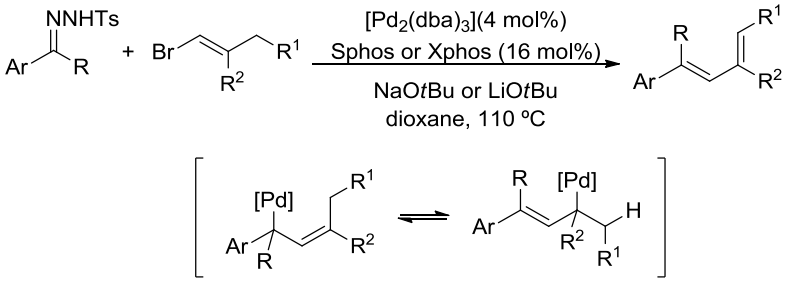
[74] The methodology has been also extended to different electrophile, such as aryl nonaflates: J. Barluenga, L. Florentino, F. Aznar, C. Valdés, *Org. Lett.* **2010**, *13*, 2011.
[75] J. Barluenga, C. Valdés, M, Tomás-Gamasa, P, Moriel, F. Aznar, *Chem. Eur. J.* **2008**, *14*, 4792.
[76] This *one-pot* methodology could be also employed to synthesize 2-arylacrylates from ethyl pyruvate and different halides: J. Barluenga, C. Valdés, M, Tomás-Gamasa, F. Aznar, *Chem. Eur. J.* **2010**, *16*, 12801.



Scheme I.36. Straightforward synthesis of 4-aryl tetrahydropyridines from 4-piperidones.

Synthesis of dienes

The one-pot methodology described above was evaluated for different substrates for the purpose of expanding the scope of the reaction. The procedure was applied to α,β-unsatured ketones, to obtain different conjugated dienes (Scheme I.37). These structures are obtained through a new reaction pathway in the catalytic cycle, where, a formal δ-hydride elimination takes place involving a π-allylpalladium intermediate.[77]



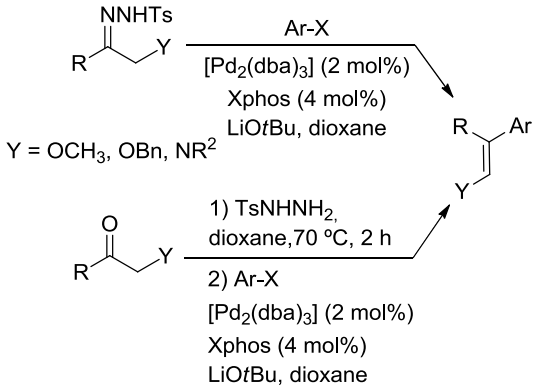
Scheme I.37. Synthesis of conjugated dienes from α,β-unsatured ketones.

Synthesis of functionalized olefins

The usefulness of this transformation was also applied to a variety of α-functionalized ketones and aldehydes to achieve the synthesis of different olefins derived from enol ether and enamines (Scheme I.38). This methodology provides a masked carbonyl group since enol ether could be hydrolyzed to obtain the

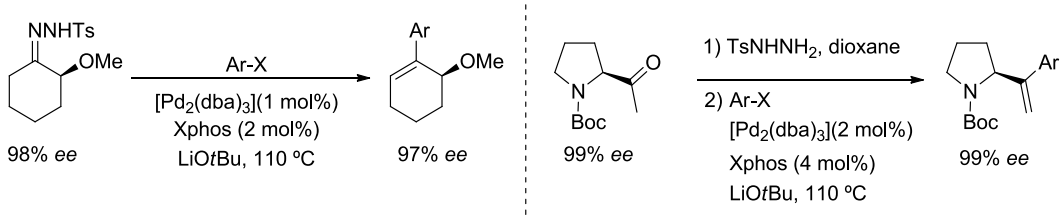
[77] J. Barluenga, C. Valdés, M, Tomás-Gamasa, F. Aznar, *Adv. Synth. Cat.* **2010**, *352*, 3235.

corresponding carbonyl compound. In this way, it could be deprotected at the desired point of the synthesis.[78]



Scheme I.38. Synthesis of functionalized olefins from α-functionalized ketones and aldehydes.

In the case of enantiomerically enriched 2-methoxycyclohexanone, this kind of hydrazones have two enolizable positions, however the process was regioselective affording the less substituted olefin.[79] It is remarkable that the reaction underwent with preservation of the configuration when enantiomerically enriched ketones were used. In addition, this methodology was likewise applied to others α-chiralmethylketones derived from different aminoacids observing no erosion in the chirality of the stereogenic centre Scheme I.39.



Scheme I.39. Synthesis of enantiomerically allylic ethers and amines.

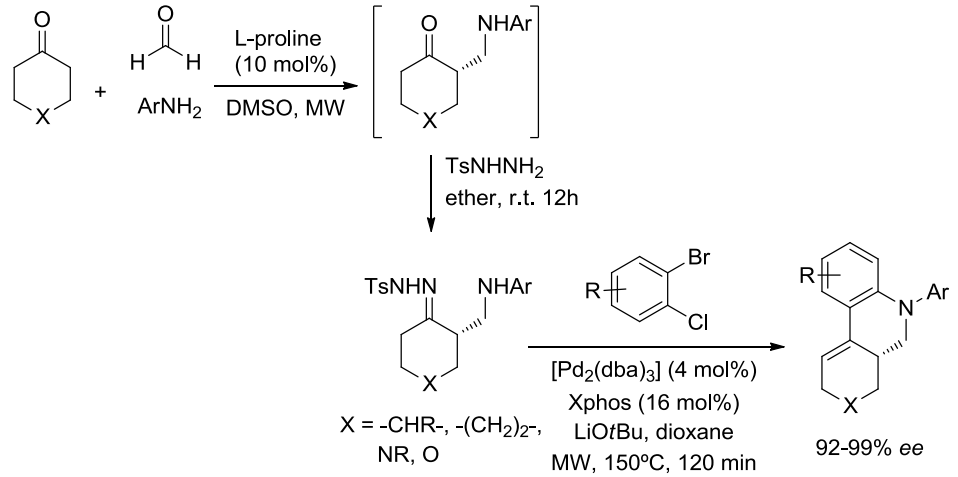
I.4.1.2. *N*-Tosylhydrazones in autotandem catalysis.

The synthetic potential of this methodology has been also demonstrated in autotandem reactions in which a single catalyst is able to promote distinct reactions. The first transformation developed consisted in a palladium-catalyzed cross-coupling

[78] J. Barluenga, C. Valdés, M. Escribano, P. Moriel,F. Aznar, *Chem. Eur. J.* **2009**, *15*,13291.
[79] J. Barluenga, M. Escribano, F. Aznar, C. Valdés, *Angew. Chem. Int. Ed.* **2010**, *49*, 6856.

reaction to generate a C-C bond followed by an intramolecular C-N forming reaction. Therefore, the reaction between tosylhydrazones derived from β-aminoketones and 1,2-dihalogenated compounds under appropriate conditions provided quinoline derivatives in good yields.[80]

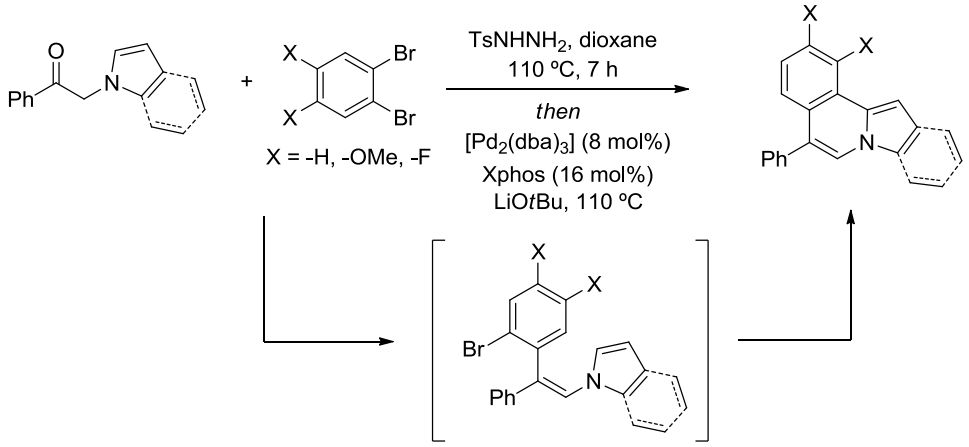
Additionally, this process was also described with enantiomerically enriched aminoketones to access to tetrahydrophenanthridines with excellent *ee*. These results demonstrated that the stereochemistry was again preserved during the overall transformation. This represents an excellent example combining organocatalysis and palladium autotandem catalysis (Scheme I.40).



Scheme I.40. Synthesis of enantiomerically enriched quinolines derivatives from Mannich adducts and *o*-bromochlorobenzene.

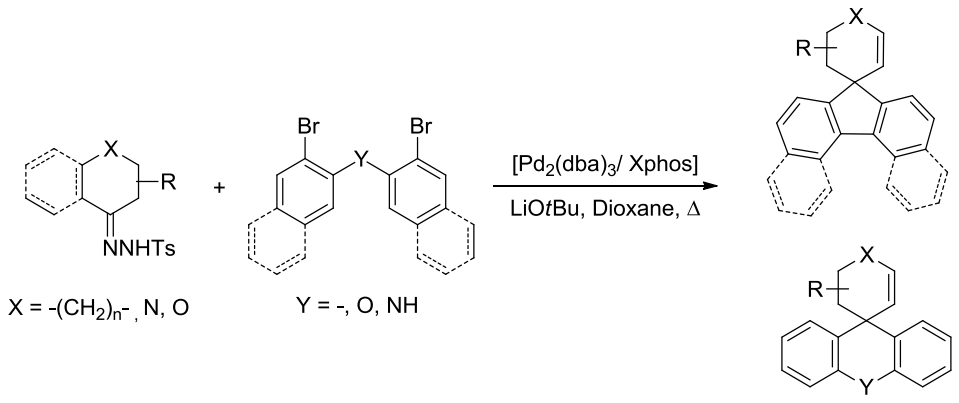
Autotandem catalyzed processes have been next extended to other hydrazones, particularly to those derived from α-*N*-azoleacetophenones.[81] In this way, a new process through a C-C/C-C sequence was carried out to synthesize pyrrolo isoquinolines. The reaction proceeds through a palladium-catalyzed cross-coupling reaction followed by a C-H functionalization via intramolecular Heck-type reaction (Scheme I.41).

[80] J. Barluenga, N. Quiñones, M.-P. Cabal, F. Aznar, C. Valdés, *Angew. Chem. Int. Ed.* **2011**, *50*, 2350.
[81] L. Florentino, F. Aznar, C. Valdés, *Chem. Eur. J.* **2013**, *19*, 10506.



Scheme I.41. Synthesis of indolo- and pyrrolo[2,1-*α*]isoquinolines through a palladium-catalyzed autotandem process.

Finally, in order to demonstrate the feasibility of C-C/C-C autotandem process a sequence that might involve a tosylhydrazone cross-coupling followed by an intramolecular Heck reaction has been recently described.[82] This challenge involves tosylhydrazones of cyclic ketones and 2,2-dibromobiphenyls and related systems. Depending on the starting dihalide, this methodology allows direct access to a set of spirocompounds as is shown in Scheme I.42. The spirocycles generated, particularly spirofluorenes, have arosed interest since they are employed in electroluminescent and optoelectronic materials.



Scheme I.42. Synthesis of spirocompounds through a sequence of tosylhydrazones cross-coupling followed by a Heck reaction.

[82] R. Barroso, R. A. Valencia, M.-P. Cabal, C. Valdés, *Org. Lett.* **2014**, *16*, 2264.

I.4.2. Transition metal-free coupling reactions.

Transition-metal-catalyzed cross-coupling reactions could be considered one of the major topics in organic chemistry. Despite of the success and recognition of metal-catalyzed reactions, they are still possessing some limitations that need to be taken into account:

- Transition metal-catalysts and ligands are usually very expensive and the latter, difficult to prepare sometimes.
- The most typical transition metals employed in cross coupling reactions, such as Pd, Pt or Ni, are toxic in most of the cases. For that reason, it is necessary remove traces from final products.
- Transition metal complexes may be sensitive to oxygen and moisture, so a thorough manipulation should be carried out.
- In many cases, additives and co-catalyst are needed to obtain good yields in terms of efficiency and selectivity.

In order to avoid some of these drawbacks, the search for more sustainable processes from both economical and environmental perspectives, are currently areas that concentrate a great deal of attention.[83] In this context, transition metal-free reactions that provide similar results than those catalyzed by transition metal are intensely pursued nowadays. Nevertheless, some arguments exist about the significance of the "metal-free" term being nowadays quite broad. In addition, on account that metal traces are difficult to determine and remove from starting materials, reagents, additives, as well as solvents, some questions may arise as to whether very small amounts of a metal could really catalyze the process.[84] However, it is in the mechanistic pathways, and in the way that the formation of the products could be explained, where the difference between metal-catalyzed and metal-free reactions are notorious. Furthermore, typical transition-metal-free coupling-reactions could be classified taking into account the principal step involved as it is summarized below and in Scheme I.43.[85]

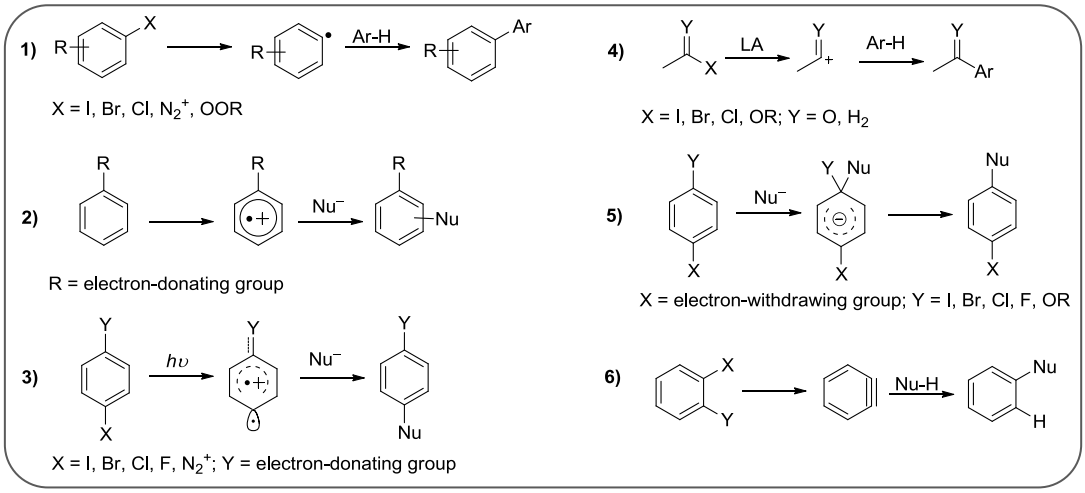
1- Homolytic aromatic substitution (HAS).

2- Oxidative coupling reactions that include the participation of a radical cation, specifically hyperiodine-mediated reactions.

3-DDQ-promoted oxidative coupling reactions and photoinduced reactions via formation of triplet aryl cations.

[83] P. T. Asastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford: Oxford University Press, **1998**.
[84] I.Thomé, A. Nijs, C. Bolm, *Chem. Rev. Soc.* **2012**, *41*, 979.
[85] See review of transition metal-free coupling reactions: C.-L. Sun, Z. J. Shi, *Chem. Rev.* **2014**, *114*, 9219 and references therein.

4-Electrophilic aromatic substitution reactions.
5-Nucleophilic aromatic substitution reactions.
6-Cross-coupling reactions via aryne pathway.
7-Organocatalytic reactions.



Scheme I.43. Typical transition-metal-free cross-coupling-reactions.

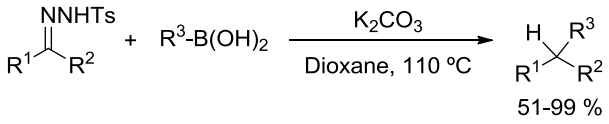
It is noteworthy that traditional substitution reactions that involve stoichiometric organometallic reagents as well as *N*-tosylhydrazones, are not enclosed in this classification. The chemistry of metal-free reactions is very extensive, well-reviewed[88] an out of the scope of this chapter. Consequently, it will be not entirely discussed in this Introduction and only a specific revision of the role of tosylhydrazones is carried out below.

I.4.2.1. *N*-Tosylhydrazones in metal-free cross-coupling reactions: carbon-carbon bond formation.

In the previous sections, it has been shown that tosylhydrazones are a very effective source of diazo compounds, that can participate in a variety of metal catalyzed processes. Indeed, it has been demonstrated through the palladium-catalyzed-reactions, that tosylhydrazones can act as diazo compounds precursors with no restriction regarding the structure of the hydrazone. Additionally, due to the high reactivity of the diazo functionality, some processes that do not require the participation of a metal catalyst have been also devised.

The reductive coupling of tosylhydrazones with organometallic compounds is well-known and was commented at the beginning of this Introduction (Section I.2.3). Nevertheless, the marked reactivity of the reagents that have been used so far is unpredictable. In addition, they are incompatible with some functional groups. For that reason, other coupling partners and different conditions in absence of metal catalyst, have been examined with the aim of improving the scope of the reaction.

In fact, a turning point in the employment of tosylhydrazones in transition-metal-free cross-couplings came in 2009, when in our research group, it was discovered the reductive coupling of tosylhydrazones with boronic acids (Scheme I.44).



Scheme I.44. Reductive coupling of *N*-tosylhydrazones with boronic acids

This transformation will be discussed in detail in Chapter 1. Nevertheless, to provide a complete picture of the state of the art in this fast evolving field, some other examples of metal-free transformations employing sulfonylhydrazones will be presented herein. Noteworthy, most of them have been published simultaneously or after the realization of the work presented in this Thesis.

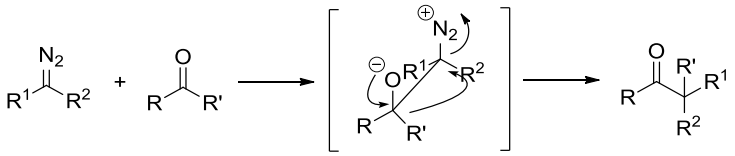
Homologation of aldehydes

Homologation of carbonyl compounds is a broad synthetic method to prepare useful compounds. In this context, a formal diazo carbon insertion is a valuable tool for this purpose.[86,87] Mainly, this process consists of two steps in which carbonyl compounds

[86] Formal diazo carbon insertion to carbonyl C-C bond: a)W. S. Johnson, M. Neeman, S. P. Birkeland, N. A. Fedoruk, *J. Am. Chem. Soc.* **1962**, *84*, 989; b) K. Maruoka, A. B. Concepcion, H. Yamamoto, *Synthesis* **1994**, 1283; c) K. Maruoka, A. B. Concepcion, H. Yamamoto, *J. Org. Chem*. **1994**, *59*, 4725; d) T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc*. **2008**, *130*, 2434; e) D. C. Moebius, J. S. Kingsbury, *J. Am. Chem. Soc.* **2009**, *131*, 878; f) T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 6614; g) T. Hashimoto, Y. Naganawa, K. Maruoka, *Chem. Commun.* **2010**, *46*, 6810; h) J. A. Dabrowski, D. C. Moebius, A. J. Wommack, A. F. Kornahrens, J. S. Kingsbury, *Org. Lett.* **2010**, *12*, 3598; i) T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 8834; j) V. L. Rendina, D. C. Moebius, J. S. Kingsbury, *Org. Lett.* **2011**, *13*, 2004; k)W. Li, X. Liu, X. Hao, Y. Cai, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2012**, *51*, 8644.

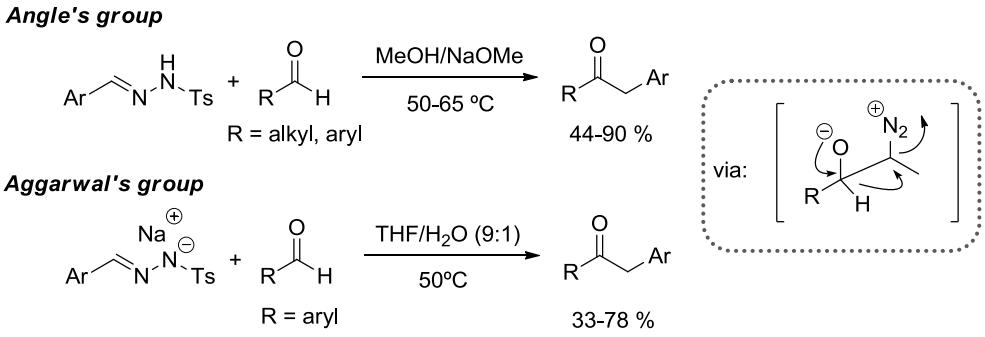
[87] Formal diazo carbon insertion into carbonyl C-H bond: a) C. A. Loeschorn, M. Nakajima, P. J. McCloskey, J.-P. Anselme, *J. Org. Chem*. **1983**, *48*, 4407; b) C. R. Holmquist, E. J. Roskamp, *J. Org. Chem*. **1989**, *54*, 3258; c) R. M.Werner, O. Shokek, J. T. Davis, *J. Org. Chem.* **1997**, *62*, 8243; d) S. J. Mahmood, A. K. Saha, M. M. Hossain, *Tetrahedron* **1998**, *54*, 349; e) E. L. Dias, M. Brookhart, P. S. White, *J. Am. Chem. Soc.* **2001**, *123*, 2442; f) T. Hashimoto, H. Miyamoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 11280; g) A. J.Wommack,D. C. Moebius,A. L. Travis, J. S. Kingsbury, *Org. Lett.* **2009**, *11*, 3202; h)W. Li, J.Wang, X. L. Hu, K.

firstly react with diazo compounds to give alkoxide diazonium intermediates, followed by 1,2-shift of the corresponding R group with the loss of a molecule of nitrogen (Scheme I.45).



Scheme I.45. Formal Diazo Carbon Insertion into Carbonyl Groups.

Tosylhydrazones have been employed as *in situ* diazo compounds sources in the convertion of aldehydes to ketones. Angle and co-workers[88] and Aggarwal and co-workers[89] simultaneously described very similar methodologies to achieve the homologation of aldehydes via a carbon insertion into the formyl C-H bond (Scheme I.46).



Scheme I.46. Homologation of aldehydes from tosylhydrazones.

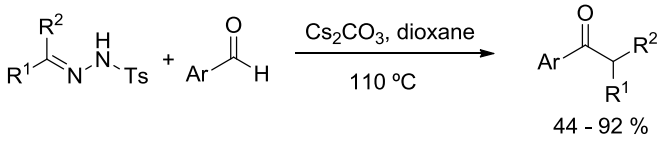
Very recently, the methodology could be extended to alkyl tosylhydrazones using totally different conditions.[90] Thus, the reaction between tosylhydrazones derived from dialkylketones and aryl aldehydes was carried out with Cs_2CO_3 as base and dioxane to give unsymmetrical ketones (Scheme I.47).

Shen, W. T. Wang, Y. Y. Chu, L. L. Lin, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 8532; i) L. Gao, B. C. Kang, G.-S. Hwang, D. H. Ryu, *Angew. Chem. Int. Ed*. **2012**, *51*, 8322.

[88] S. R. Angle, M. L. Neitzel, *J. Org. Chem*. **2000**, *65*, 6458.

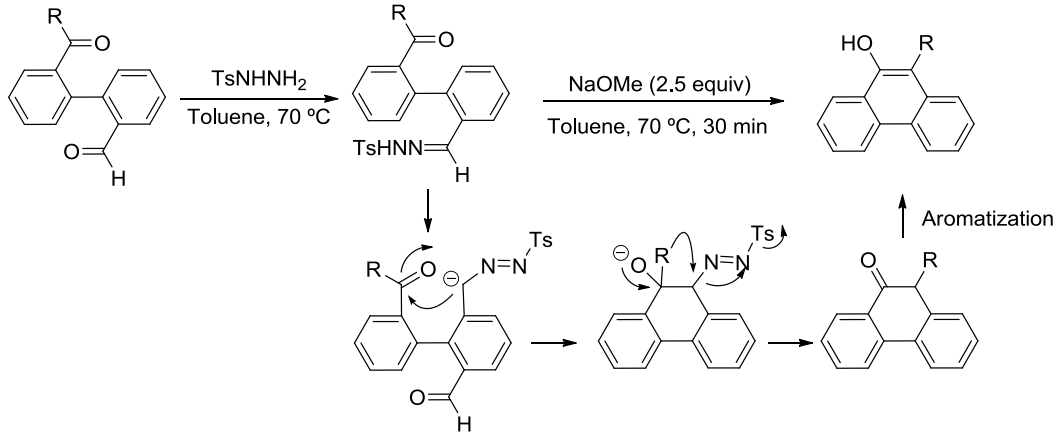
[89] V. K. Aggarwal, J. de Vicente, B. Pelotier, I. P. Holmes, R. V. Bonnert, *Tetrahedron Lett.* **2000**, *41*, 10327.

[90] D. M. Allwood, D. C. Blakemore, S. V. Ley, *Org. Lett.* **2014**, *16*, 3064.



Scheme I.47. Synthesis of unsymmetrical ketones from tosylhydrazones.

An intramolecular version of the same transformation was reported by Wang and co-workers in 2013[91] leading to a set of phenantrol and naphtol derivatives from aromatic systems featuring a tosylhydrazone and a formyl functionality.



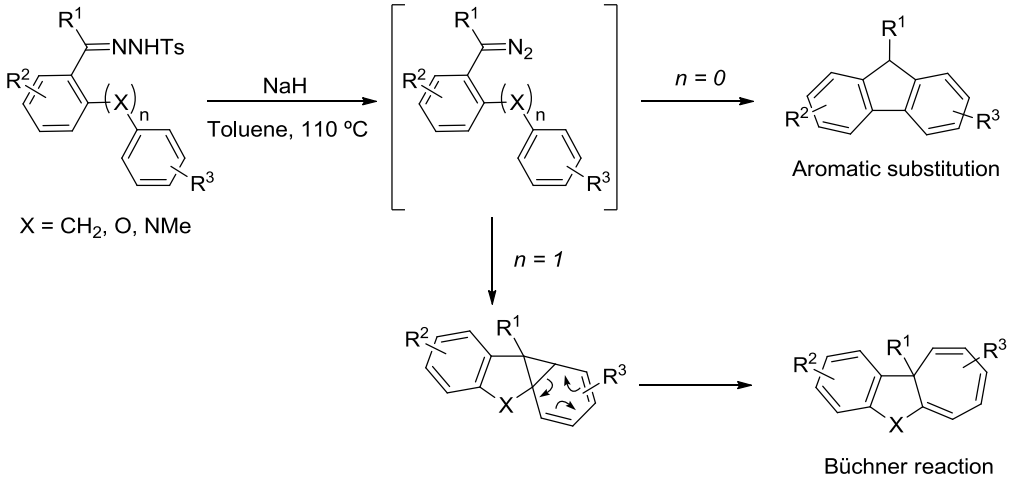
Scheme I.48. Synthesis of hydroxyl-substituted polycyclic aromatic compounds and a plausible mechanism.

As it is indicated in Scheme I.48, the process was carried out stepwise. First, the selective formation of hydrazone on the aldehyde would take place. Then, the formal C-C bond insertion is promoted by treatment with a base. Subsequent aromatization occurs, leading to the final product in good yields. The reaction is quite general admitting different migrating groups as aryl, alkenyl, alkynyl and alkyl groups. Furthermore, different aromatic structural motifs could be also employed, synthesizing a variety of hydroxyl-substituted polycyclic aromatic compounds (PACs).

Other polycyclic compounds such as fluorenes and [6,5,7]benzo-fused rings were synthesized by this same group. Here, Wang co-workers [92] presented in 2015 an intramolecular reaction using *N*-tosylhydrazones as non-stabilized diazo compound precursors, which depending upon the substrates, could lead to intramolecular aromatic

[91] Y. Xia, P. Qu, Z. Liu, R. Ge, Q. Xiao, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2543.
[92] Z. Liu, H. Tan, L. Wang, T. Fu, Y. Xia, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 3056.

substitution or intramolecular Büchner reaction.[93] These different reactivities are reflected in Scheme I.49. It should be pointed out that these classical reactions of diazocarbonyl compounds need transition metal or acid catalyst to achieve the final products, whereas in this protocol is not necessary.[94] Finally, the reaction could be performed in a one-pot step directly from the carbonyl compound.



Scheme I.49. Synthesis of fluorenes and [6,5,7]benzo-fused ring.

Other reactions

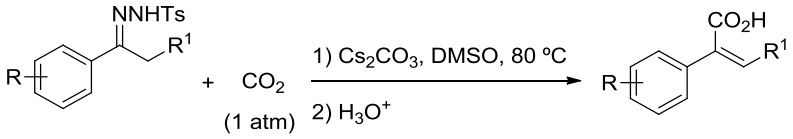
Also in 2015, Cheng and co-workers extended the use of sulfonylhydrazones reporting a carboxylation of tosylhydrazones with atmospheric CO_2 promoted by Cs_2CO_3 to accomplish the synthesis of α-arylacrylic acids without metal catalyst (Scheme I.50).[95] In this reaction, the solvent and the base were essential and their modification affected

[93] Related studies using tosylhydrazones: a) K. L. M. Stanley, J. Dingwall, J. T. Sharp, T. W. Naisby, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1433; b) D. P. Munro, J. T. Sharp, *J. Chem. Soc. Perkin Trans. 1* **1984**, 541; c) M. Akiba, Y. Kosugi, T. Takada, *J. Org. Chem.* **1978**, *43*, 4472; d) N. Krogsgaard-Larsen, M. Begtrup, M. M. Herth, J. Kehler, *Synlett* **2010**, 4287.

[94] a) H. Duddeck, M. Kennedy, M. A. Mckervey, F. M. Twohig, *J. Chem. Soc. Chem. Commun*. **1988**, 1586; b) C. J. Moody, S. Miah, A. M. Z. Slawin, D. J. Mansfleld, I. C. Richards*, J. Chem. Soc. Perkin Trans. 1* **1988**, 4067; c) M. P. Doyle, D. G. Ene, D. C. Forbes, T. H. Pillow, *Chem. Commun.* **1999**, 1691; d) A. Padwa, D. J. Austin, A. T. Price, M. A. Semones, M. P. Doyle, M. N. Protopopova, W. R. Winchester, A. Tran, *J. Am. Chem. Soc.* **1993**, *115,* 8669; e) A. A. Cordi, J. M. Lacoste, P. Hennig*, J. Chem. Soc. Perkin Trans. 1* **1993**, 3; f) C. A. Merlic, A. L. Zechman, M. M. Miller*, J. Am. Chem. Soc.* **2001**, *123*, 11101; g) M. P. Doyle, W. Hu, D. J. Timmons, *Org. Lett.* **2001**, *3*, 933; h) M. P. Doyle, I. M. Phillips, *Tetrahedron Lett.* **2001**, *42*, 3155; i) A. R. Maguire, P. O_Leary, F. Harrington, S. E. Lawrence, A. J. Blake, *J. Org. Chem.* **2001**, *66*, 7166; j) J. L. Kane, K. M. Shea, A. L. Crombie, R. L. Danheiser, *Org. Lett.* **2011**, *13*, 1081; k) O. A. McNamara, N. R. Buckley, P. O_Leary, F. Harrington, N. Kelly, S. O_Keeffe, A. Stack, S. O_Neill, S. E. Lawrence, C. N. Slattery, A. R. Maguire, *Tetrahedron* **2014**, *70*, 6870.

[95] S. Sun, J,-T. Yu, Y. Jiang, J. Cheng, *J. Org. Chem.* **2015**, *80*, 2855.

directly to the yield. It is noteworthy that the transformation is stereoselective and therefore only *Z*-products were obtained.

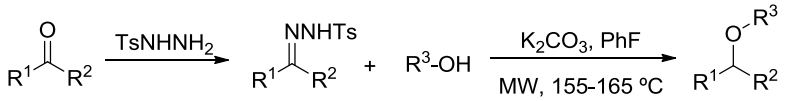


Scheme I.50. Synthesis of α-arylacrylic acids.

I.4.2.2. *N*-Tosylhydrazones in metal-free cross-coupling reactions: carbon-heteroatom bond formation.

The discovery of new methods to form carbon-carbon bonds is a challenge in Organic Chemistry. Novel protocols employing *N*-tosylhydrazones as coupling partner have emerged as a significant alternative for this purpose. One step further would consist in the design of efficient new processes, both in metal-catalyzed or metal-free reactions, to create carbon-heteroatom bonds employing tosylhydrazones. In this context, our research group and others have uncovered new methodologies in transition-metal-free reductive couplings.

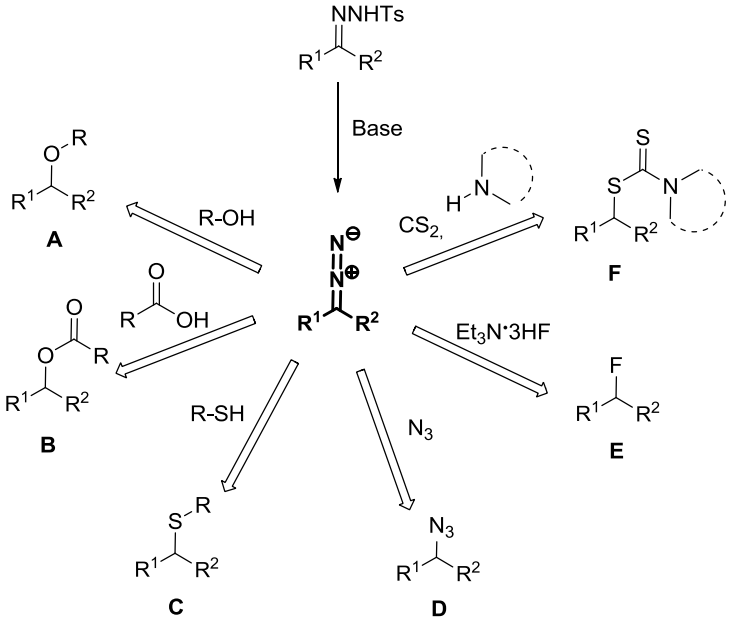
In 2010, our research group developed a metal-free reductive etherification of tosylhydrazones with phenols or alcohols (Scheme I.51).[96] The reaction would proceed through an insertion step of the incipient carbene generated from tosylhydrazone into the O-H bond of a hydroxylic compound to form ethers. This novel synthesis was carried out by conventional heating of MW in presence of K_2CO_3 with a remarkable operational simplicity. Considering that the tosylhydrazones are readily obtained from carbonyl compounds, this reaction can be seen as a reductive etherification of carbonyl compounds, a transformation that requires several steps through alternative methodologies.



Scheme I.51. Metal-free reductive etherification of tosylhydrazones with alcohols.

[96] J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Angew. Chem. Int. Ed.* **2010**, *49*, 4993.

The methodology described above has been later explored using different nucleophiles to generate esters (Scheme I.52.**B**),[97] primary and secondary azides (Scheme I.52.**C**),[98] unsymmetrical benzylic thioethers (Scheme I.52.**D**)[99] and fluoroalkanes (Scheme I.52.**E**).[100] Furthermore, recently, a one-pot reaction to synthesize *S*-secondary alkyl dithiocarbamates, which involve *N*-tosylhydrazones, amines and carbon disulfide, has been described (Scheme I.52.**F**).[101] A general scheme of the employment of tosylhydrazones in C-X reductive couplings is collected in Scheme I.52.



Scheme I.52. Free metal reductive coupling reactions from tosylhydrazones.

[97] A.-H. Garcia-Muñoz, M. Tomás-Gamasa, M. C. Pérez-Aguilar, E. Cuevas-Yañez, C. Valdés, *Eur. J. Org. Chem.* **2012**, 3925.
[98] J. Barluenga, M. Tomás-Gamasa, C. Valdés, *Angew. Chem. Int. Ed.* **2012**, *51*, 5950.
[99] Q. Ding, B. Cao, J. Yuan, X. Liu, Y. Peng, *Org. Biomol. Chem.* **2011**, *9*, 748.
[100] A. K. Yadav, V. P. Sriwastava, L. D. S. Yadav, *Chem. Commun.* **2013**, *49*, 2154.
[101] Q. Sha, Y,-Y. Wei, *Org. Biomol. Chem.* **2013**, *11*, 5615.

I.5. Conclusions

To conclude this General Introduction is necessary to remark that the tosylhydrazones are very versatile intermediates to carry out different transformations of carbonyl compounds through non conventional reactions.

In spite of these reagents have been employed in Organic Synthesis during more than 70 years, new chemistries have emerged in the last decade.

The capacity of tosylhydrazonesn to behave as a general source of diazocompounds without any limitation in the structure of carbonyl precursor, offers wide possibilities in synthesis in metal-catalyzed cross-coupling reactions as well as in metal-free cross-coupling transformations.

Despite the wide development that this field has experimented in only seven years, the chemistry of tosylhydrazones continues providing opportunities to discover new transformations. This is the context in which this Thesis is framed.

Capítulo 1.

Olefination of carbonyl compounds through Reductive Coupling of Alkenylboronic Acids and Tosylhydrazones

1.1. INTRODUCTION

1.1.1. The employ of boronic acids as nucleophilic coupling partners.

Throughout the General Introduction, it has been demonstrated the versatility of *N*-tosylhydrazones as coupling partners, both in metal-catalyzed cross-coupling and in transition-metal-free reactions. As it was commented, those processes in which the presence of a metal catalyst is not necessary are highly desirable. Consequently, different methodologies and reaction conditions have been explored in order to improve the efficiency and selectivity of transition-metal-free transformations. For that reason, the discovery of new nucleophiles that allow to carry out this kind of reactions in the same way has attracted a lot of attention.

In this context, organoboron reagents have emerged as suitable candidates due to their properties and reactivity profile:[102]

- Their stability toward air and water and in consequence, their easy handling.

- The low toxicity and their ultimate degradation in boric acid that make them "green" compounds.

- The tolerance to several functional groups.

- Their ready availability.

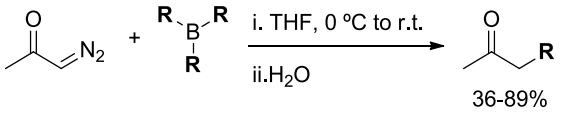
Since their isolation in 1860,[103] boronic acids have been broadly used in a wide number of transformations. Particularly, these reagents have been very important as nucleophilic partner in palladium-catalyzed cross-couplings with organic halides commonly known as Suzuki-Miyaura reaction.[104] However, until the discovery of our group in 2009 of the reaction between tosylhydrazones and boronic acids reactions between organoboron compounds and diazo compounds had involved stabilized diazo compounds. This was owing to the instability and toxicity derived from aliphatic diazo compounds.

[102] D. G. Hall, *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*, Wiley-VCH (Weinheim), **2005**.
[103] a) E. Frankland, B. F. Duppa, Justus *Liebig Ann. Chem.* **1860**, *115*, 319; b) E. Frankland, B. F. Duppa, *Proc. Royal Soc. (London)* **1860**, *10*, 568; c) E. Frankland, *J. Chem. Soc.* **1862**, *15*, 363.
[104] See reference 60 of General Introduction.

This chapter is specifically included in the framework of metal-free cross-coupling reactions between boronic acids and *N*-tosylhydrazones. Therefore, a revision of this topic will be examined in detail in this chapter.[105]

1.1.2. First examples of reactions between organoboron compounds and stabilized diazo compounds.

The earliest example in which diazocarbonyl compounds and organoboron compounds were involved, was described by Hooz and co-workers in 1968. The strategy employed stabilized diazo compounds with electron-withdrawing groups such as diazoketones and trialkylboranes reagents as is indicated in Scheme 1.1. In this way, the C-C bond formation was achieved through the transfer of one of the R groups from boron to the diazo carbon introducing an alkyl group adjacent to a carbonyl group. Then, it was necessary an alkaline hydrolysis to afford the corresponding ketones.[106]

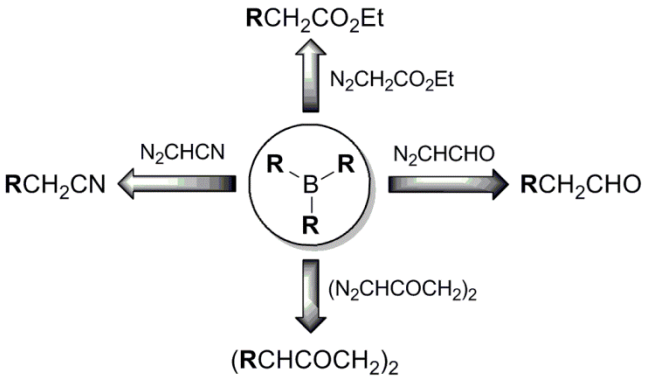


Scheme 1.1. Reaction of diazo acetone with trialkylboranes described by Hooz.

The scope of the reaction developed by Hooz was restricted to trialkyl boranes and moreover, the yield was affected when sterically hindered organoboranes were used.

During subsequent years, this group explored the scope of the reactions of organoboranes extending the methodology to diazonitrile,[107a] diazoacetate (EDA),[107a] diazoacetaldehyde[107b] and bisdiazoketones.[107c] These reactions allowed the synthesis of nitriles, esters, aldehydes and diketones, respectively (Scheme 1.2).

[105] H. Li, Y. Zhang, J. Wang, *Synthesis* **2013**, *45*, 3090.
[106] J. Hooz, S. Linke, *J. Am. Chem. Soc.* **1968**, *90*, 5936.
[107] a) J. Hooz, S. Linke, *J. Am. Chem. Soc.* **1969**, *91*, 6891; b) J. Hooz, G. F. Morrison, *Can. J. Chem*. **1970**, *48*, 868; c) J. Hooz, D. Gunn, *J. Chem. Soc., Chem. Commun.* **1969**, 139.



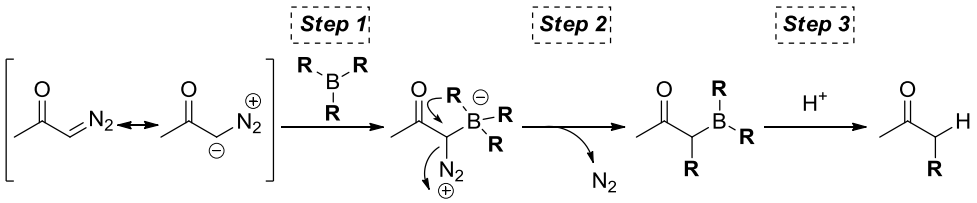
Scheme 1.2. Hooz reaction employing different diazo compounds.

Detailed mechanistic studies were not carried out. However, the authors proposed the following mechanism shown in Scheme 1.3:

1. The reaction would start with the nucleophilic attack of the diazo compound to the trialkyl borane generating a quaternary boronate intermediate.

2. Then, a rapid boron to carbon 1,2-alkyl shift with simultaneous expulsion of nitrogen would occur.

3. Finally, boron-carbon bond cleavage would provide the corresponding alkylation products.



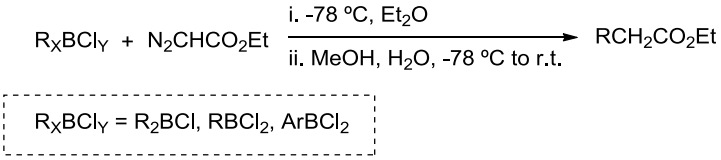
Scheme 1.3. The proposed mechanism for the alkylation of α-diazocarbonyl compounds.

1.1.3. Reactions with organochloroboranes.

Due to the important limitations that the Hooz methodology possessed, this unexplored field demanded more accurate studies.[108] Further modifications broadened

[108] a) D. J. Pasto, P. W. Wojtkowski, *Tetrahedron Lett.* **1970**, 215; b) D. J. Pasto, P. W. Wojtkowski, *J. Org. Chem.* **1971**, *36*, 1790; c) H. Newman, *J. Org. Chem.* **1974**, *39*, 100; d) J. Hooz, J. N. Bridson, *J. Am. Chem. Soc.* **1973**, *95*, 602; e) J. Hooz, J. Oudenes, J. L. Roberts, A. Benderly, *J. Org. Chem.* **1987**, *57*, 1347.

the scope of organoboranes such as more active dialkylchloroboranes or alkyl-, alkenyl- or aryldichloroboranes, which provided milder conditions and more generality than the protocol previously described (Scheme 1.4).[109] This improvement of reactivity proceeds from the introduction of more electronegative rests such as chloro, that result in an increase of the Lewis acidity of the organoboron compound and in consequence, the step where the coordination with the diazo compound occurs is facilitated.



Scheme 1.4. Reaction between organochloroboranes and ethyl diazoacetate.

The reactions with organochloroboranes proceeded with excellent yields under mild conditions and allowed the employment of bulky alkyl groups which was unfeasible in Hooz protocol.

In spite of this increase of reactivity, this protocol presented some limitations since secondary products could be observed as result of the competitive transfer of chlorine from boron to carbon, instead of the migration of the alkyl group. The mechanism proposed was quite similar to the one that was presented for trialkylboranes.

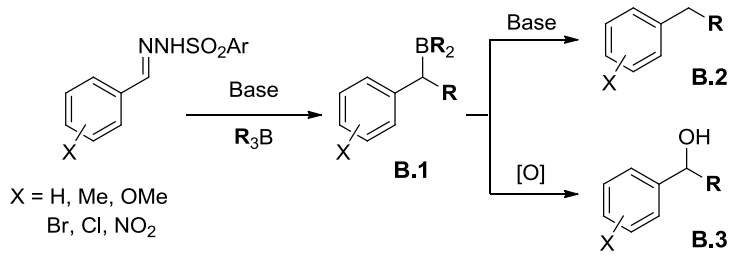
Even though this reaction provides a highly useful and operationally simple method for the alkylation of diazo compounds, it was indeed scarcely applied. Nevertheless, it was expanded by Brown and Salunkhe to alkenyldichloroboranes to synthesize β,γ-unsatured esters.[110] The low applicability of these transformations could be due to the sensitivity of the reaction to steric hindrance and the low availability, high instability and relative toxicity of required boranes.

1.1.4. Reactions of *N*-tosylhydrazones with trialkylboranes.

Alkylation of carbonyl compounds employing trialkylboranes was reported by Kabalka and co-workers in 1994.[111] In this methodology, aryl aldehyde tosylhydrazones

[109] a) H. C. Brown, M. M. Midland, A. B. Levy, *J. Am. Chem. Soc.* **1972**, *94*, 3662; b) J. Hooz, J. N. Bridson, J. G. Calzada, H. C. Brown, M. M. Midland, A. B. Levy, *J. Org. Chem*. **1973**, *38*, 2574.
110 H. C. Brown; A. M. Salunkhe, *Synlett* **1991**, 684.
[111] G. W. Kabalka, J. T. Maddox, E. Bogas, *J. Org. Chem*. **1994**, *59*, 5530.

were involved, which depending on the employed reaction conditions, could afford the corresponding alkanes or alcohols (Scheme 1.5). On one hand, when a strongly nucleophilic base as Bu_4NOH or NaH was used, it was therefore observed the formation of the corresponding alkane **B.2**. By contrast, the employment of non nucleophilic base such as DBU followed by an oxidation step with $NaBO_3$ gave rise to the synthesis of alcohol **B.3**.



Scheme 1.5. Synthesis of alkanes and alcohols employing aryl aldehyde (arenesulfonyl)hydrazones and trialkylboranes.

The reaction was very general and took place with good yields in presence of different substituents. Only the electronegativity of the substituents presented in the borane partner could affect the amount of final product.[112] Moreover, the aryl aldehyde tosylhydrazones could be previously prepared or generated *in situ*.

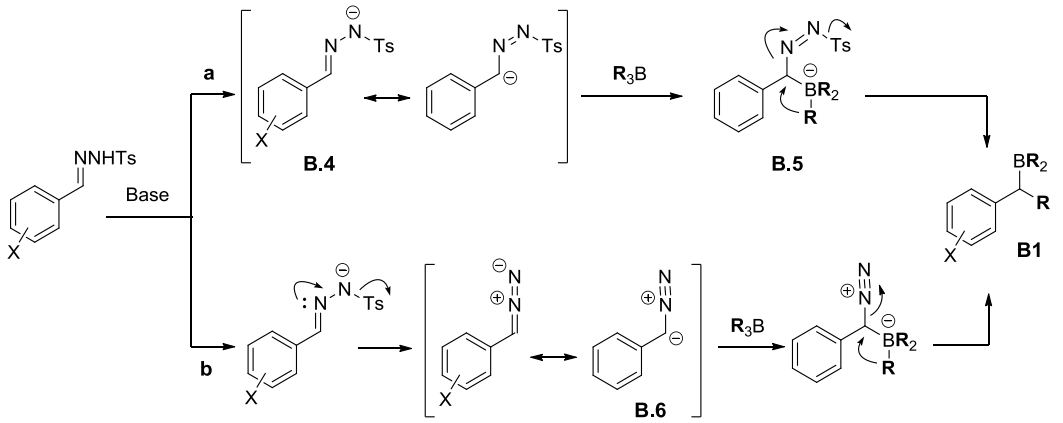
The methodology was extended to aryl aldehyde trisylhydrazones leading to the same products.[113] The reaction proceeded even more effectively than employing tosylhydrazones and furthermore, milder reaction conditions were employed. In any case, the transformation appeared limited to aryl aldehyde derivatives.

Further mechanistic studies were carried out by the same research group in order to determine the appropriate reaction pathway.[114] In consequence, two possible mechanistic courses were proposed for the generation of the intermediate **B.1**:

a- The intermediate **B.1** is formed through an anionic mechanism. Initially, the starting tosylhydrazone would generate an anion **B.4** which would then react with the trialkylborane compound to form the organoborane intermediate **B.5**. This intermediate would undergo a 1,2-alkyl shift with concomitant release of nitrogen and the *p*-toluenesulfinate anion, giving rise to trialkylborane **B.1**.

[112] H. C. Brown, R. L. Sharp, *J. Am. Chem. Soc.* **1966**, *88*, 5851.
[113] G. W. Kabalka, J. T. Maddox, E. Bogas, D. Tejedor, E. J. Ross, *Synth. Commun*. **1996**, *26*, 999.
[114] G. W. Kabalka, J. T. Maddox, E. Bogas, S. W. Kelley, *J. Org. Chem.* **1997**, *62*, 3688.

b- The intermediate **B.1** is formed through a diazo mechanism. The tosylhydrazone would decompose in the presence of the base to generate the diazo compound **B.6**. Again, this diazo compound would react with the trialkylborane and would also suffer a spontaneous 1,2-alkyl shift leading to trialkylborane **B.1**.



Scheme 1.6. The proposed mechanism for the synthesis of the intermediate **XV** between tosylhydrazones and trialkylboranes.

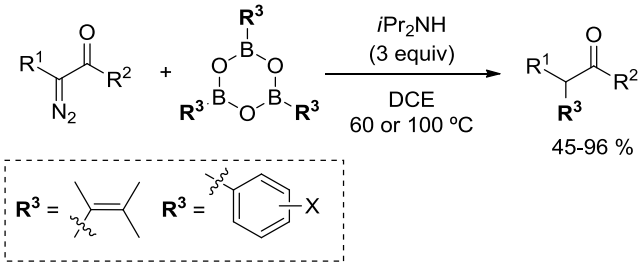
This methodology represents the first reaction between organoboranes and sulfonylhydrazones. However, the usefulness of the transformation was restricted to the employment of hydrazones of aromatic aldehydes and a very limited range of trialkylboranes.

1.1.5. Reactions of diazo compounds with boroxines.

In 2009, Wang and co-workers described a general α-arylation and α-vinylation of carbonyl compounds by the reaction of different α-diazocarbonyl compounds with aryl or vinylboroxines in the absence of a metal catalyst.[115,116] The general reaction is shown below in Scheme 1.7.

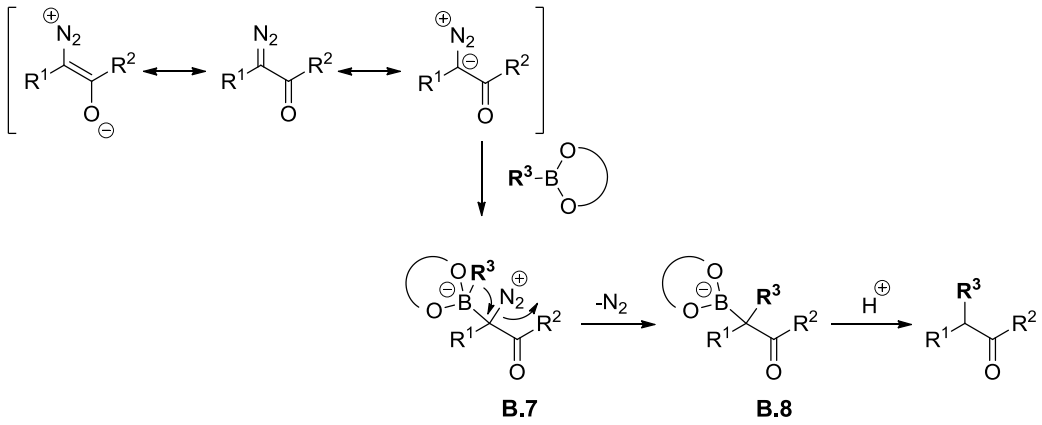
[115] C. Peng, W. Zhang, G. Yan, J. Wang, *Org. Lett.* **2009**, *11*, 1667.

[116] The Pd-catalyzed oxidative coupling between α-diazocarbonyl compounds and boronic acids was also described by Wang and co-workers to access to α-aryl-α,β-unsaturated carbonylic compounds: C. Peng, Y. Wang, J. Wang, *J. Am. Chem. Soc.* **2008**, *130*, 1566.



Scheme 1.7. Reaction of diazocarbonyl compounds with boroxines.

The proposed mechanism is quite similar to those of the reactions of α-diazocarbonyl compounds with trialkylboranes commented in Section 1.1.2. The reaction might be initiated with the nucleophilic attack from the diazo compound to the boroxine, generating the quaternary boronate intermediate **B.7**, followed by the subsequent 1,2-migration of R^3 from boron to carbon to give **B.8**. Finally, a hydrolysis step would lead to the final product (Scheme 1.8).

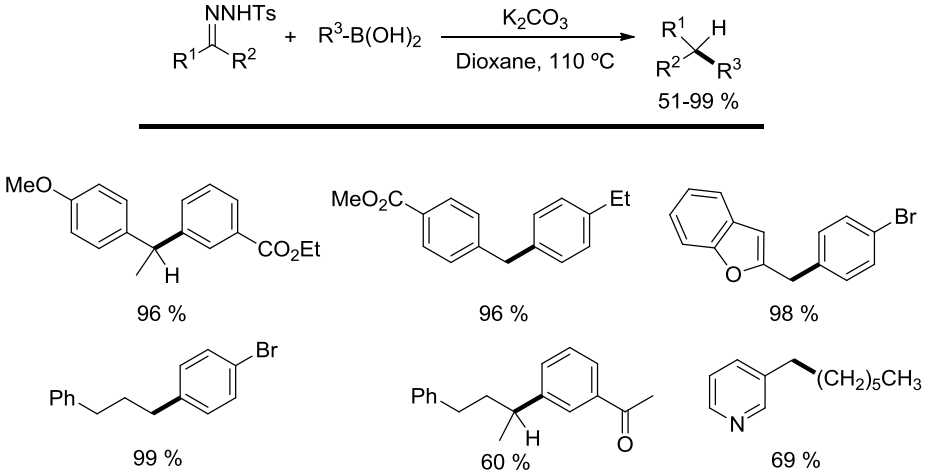


Scheme 1.8. The proposed mechanism for the reaction of diazocarbonyl compounds with boroxines.

1.1.6. Reactions of *N*-tosylhydrazones with boronic acids.

As it was previously mentioned, sulfonylhydrazones allow to prepare *in situ* non stabilized diazo compounds without the associated risk that they normally present. In this context, our research group was pioneer developing a transition-metal-free

reductive cross-coupling reaction between tosylhydrazones and boronic acids.[117] The procedure of the reaction is very simple and proceeds successfully by heating both reagents in dioxane using potassium carbonate as base (Scheme 1.9). [118] This new C-C bond forming reaction is very general, selective and tolerates a great diversity of functional groups present in both coupling partners. Moreover, inert atmosphere or dry solvents are not necesary providing an excellent operational simplicity.

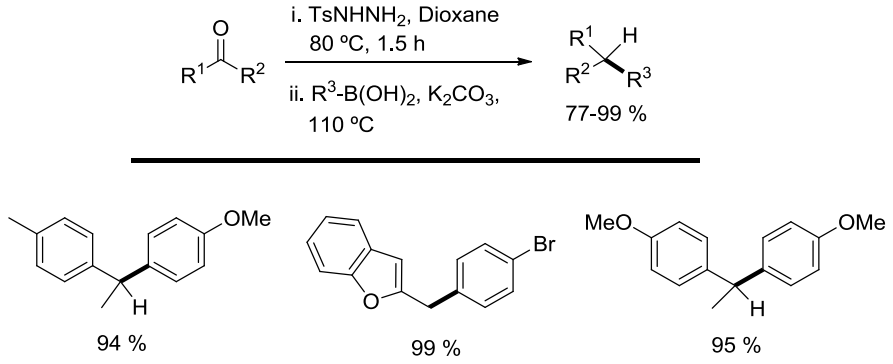


Scheme 1.9. Reductive coupling of *N*-tosylhydrazones with boronic acids.

Furthermore, this process could take place in one-pot fashion directly from the carbonyl compound observing no erosion in the efficiency of the transformation. Noteworthy this reaction could be envisioned from the synthetic point of view as a direct reductive coupling of carbonyl compounds, a transformation that requires several synthetic steps through other procedures (Scheme 1.10).

[117] The palladium catalysed oxidative cross-coupling reaction between *N*-tosylhydrazones and boronic acids has been reported: X. Zhao, J. Jing, K. Lu, Y. Zhang, J. Wang, *Chem. Commun.* **2010**, *46*, 1724.

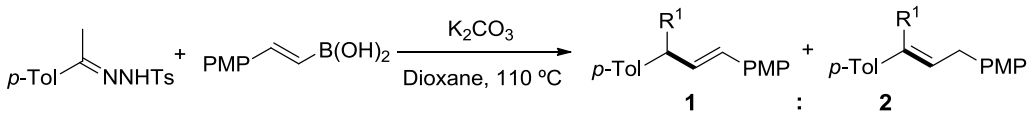
[118] J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Nat. Chem*. **2009**, *1*, 494.



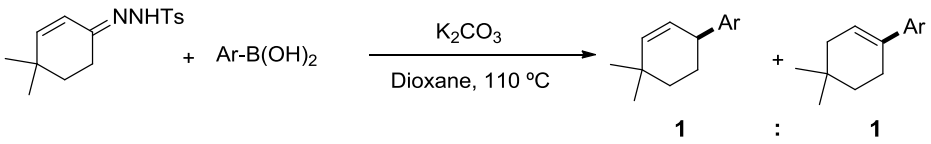
Scheme 1.10. One-pot reductive coupling of *N*-tosylhydrazones with boronic acid.

Additionally, the reaction could be carried out with alkenyl boronic acids as coupling partners. Indeed, the reaction of 2-styrylboronic acid with tosylhydrazones of acetophenones led to the corresponding reductive coupling products, but as a mixture of two regioisomers differing in the position of the double bond (Scheme 1.11.**A**). Similarly a mixture of regioisomers was also obtained in the reaction of a α,β-unsaturated tosylhydrazone with an aryl boronic acids (Scheme 1.11.**B**). Both mixtures of regioisomers of the double bond could be explained considering a borotropic [1,3]-rearrangement. The protodeboronation of the different species would lead to the final products. Thus, the experiments carried out in this work, indicated the presence of an allylboronic acid as intermediate of the process. Nevertheless, this kind of reaction will be deeply studied in Section 1.2 of this Chapter.

A- Employment of alkenyl boronic acids



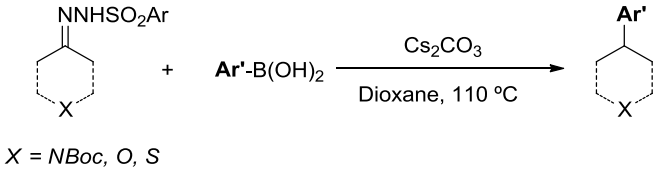
B- Employment of α,β-unsatured tosylhydrazones



Scheme 1.11. A- Reaction of tosylhydrazone with alkenyl boronic acid; **B-** Reaction of a α,β-unsaturated tosylhydrazones with aryl boronic acid.

1.1.6.1. Applications of the reductive coupling of boronic acids in medicinal chemistry.

Considering all the synthetic advantages, this coupling could be potentially used to prepare diverse sets of attractive compounds and has therefore attracted the attention of several research groups in the medicinal chemistry area. For instance, this methodology has been applied to synthesize a range of small polar molecules with physiochemical properties through parallel chemistry techniques.[119] Moreover, Ley and co-workers extend the scope of the reaction to 4-, 5- and 6-membered saturated heterocyclic rings with aryl boronic acids (Scheme 1.12).[120] The only modification from the original protocol was the replacement of Na_2CO_3 by Cs_2CO_3, which provided higher yields.



Scheme 1.12. Metal-free coupling between different heterocyclic hydrazones and boronic acids.

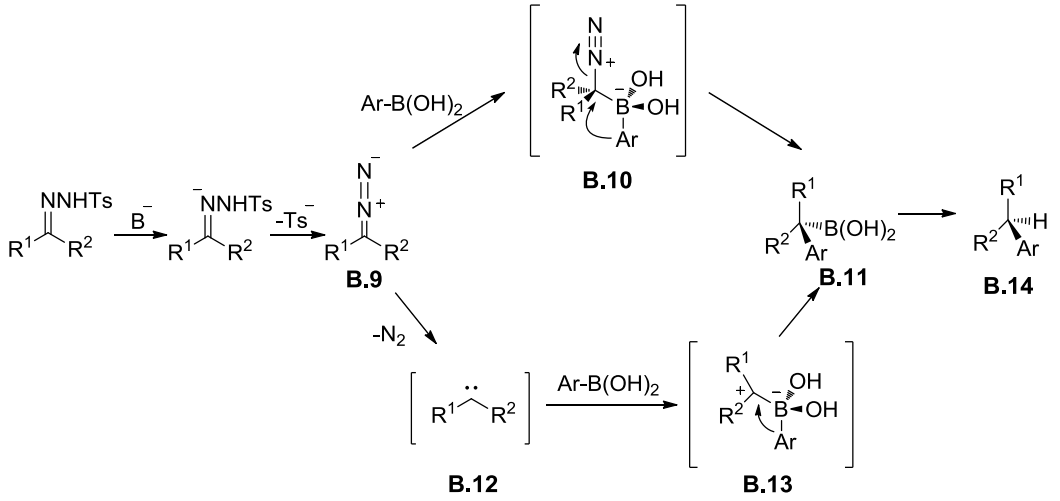
Furthermore, the reaction was also adapted towards its application in flow chemistry. Kirschning developed a protocol performed in a continuous flow system that follows the same sequence described by our research group.[121] More recently, in 2015, Ley and co-workers have also carried out a metal-free sp^2-sp^3 coupling between arylboronic acids and diazo compounds employing flow chemistry techniques. In this method the generation of the diazo compound is achieved using manganese dioxide as oxidant.[122]

1.1.6.2. Mechanism proposal for the reductive coupling of boronic acids.

From the point of view of the mechanism, the transformation could be explained postulating two different pathways. In the presence of the base, the *N*-tosylhydrazone decomposes under thermal conditions to lead to diazo compound **B.9**. Then, this diazo compound could react with the boronic acid generating a boronate intermediate **B.10**

[119] S. Nakagawa, K. A. Bainbridge, K. Butcher, D. Ellis, W. Klute, T. Ryckmas, *ChemMedChem*. **2012**, 7, 233.
[120] D. M. Allwood, D. C. Blakemore, A. D. Brown, S. V. Ley, *J. Org. Chem.* **2014**, *79*, 328.
[121] L. Kupracz, A. Kirschning, *J. Flow. Chem.* **2012**, *3*, 11.
[122] D. N. Tran, C. Battilocchio, S,-B Lou, J. M. Hawkins, S. V. Ley, *Chem. Sci.* **2015**, *6*, 1120.

that would evolve losing nitrogen to give benzylboronic acid **B.11**.[123] Formation of **B.11** could be also explained by an alternative dissociative mechanism, in which carbene **B.12**, generated by thermally induced N_2 release, would react with the aryl boronic acid through a zwitterionic intermediate **B.13**. Finally, protodeboronation of the benzyl boronic acid **B.11** under basic conditions would lead to the final product **B.14** (Scheme 1.13).



Scheme 1.13. Mechanism of reductive coupling between *N*-tosylhydrazones and boronic acids.

A similar procedure was described by Zou and co-workers in 2012, but employing diarylborinic acids or their anhydrides. These compounds in presence of tosylhydrazones gave rise to symmetrical and unsymmetrical diarylmethanes.[124]

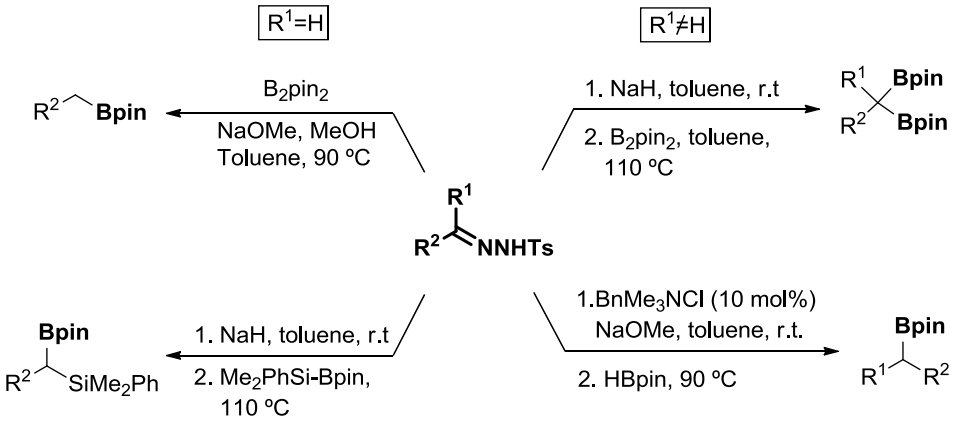
1.1.7. Reactions of diazo compounds with boronic esters.

Boronic esters are less polar and easier to handle than boronic acids due to the loss of the hydrogen bond donor capability of the hydroxyl groups. Consequently, boronic ester derivatives are less reactive and this reactivity can be tuned by the choice of the substituents.

The relevance of the reaction developed by our research group has given rise to a starting point for different studies with others borylation reagents. Subsequent works

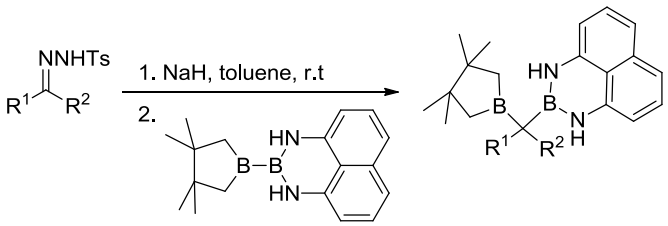
[123] The benzylboronic acid intermediate has been detected in the reactions with diazo compounds under flow conditions (See reference 122)
[124] X. Li, Y. Feng, L. Lin, G. Zou*, J. Org. Chem*. **2012**, *77*, 10991.

have been reported during the realization of this thesis that involve *N*-tosylhydrazones and pinacolborane, bis(pinacolato)diboron (B_2pin_2) or silylborane reagents to generate a set of boron compounds (Scheme 1.14).[125]



Scheme 1.14. Metal-free carbon insertion of *N*-tosylhidrazones into different species of boron.

To further extend this reaction, very recently, professor Elena Fernández and co-workers have described a unsymmetrical 1,1-diboration of diazo compounds generated *in situ* from aldehydes or ketones (Scheme 1.15).[126] The strategy followed involved the employment of the diboron reagent Bpin-Bdan (Bdan=1,8-naphthalenediaminatoboryl) that features a unsymmetrical B-B bond. The advantage of this reaction over the Wang´s protocol is the possibility of a selective deborylation of Bpin. Moreover, employing cyclic ketones a set of diborylated compounds in a diastereoselective manner.



Scheme 1.15. Metal-free carbon insertion of *N*-tosylhydrazones into Bpin-Bdan

[125] a) H. Li, L. Wang, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 2943; b) H. Li, X. Shangguan, Z. Zhang, S. Huang, Y. Zhang, J. Wang; *Org. Lett.* **2014**, *16*, 448.

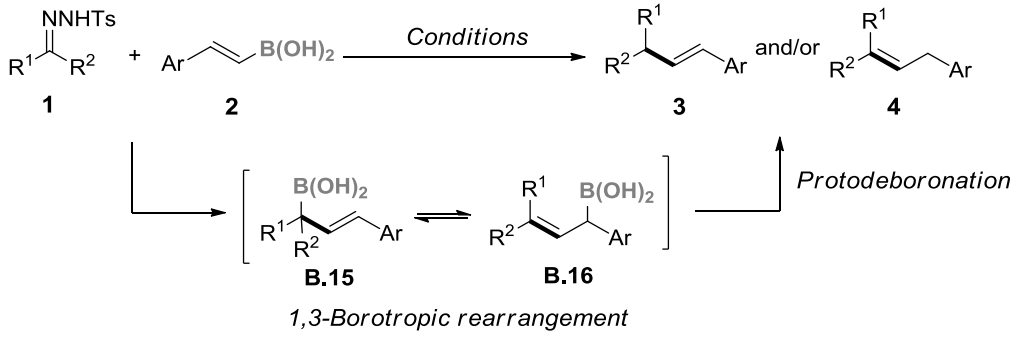
[126] A. B. Cuenca, J. Cid, D. García-López, J. J. Carbó, E. Fernández, *Org. Biomol. Chem*. **2015**, DOI: 10.1039/c5ob01523e.

1.2. RESULTS AND DISCUSSION.

1.2.1. Objetives

The selective creation of carbon-carbon bonds is a fundamental transformation of organic chemistry. As shown in the General Introduction of this thesis, our group has been working in recent years in the discovery of new free-metal methodologies to form C-C or C-X bond through the use of tosylhydrazones as diazo compounds precursors and different coupling partners. Particularly, as was previously commented (see section 1.1.6), a new method that involves alkyl or aryl boronic acids and tosylhydrazones was reported by our research group. The reaction proceeded efficiently without the need of a metal catalyst.

In this context, alkenyl boronic acids are very useful substrates in transition-metal-catalyzed cross-couplings reactions to access to substituted olefins and dienyl moieties.[1] In an attempt to go further in this field (see section 1.1.6), an interesting extension of this methodology would be the employment of alkenyl boronic acids and *N*-tosylhydrazones in transition-metal-free reactions (Scheme 1.16). However, the initial experiments employing alkenylboronic acids revealed a lack of regioselectivity, leading to a mixture double bond-positional isomers, that diminished the synthetic usefulness of the transformation. The formation of both isomers could be initially explained considering a 1,3-borotropic rearrangement[127] on the intermediate boronic acid **B.15**, followed by the protodeboronation of each isomer **B.16**. For that reason, the final objective would be to develop the reaction conditions that would lead to one single isomer of the reductive coupling product, and therefore, convert these transformations into more relevant synthetic processes.



Scheme 1.16. Objectives employing alkenyl boronic acids as coupling partners.

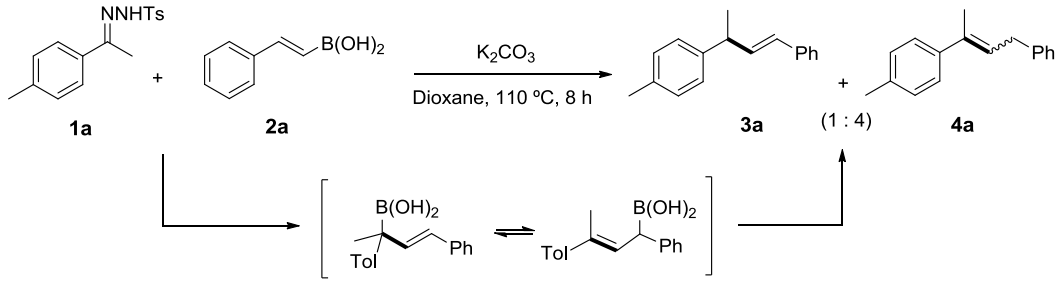
[127] H. C. Brown, P. K. Jadhav, K. S. Bhat, *J. Am. Chem. Soc.* **1985**, *107*, 2564.

Therefore, it was decided to investigate on the suitable reaction conditions and the importance of the synthetic transformation. The results are recovered below.

1.2.2. Reaction of alkenyl boronic acids 2 and tosylhydrazones 1a.

1.2.2.1. Preliminary studies.

The proposed reaction was initially studied with the tosylhydrazone **1a**, derived from 4-methylacetophenone and 2-phenylvinyl boronic acid **2a** as coupling partner. In the preliminary investigation, the selected conditions were the same as those employed for aryl and alkyl boronic acids but increasing the amount of base. Thus, the reaction between the tosylhydrazone **1a** and the alkenyl boronic acid **2a** (2 equiv) was carried out in the presence of K_2CO_3 (2 equiv) as base in dioxane and heating for 8 hours. Nevertheless, a mixture of isomers of position of the double bond **3a** and **4a** were obtained in a ratio 1:4, respectively. Noteworthy, both Z/E stereoisomers of **4a** were also observed (Scheme 1.17).

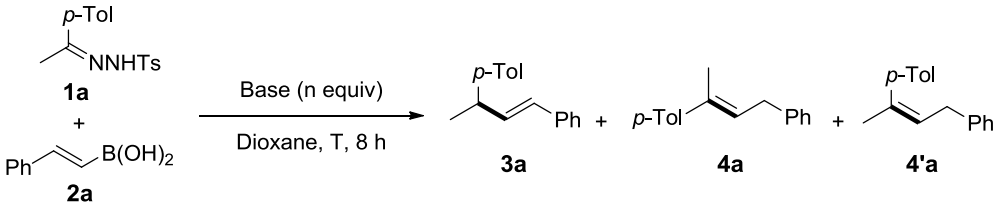


Scheme 1.17. Preliminary experiment.

1.2.2.2. Optimisation studies.

It was decided to carry out a deep study of reaction conditions including a variety of bases and different mixtures of them, in an attempt to drive the transformation into a single compound. Our initial hipothesis was to consider a base-assisted protodeboronation. For this reason, we decided to incorporate CsF and TBAF, in the idea that the presence of the fluorine anion might favor the protodeboronation towards the isomerization, and therefore, modify the ratio of the positional isomers. In the same sense, stronger bases, such as NaOH and LiOH were also tested. Moreover, the reaction was performed at different temperatures as is shown in the table below (Table 1.1).

Table 1.1. Influence of the base in the reductive coupling between **1a** and **2a**.



Entry	Base	(*n* equiv)	T (°C)	Yield (%)[a]	3a : 4a : 4'a
1	**K_2CO_3**	2	110	80	1 : 4 : 1
2	**CsF**	2	110	36	1 : 4 : -
3	**K_2CO_3 + CsF**	2 (1:1)[b]	110	67	1 : 10 : 1
4	**LiOH**	2	110	61	1 : 1 : -
5	**LiOH + CsF**	2 (1:1) [b]	110	62	2 : 15 : 1
6	**K_2CO_3 + CsF**	2 (1:2) [b]	110	60	1 : 10 : 1
7	**K_2CO_3 + CsF**	2 (1:1) [b]	90	48	4 : 20 : 1
8	**LiOH**	2.5	110	92	8 : 8 : 1
9	**KOH**	2	110	10	2 : 10 : 1
11	**KOH+CsF**	2 (1:1) [b]	110	28	1 : 8 : 1
12	**NaOH**	2	110	30	2 : 8 : 1
13	**NaOH+CsF**	2 (1:1) [b]	110	71	1 : 15 : 2
14	**K_2CO_3 + TBAF**	2 (1:1) [b]	110	43	1 : 3 : -

[a] Yields of the mixture. [b] Mixture of bases indicated in brackets. [c] The relative ratio of **3a**, **4a**, **4'a** was established by integration of the identified signals on ^{1}H-NMR.

As it was shown in the Table 1.1, the reaction tolerated bases of different nature providing a mixture of the regioisomeric coupling products with moderate to excellent yield. At this point, it is remarkable that the product that came from the intermediate **B.16** in which the double bond has migrated, (Scheme 1.17) was the main product in any case. This could be due to the favoured protodeboronation of the secondary boronic acid against the tertiary one. In consequence, the stereoisomeric compounds **4a** and **4'a**

were always obtained as major product. Nevertheless, a moderate influence of the base employed could be observed.

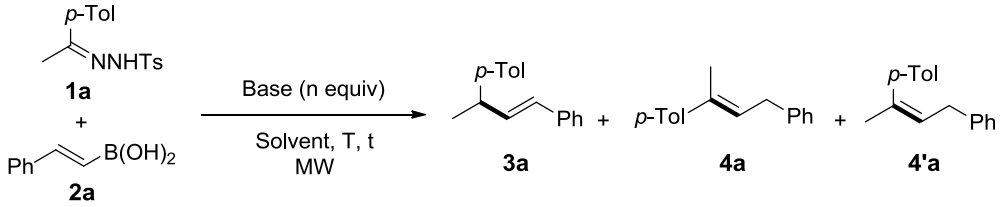
The best outcomes in terms of yield were obtained when the reaction was carried out with an increase of K_2CO_3 or with a large excess of LiOH (entry 1 and 8), although no improvement was observed in the ratio between different isomers.

It is known that fluoride bases have been studied to avoid the difficulties in the protodeboronation step, particularly, of tertiary boronic esters.[128] Nevertheless, in our case, the employment of CsF gave rise to very low yields and no significant changes in the ratio of the final products (entry 2). However, when K_2CO_3 and NaOH were used as the base in combination with an amount of CsF, the results in terms of selectivity were improved (entry 3 and 13). Particularly, the equimolar mixture of NaOH and CsF reduced the product in which the double bond is retained in the original position **3a** to only 6%.

Moreover, variations of the temperature (entry 7) and the ratio between reagents (entry 6) were almost ineffective in order to alter the products distribution.

At this point, it was decided to employ the microwave heating as an alternative energy source for this transformation. Some selected results are presented in Table 1.2 .

Table 1.2. Influence of the base and reaction conditions in the reaction between tosylhydrazone **1** and alkenyl boronic acid **2a** under microwave heating.



Entry	Base	T (°C)	t (min)	3a : 4a : 4'a[b]	Yield[a]
1	**LiOH**	110	5	3: 1 : -	44
3	**LiOH**	110	120	-	-
4	**LiOH**	150	5	1 : 5: -	
5	**LiOH**	150	20	6 : 1 : -	20

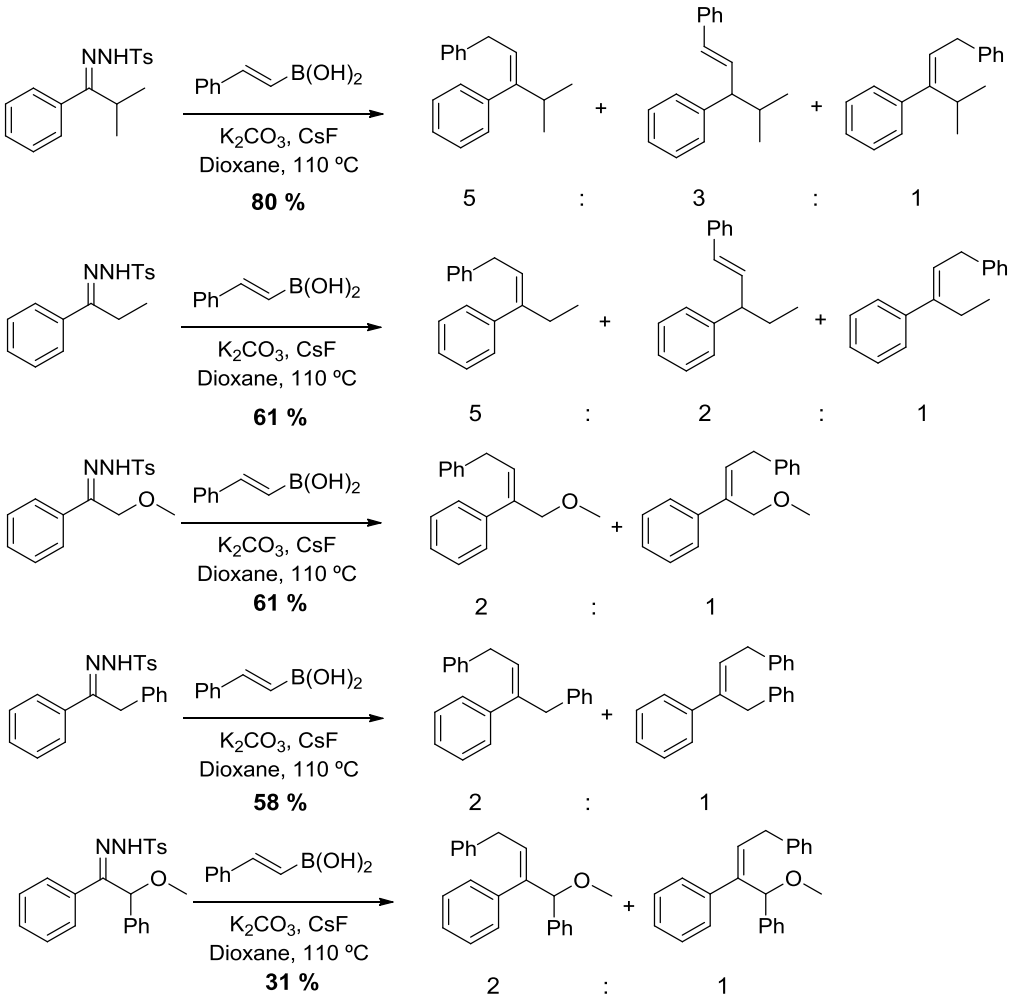
[128] S. Nave, R. P. Sonawane, T. G. Elford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 17096.

6	**LiOH**	150	60	4 : 1 : -	28
7	**LiOH**	160	20	10 : 1 : -	26
8	**LiOH**	160	60	6 : 1 : -	28
10	**K_2CO_3**	110	5	1 : 5 : 1	65
11	**K_2CO_3**	150	5	4 : 20 : 1	16
13	**K_2CO_3 + CsF**	150	5	1 : 6 : -	-

[a] Yields of the mixture. [b] The relative ratio of **3a**, **4a**, **4'a** was established by integration of the identified signals on ^{1}H-NMR.

The reaction was tested modifying the base, the temperature, the solvent and the reaction time. It is noteworthy that the employ of LiOH led to **3a** as major isomer which is the opposite to that expected. However, despite the extensive experimentation performed, the reaction could not be driven to a single isomer.

At this point, it was decided to modify the model reaction. Particularly, the α-substitution of the hydrazone in order to study the scope of the reductive couplings well as the influence of the structure of the ketone in the ratio of the isomers (Scheme 1.18).



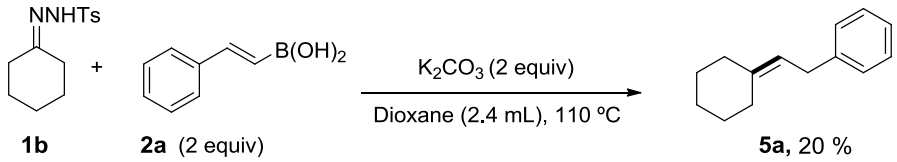
Scheme 1.18. Some examples employing alkyl aryl ketones with different substituents at α-position.

In an initial approximation, the reactions were conducted with differently substituted aryl alkyl hydrazones. As it could be observed in the scheme, these hydrazones led to the olefination product as major positional isomer, but as a mixture of *Z*/*E*-stereoisomers **4** and **4'**. In some cases, small amounts of the regioisomer **3** were found. Again, although the overall yields were promising in most of the examples, a single isomer could not be obtained.

1.2.3. Reaction of alkenyl boronic acids 2 and tosylhydrazones 1b.

1.2.3.1. Preliminaries studies.

Taking into consideration the results obtained above, it was decided to change the structure of the tosylhydrazone. It was selected the hydrazone derived from the cyclohexanone which would not present the problem of *Z/E* isomers. In an initial experiment, the same conditions of aryl and alkyl boronic acids were employed. The product of the reaction was isolated in a poor 20% yield but surprisingly, as a single isomer (Scheme 1.19). The observed isomer **5a** corresponded to the product in which the double bond had migrated.



Scheme 1.19. Preliminary study of the reaction between the tosylhydrazone derived from cyclohexanone **1b** and alkenyl boronic acid **2a**.

Although the yield was very poor, it was a promising result for various reasons:

1. These hydrazones derived from cyclic ketones provided extremely poor yields in the reductive coupling with arylboronic acids.

2. The obtained products are the thermodynamically unstable isomers which present an exocyclic double bond and are not conjugated with the aromatic ring.

3. This transformation could be envisioned as a new type of olefination reaction of carbonyl compounds.[129]

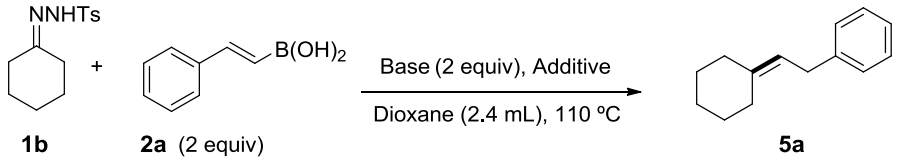
1.2.3.2. Optimisation of the reaction conditions.

The previously obtained result encouraged us to find the combination of conditions that might lead to best outcomes. A wide range of variables was studied such as the different mixture of bases, temperature, the ratio between the reagents, the solvent and finally, the heating source.

[129] T. Takeda, *Modern carbonyl olefination*, Wiley-VCH, (Weinheim), **2004**.

In the reaction with tosylhydrazones derived from methyl aryl ketones it was observed some dependence on the selected base. For that reason, it was firstly decided to test different bases as well as the presence of a fluorine source as additive. The results are outlined in Table 1.3.

Table 1.3. Influence of the base in the reaction of tosylhydrazone **1b** and alkenyl boronic acid **2a**.



1b **2a** (2 equiv) **5a**

Entry	Base	T (°C)	t (h)	Solvent (mL)	Additive[a]	Ratio 1b: 2b: Base[b]	Yield (%)
1	K_2CO_3	110	12	2.3	-	0.5: 1: 1	20
2	CsF	110	12	2.3	-	0.5: 1: 1	12
3	K_2CO_3	110	12	2.3	CsF	0.5: 1: 1	63
4	LiOH	110	12	2.3	-	0.5: 1: 1	-
5	K_2CO_3	70	12	2.3	CsF	0.5: 1: 1	-
6	K_2CO_3	90	12	2.3	CsF	0.5: 1: 1	38
7	K_2CO_3	110	12	2.3	CsF+TBAB	0.5: 1: 1	22
8	K_2CO_3	110	18	2.3	CsF	0.5: 1: 1	39
9	K_2CO_3	110	12	2.3	CsF	0.5: 0.75: 1	37
10	K_2CO_3	110	12	2.3	CsF	1: 1: 1	44
11	K_2CO_3	110	12	2.3	CsF	0.5: 1: 2	24
12	K_2CO_3	110	18	2.3	CsF	1: 0.5: 1	58

13	K_2CO_3	110	12	1.5	CsF	0.5: 1: 1	27
14	K_2CO_3	110	12	3	CsF	0.5: 1: 1	17
15	K_2CO_3	110	12	5	CsF	1: 0.5: 1	16

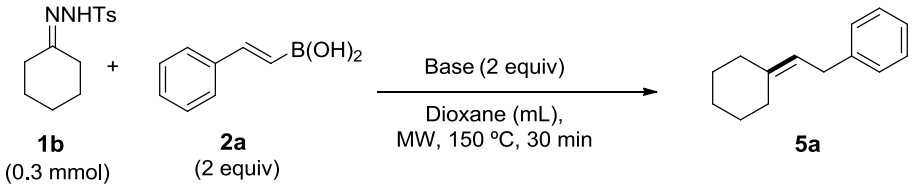
[a] A 1 : 1 ratio, base: additive was employed. [b] The table indicates the amount in mmol of each reagent.

First of all, it is important to note that regardless of the reaction conditions, the oleofination product **5a** was the only coupling product obtained, while the isomer **3** was not even detected.

Moreover, as it can be observed in the table, a dependence with the base was found. Some differences regarding methyl aryl hydrazones were observed, since the reaction did not take place when the LiOH was selected as base (entry 4). Indeed, the best results were obtained when a mixture with K_2CO_3 and CsF was employed (entry 3). Although the process can be performed at low temperatures, the best outcomes were collected at 110 °C (entry 3-5 and 6). Moreover, when the reaction was carried out in the presence of a phase-transfer catalyst[128] in order to facilitate the dissolution of the tosylhydrazone (entry 7), no improvement was observed.Other variables were considered such as the ratio between different reagents (entries 9-12), the reaction time (entry 8) and the amount of solvent (entries 13-15). Nevertheless, the isolated yield of **5a** could not be improved.

In an attempt to further study the process, the heating source was also optimized as is shown Table 1.4. Therefore, all the reactions were performed employing microwave irradiation at 150 °C during 30 min.

Table 1.4. Influence of the heating source in the reaction of tosylhydrazone **1b** and alkenyl boronic acid **2a**.



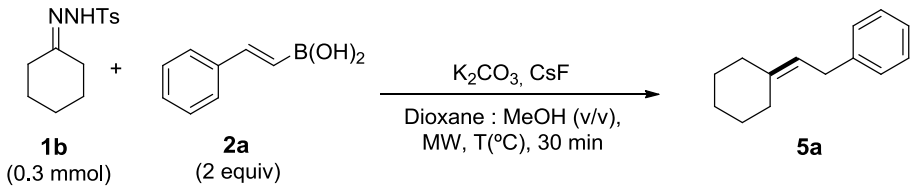
Entry	Base	Vol (mL)	Yield (%)
1	**K_2CO_3**	1.4	-

2	**CsF**	1.4	20
3	**K_2CO_3 + CsF**	1.4	71
4	**LiOH**	1.4	-
5	**LiO*t*Bu**	1.4	23
6	**K_2CO_3 + CsF**	2	88
7	**K_2CO_3 + CsF**	3	87

Again, the mixture of K_2CO_3 and CsF was the most suitable combination of bases, increasing the yield of the process (entry 3). Moreover, it is known that the reactions performed using microwave irradiation can be influenced by the amount of solvent. In this context, the highest yield was obtained employing the amount of 2 mL of dioxane for 0,3 mmol of starting hydrazone (entry 6). Delightfully, the reaction times were dramatically reduced from 8 hours to 30 minutes and the yield was significantly improved.

Finally, it was postulated that the cesium fluoride base might be necessary to generate a quaternary boron intermediate, facilitating the protodeboronation to give rise to the final product. It is known than other reagents, particularly alcohols, are also able to coordinate to the boron centre and assist the protodeboronation step.[130] In our case, methanol was chosen as an alternative reagent to promote the protodeboronation (Table 1.5).

Table 1.5. Influence of the MeOH as reagent to protodeboronate in the reaction of tosylhydrazone **1b** and alkenyl boronic acid **2**.

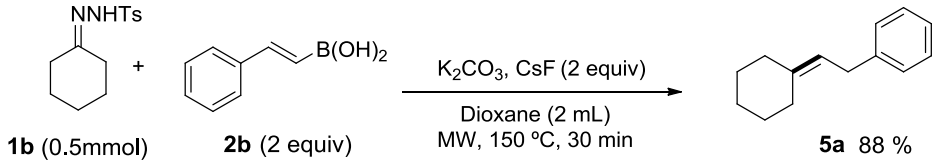


[130] H. C. Brown, K. J. Marray, *Tetrahedron* **1986**, *42*, 5497.

Entry	Base	Yield (%)	Entry	Solvent (mL)	Yield (%)
1	110	31	**4**	MeOH (1 equiv): Dioxane 2 mL	20
2	130	60	**5**	MeOH: Dioxane (v/v = 1:1)	63
3	150	78	**6**	MeOH	12

The reaction was studied at different temperatures and testing different amounts of MeOH:Dioxane. Unfortunately, these attempts did not lead to significant improvements in the efficiency of the reaction.

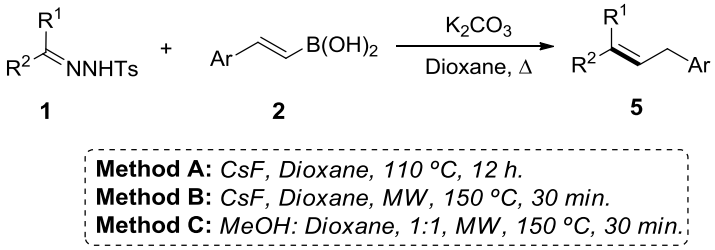
In conclusion, the best conditions found for achieving this transformation at the 0.3 mmol scale were a combination of K_2CO_3 (2 equiv) and CsF (2 equiv) in 2 mL of dioxane heating 30 min at 150 °C under microwave irradiation (Scheme 1.21).



Scheme 1.20. Optimal conditions for the reductive coupling of tosylhydrazone **1b** and alkenyl boronic acid **2a.**

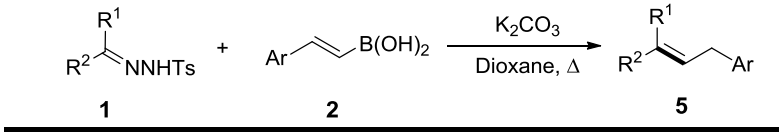
1.2.3.3. Scope of the reaction employing arylalkenyl boronic acids 2.

These optimized conditions were subsequently applied to a wide range of structurally diverse *N*-tosylhydrazones **1** and different styrylboronic acids **2**. At this point, it should be remarked that in the course of the study, the conditions had to be optimized for each *N*-tosylhydrazone. Therefore, there were thereby established three methods as is shown in Scheme 1.21. The employed method will be indicated for each example.

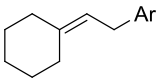


Scheme 1.21. Established methods for the olefination of tosylhydrazone **1** and alkenyl boronic acid **2**

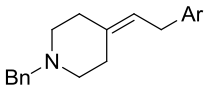
As was represented in Scheme 1.22, from the point of view of the tosylhydrazone, the olefination reaction was very general. Therefore, the reaction could be carried out with hydrazones derived from cyclohexanone (**5a**-**5be**) or 4-substituted cyclohexanone (**5ea**-**5h**) as well as heterocyclic ketones, such as *N*-benzyl piperidone (**5ca**-**5cc**) or tetrahydro-4*H*-pyran-4-one (**5d**), giving rise to the corresponding olefination products from good to excellent yields. Moreover, the reaction allowed the employment of carbocyclic systems with varied ring-sizes such as hydrazones derived from cyclopentanone (**5i**) or cycloheptanone (**5j**).



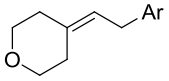
1 **2** **5**



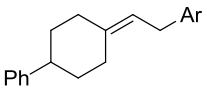
5a, Ph, *Method B*, 88 %
5bb, 4-$MeOC_4H_6$, *Method B*, 92 %
5bc, 4-$CF_3C_6H_4$, *Method B*, 52 %
5bd, 3-F-C_6H_4, *Method B*, 89 %
5be, 4-Cl-C_6H_4, *Method B*, 76 %



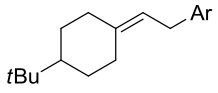
5ca, Ph, *Method B*, 82 %
5cb, 4-$MeOC_4H_6$, *Method A*, 57 %
5cc, 4-$CF_3C_6H_4$, *Method B*, 68 %



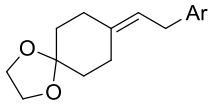
5d, Ph, *Method B*, 82 %



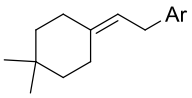
5ea, Ph, *Method C*, 81 %
5eb, 4-$MeOC_4H_6$, *Method C*, 70 %
5ec, 4-$CF_3C_6H_4$, *Method C*, 83 %
5ed, 3-F-C_6H_4, *Method C*, 93 %
5ee, 4-Cl-C_6H_4, *Method C*, 79 %



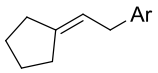
5f, Ph, *Method B*, 86 %



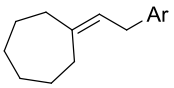
5g, Ph, *Method B*, 77 %



5h, Ph, *Method C*, 80 %



5i, Ph, *Method C*, 78 %



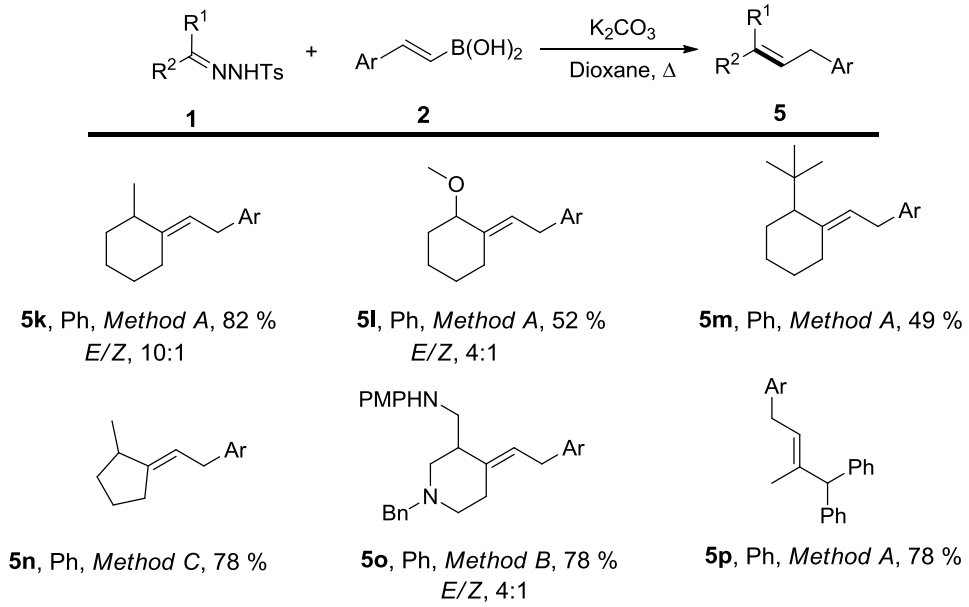
5j, Ph, *Method B*, 89 %

Scheme 1.22. Scope of the reaction with alkenyl boronic acids **2** and tosylhydrazones **1**.

This transformation was also extended to various alkenyl boronic acids, featuring either electron-withdrawing or electron-donating substituents (**5b**-**5cc**, **5ea**-**5ee**) furnishing the olefination products with similar good yields.

In the following step, the scope of the transformation was evaluated with unsymmetrical cyclic as well as α-substituted acyclic ketones (Scheme 1.23). Interestingly, these hydrazones provided different ratio of *Z/E* stereoisomers depending on the size of substituent. Thus, employing bulky groups (**5m**, **5n, 5p**), the reaction led exclusively to a single isomer. However, with substituents of a smaller size, a mixture of stereoisomers were observed (**5k**, **5l**, **5o**). Particularly interesting is the example **5o** in which the hydrazone derived from a Mannich adduct, featuring an amine free NH, is able to participate in the process leading to a separable mixture of the *Z/E* isomers (4:1)

with very good yield. The major isomer in all cases, featured a double bond wherein the benzyl group is on the opposite side to the bulkier group (Scheme 1.23).



Scheme 1.23. Scope of the reaction with alkenyl boronic acids **2** and tosylhydrazones **1** employing hydrazones derived from unsymmetrical ketones.

The stereochemistry of the major isomer was determined based on selective nOe experiments. A representative example is shown below in Figure 1.1.[131] Irradiation of the signal of the alkene H_a, that appears at 5,52 ppm, produces positive nOe on the signal at 3,62 ppm, that corresponds to the methynic proton H_b. Thus, the proximitiy between both protons establishes the *E* stereochemistry for the double bond.

[131] See NMR Spectra Appendix.

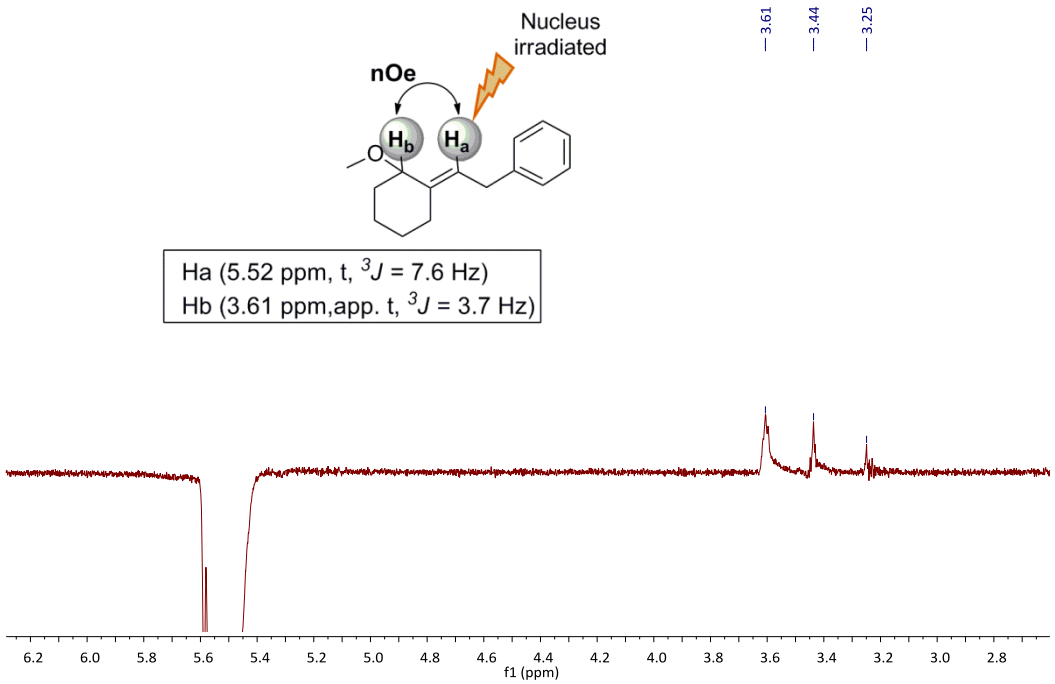
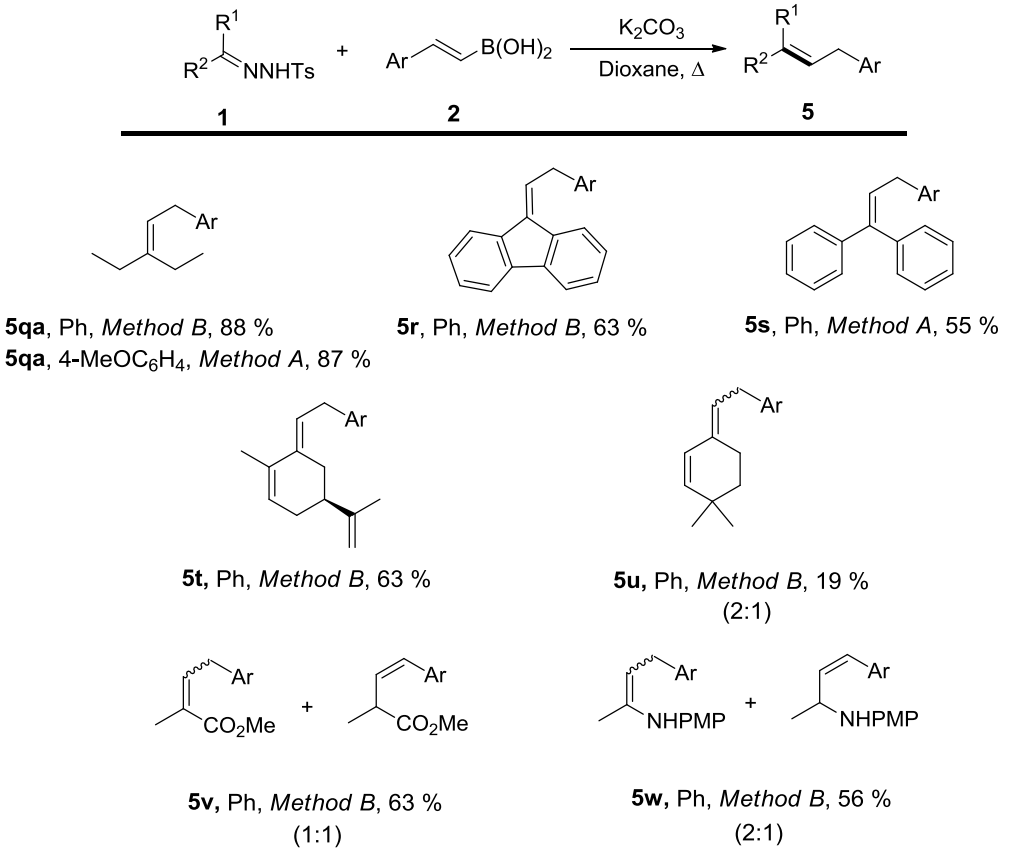


Figure 1.1. Determination of the major isomer through a selective nOe experiment.

Finally, the scope of the reaction was also evaluated employing cyclic an acyclic ketones with a variety of substutitions (Scheme 1.24).

The regioselective reaction could be carried out not only with acyclic dialkyl ketones (**5qa**, **5qb**) but also diarylsubstituted hydrazones derived from benzophenone (**5s**) as well as from fluorenone (**5r**), which provided exclusively the olefination isomer as product. It should be also remarked that α,β-unsaturated hydrazones derived from cyclohexenones gave rise also to a single regioisomer (**5t**,**5u**). Here, it was provided a representative example of the influence of the substituent when the hydrazone of the carvone was employed. Due to the bulky methyl group at the α-position, the olefination of this hydrazone led to a single stereoisomer. In consequence, a regioselective and stereoselective process was developed.

Nevertheless, when ethyl pyruvate or pyruvic amides were used, it was obtained a (1:1) mixture of both double bond positional regioisomers (**5v**, **5w**). Clearly, the presence of the electronwithdrawing groups had a negative effect on the regioselectivity of the coupling reaction.

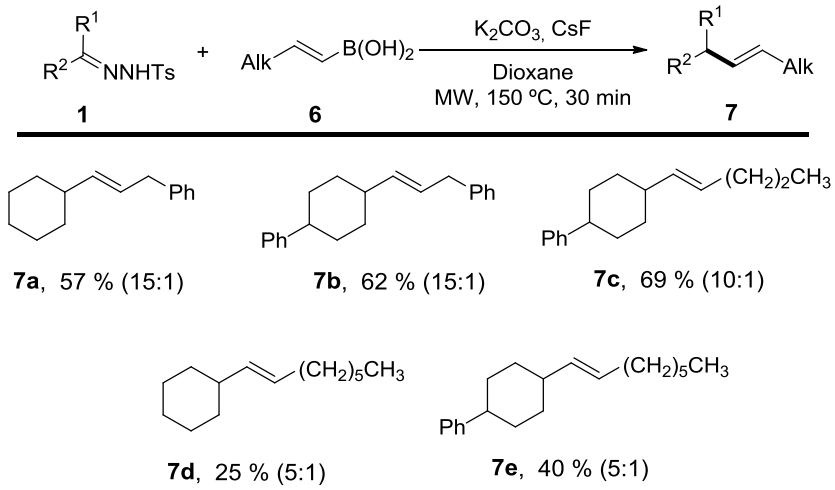


Scheme 1.24. Scope of the reaction reaction with alkenyl boronic acids **2** and tosylhydrazones **1** employing dialkyl, diaryl and α,β-unsaturated hydrazones.

1.2.3.4. Scope of the reaction employing 2-alkylalkenyl boronic acids 6.

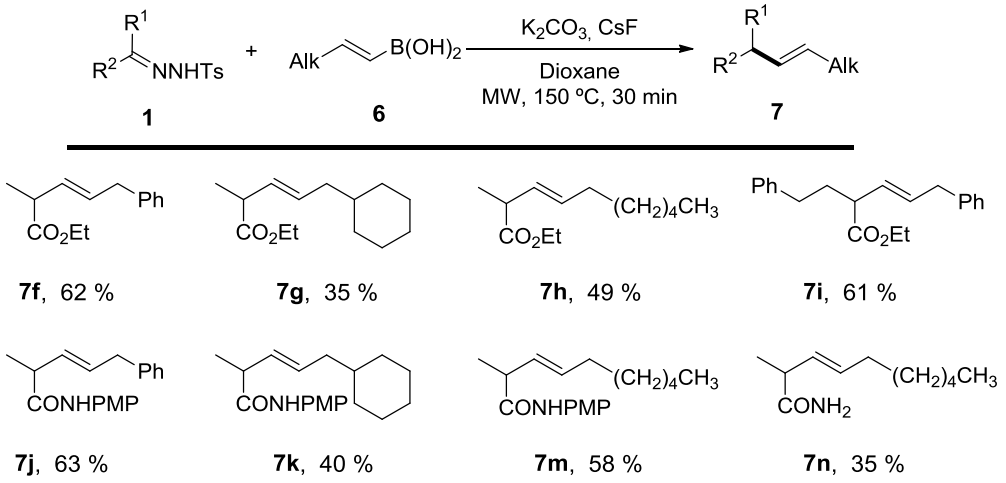
So far, all the reactions had been studied with alkenylboronic acids which feature an aromatic ring directly attached at the double bond. To further demonstrate the utility of this transformation, we turned our attention to investigate the corresponding 2-alkyl substituted alkenylboronic acids. The reactions with 2-alkylalkenyl boronic acids as substrates needed to be again optimized to reach completion. Thus, the best conditions found for this transformation consisted on using K_2CO_3 as base and dioxane as solvent under microwave irradiation during 30 min at 150 °C. It was also observed that the process could be significantly improved by adding CsF as additive (Scheme 1.25). However, despite of the efforts, only moderate yields were obtained employing hydrazones derived from cyclohexanone. Surprisingly, in these reactions, where the aryl group was replaced by an alkyl group, the regioselectivity of the reaction drastically

changed. Now, it was obtained as major isomer the one that preserved double bond in the original position. Particularly, employing hydrazones derived from dialkyl ketones, the reactions were accomplished with remarkable regioselectivity and only little amounts of the other regioisomer of were observed (**7a**-**7e**).



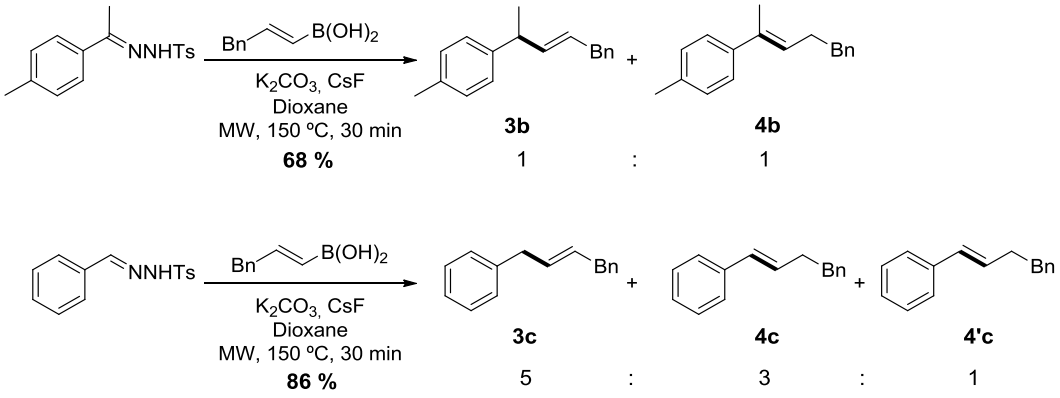
Scheme 1.25. Scope of the reaction with alkenyl boronic acids **6** and tosylhydrazones derived from different cyclohexanones. The major isomer is represented in the table and the ratio between both isomers is indicated in parenthesis.

At this point, with these results in hands, different hydrazones were further studied in order to evaluate the influence of the structure of the hydrazone in the course of the reaction (Scheme 1.26). Interestingly, complete regioselectivity was achieved when the reaction was carried out employing hydrazones derived from ethyl pyruvate and pyruvic amides in contrast with the reactions of these hydrazones with the styrylboronic acids. Therefore, disubstituted alkenes were obtained as unique positional isomer in moderate yield. It is noteworthy the functional-group tolerance of the process, which could be carried out even in the presence of unprotected NH_2. Furthermore, this new reaction is also remarkable because the stereochemistry of the alkenyl boronic acid was retained during the process and in consequence, the *E* olefin was obtained in every instance.



Scheme 1.26. Scope of the reaction with alkenyl boronic acids **6** and tosylhydrazones derived from ethyl pyruvate and pyruvic amides.

However, using hydrazones derived from alkyl aryl ketones as well as aldehydes, the regioselectivity of the reaction was lost, and a mixture of different isomers was obtained. These results indicate that a precise combination of substituents of both coupling partners is required in order to achieve a regioselective reaction.



Scheme 1.27 Unselective reactions of alkenyl boronic acids **6** and tosylhydrazones derived from alkyl aryl ketones and aldehydes.

1.2.3.5. Diastereoselective processes.

A particular interesting result was obtained when the reaction was carried out with the tosylhydrazones derived from 4-phenylcyclohexanone, because the final 1,4-disubstituted cyclohexanones (Scheme 1.25, **7b**, **7c** and **7e**) were obtained with total diastereoselectivity. Only one of the two possible diastereosisomers was observed in the reaction crude, that corresponded to the incorporation of the R group in the equatorial position. The relative stereochemistry of the substituents was determined by ^{1}H-NMR ($CDCl_3$, 600 MHz) spectra. Particularly, the spectrum of product **7b** was studied as a representative example. As is shown in Figure 1.2, the signal for H^1 appears as a triple triplet at 2.49 ppm, ($^{3}J_{H1\text{-}H2eq}$= 3.2 Hz, $^{3}J_{H1\text{-}H2ax}$=12.9 Hz) and the signal for H^{2ax} appears at 1.27 ppm as a quadruple doblet ($^{3}J_{H2ax\text{-}H3eq}$= 3.2 Hz, $^{3}J_{H1\text{-}H2ax}$=$^{3}J_{H2ax\text{-}H3ax}$ =$^{2}J_{H2eq\text{-}H2ax}$ = 12.9 Hz) establishing the equatorial arrangement of the phenyl ring. The signal for H^{3ax} appears also as a quadruple doblet ($^{3}J_{H3ax\text{-}H2eq}$= 3.2 Hz, $^{3}J_{H4\text{-}H3ax}$=$^{3}J_{H2ax\text{-}H3ax}$ =$^{2}J_{H3eq\text{-}H3ax}$ = 12.9 Hz) and establishes the axial arrangement of H^4 and therefore, the equatorial arrangement of the alkenyl substituent. These results are remarkable, as they represent a rare example of a stereoselective reaction based on diazo compounds, but in the absence of any metal catalyst.

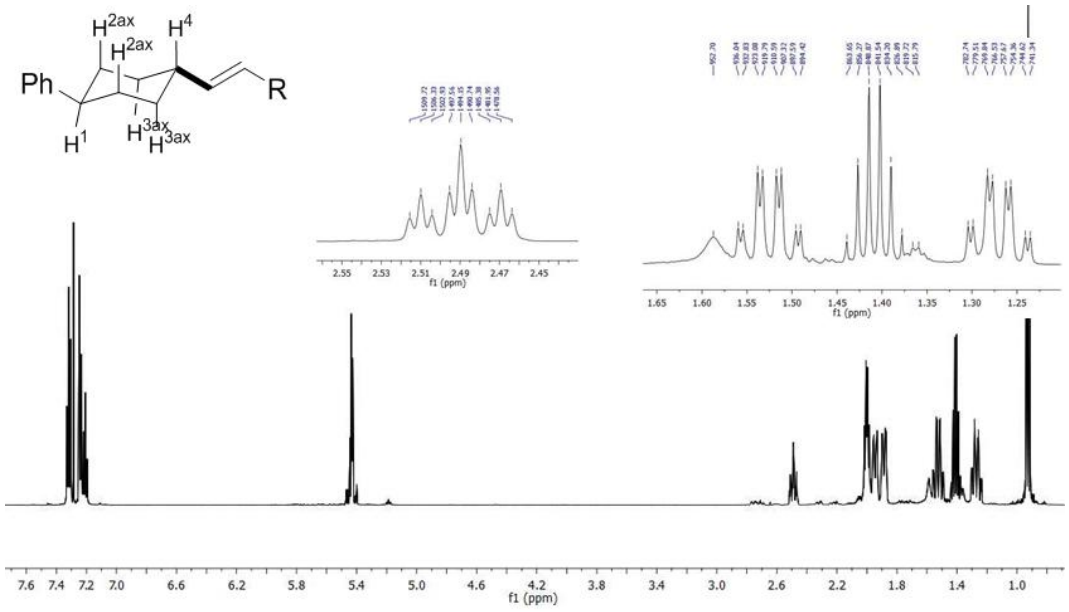
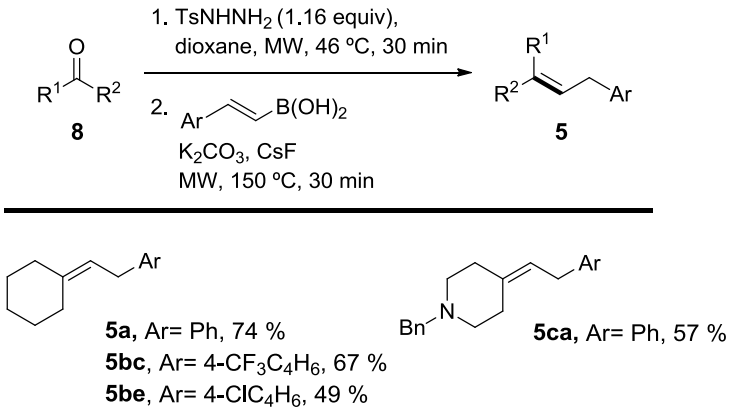


Figure 1.2. ^{1}H-NMR spectrum ($CDCl_3$, 600 MHz) of **7b**.

1.2.3.6. Development of a "one-pot" methodology in the reaction between tosylhydrazones 1 and alkenyl boronic acids 2.

In our research group, different methodologies involving hydrazones have been developed in which the reaction can be carried out directly from the carbonyl compound. At this point, it was decided to apply this *in situ* generation of the tosylhydrazone to our reaction.

The protocol consists in combining the corresponding carbonyl compound with the tosylhydrazide employing dioxane as solvent and heating the mixture under microwave irradiation for 30 min at 46 °C. In this step, the tosylhydrazone is generated *in situ* suppressing the isolation and purification steps. After that, the rest of the reagents are added and mixture is heated at 150 °C for 30 min (Scheme 1.28). In this manner, the final products are obtained in a one-pot fashion with total regioselectivity albeit in slighty lower yields than the reactions from the preformed hydrazone (**5a**, **5bc**, **5be** and **5ca**).

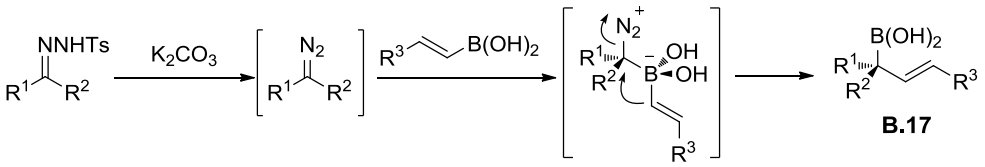


Scheme 1.28. One-pot reaction of alkenyl boronic acids **2** and ketones **8.**

1.2.3.7. Mechanistic proposal

The proposed mechanisms for both the olefination and the alkenylation reactions are similar to that postulated for the reductive couplings with arylboronic acids previously described.[17] It would begin with the formation of the diazo compound by decomposition of the tosylhydrazone in the presence of the base. This *in situ* generated diazo compound would react with the alkenyl boronic acid leading to the formation of allylic boronic acid intermediate **B.17** through a boronate type of transition state

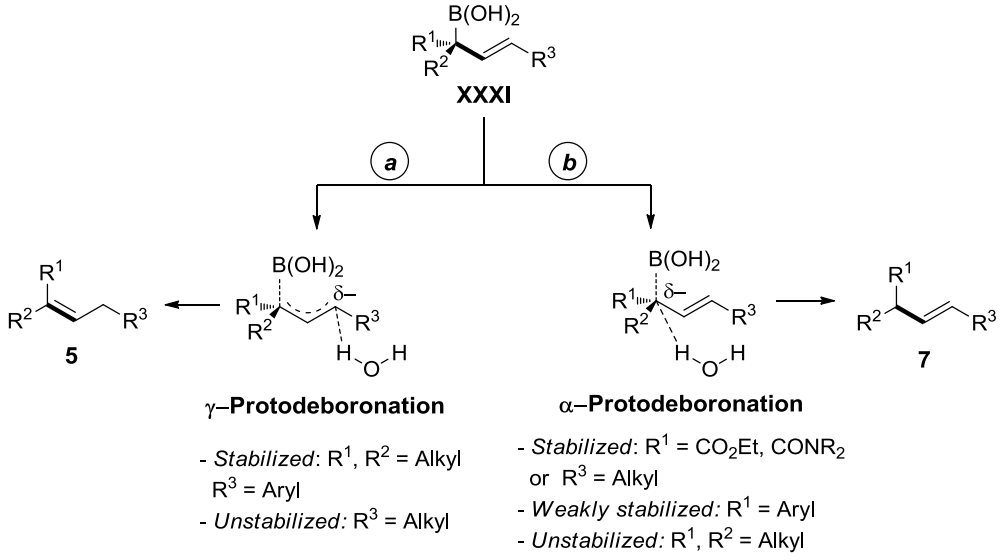
(Scheme 1.29).[132] The evolution of the intermiate **B.17** will determine the products distribution. In fact, the recovered results along the experimental work depend exclusively on the relative ratio of α or γ protodeboronation that undergoes this intermediate (Scheme 1.29). In addition, this ratio is directly affected by the substitution of the allylic intermediate **B.17**.



Scheme 1.29. Formation of the allylic boronic acid intermediate **B.17**.

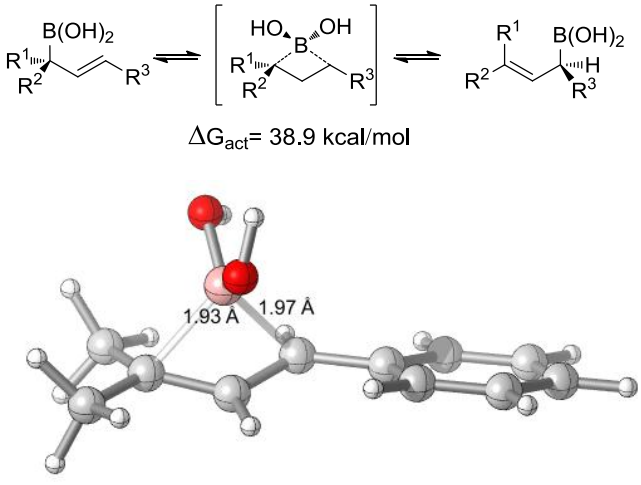
A possible explanation for the influence of the substituents on the protodeboronations could be based on the relative stabilization of the partial negative charge that is developed in this process. As is shown in Scheme 1.30, when the reaction is carried out with styrylboronic acid, the generated incipient negative charge is stabilized at benzylic position favouring the γ-protodeboronation (*Route **a***). In consequence, the trisubstituted olefin is obtained as major product of the reaction. In contrast, when 2-alkyl alkenyl boronic acids are employed (*Route **b***), that effect does not exist and therefore, α-protodeboronation might take place. In this case, the stereochemistry of double bond of the starting boronic acid is retained. Similarly, the presence of electronwithdrawing groups in the hydrazone (R^1 = CO_2Me or CONHR) will stabilize the incipient negative charge at the α position, favouring the α-protodeboronation. In these cases, the combination of both effects will determine the final outcome. The reactions with alkyl substituted boronic acids are completely regioselective. However, the reactions with aryl substituted boronic acids, in which to opposing effects take place, give rise to 1:1 mixtures of positional isomers. A summary of the influence of the different substiuents is presented in Scheme 1.30.

[132] Computational studies carried out in our lab indicate that the boronate is indeed a transition state and not an intermediate in the potential energy surface.



Scheme 1.30. Influence of the substitution of intermediate **XXXI** in the protodeboronation step.

Other plausible explanation would be that the allylboronic acid intermediate could undergo a reversible borotropic-[1,3]-rearrangement and the subsequent protodeboronation might give rise to the corresponding final products (Scheme 1.31). However, computational studies carried out by our research group suggest that the activation free energy for this equilibrium is very high (**ΔGact** = 39.8 kcal·mol^{-1}) and in consequence, it is not expected to occur spontaneously.



Scheme 1.31. Proposed mechanism through borotropic-[1,3]-rearrangement and representation of the transition state. Theoretical studies computed at the b3lyp/6-31++G(2d,2p) level.

To understand the diastereoselectivity of the reaction, computational studies have been carried out with a 4-substituted cyclohexanone. It has been previously shown by Aggarwal[128] that the protodeboronation step occurs with retention of configuration and the hydrogen atom is incorporated at the position occupied by the boron atom. With this consideration, the stereochemistry should be defined in the initial step, when the C-B and the C-C bond are formed. For this reason, the modeling studies were focused on this particular step. The calculations have been performed using the density functional theory (DFT), employing the functional b3lyp and the 6-31++G(2d,2p) basis functions. The selected model for the calculation is shown in Figure 1.3. Two different transition states were located, that corresponded to the approach of the alkenyl boronic acid to the *in situ* generated diazo compound following either equatorial or axial trajectories. Attending to the difference in activation free energy between both transition states (**TSax**= 31.1 Kcal/mol, **TSeq**= 26.3 Kcal/mol), it can be determined that the equatorial approach is energetically more stable than the axial one. Therefore, the alkenyl group should occupy the equatorial position at the end of the reaction, in agreement with the diastereoselectivity experimentally observed.

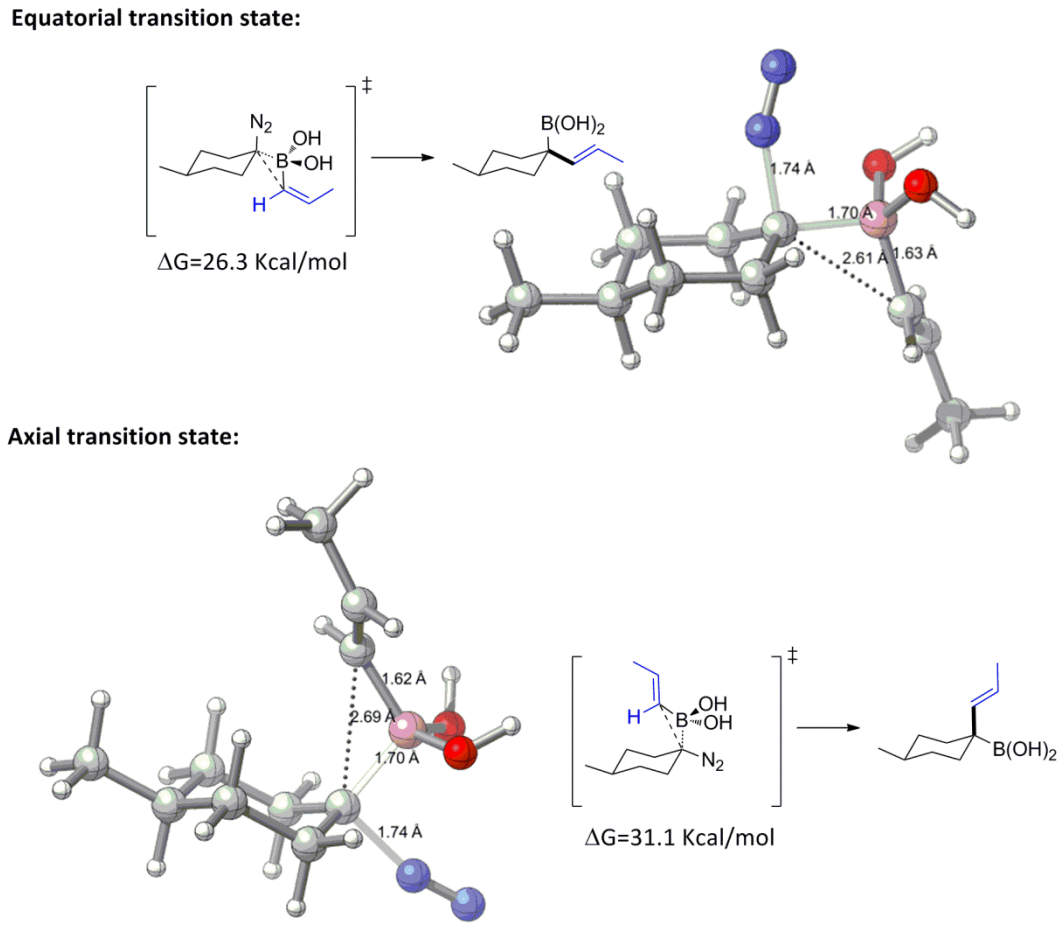


Figure 1.3. Representation of the transition states corresponding to the different approaches of the alkenyl boronic acid to the diazocompound computed by b3lyp/6-31++G(2d,2p). Relevant atom distances in Å are shown.

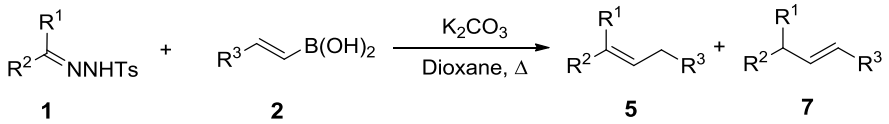
1.2.3.8. Reductive coupling of alkenyl boronic acids: A predictable reaction.

Attending to the results obtained throughout this section, it would seem quite obvious that the double bond positional isomer obtained depends on the substituents of both coupling partners. In fact, the nature of this reagent has a dramatic influence on the regioselectivity of the process. Very importantly, the final outcome of the reaction

could be determined beforehand in ***a predictable way*** by considering the substituents on the alkenylboronic acid and the tosylhydrazone.

Based on our experimental results, we have built a table(Table 1.6) to represent the double bond positional isomer which is expected considering the substituents of both coupling partners. It must be highlighted, that many combinations afford one major or unique isomer.

Table 1.6. Summary of the expected product distribution depending on the substituents of the coupling partners.



1 **2** **5** **7**

R^1	**R^2**	**R^3**	**5**	**7**
Alkyl	Aryl	Aryl	**95-90**	5-10
Alkyl	Alkyl	Aryl	**100**	0
Aryl	Aryl	Aryl	**100**	0
Alkyl	COX	Aryl	50	50
Alkyl	Aryl	Alkyl	50	50
Alkyl	Alkyl	Alkyl	5-10	**95-90**
Alkyl	COX	Alkyl	0	**100**

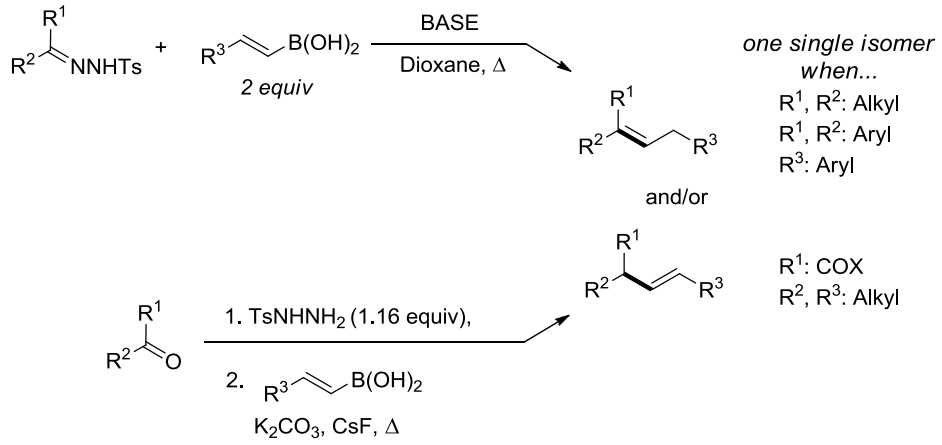
1.3. CONCLUSIONS

In Chapter 1, it has been described a very general and simple reductive coupling between tosylhydrazones and alkenyl boronic acids, both ready available or commercial reagents. The reactions take place in the presence of a base, and do not require any transition metal catalyst. Depending on the substituents of both coupling partners, olefination of reductive alkenylation products are obtained.

It is remarkable that the reaction depends exclusively on the nature of the substituents and allows to predict beforehand the isomer obtained.

From a synthetic point of view, these transformations could be envisioned as new type of olefination and reductive alkylations of carbonyl compounds, a very useful methodologies in Organic Chemistry. Furthermore, the process does not need the inert atmosphere and could be carried out in a one-pot fashion directly from the carbonyl reagent.

1.4. GRAPHIC SUMMARY



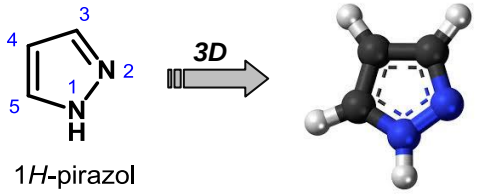
Capitulo 2

Síntesis de pirazoles polisustituidos

2.1. INTRODUCCIÓN

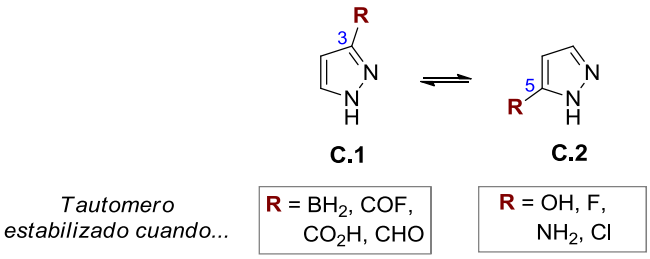
2.1.1. Pirazoles. Características generales.

Los pirazoles son estructuras muy importantes en Química Orgánica perteneciente a la familia de los 1,2-azoles. Concretamente, estos compuestos son heterociclos de cinco eslabones con dos nitrógenos adyacentes y en su mayoría, son sólidos estables (Esquema 2.1).



Esquema 2.1. Estructura, numeración y representación en tres dimensiones de la molécula del pirazol.

Desde el punto de vista estructural, existe una tautomería anular del N-H del ciclo de considerable importancia. Si el pirazol no se encuentra sustituido, la migración del H da lugar a estructuras idénticas debido a la simetría de la propia molécula. Sin embargo, cuando el ciclo se encuentra sustituido en las posiciones 3 o 5 se observan dos formas tautómeras (Esquema 2.2). La estabilización de un tautómero sobre otro depende exclusivamente de la sustitución del propio anillo. Así, por ejemplo, los sustituyentes atractores de electrones hacen que predomine la especie **C.1**.



Esquema 2.2. Tautomeria en pirazoles asimétricamente sustituidos.

Aunque el anillo de pirazol raramente está presente en productos naturales, son moléculas que juegan un papel muy importante en la industria química, farmacéutica y agroquímica.[133] Los derivados de pirazol poseen un amplio rango de actividades

[133] J. Elguero, P. Goya, N. Jagerovic, A. M. S. Silva en *Targets in Heterocyclic Systems* (Eds: O. A. Attanasi, D. Spinelli), Royal Society of Chemistry, Cambridge, **2002**, Vol. 6, pag. 52.

biológicas y en consecuencia, son empleados como analgésicos, antiinflamatorios, antipiréticos, antiarrítmicos, antifúngicos, antibacterianos o tranquilizantes. Por ejemplo, el sildenafil[134] se comercializó como Viagra® contra la disfunción eréctil, el celecoxib[135] es un inhibidor selectivo de la enzima COX-2 y se emplea como potente antiinflamatorio no esteroideo en tratamientos contra la artritis reumatoide y artritis osea, y el lonazolac[136] como analgésico con propiedades antipiréticas (Figura 2.1). También, los derivados de pirazol se han empleado en tratamientos para la ansiedad, contra el Alzheimer, psoriasis o asma.

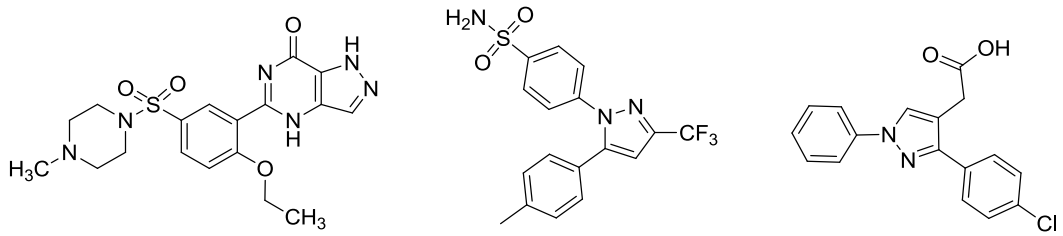


Figura 2.1.

Además de las aplicaciones derivadas de sus propiedades biológicas, el esqueleto del pirazol también es utilizado como estructura fundamental en moléculas empleadas en la química supramolecular,[137] en polímeros,[138] como cristales líquidos,[139] en la industria alimentaria y cosmética, así como ligandos para metales de transición.[140] Todos estos usos ponen de manifiesto la gran utilidad y versatilidad que posee el heterociclo de pirazol. Por ello, la búsqueda de nuevas rutas sintéticas eficientes de pirazoles polisustituidos ha generado gran interés y continúa siendo hoy en día de gran actualidad.

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[134] M. Boolell, M. J. Allen, S. A. Ballard, S. Gepi-Attee, G. J. Muirhead, A. M. Naylor, I. H. Osterloh, C. Gingell , *Int. J. Impot. Res.* **1996**, *8*, 47.

[135] T. D. Pening, J. J. Talley,S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton. J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert. A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347.

[136] R. Riedel, *Arzneim.-Forsch.* **1981**, *31*, 655.

[137] a) S. Nieto, J. Pérez, L. Riera, V. Riera, D. Miguel, *Chem. Eur. J.* **2006**, *12*, 2244; b) S. Moyano, J. L. Serrano, A. Elduque, R. Gimenez, *Soft Matter* **2012**, *8*, 6799.

[138] J. A. R. Navarro, B. Lippert, *Coord. Chem. Rev.* **2001**, *222*, 219.

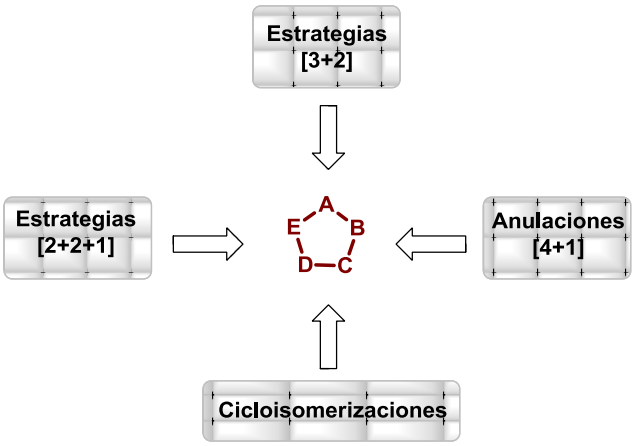
[139] E. Cavero, S. Uriel, P. Romero, J. L. Serrano, R. Giménez, *J. Am. Chem. Soc.* **2007**, *129*, 11608.

[140] (a) O. Das, T. Malakar, A. Mandal, A. Paul, T. K. Paine, *Chem. Asian J.* **2012**, *8*, 623; b) S. O. Ojwach, J. Darkwa, *Inorg. Chim. Acta* **2010**, *363*, 1947; c) X. Deng, N. S. Mani, *Org. Lett.* **2008**, *10*, 1307; d) R. A. Singer, M. Doré, J. E. Sieser, M. A. Berliner, *Tetrahedron Lett.* **2006**, *47*, 3727.

En este contexto está enmarcado el trabajo de investigación que constituye este segundo capítulo. A continuación, se presentará una revisión de los métodos más empleados en la síntesis de pirazoles, así como un breve resumen de su reactividad. Además, en concreto, se presentará una sección dedicada al empleo de las tosilhidrazonas en la construcción de pirazoles polisustituidos. Adicionalmente, debido a la estrecha relación que posee con la discusión mecanística, el reagrupamiento [1,5]-sigmatrópico, en especial en los 3*H*-pirazoles, será discutido en detalle. Finalmente, se mostrarán ejemplos de síntesis de pirazoles que involucran un paso de cicloadición 1,3-dipolar seguido de un reagrupamiento [1,5]-sigmatrópico.

2.1.2. Síntesis de pirazoles.

A la hora de abordar la síntesis de carbociclos y heterociclos de cinco eslabones, se pueden encontrar en la bibliografía cuatro métodos bien diferenciados, como se muestran en el Esquema 2.3.[141]



Esquema 2.3. Estrategias generales para la síntesis de carbociclos y heterociclos de cinco eslabones.

Para acceder al esqueleto de pirazol existe un gran número de posibilidades. Una sencilla revisión de la bibliografía, revela la enorme cantidad de rutas sintéticas y protocolos descritos y estudiados. De este modo, se desvela la gran importancia que posee esta estructura *a priori* tan simple. En primer lugar, la síntesis de pirazoles sustituidos se puede abordar a través de diferentes estrategias: se puede funcionalizar el

[141] a) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Rev.* **2015**, *115*, 5301 y las referencias contenidas en el articulo; b) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366.

anillo de pirazol ya formado, o bien, se puede partir de precursores acíclicos para formar el anillo de pirazol.[142,143] Adicionalmente, los métodos sintéticos se puede clasificar en dos grandes grupos:

- *Métodos convencionales*: anulaciones [3+2] y [4+1],[137a] cicloadiciones intramoleculares,[144] ciclaciones electrofílicas[145] y síntesis a partir de otros heterociclos.[146]
- *Métodos modernos*: reacciones de acoplamiento cruzado catalizados por metales de transición[147] y reacciones multicomponente.[148]

Una revisión exhaustiva de los métodos de síntesis de pirazoles excede los objetivos de esta memoria. En este contexto, existen revisiones recientes muy completas como las que se pueden encontrar en las referencias 10 y 11. En cualquier caso, los métodos basados en la aproximación general [3+2], a través de reacciones de ciclación o cicloadición, han sido los más empleados y los más relacionados con la estrategia que va a ser objeto de estudio de este Segundo Capítulo. Debido a tal similitud, esta revisión se centrará principalmente en estas metodologías. Dentro de las estrategias [3+2] pueden distinguirse dos aproximaciones fundamentales para la construcción del ciclo de cinco eslabones:

- La formación de dos enlaces C-N mediante la condensación de hidracinas con compuestos 1,3-dicarbonílicos o los correspondientes equivalentes 1,3-dielectrófilos (Esquema 2.4, A).[149]
- La generación de un enlace C-N y un enlace C-C mediante cicloadiciones 1,3-dipolares (Esquema 2.4, B).[150]

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[142] S. Fusteros, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev.* **2011**, *111*, 6984.

[143] J. Elguero, A. M. S. Builla, J. Barluenga en *Modern Heterocyclic Chemistry*, Wiley-VCH, Weinheim, **2011**, Vol.2, pag. 635.

[144] a) R. Martín, M. R. Rivero,S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 7079; b) S. J. Hayes, D. W. Knight, M. O'Halloran, S. R. Pickering, *Synlett* **2008**, 2188; c) Y. T. Lee, Y. K. Chung, *J. Org. Chem.* **2008**, *73*, 4698; d) T. Okitsu, K. Sato, A. Wada, *Org. Lett*. **2010**, *12*, 3506.

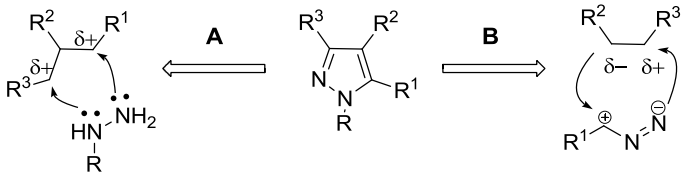
[145] M. Yosimatsu, K. Ohta, N. Takahashi, *Chem. Eur. J.* **2012**, *18*, 15602.

[146] a) D. C. G. A. Pinto, A. M. S. Silva, J. A. S. Cavaleiro, *J. Het. Chem*. **2000**, *37*, 1629; b) T. Tsuchiya, C. Kaneko, H. Igeta, *J. Chem. Soc., Chem. Commun*, **1975**, 528.

[147] a) D. J. Babinski, H. R. Aguilar, R. Still, D. E. Frantz, *J. Org. Chem.* **2011**, *76*, 5915; b) R. Martín, M. Rodríguez-Rivero, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 7079.

[148] a) R. Harigae, K. Moriyama, H. Togo, J. Org. Chem. 2014, 79, 2049; b) H. Liu, H. Jiang, M. Zhang, W. Yao, Q. Zhu, Z. Tang, *Tetrahedron Lett.* **2008**, *49*, 3805; c) B. Willy and T. J. J. Müller, *Eur. J. Org. Chem*. **2008**, 4157; d) M. S. M. Ahmed, K. Kobayashi, A. Mori, *Org. Lett.* **2005**, *7*, 4487; d) M. Adib, B. Mohammadi, H. R. Bijanzadeh, *Synlett*, **2008**, *20*, 3180.

[149] a) J. Elguero en *Comprehensive Heterocyclic Chemistry II*, (Eds: A. R. Katritzky, C. W. Rees, E. F. Scriven), Pergamon Press: Oxford, UK., **1996**, Vol. 3, pag. 1; b) Yet. L. en *Comprehensive Heterocyclic Chemistry III*, (Eds: A. R. Katritzky, C. W. Rees, E. F. V. Scriven, R. J. K. Taylor), Elsevier: Oxford, UK., **2008**, Vol. 4, pag. 1.

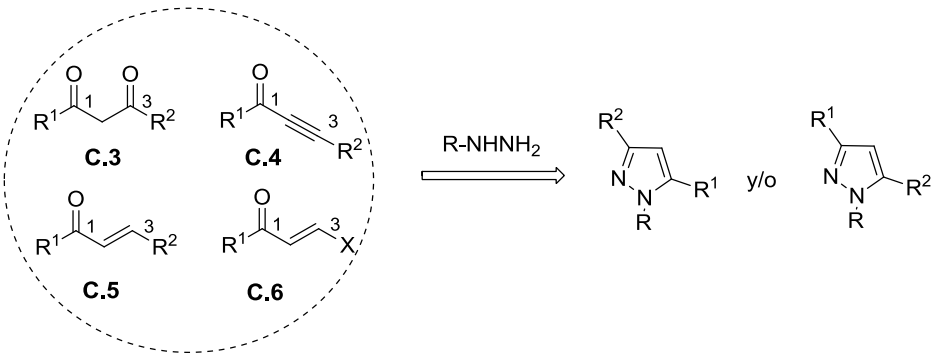


Esquema 2.4. Estrategias convencionales para sintetizar el anillo de pirazol.

A continuación, se va a realizar una breve revisión de los métodos más generales encontrados en la literatura que permiten acceder a la construcción de este heterociclo.

2.1.2.1. Ciclocondensaciones de 1,3-dielectrófilos con hidracinas.

Una de las rutas más versátiles y empleadas en la síntesis de pirazoles es la adición de hidracinas, las cuales actúan como doble nucleófilo, a unidades de tres átomos de carbono que poseen dos carbonos electrófilos en relación 1,3. Dentro de esta metodología, el empleo de compuestos 1,3-dicarbonílicos como β-cetoaldehidos, β-cetoésteres, β-cetoamidas o β-cetonitrilos (Esquema 2.5, **C.3**), ha sido la ruta comúnmente seguida para generar el anillo de pirazol. Además, existen otros compuestos 1,3-dielectrófilos equivalentes que también reaccionan con hidracinas para dar pirazoles, como son los compuestos carbonílicos α,β-insaturados y sus derivados (Esquema 2.5, **C.4**, **C.5**, **C.6**).[151]



Esquema 2.5. Representación de los compuestos 1,3-dielectrófilos que se pueden emplear en la síntesis de pirazoles.

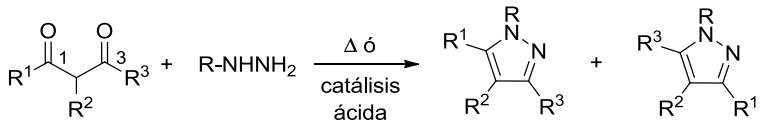
[150] A. Padwa, W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry towards Heterocycles and Natural Products*, John Wiley and Sons, New York, **2002**.

[151] a) B. A. Bhat, S. C. Puri, M. A. Qurishi, K. L. Dhar, G. N. Qazi, *Synth. Commun.* **2005**, *35*, 1135; b) O. Prakash, D. Sharma, R. Kamal, R Kumar, R. R. Nair, *Tetrahedron* **2009**, *65*, 10175.

Sin embargo, en algunos casos, el empleo de 1,3-dielectrófilos presenta ciertas limitaciones como es el acceso a los reactivos de partida apropiados y principalmente, la regioselectividad que presenta el proceso.[152] De este modo, cuando se usan 1,3-dielectrófilos sustituidos asimétricamente se obtienen los dos regioisoméros posibles del pirazol como se muestra en el Esquema 2.5.

2.1.2.1.A. Compuestos 1,3-dicarbonílicos.

Los compuestos 1,3-dicarbonílicos se condensan con hidracinas para dar pirazoles sustituidos tanto con restos alquilos como con restos arilos (Esquema 2.6).



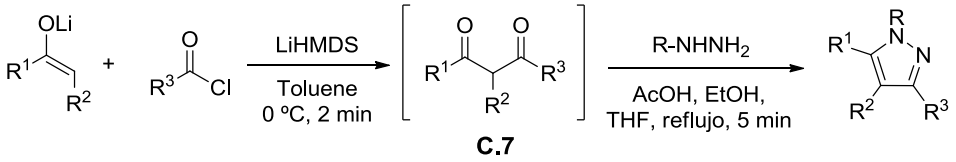
Esquema 2.6. Esquema general para la síntesis de pirazoles a partir de compuestos 1,3-dicarbonílicos.

En la mayoría de las síntesis descritas, los compuestos 1,3-dicarbonílicos empleados necesitan ser preparados con anterioridad y además, purificados convenientemente. Esta desventaja se suma a las mezclas de regioisomeros obtenidas en los productos finales después de la condensación. No obstante, en los últimos años han emergido numerosos métodos orientados a mejorar la eficiencia de los procesos descritos con anterioridad.[138]

En este contexto, Heller y Natarajan[153] han desarrollado un método *one-pot* para sintetizar pirazoles 3,5- ,1,3,5- y 3,4,5- sustituidos de una forma eficiente, rápida y muy general. Para generar el compuesto dicarbonilo intermedio **C.7**, se emplean como producto de partida cetonas enolizables y cloruros de ácido (Esquema 2.7). De esta manera, el intermedio no es aislado sino que seguidamente se añade la hidracina apropiada.

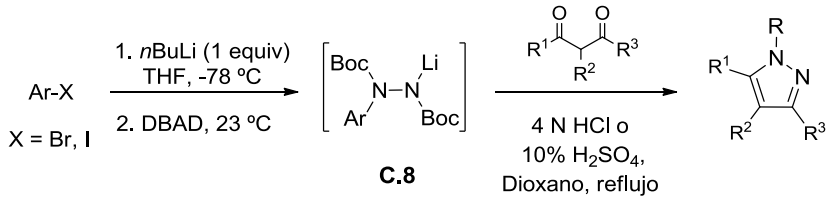
[152] El estudio de la propia regioselectividad del proceso así como la influencia de las condiciones de reacción, los efectos estéricos y electrónicos se encuentran recogidos en los siguientes trabajos: a) S. R. Singh, D. Kumar, H. Batra, R. Naithani, I. Rozas, J. Elguero, *Can. J. Chem.* **2000**, *78*, 1109; b) S. K. Singh, M. S. Reddy, S. Shivaramakrishna, D. Kavitha, R. Vasudev, J. M. Babu, A. Sivalakshmidevi, Y. K. Rao, *Tetrahedron Lett*. **2004**, *45*, 7679; c) N. C. Duncan, C. M. Garner, T. Nguyen, F. Hung, K. Klausmeyer, *Tetrahedron Lett*. **2008**, *49*, 5766.

[153] S. T. Heller, S. R. Natarajan, *Org. Lett*. **2006**, *8*, 2675.



Esquema 2.7. Síntesis *one-pot* de pirazoles 3,5- ,1,3,5- y 3,4,5- sustituidos a partir de cetonas enolizables y cloruros de ácido.

Estas metodologías requieren el acceso a la arilhidracina sustituida de forma adecuada y en ocasiones, cuando no son comerciales, su síntesis requiere numerosos pasos de reacción. Además, la hidracina libre no es compatible con otros grupos funcionales presentes en el medio. Como alternativa, se propuso otra ruta sintética, llevada a cabo de nuevo de forma *one-pot*, basada en la ciclocondensación de compuestos 1,3-dielectrófilos con arilhidracinas bis-Boc protegidas, para dar lugar a *N*-arilpirazoles sustituidos (Esquema 2.8).[154]



Esquema 2.8. Síntesis *one-pot* de *N*-arilpirazoles halogenuros de arilos, di-*tert*-butilazodicarboxilato y compuestos 1,3-dicarbonílicos.

De este modo, la síntesis consta de dos pasos. En primer lugar, para generar el intermedio **C.8**, se produce un intercambio metal-halogeno en el halogenuro de arilo seguido del tratamiento con di-*tert*-butilazodicarboxilato como fuente para generar la hidracina. En segundo lugar, para obtener el pirazol deseado, este intermedio **C.8** es desprotegido *in situ* usando una disolución de HCl o H_2SO_4 en dioxano en presencia del compuesto 1,3-dicarbonílico. Este procedimiento *one-pot* se puede llevar a cabo con 1,3-dialdehidos, 1,3-dicetonas, β-aminoacroleinas y β-aminovinilmetilcetonas.

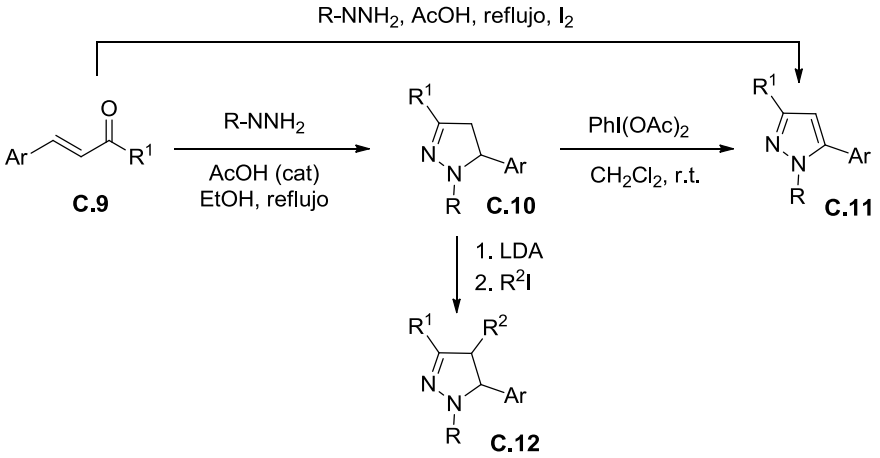
El empleo de compuestos 1,3-dicarbonílicos para sintetizar pirazoles altamente sustituidos también ha experimentado un desarrollo tanto en fase sólida[155] como en ausencia de disolventes.[156] Estos últimos, son procesos muy deseables en Química Orgánica debido a que se reducen costes, son métodos más seguros y en consecuencia, más beneficiosos con el medio ambiente.

[154] B. S. Gerstenberger, M. Rauckhorst, J. T. Starr, *Org. Lett.* **2009**, *11*, 2097.
[155] D.-M. Shen, M. Shu, K. T. Chapman, *Org. Lett.* **2000**, *2*, 2789.
[156] Z.-X. Wang, H.-L. Qin. *Green Chem.* **2004**, *6*, 90.

2.1.2.1.B. Compuestos α,β-insaturados y derivados.

En general, los compuestos α,β-insaturados se condensan regioselectivamente con hidracinas generando pirazolinas, las cuales deben ser oxidadas posteriormente para dar lugar a los correspondientes pirazoles.

En este contexto, se ha descrito una síntesis de pirazoles **C.11** partiendo de calconas (1,3-diaril-2-propen-1-ona) **C.9** e hidracinas, a través de una secuencia consistente en una ciclocondensación en presencia de cantidades catalíticas de ácido acético glaciar, para dar la pirazolina intermedia **C.10** y a continuación, un paso de oxidación en presencia de I(III) (Esquema 2.9). La reacción puede transcurrir en dos pasos aislando el intermedio de la pirazolina[157] o a través de un proceso *one-pot*.[158,159] Además, la posición 4 del anillo de pirazolina puede ser alquilada o arilada empleando LDA como base seguido de la adición de un yoduro de alquilo o arilo generando el intermedio **C.12**.[160] Este intermedio mediante una etapa de oxidación daría lugar al correspondiente pirazol tetrasustituido.

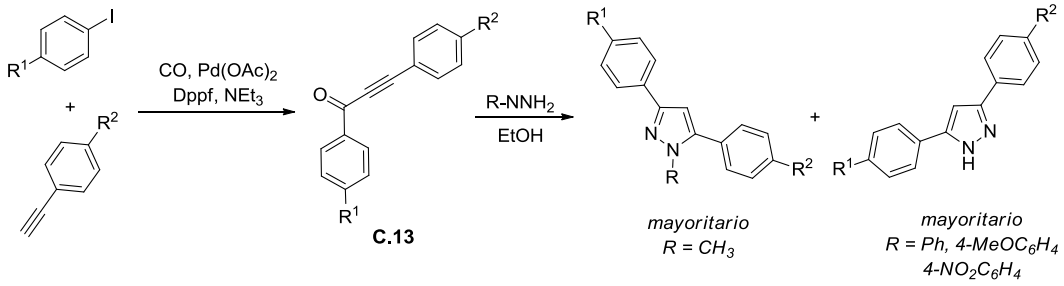


Esquema 2.9. Síntesis por pasos y *one-pot* de anillo de pirazol empleando compuestos α,β-insturados.

La síntesis de pirazoles sustituidos en las posiciones 1,3- y 1,5- a partir de alquinil cetonas terminales e hidracinas ha sido ampliamente estudiada. Sin embargo, la regioselectividad de estos procesos es altamente dependiente de las condiciones de

[157] Prakash, A. Kumar, M. Kinger, S. P. Singh, *Indian J. Chem.* **2006**, *45B*, 456.
[158] S. Ponnala, D. P. Sahu, *Synth. Commun.* **2006**, *36*, 2189.
[159] X. Zhang, J. Kang, P. Niu, J. Wu, W. Yu, J. Chang, *J. Org. Chem.* **2014**, *79*, 10170.
[160] Y. R. Huang, J. A. Katzenellenbogen, *Org. Lett.* **2000**, *2*, 2833.

reacción empleadas.[161,162] Por otro lado, el empleo de alquinil cetonas sustituidas en el triple enlace da lugar a la síntesis regioselectiva y simple de pirazoles 1,3,5-trisustituidos.[163] Las correspondientes alquinil cetonas de partida **C.13** son previamente preparadas a través de una carbonilación catalizada por paladio entre yoduros de arilo y fenilacetileno (Esquema 2.10). La regioselectividad observada se debe a que en primer lugar, se produce una adición conjugada 1,4 del nitrógeno más nucleofílico de la hidracina al triple enlace. A continuación, se produce una ciclación 5-exo-*trig* del otro nitrógeno de la hidracina al grupo carbonilo, que tras la consiguiente deshidratación conduce al pirazol final. Es de resaltar que en esta reacción la naturaleza del sustituyente está íntimamente relacionada con la regioselectividad obtenida.



Esquema 2.10. Síntesis de pirazoles 1,3,5-trisustituidos a partir de yoduros de arilo y los correspondientes fenilacetilenos.

2.1.2.1.C. Compuestos α,β-insaturados que poseen un grupo saliente.

Las vinilcetonas β-alcoxi y β-aminosutituidas son equivalentes sintéticos de compuestos 1,3-dicarbonílicos, por ello, han sido muy empleados en la síntesis de pirazoles.

De este modo, una familia de pirazoles 4,5-disustituidos ha sido sintetizada a partir de β-dimetilaminovinilcetonas y sulfato de hidracina empleando ácido *p*-toluensulfónico como catalizador en un proceso que transcurre en ausencia de disolventes (Esquema 2.11).[164]

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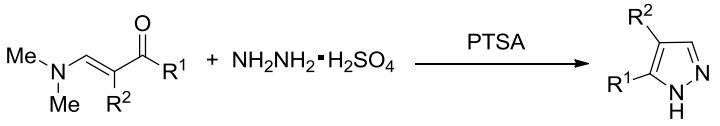
[161] a) A. Engelmann, W. Kirmse, *Chem. Ber.* **1973**, *106*, 3092; b) R. D. Miller, O. J. Reiser, *Heteroclyc. Chem*. **1993**, *30*, 755; c) R. M. Adlington, J. E. Baldwin, D. Catterick, G. J. Pritchard, L. T. Tang, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2311.

[162] M. C. Bagley, M. C. Lubinu, C. Mason, *Synlett*, **2007**, 704.

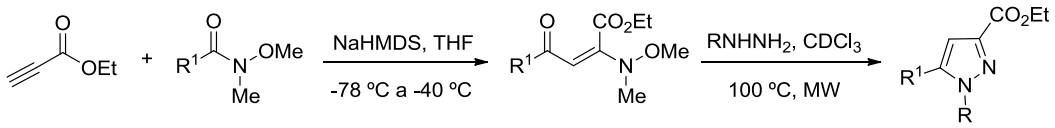
[163] B. C. Bishop, K. M. J. Brands, A. D. Gibb, D. J. Kennedy, *Synthesis* **2004**, 43.

[164] K. Longhi, D. N. Moreira, M. R. B. Marzari, V. M. Floss, H. G. Bonacorso, N. Zanatta, M. A. P. Martins, *Tetrahedron Lett*. **2010**, *51*, 3193.



Esquema 2.11. Síntesis de pirazoles 4,5-disustituidos a partir de β-dimetilaminovinilcetonas y sulfato de hidracina

Como una extensión interesante del método anterior, las amidas de Weinreb también han sido empleadas por Persson y Nielsen para generar pirazoles sustituidos en la posición 3 por un grupo carboxilato de alquilo[165] de una forma totalmente regioselectiva (Esquema 2.12).[166] El paso clave de la síntesis es la generación del compuesto carbonílico α,β-insaturado intermedio, el cual, es el que sufre posteriormente la reacción de la condensación con la hidracina.



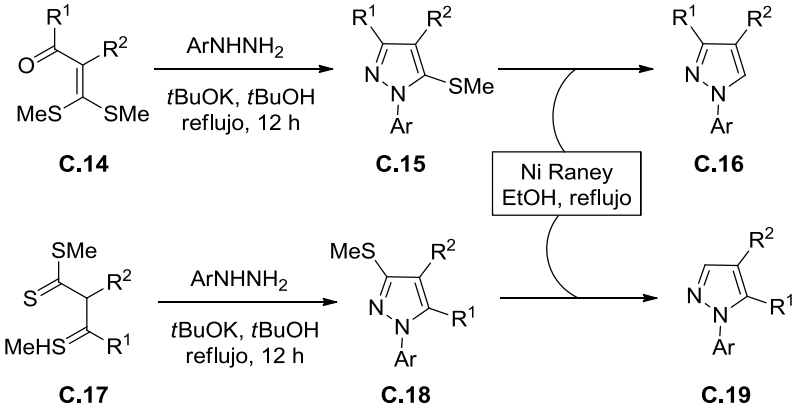
Esquema 2.12. Síntesis de pirazoles sustituidos por un grupo carboxilato empleando de amidas de Weinreb.

Los pirazoles sustituidos con heteroátomos tales como restos sulfuros, trialquilsililos o halógenos, son estructuras muy interesantes debido a la fácil eliminación o sustitución de estos grupos por sustituyentes tanto carbonados como heterocarbonados una vez formado el anillo. Así, a partir de la condensación de arilhidracinas con los ditioacetales **C.14** y los β-oxoditioésteres **C.17**, se pueden obtener los pirazoles 1-aril-3,4-sustituido-5-tiometil **C.15** y 1-aril-3-tiometil-4,5-sustituido **C.18** respectivamente. La correspondiente desulfuración empleando Ni Raney da lugar de forma regioselectiva a los pirazoles **C.16** y **C.19** que poseen diferente patrón de sustitución (Esquema 2.13).[167]

[165] Estos pirazoles-3/5-carboxilatos sustituidos son muy importantes en la industria farmaceutica debido a que presentan actividad biológica: Y. L. Janin, *Mini-Rev Org. Chem.* **2010***, 7*, 314.

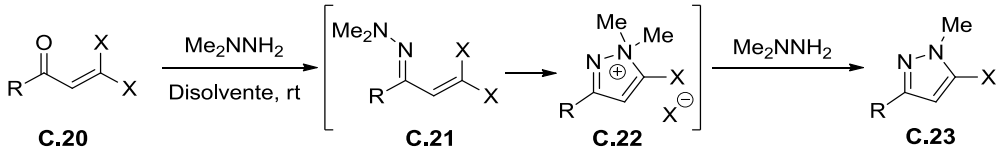
[166] T. Persson, J. Nielsen*, J. Org. Chem*. **2006**, *8*, 3219.

[167] S. Peruncheralathan, T. A. Khan, H. Ila, H. Junjappa, *J. Org. Chem.* **2005**, *70*, 10030.



Esquema 2.13. Síntesis de pirazoles sustituidos en las posiciones 3,4- y 4,5 a partir del compuesto ditioacetal **C.14** y el β-oxoditioester **C.17**.

Por último, los halopirazoles son accesibles a partir de la reacción entre 1,1-dimetilhidracina y las β,β-dihaloenonas **C.20**. El mecanismo de la reacción comenzaría con la formación de la hidrazona **C.21**, seguido de un ataque nucleófilo intramolecular del grupo dimetilamino al C beta de grupo vinilo para dar **C.22**. La correspondiente desmetilación de este intermedio daría lugar al pirazol final **C.23** (Esquema 2.14).[168]



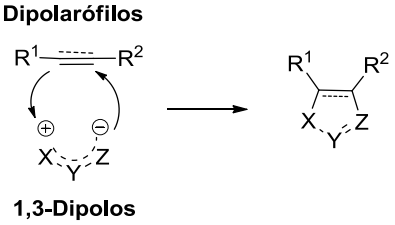
Esquema 2.14. Síntesis de pirazoles sustituidos con un átomo de halógeno.

La presencia de un sustituyente halógeno en el anillo de pirazol resulta muy atractivo desde el punto de vista sintético. Esto es debido a que se puede llevar a cabo la sustitución de ese átomo a través de reacciones de acoplamiento cruzado catalizadas por metales de transición. De hecho, las reacciones de acoplamiento cruzado son consideradas, hoy en día, como uno de los métodos más populares a la hora de sintetizar pirazoles polisustituidos de forma regioselectiva. Este tipo de reacciones serán vistas en la Sección 2.1.3.

[168] G. G. Levkovskaya, G. V. Bozhenkov, L. I. Larina, A. N. Mirskova, Russ. *J. Org. Chem.* **2002**, *38*, 1501.

2.1.2.2. Cicloadiciones 1,3-dipolares.

Las cicloadiciones 1,3-dipolares constituyen uno de los métodos más empleados y versátiles en la obtención de pirazoles sustituidos (Esquema 2.15).



Esquema 2.15. Esquema general para las adiciones 1,3-dipolares.

De un modo más concreto, existen tres tipos de 1,3-dipolos útiles en la síntesis de pirazoles (Figura 2.2), los cuales contribuyen con el fragmento [*CNN*]: diazoalcanos, nitriliminas e iluros de azometano. El fragmento [*CC*] restante proviene del dipolarófilo que puede ser un alqueno o alquino con la funcionalización apropiada.

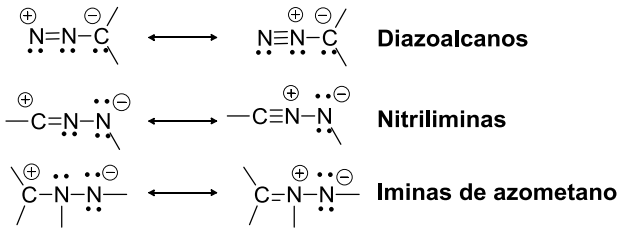


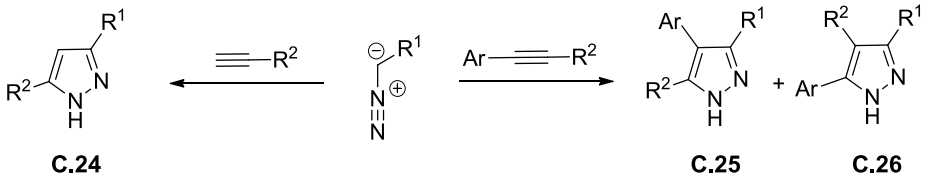
Figura 2.2. Clases de 1,3-dipolos empleados en las cicloadiciones 1,3-dipolares.

Si compramos esta metodología con la ciclocondensación, las cicloadiciones dipolares son reacciones intrínsecamente más regioselectivas debido a que la polarización tanto del dipolo como del dipolarófilo determinan la orientación en la reacción de cicloadición.

2.1.2.2.A. Diazoalcanos.

La reacción entre diazoalcanos y diferentes alquinos terminales da lugar a los pirazoles **C.24** con alta regioselectividad. En este caso, la regioselectividad viene dada por la polarización del triple enlace. Así, el carbono más nucleofílico del dipolo reacciona con el carbono terminal del alquino. Por el contrario, empleando alquinos internos da lugar a una mezcla entre diferentes pirazoles **C.25** y **C.26**. La regioselectividad, en este

caso, depende fuertemente de la sustitución del diazocompuesto empleado (Esquema 2.16).[169]

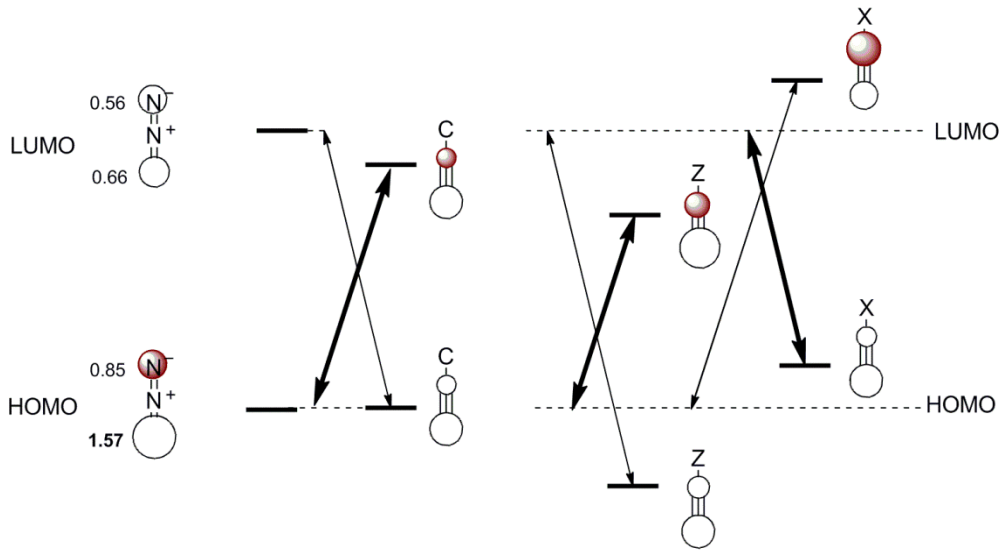


Esquema 2.16. Síntesis de pirazoles empleando diazoalcanos y alquinos terminales e internos.

La regioquímica en las reacciones de cicloadición 1,3-dipolar entre diazo compuestos y alquinos se puede explicar de forma satisfactoria a partir de la teoría de los orbitales moleculares frontera (TOMF). En la TOMF se asume que los procesos de cicloadición 1,3-dipolar se encuentran controlados por la interacción entre el HOMO del dipolo y el LUMO del dipolarófilo, o bien al contrario, dependiendo de las energías relativas de los orbitales frontera de ambas especies (Esquema 2.17). En la mayoría de los casos, la diferencia de energía $HOMO_{dipolo}$-$LUMO_{dipolarófilo}$ es más pequeña, y por tanto, la interacción entre dichos orbitales es dominante. Esto ocurre para alquinos con sustituyentes de tipos Z (electrón atractores) o de tipo C (sistemas conjugados). En estos casos, la regioquímica de las cicloadiciones, vendrá determinada por la polarización de los orbitales frontera responsables de la interacción dominante: HOMO del diazocompuesto y LUMO del alquino. Como se muestra en Esquema 2.17, los diazocompuestos presentan el coeficiente mayor del HOMO sobre el átomo de carbono, mientras que los alquinos terminales C y Z sustituidos presentan el coeficiente mayor del LUMO en su posición terminal. La interacción entre los átomos con los coeficientes de mayor tamaño en HOMO y LUMO, respectivamente de ambas especies, determinan la estereoquímica observada en las reacciones. Finalmente, en el caso de alquinos X-sustituidos, tales como inaminas o inoléteres, se esperaría que la reacción fuese controlada por la interacción contraria: $LUMO_{dipolo}$-$HOMO_{dipolarófilo}$, que debido a la polarización de dichos orbitales, daría lugar también a la misma regioquímica.

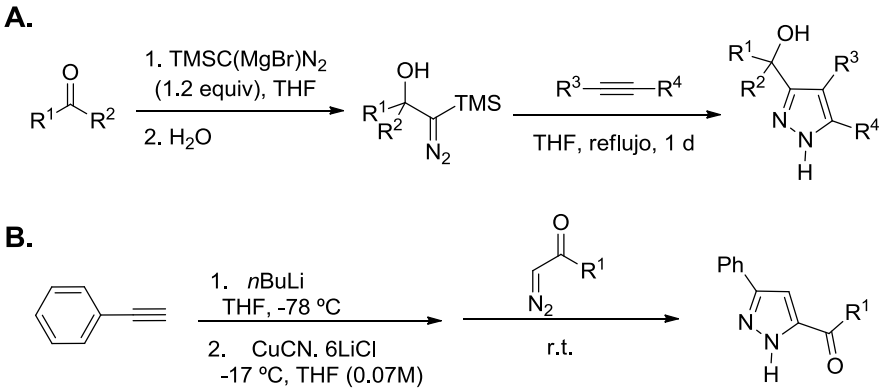
En efecto, en la reacciones entre diazocompuestos y alquinos terminales se obtiene el regioisómero predicho por la teoría de orbitales moleculares frontera, donde tiene lugar la formación del enlace C-C entre la posición terminal del alquino y el átomo de carbono del diazocompuesto.

[169] a) J. Bastide, O. Henri-Rousseau, L. Aspart-Pascot, *Tetrahedron* **1974**, *30*, 3355 ; b) T. Sasaki, K. Kanematsu, *J. Chem. Soc. C* **1971**, 2147.



Esquema 2.17. Representación de los orbitales frontera para un diazocompuesto y un alquino.[170]

En la literatura se pueden encontrar numerosas cicloadiciones entre diferentes diazocompuestos estabilizados y alquinos. Así, por ejemplo, se han utilizado diazocompuestos α-trimetilsililados (Esquema 2.18.**A**)[171] y compuestos α-diazocarbonilicos (Esquema 2.18.**B**)[172] para acceder a la síntesis de compuestos tri- y di-sustituidos, respectivamente.

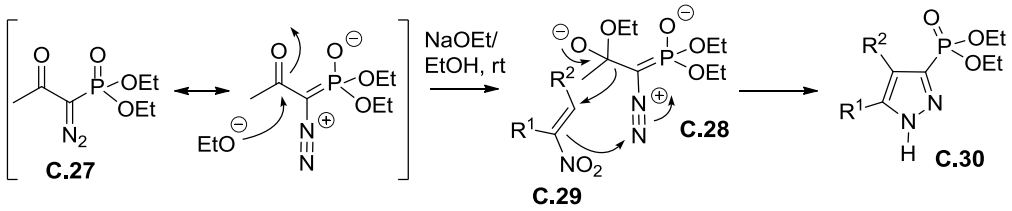


Esquema 2.18. Síntesis de pirazoles a partir de diazocompuestos estabilizados.

Además del empleo de alquinos como dipolarófilos, las olefinas han sido empleadas con este fin. En concreto, se han elegido olefinas sustituidas con grupos

[170] I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Wiley and Sons, Chichester, UK, **2010**.
[171] Y. Hari, S. Tsuchida, R. Sone, T. Aoyama, *Synthesis* **2007**, 3371.
[172] X. Qi, J. M. Ready, *Angew. Chem. Int. Ed.* **2007**, *46*, 3242.

aceptores de electrones debido a que suministran mejores rendimientos que aquellas que poseen un grupo dador.[173] En este contexto, se ha llevado a cabo una cicloadición 1,3-dipolar *one-pot* del anión de 1-diazometilfosfonato de etilo **C.28** con nitro olefinas **C.29** para dar los fosfonilpirazoles de forma totalmente regioselectiva **C.30**. El 1,3-dipolo **C.28** es generado *in situ* a partir del reactivo de Bestman-Ohira **C.27**. Las reacciones son llevadas a cabo en presencia de NaOEt como base nucleófila en un disolvente prótico como es el etanol. En estas condiciones, se produce la pérdida espontánea del grupo nitro (Esquema 2.19).[173b]



Esquema 2.19. Síntesis de fosfonilpirazoles a partir del reactivo de Bestman-Ohira y nitroolefinas.

Como ya se comentó en la Introducción General, los diazocompuestos presentan la desventaja que son difíciles tanto de manejar como de preparar. Esto es debido a la toxicidad que presentan y a su naturaleza explosiva. Un método muy conveniente y empleado ha sido la utilización de las tosilhidrazonas como precursoras para generar *in sit*u diazocompuestos. Debido a que las tosilhidrazonas son el hilo conductor de esta tesis, su papel en la síntesis de pirazoles será tratado con más detalle en la Sección 2.1.3.

2.1.2.2.B. Nitriliminas.

Las nitriliminas son también intermedios muy interesantes a la hora de sintetizar pirazoles. Estos compuestos se pueden generar *in situ* mediante el tratamiento de haluros de hidrazoilo con una base.

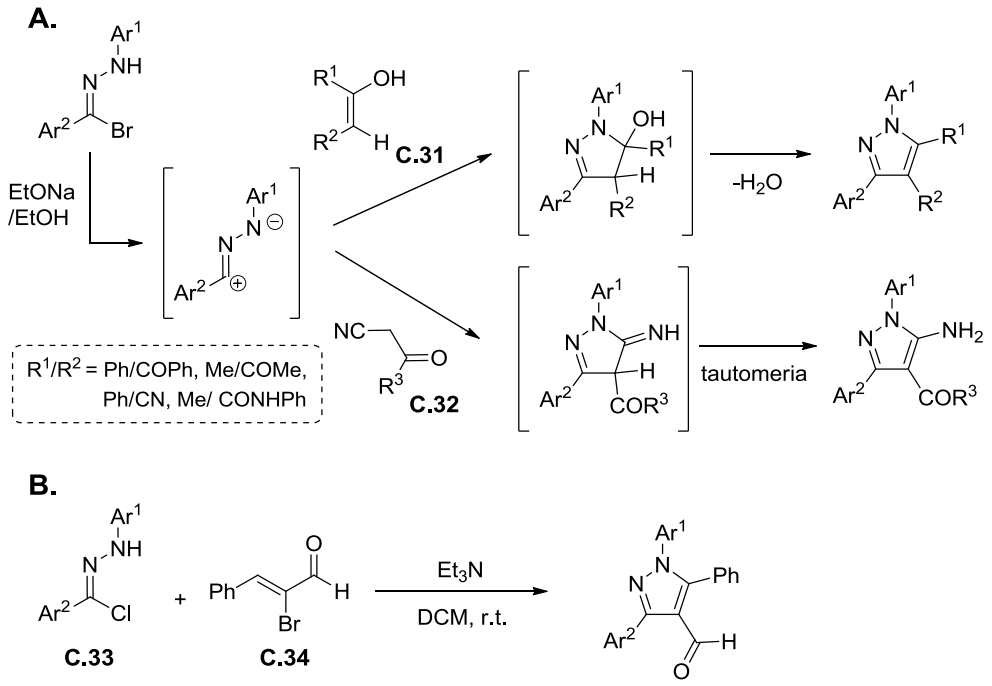
Las nitriliminas permiten el acceso a pirazoles polisustituidos empleando dipolarófilos que posean un grupo que pueda ser eliminado en las propias condiciones de reacción. De este modo, la reacción entre los enoles **C.31** y los compuestos carbonílicos del tipo **C.32** con las correspondientes nitriliminas generadas *in situ* dan lugar a pirazoles 1,3,4,5- tetrasustituidos (Esquema 2.20.**A**).[174,175] Además, también se

[173] a) D. Luvino, C. Amalric, M. Smietana, J.-J. Vasseur, *Synlett* **2007**, 3037; b) R. Muruganantham, S. M. Mobin, N. N. Namboothiri, *Org. Lett.* **2007**, *9*, 1125; c) J.-W. Xie, Z. Wang, W.-J. Yang, L.-C, Kong, D.-C. Xu, *Org. Biomol. Chem.* **2009**, *7*, 4352; d) K. Mohanan, A. R. Martin, L. Toupet, M. Smietana, J.-J, Vasseur, *Angew. Chem. Int. Ed.* **2010**, *49*, 3196.

[174] N. M. Abunada, H. M. Hassaneen, N. G. Kandile, O. A. Miqdad, *Molecules* **2008**, *13*, 1501.

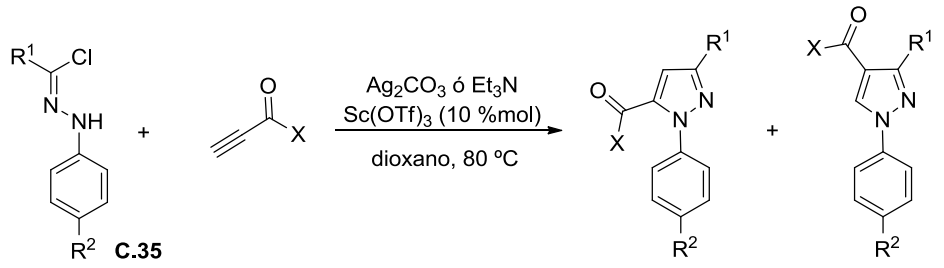
[175] A. Sun, J.-H. Ye, H. Yu, W. Zhang, X. Wang, *Tetrahedron Lett.* **2014**, *55*, 889.

puede acceder a estos pirazoles polisustituidos a través de una cicloadición 1,3-dipolar de forma regioselectiva entre los precursores de las correspondientes nitriliminas **C.33** y bromocinamaldehidos **C.34** (Esquema 2.20.**B**).



Esquema 2.20. Síntesis de pirazoles polisustituidos a partir de nitriliminas y alquenos activados.

Las cicloadiciones entre nitriliminas y derivados de alquinos también han sido descritas, aunque mucho menos extendidas. En este caso, el proceso se lleva a cabo a partir de las nitrilaminas generadas a partir de **C.35** y diferentes propiolatos, empleando un catalizador de Sc. Sin embargo, a pesar de los esfuerzos no se pudo dirigir la reacción a uno sólo de los regioisómeros (Esquema 2.21).[176]



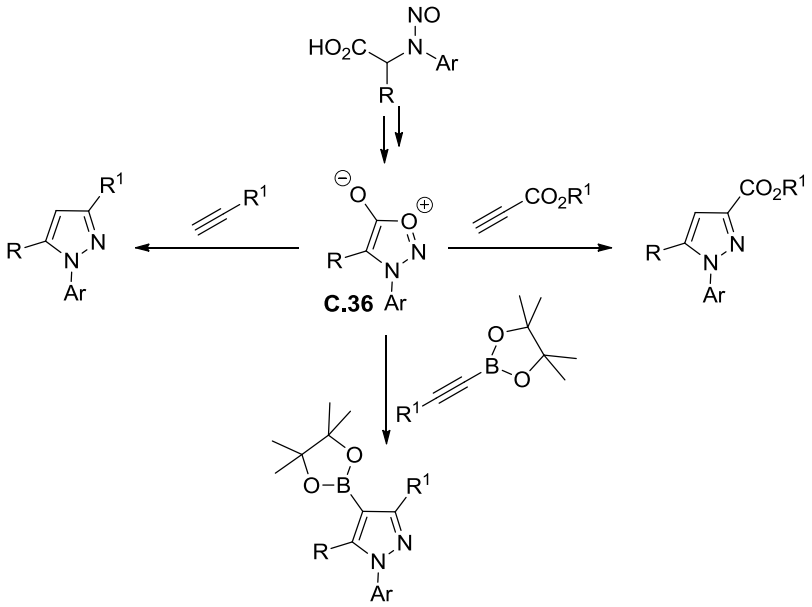
Esquema 2.21. Síntesis de pirazoles a partir de nitriliminas y alquinos.

[176] B. F. Bonini, M. C. Franchini, D. Gentili, E. Locatelli, A. Ricci, *Synlett* **2009**,2328.

2.1.2.2.C. Iminas de azometano: Sidnonas.

Las sidnonas **C.36** son oxadiazoles que tienen un oxígeno en la posición 5. Son compuestos mesoiónicos con carga positiva y negativa deslocalizada. En numerosas ocasiones, se han empleado como dipolos debido a que se pueden sintetizar fácilmente a partir de la ciclodeshidratación de *N*-nitrosoamino ácidos sustituidos en el nitrógeno en presencia de ácido acético.

Estos compuestos experimentan la cicloadición 1,3-dipolar con acetilenos deficientes en electrones para generar pirazoles tras la extrusión de dióxido de carbono (Esquema 2.22).[177]



Esquema 2.22. Síntesis de pirazoles a partir del uso de sidnonas.

Recientemente, estos reactivos han estado involucrados en reacciones catalizadas por metales con el fin de preparar pirazoles con diferentes patrones de sustitución.[178]

[177] a) E.-M. Chang, T.-H Chen, F. F. Wong, E.-C. Chang, M.-Y. Yeh, *Synlett* **2006**, 901; b) R. S. Foster, J. Huang, J. F. Huang, J. F. Vivat, D. L. Browne, J. P. A. Harrity, *Org. Biomol. Chem.* **2009**, *7*, 4052; c) D. L. Browne, J. B. Taylor, A. Plant, J. P. A. Harriry, *J. Org. Chem.* **2010**, *75*, 984.

[178] a) E. Decuypere, S. Specklin, S. Gabillet, D. Audisio, H. Liu, L. Plougastel, S. Kolodych, F. Taran, *Org. Lett.* **2015**, *17*, 362 ; b) E. Decuypere, S. Specklin, S. Gabillet, D. Audisio, H. Liu, L. Plougastel, S. Kolodych, F. Taran, *Org. Lett.* **2015**, *17*, 1062; c) A. W. Brown, J. P. A. Harrity, *J. Org. Chem.* **2015**, *80*, 2467.

2.1.3. Síntesis de pirazoles a partir de *N*-tosilhidrazonas.

El empleo de las *N*-tosilhidrazonas en la síntesis de pirazoles comienza a estar bastante extendido. Así, se pueden encontrar como precursoras de diazocompuestos, tanto en reacciones de cicloadición dipolar como en reacciones de electrociclación, así como componente *NN* o *CNN* en reacciones de ciclocondensación. A continuación, se presenta una revisión de los trabajos más representativos que se han hallado en la literatura. Con el fin de proporcionar una visión completa del estado actual de este campo, se incluyen tanto los trabajos anteriores como los que se han publicado en el transcurso de la realización de esta tesis.

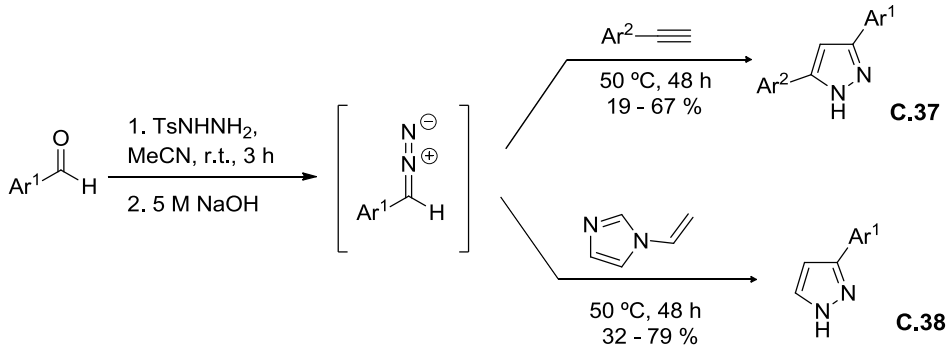
2.1.3.1. Estrategias [3+2] intermoleculares.

Las cicloadiciones 1,3-dipolares entre diazocompuestos y alquinos transcurre de un modo eficiente bajo condiciones térmicas para la preparación de pirazoles. En esta estrategia, debido a las limitaciones que supone el uso de diazocompuestos no estabilizados, se pueden emplear tosilhidrazonas para generarlos *in situ* de forma segura. En consecuencia, el proceso adquiere mayor versatilidad y generalidad puesto que permite utilizar una gama mucho más amplia de diazocompuestos.

En este contexto, en 2003, el profesor Aggarwal y colaboradores[179] describieron una síntesis *one-pot* de 1*H*-pirazoles a partir de tosilhidrazonas derivadas de aldehídos. En este trabajo, los autores proponen dos estrategias a la hora de abordar la preparación de pirazoles. Por un lado, se obtienen los pirazoles disustituidos en las posiciones 3 y 5 **C.37** con una alta regioselectividad cuando se emplea un alquino terminal. Por otro lado, la elección de un equivalente sintético del acetileno terminal, como es el *N*-metilimidazol, da lugar al anillo de pirazol monosustituido en la posición 3 **C.38** (Esquema 2.23). En este caso el proceso implica la reacción de cicloadición seguida de la aromatización por eliminación del imidazol. Es de destacar que en este último caso es muy importante el grupo saliente elegido para obtener el pirazol con rendimientos satisfactorios.[180]

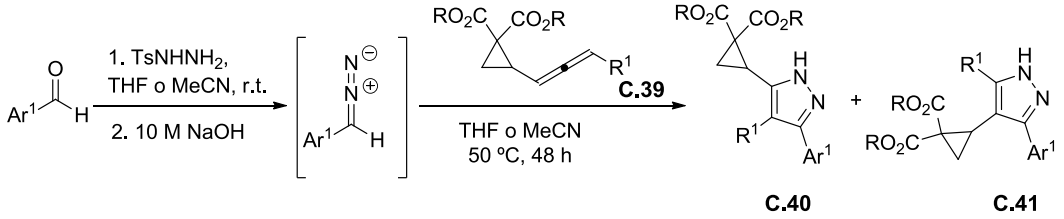
[179] V. K. Aggarwal, J. de Vicente, R. V. Bonnert, *J. Org. Chem.* **2003**, *68*, 5381.

[180] Las reacciones de tosilhidrazonas con un alquino terminal en presencia de CuI como catalizador transcurren de una forma totalmente diferente a aquellas que lo hacen en ausencia del catalizador metálico, dando lugar a alenos: a) Q. Xiao, Y. Xia, H. Li, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 1114; b) F. Ye, X. Ma, Q. Xiao, H. Li, Y. Zhang, J. Wang. *J. Am. Chem. Soc*. **2012**, *134*, 5742.



Esquema 2.23. Síntesis de pirazoles mono y disustituidos empleando aldehídos y acetileno.

Esta misma estrategia en la cual la generación *in situ* del diazocompuesto se lleva a cabo a partir de la descomposición básica de la tosilhidrazona, se ha desarrollado también empleando como equivalentes de alquinos los vinilidenciclopropanos **C.39** (VDCPs) para la obtención de los 1*H*-pirazoles trisustituidos **C.40** y **C.41.**[181] La regioselectividad del proceso depende exclusivamente de la sustitución del VDCP. De este modo, cuando R^1 = H, da lugar a mezclas de pirazoles 3,5- y 3,4-disustituidos, en cambio, cuando R^1 = Ar, la reacción es completamente regioselectiva, observándose como único producto el regioisomero **C.41** (Esquema 2.24).

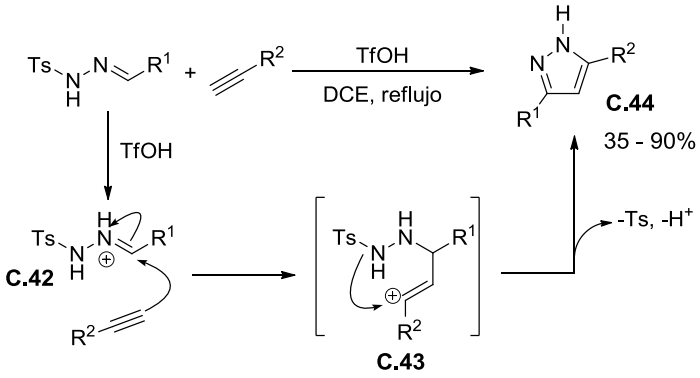


Esquema 2.24. Síntesis de pirazoles tri- y disustituidos a partir de vinilidenciclopanos y tosilhidrazonas.

Como equivalentes de triples enlaces, también se han empleado *gem*-dibromoalquenos para generar *in situ* en medio básico bromoalquinos, los cuales reaccionan con el diazocompuesto, que se encuentra en el medio, para dar bromo pirazoles.[182] Estos sustratos resultan muy útiles a la hora de la posterior funcionalización del anillo del pirazol.

[181] L. Wu, M. Shi, *J. Org. Chem.* **2010**, *75*, 2296.
[182] Q. Sha, Y. Wei, *Synthesis* **2013**, *45*, 413.

De forma complementaria, Lin y colaboradores han descrito la síntesis de pirazoles disustituidos en las posiciones 3 y 5, de forma mayoritariamente regioselectiva, mediante la adición catalizada por ácido trífico (TfOH) entre un alquino terminal y una tosilhidrazona (Esquema 2.25).[183]

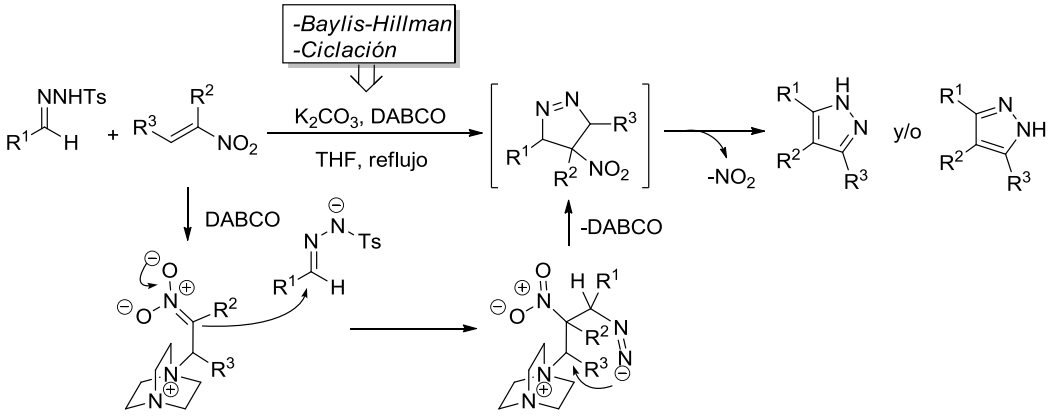


Esquema 2.25. Síntesis de pirazoles entre tosilhidrazonas y alquinos promovida por ácido.

En el mecanismo propuesto para la reacción, la tosilhidrazona es inicialmente protonada por el TfOH generando el cation **C.42**. A continuación, el alquino se adiciona a la tosilhidrazona protonada para dar el intermedio **C.43**, el cual, evoluciona mediante un ataque intramolecular del N al carbocatión viníco formado y la consiguiente pérdida del grupo tosilo, para dar el correspondiente pirazol **C.44**. Si comparamos este procedimiento con la cicloadición 1,3-dipolar, es intrínsecamente distinto ya que no se genera el diazocompuesto intermedio.

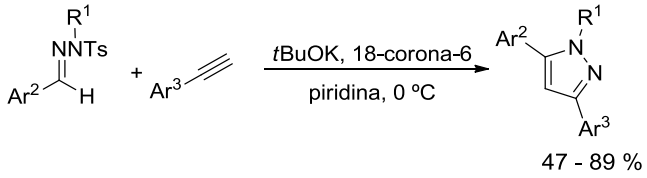
Otro procedimiento donde no se genera el diazocompuesto intermedio es el publicado por Kong y colaboradores. [184] Esta síntesis de pirazoles trisustituidos se lleva a cabo a partir de tosilhidrazonas y olefinas activadas, como son los nitroalquenos. Esta reacción transcurre a través de una reacción de tipo Baylis-Hillman promovida por DABCO. Seguidamente, se produce una ciclación con pérdida del grupo nitro, obteniéndose el pirazol final (Esquema 2.26).

[183] P. Liu, Q.-Q. Xu, C. Dong, X. Lei, G.-Q. Lin, *Synlett* **2012**, *23*, 2087.
[184] M. Tang, W. Zhang, Y. Kong, *Org. Biomol. Chem.* **2013**, *11*, 6250.



Esquema 2.26. Síntesis de pirazoles a partir de tosilhidrazonas y nitroalquenos.

También se ha descrito un método para acceder a pirazoles 1,3,5-trisustituidos de forma regioselectiva a partir de tosilhidrazonas *N*-alquiladas y alquinos terminales en presencia de una base y un éter corona (Esquema 2.27).[185]



Esquema 2.27. Síntesis de pirazoles a partir de tosilhidrazonas N-alquiladas y alquinos terminales.

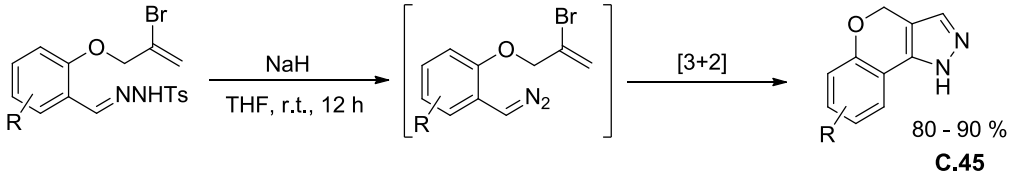
Esta reacción se produce mediante una adición nucleófila del acetiluro de potasio formado en el medio a la tosilhidrazona con la consiguiente ciclación intramolecular. Aunque el protocolo admite numerosos grupos funcionales, la metodología está limitada al empleo de hidrazonas derivadas de aldehídos arómaticos y a acetilenos aromáticos.

2.1.3.2. Estrategias [3+2] intramoleculares.

Numerosos pirazoles que poseen ciclos fusionados, presentan actividad biológica y propiedades farmacéuticas, por ello, su síntesis de un modo eficiente ha cobrado mucho interés.

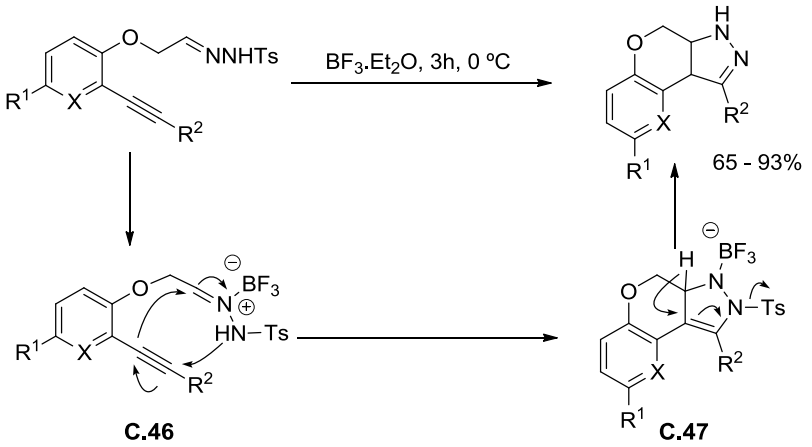
[185] Y. Kong, M. Tang, Y. Wang, *Org. Lett*. **2014**, *16*, 576.

En este campo, en 2001, Chandrasekhar publicó una cicloadicion [3+2] intramolecular a partir de tosilhidrazonas y de alquenos terminales para sintetizar 1,4-dihidrobenzopiranona[4,3-*c*]pirazol y quinolinopirazoles **C.45** de un modo sencillo (Esquema 2.28).[186]



Esquema 2.28. Síntesis de pirazoles fusionados a través de una ciclación [3+2] intramolecular entre alquenos terminales y tosilhidrazonas.

Más recientemente, Deng y colaboradores extendieron esta ciclación intramolecular a tosilhidrazonas y alquinos promovida por un ácido de Lewis como el $BF_3.Et_2O$.[187] Esta ciclación da lugar a los mismos anillos sintetizados por Chandrasekhar pero aportando un nuevo patrón de sustitución (Esquema 2.29).



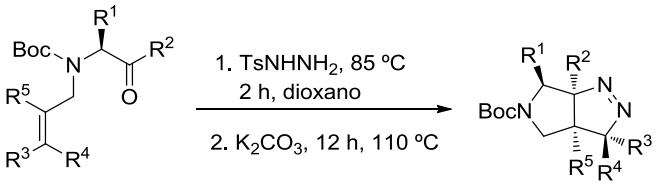
Esquema 2.29. Síntesis de pirazoles fusionados a través de una ciclación [3+2] intramolecular entre alquinos y tosilhidrazonas.

La diferencia entre los dos protocolos radica en que mientras las cicloadiciones de las tosilhidrazonas a olefinas transcurre bajo condiciones térmicas a través del dipolo generado *in situ* y es este dipolo el que reacciona con el dipolarófilo de un modo

[186] S. Chandrasekhar, G. Rajiah, P. Sirihari, *Tetrahedron Lett.* **2001**, *42*, 6599.
[187] W.-L. Wang, Y.-L. Feng, W.-Q Gao, X. Luo, W.-P. Deng, *RSC Advances,* **2013**, *3*, 1687.

concertado, el cierre catalizado por un ácido de Lewis transcurre a través de intermedio carbocatiónicos como **C.46** y **C.47**.[188]

La reacción intramolecular entre tosilhidrazonas y alquenos que no poseen un grupo saliente da lugar a pirazolinas.[189] En este contexto, en nuestro grupo de investigación, se ha desarrollado una versión intramolecular de la cicloadición [3+2] entre tosilhidrazonas y alquenos. En este caso, se emplean α-alilaminocetonas a partir de las cuales se generan de forma one-pot las correspondientes tosilhidrazonas. La descomposición de las tosilhidrazonas en medio básico da lugar a diazocompuestos, que experimentan una cicloadición dipolar para dar lugar a estructuras de tetrahidropirrolo[3,4-*c*]pirazoles de forma diastereoselectiva (Esquema 2.30).[190,191]



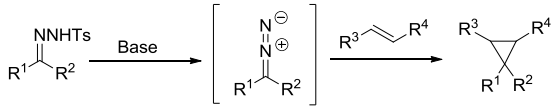
Esquema 2.30. Síntesis de tetrahidropirrolo[3,4-*c*]pirazoles.

[188] E. Frank, Z. Mucsi, I. Zapkó, B. Réthy, G. Falkay, G. Scheneider, J. Wölfling, *J. Am. Chem. Soc.* **2009**, *131*, 3894.

[189] a) A. Padwa, H. Ku, *J. Org. Chem.* **1980**, *45*, 3756; b) U. H. Brinker, T. Schrievers, L. Xu, *J. Am. Chem. Soc.* **1990**, *112*, 8609; c) P. C. Miller, P. P. Gaspar*, J. Org. Chem*. **1991**, *56*, 5101; d) E. C. Ashby, B. Park, G. S. Patil, K. Gadru, R. Gurumurthy, *J. Org. Chem*. **1993**, *58*, 424; M. E. Jung, A. Huang, *Org. Lett.* **2000**, *2*, 2659; e) D. F. Taber, P. Guo, *J. Org. Chem.* **2008**, *73*, 9479; D. F. Taber, P. Guo, N. Guo *J. Am. Chem. Soc.* **2010**, *132*, 11179.

[190] R. Barroso, M. Escribano, M.-P. Cabal, C. Valdés, *Eur. J. Org. Chem*. **2014**, *8*, 1672.

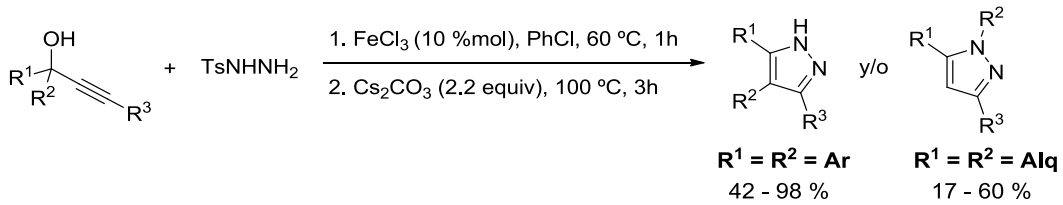
[191] La reacción en ausencia de catalizador metálico en presencia de una tosilhidrazona y un alqueno de forma intermolecular, da lugar a la formación del correspondiente ciclopropano: a) L. A. Adams, V. K. Aggarwal, R. V. Bonnert, B. Bressel, R. J. Cox, J. Shepherd, J. de Vicente, M. Walter, W. G. Wittingham, C. L. Winn, *J. Org. Chem.* **2003**, *68*, 9433; b) J. Barluenga, N. Quiñones, M. Tomás-Gamasa, M.-P. Cabal, *Eur. J. Org. Chem.* **2012**, 2312.



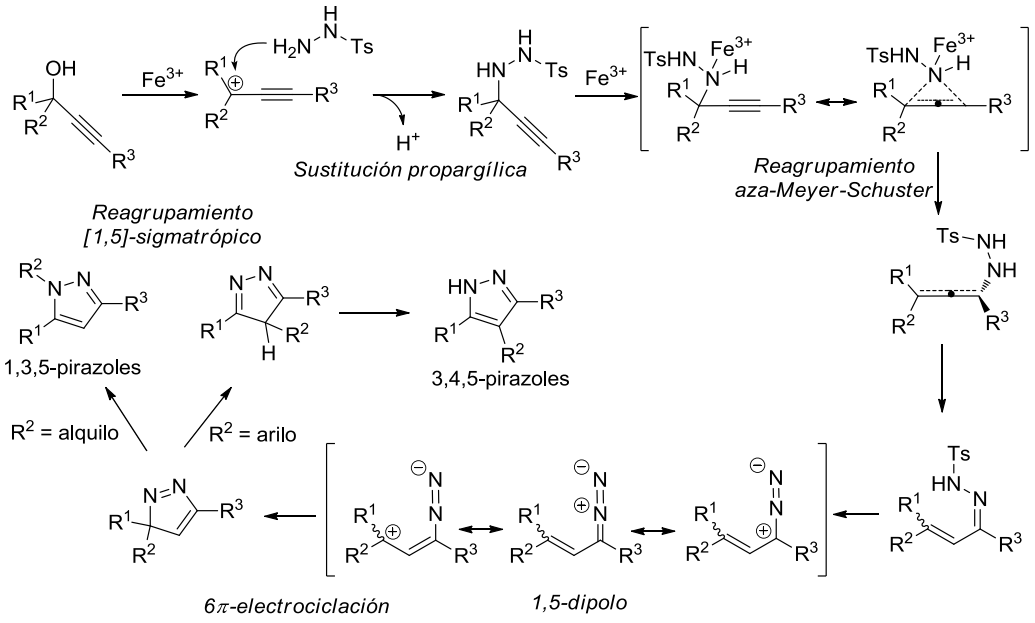
En cambio, el empleo de olefinas desactivadas con grupos atractores de electrones como son nitroalquenos, cianoalquenos, enonas y esteres α,β-insturados, dan lugar a una mezcla compleja de ambos regioisomeros del pirazol con muy bajos rendimientos: c) J.-W. Xie, Z. Wang, W.-J. Yang, L.-C. Kong and D.-C. Xu, *Org. Biomol. Chem.* **2009,** *7*, 4352; d) A. Jończyk, J. Włostowskab and M. Mąkosza, *Tetrahedron* **2001**, *57*, 2827.

2.1.3.3. Reacciones electrocíclicas.

Las reacciones electrocíclicas han sido muy empleadas en las síntesis de heterociclo de una forma eficiente, regioselectiva y enantioselectiva. En el año 2013, Zhan y colaboradores desarrollan una metodología para preparar pirazoles 3,4,5- y 1,3,5-trisustituidos a partir de alcoholes propargílicos terciarios y *p*-toluensulfonilhidracina (Esquema 2.31).[192] De este modo, la tosilhidrazona es un intermedio de la reacción generada *in situ*. La síntesis de estos pirazoles se lleva a cabo a través de un proceso *one-pot,* en el cual, se dan cuatro reacciones secuenciales: una sustitución propargílica catalizada por $FeCl_3$, un reagrupamiento aza-Meyer-Schuster, una electrociclación de 6π electrones y un reagrupamiento [1,5]-sigmatrópico.



Esquema 2.31. Síntesis de pirazoles trisustituidos a partir de alcoholes propargílicos terciarios y *p*-toluensulfonilhidracina.



Esquema 2.32. Mecanismo propuesto para la reacción entre alcoholes propargílicos terciarios y *p*-toluensulfonilhidracina .

[192] L. Hao, J.-J. Hong, J. Zhu, Z.-P Zhan, *Chem. Eur. J.* **2013**, *19,* 5715.

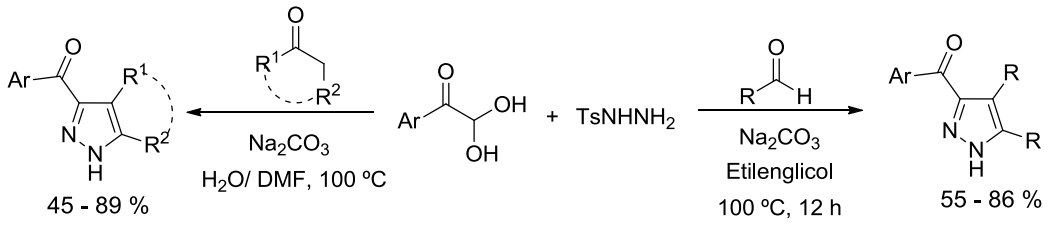
La reacción es totalmente regioselectiva cuando los alcoholes propargílicos empleados son simétricos $R^1 = R^2$ = arilo, obteniéndose exclusivamente el pirazol 3,4,5-trisustituido. En cambio, cuando $R^1 \neq R^2$ = arilo, se observa una mezcla de los dos regioisómeros. Por otro lado, cuando R^1 = arilo y R^2 = alquilo la reacción transcurre regioselectivamente hacia el pirazol 1,3,5-trisustituido.

Como se verá en el apartado de discusión, la regioselectividad observada en la reacción de reagrupamiento sigmatrópico [1,5] guarda similitud con nuestros propios resultados. Hay que destacar también que es trabajo fue realizado y apareció publicado de forma simultánea a nuestra propia contribución.

2.1.3.4. Reacciones multicomponente (MCR).

Las reacciones multicomponente (MCR) son especialmente relevantes. Esto es debido a que partiendo de tres o más sustratos de partida se pueden obtener los productos deseados en un solo paso de reacción a través de la formación de dos o más enlaces sin necesidad de aislar o purificar los compuestos intermedios generados. En este apartado se mostrarán ejemplos de estas reacciones, en las cuales, la hidrazona es un intermedio de la transformación.

En 2015, Wu y colaboradores han presentado una síntesis de pirazoles polisustituidos, los cuales, son preparados de forma regioselectiva a partir del monohidrato de arilglioxal, tosilhidracina y aldehídos o cetonas (Esquema 2.33).[193]

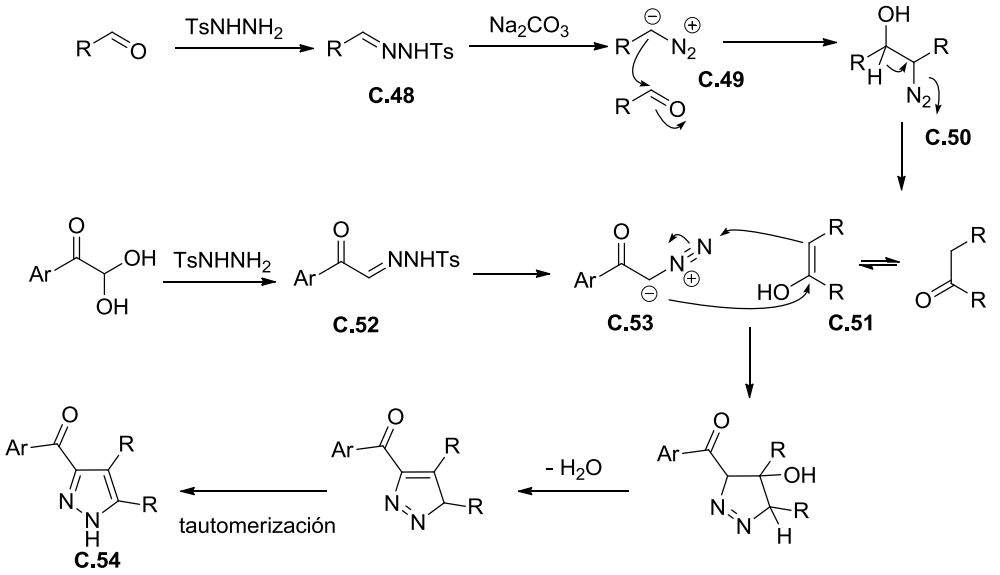


Esquema 2.33. Síntesis de pirazoles funcionalizados de forma multicomponente.

El mecanismo propuesto para la reacción comenzaría con la condensación del carbonilo para dar lugar a la hidrazona **C.48** que descompone en presencia de la base dando el diazocompuesto **C.49**. El diazocompuesto **C.49** reacciona con otra molécula de carbonilo para dar el intermedio **C.50** que mediante la transferencia de un protón y la posterior pérdida de nitrógeno, generan el enol **C.51**. Simultáneamente, el monohidrato

[193] W.-M. Shu, K.-L. Zheng, J.-R. Ma, H.-Y. Sun, M. Wang, A.-X. Wu, *Org. Lett.* **2015**, *17*, 1914.

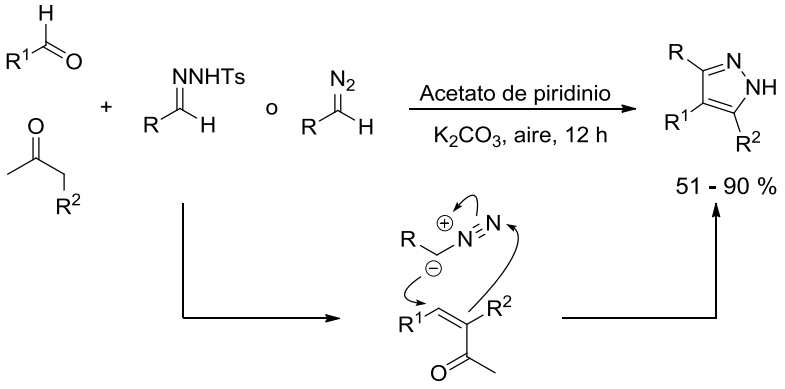
de arilglioxal reacciona con la tosilhidracina para dar la hidrazona **C.52** descomponiendo para la obtención de nuevo del diazocompuesto **C.53**. Este intermedio **C.53** experimenta una cicloadición 1,3-dipolar con **C.51** que seguido de una pérdida de H_2O y tautomerización permiten el acceso a **C.54** (Esquema 2.34).



Esquema 2.34. Mecanismo propuesto para la reacción multicomponente.

En otra contribución muy semejante también publicada en 2015, se ha desarrollado la síntesis de una serie de pirazoles polisustituidos a partir de de aldehídos, compuestos 1,3 dicarbonílicos y diazocompuestos, así como con hidrazonas (Esquema 2.35).[194] La síntesis se alcanza a través de tres pasos: una condensación de Knoevenagel, una cicloadición 1,3-dipolar y una aromatización a través de una oxidación en ausencia de metales de transición.

[194] A. Kamal, K. N. V. Sastry, D. Chandrasekhar, G. S. Mani, P. R. Adiyala, J. B. Nanubolu, K. K. Singarapu, R. A. Maurya, *J. Org. Chem.* **2015**, *80*, 4325.

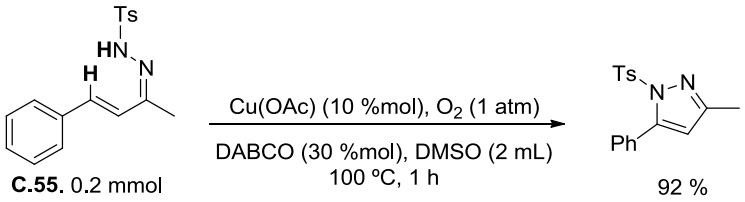


Esquema 2.35. Síntesis de pirazoles polisustituidos a partir de aldehídos, compuestos 1,3-dicarbonilos y diazocompuestos.

2.1.3.5. Activación C-H.

La aminación directa de un enlace C-H sin la prefuncionalización de los sustratos de partida, supone una estrategia muy eficiente desde el punto de vista de la economía atómica. De este modo, la funcionalización C-H catalizada por un metal de transición seguida de la formación de un enlace C-N representa un método muy versátil y práctico para instalar un grupo nitrogenado.

En este contexto, en 2013, se desarrolló una aminación aeróbica oxidativa de un enlace C (sp^2)-H catalizada por cobre para generar pirazoles trisustituidos a partir de la tosilhidrazona α,β-insaturada **C.55** (Esquema 2.36).[195] Estos pirazoles se obtienen con muy buenos rendimientos y además, también se pueden acceder a ellos mediante una metodología *one-pot*. La reacción no es exclusiva de las sulfonilhidrazonas, sino que puede aplicarse también a la preparación de *N*-arilpirazoles partiendo de las correspondientes *N*-arilhidrazonas.



Esquema 2.36. Síntesis de pirazoles a través de una funionalización C-H seguida de una formación del enlace C-N.

[195] X. Li, L. He, H. Chen, W. Wu, H. Jiang, *J. Org. Chem*. **2013**, *78*, 3636.

2.1.4. Reacciones de Transposición Sigmatrópica.

Las reacciones de transposición sigmatrópica pertenecen a una clase de reacciones llamadas pericíclicas.[196] Dentro de las reacciones pericíclicas, se incluyen también, entre otras, las cicloadiciones y las reacciones electrocíclicas.

La característica fundamental de las recciones pericíclicas es que transcurren a través de estados de transición cíclicos, en los cuales, la ruptura y la formación de nuevos enlaces tienen lugar de forma concertada.

Las reacciones pericíclicas han sido estudiadas a través de diversos modelo teóricos, tales como la Teoría de Conservación de la Simetría Orbital, la Teoría de los Orbitales Moleculares Frontera y la Teoría de los Estados de Transición Aromáticos. La comprensión de los fundamentos de este tipo de reacciones se encuentra sistematizada a través de las bien conocidas reglas de Woodward Hoffmann. [197]

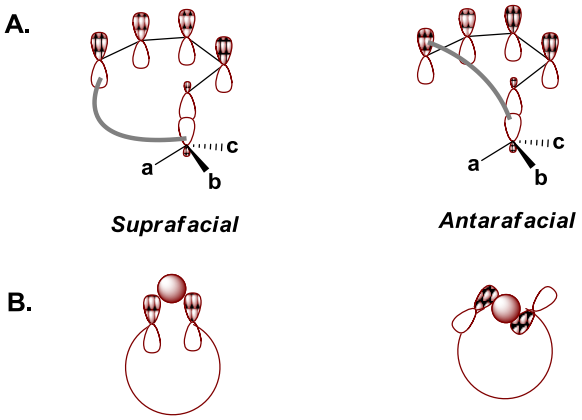
Los reagrupamientos sigmatrópicos son isomerizaciones concertadas no catalizadas. De un modo formal, involucran un estado de transición en el que se produce, de forma simultánea, la migración de un enlace σ de una posición a otra de la molécula con el correspondiente movimiento del sistema π para acomodarlo. La nomenclatura que posee el reagrupamiento está caracterizado por dos números dentro de un corchete. El primer número indica la posición de origen del enlace que migra el grupo, y el segundo, la posición final.

Para definir el curso de las reacciones sigmatrópicas, se definen ciertas notaciones esteroquímicas:

- *Migración Suprafacial* (supra): la formación y ruptura de enlaces tiene lugar por la misma cara del sistema (Esquema 2.37.**A**)

- *Migración Antarafacial* (antara): la formación y ruptura de enlaces tiene lugar por caras contrarias (Esquema 2.37.**B**).

[196] a) F. A. Carroll, *Perspectives on Structure and Mechanism in Organic Chemistry*, Brooks/Cole Publishing Company, **1998**; b) I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Wiley and Sons, Chichester, UK, **2010**.
[197] R. Hoffman, R. B. Woodward, *Accounts. Chem. Res.* **1968**, *1*, 17.



Esquema 2.37. a) Migración suparafacial y antarafacial para un reagrupamiento [1,5]; b) Conformaciones moleculares para la migración suprafacial y antarafacial.

Además, la estereoquímica del grupo que migra puede variar o no durante el proceso. Así, además de darse de forma supra o antara, el grupo puede migrar con retención o con inversión de la configuración.

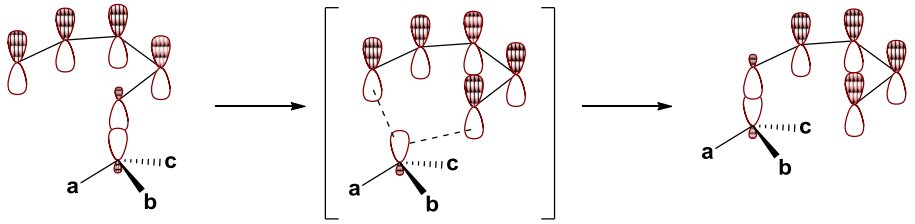
De acuerdo con las reglas de selección, que pueden deducirse a partir de cualquiera de los modelos teóricos indicados anteriormente, las transposiciones que implican el movimiento de [4*n*+2] electrones son permitidas cuanto transcurren con topología supra-supra (Esquema 2.38). Este es el caso de las transposiciones [1*s*,2*s*], [1*s*,5*s*] y [3*s*,3*s*].

Por el contrario, aquellas que implican el movimiento de 4*n* electrones, son permitidas con topología *supra-antara* o *antara-supra* (Esquema 2.38). Ejemplos de estas transposiciones son las [1*a*,3*s*] y [1*s*,7*a*].

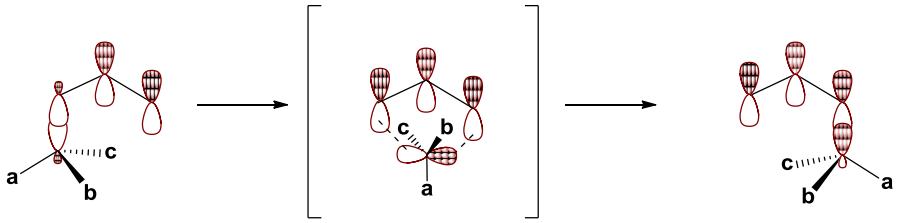
Esquema 2.38. Reglas para los reagrupamientos [*i,j*]-sigmatrópicos.

i+j	Permitidas	Prohibidas
4*n*	Supra-Antara Antara-Supra	Supra-Supra Antara-Antara
4*n*+2	Supra-Supra Antara- Antara	Supra-Antara Antara-Supra

En el caso de las transposiciones [1,*j*] donde se transpone un enlace sigma sobre un carbono con hibridación sp^3, si la transposición transcurre con topología supra con respecto a ese grupo, tiene lugar retención en la configuración de ese centro. Por el contrario, la topología antara, daría lugar a la inversión de configuración en el grupo que migra. Así, en el caso de las transposiciones [1*s*,2*s*] y [1*s*,5*s*] se debe producir retención de configuración, mientras que en las transposiciones [1*a*,3*s*] se porducirá inversión (Esquema 2.39).



[1s,5s] con retención de la configuración



[1*a*,3*s*] con inversión de la configuración

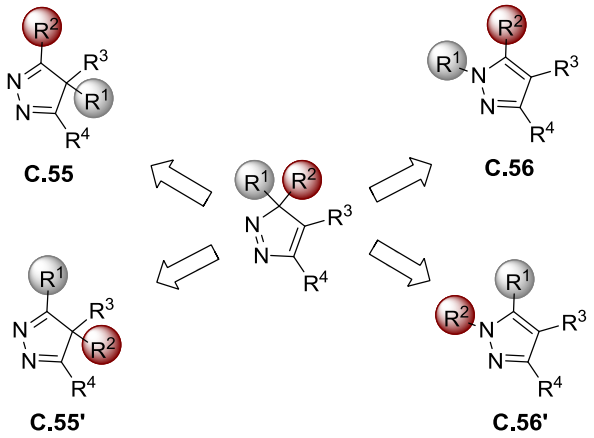
Esquema 2.39. Migraciones permitidas para: **a)** el reagrupamiento [1*s*,5*s*]-sigmatrópico; **b)** el reagrupamiento [1*a*,3*s*]-sigmatrópico.

Las reglas de Woodwarth-Hoffmann hacen referencia exclusivamente a aspectos orbitálicos, sin embargo, la viabilidad de las recciones con una topología determinada depende también de la geometría de la molécula y de los efectos estéricos. En general, las transposiciones [1*s*,5*s*] son procesos que se producen con facilidad de forma concertada, por el contrario, las transposiciones [1*a*,3*s*] y [1*s*,3*a*] son procesos muy desfavorables y, salvo ejemplos muy concretos, no se producen de forma concertada.

En este Capítulo de la memoria, se describirán procesos en los que el paso clave es precisamente una transposición [1s,5s], que obedece las reglas de Woodward-Hoffmann: la transposición [1,5] en 3*H*-pirazoles. Las principales características de esta reacción se discuten en el siguiente apartado.

2.1.4.1. Reagrupamiento térmico en los 3*H*-pirazoles.

Los 3*H*-pirazoles son heterociclos análogos al 1,3-ciclopentadieno con dos átomos de nitrógeno contiguos y al igual que ellos, pueden experimentar reagrupamientos sigmatrópicos. De este modo, sufren reagrupamientos térmicos con la correspondiente migración de un sustituyente desde el carbono tetraédrico (C-3) del 3*H*-pirazol al átomo de carbono o de nitrógeno contiguo. Así, si la transposición [1,5] de R^1 sucede en el sentido contrario a las agujas del reloj da lugar al 1*H*-pirazol **C.56** y si se produce en el sentido de las agujas del reloj se genera el 4*H*-pirazol **C.55**. Alternativamente, las dos posibles migraciones de R^2 conducirían a los pirazoles **C.55'** y **C56'**. Estas reacciones se conocen como transposiciones de van Alphen-Hüttle[198,199] y están representadas de forma general en el Esquema 2.40.



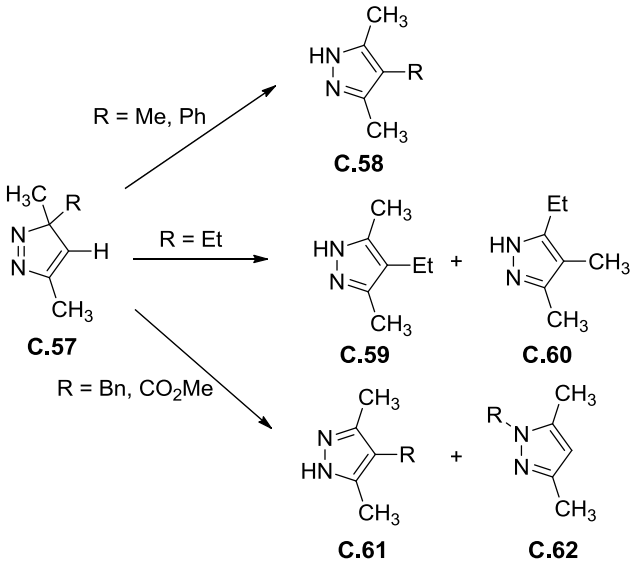
Esquema 2.40. Transposiciones de van Alphen-Hüttle.

Desde el punto de vista mecanístico, estas reacciones transcurren de manera concertada de forma suprafacial. Se ha admitido que la formación de un isómero frente a otro tiene lugar de forma competitiva[200] y que depende de la capacidad migratoria que posean los grupos susceptibles de experimentar la reacción de transposición.

En este contexto, Schiess y Stadler[201] realizaron un estudio cinético de los reagrupamientos térmicos que experimentan diferentes 3*H*-pirazoles **C.57** (Esquema 2.1). La transposición de los sustituyentes metilo y fenilo ocurren exclusivamente hacia el C-4 dando lugar a los correspondientes 1*H*-pirazoles finales **C.58**. Cuando R = Et, se

[198] J. Van Alphen, *Rec. Trav. Chim.* **1943**, *62*, 491.
[199] R. Hüttel, K. Franke, H. Martin, J. Riedl, *Chem. Ber.* **1960**, *93*, 1433.
[200] R. Baumes, J. Elguero, R. Jacquir, G. Tarrago, *Tetrahedron Lett.* **1973**, 3781.
[201] P. Schiess, H. Stalder, *Tetrahedron Lett.* **1980**, *21*,1417

obtiene una mezcla de los pirazoles **C.60** y **C.61** procedentes de la competencia entre la migración del grupo metilo y del grupo etilo, respectivamente. En cambio, la migración de los grupos bencilo y carbometoxi puede ocurrir al C-4 dando **C.62** o por el contrario, al N-2 generando **C.63**.



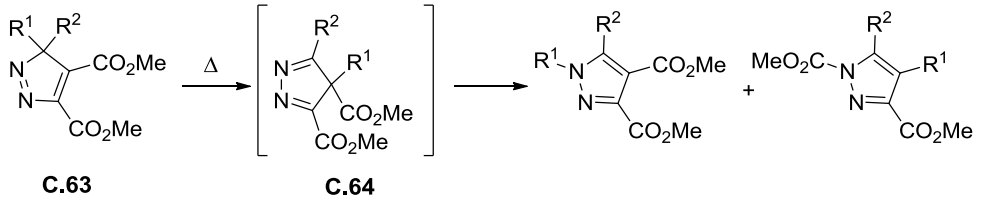
Esquema 2.41. Estudio cinético de diversos grupos con diferentes capacidades migratorias.

De estos resultados, se puede determinar la capacidad migratoria que poseen los sustituyentes. Así la tendencia a la migración en orden decreciente sería Me<etilo<bencilo<fenilo<carbometoxi.

El estudio más sistemático de la reacción de transposición de van Alphen-Hüttle ha sido llevado a cabo por el grupo de Warkentin en una serie de trabajos publicados a partir de 1990. [202] A lo largo de estos artículos, se estudian las reacciones de transposición de 3*H*-pirazoles con sustituyentes atractores de electrones, como 3*H*-pirazol-4,5-dicarboxilato y 3*H*-pirazol-5-carboxilato, presentando diferentes sustituyentes en posición 3, susceptibles de experimentar la reacción de transposición. Se observa que, dependiendo de la naturaleza del grupo que experimenta la reacción de transposición, así como de la polaridad del disolvente, se obtienen diferentes mezclas de de los productos de migración a C4 o a N1 (Esquema 2.42).[203]

[202] a) M. W. Majchrzak, E. Jefferson, J. Warketin, J. Am. Chem. Soc. 1990, 112, 2449; b) E. A. Jefferson, J. Warketin, *J. Am. Chem. Soc.* **1992**, *114*, 6318; c) E. A. Jefferson, J. Warkentin, *J. Org. Chem.* **1994**, *59*, 455.

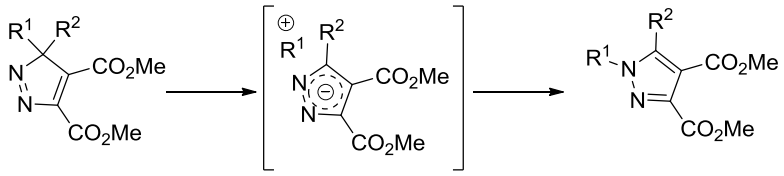
[203] La formación de un intermedio como **C.64**, fue demostrada años más tarde a partir del estudio de 3,3-espiro-(ciclopentil)pirazol: Y.-P. Yen, S.-F. Chen, Z.-C. Heng, J.-C. Huang, L.-C. Kao, C.-C, Lai, R. S. H. Liu, *Heterocycles*, **2001**, *55*, 1859.



C.63 **C.64**

Esquema 2.42. Diferentes transposiciones [1,5] del 3*H*-pirazol-4,5-dicarboxilato **C.63.**

Además, se identifican diferentes mecanismos de reacción, desde procesos típicamente concertados a procesos por pasos con formación de un par iónico. La naturaleza del mecanismo estaría determinada fundamentalmente por la capacidad del grupo que se transpone para acomodar una carga positiva. De modo simplificado, los grupos con capacidad para estabilizar la carga positiva, experimentarían preferentemente la reacción de transposición a través de procesos concertados muy polarizados o procesos por pasos involucrando pares iónicos (Esquema 2.43). Por el contrario, grupos sin capacidad para estabilizar la carga positiva, participarían en reacciones típicamente concertadas.



Esquema 2.43. Intermedio con separación de carga.

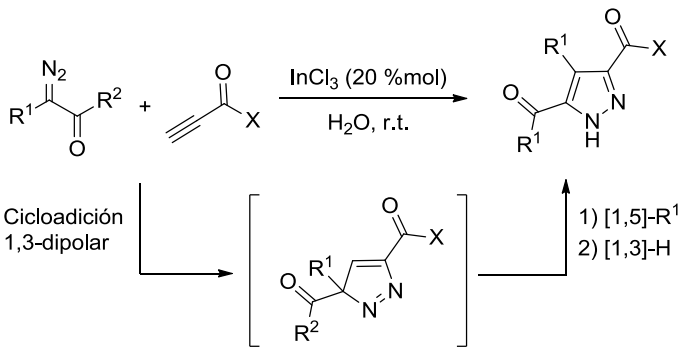
El estudio de Warkentin está directamente relacionado con los resultados descritos en esta memoria. No obstante, está limitado a pirazoles con sustituyentes electrón-atractores, y además es muy restringido en cuanto a los sustituyentes en posición 3. Esto es debido a la falta de un método general y eficiente de acceso a los 3*H*-pirazoles.

2.1.5. Ejemplos de reacciones que implican una cicloadición 1,3-dipolar seguida de un reagrupamiento [1,5]-sigmatropico

Como se ha visto en el apartado anterior, los 3*H*-pirazoles provenientes de las cicloadiciones 1,3-dipolares de diazocompuestos disustituidos, son susceptibles de sufrir posteriormente un reagrupamiento [1,5]-sigmatrópico. Debido a que el mecanismo propuesto para la generación de pirazoles descrita en la Discusión de Resultados se

produce en cascada siguiendo esta secuencia, a continuación, se mostrarán algunos ejemplos representativos.

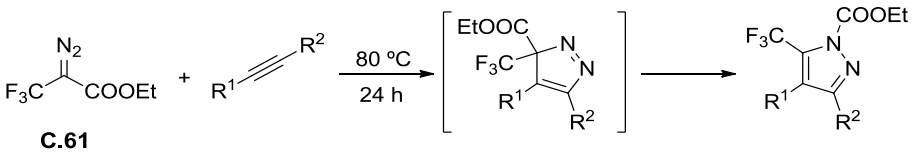
En numerosas ocasiones, las cicloadiciones 1,3-dipolares requieren un ácido de Lewis para activar el dipolarófilo y promover de esta forma la reacción. En este campo, Jiang y Li[204] publicaron por primera vez una cicloadición 1,3-dipolar intermolecular entre diazocompuestos y alquinos, en presencia de $InCl_3$ como catalizador, y en agua, para sintetizar pirazoles.[205] La secuencia que se propone para esta reacción consiste en una cicloadición 1,3-dipolar seguida de una migración [1,5] de hidrógeno, del grupo alquilo o del grupo arilo dependiendo del sustrato elegido (Esquema 2.44). Este procedimiento también se ha llevado a cabo tanto en ausencia del catalizador como del disolvente.[206]



Esquema 2.44. Síntesis de pirazoles trisustituidos mediante la secuencia cicloadicción 1,3-dipolar/transposición [1,5] catalizada por $InCl_3$.

En 2014, se empleó una metodología semejante para acceder a una familia de pirazoles trifluorometilados tri- o tetrasustituidos con buenos rendimientos.[207] Para ello, se parte de 2-diazo-3,3,3-trifluoropropanoato de etilo **C.61** y diferentes alquinos activados, en la mayoría de los ejemplos, en ausencia del disolvente (Esquema 2.45). En este caso, tras la reacción 1,3-dipolar, tiene lugar la transposición [1,5] del grupo metoxicarbonilo al átomo de nitrógeno.

[204] N. Jiang, C.-J. Li, *Chem. Commun.* **2004**, 394.
[205] Para pirazoles sustituidos con diferentes grupos funcionales: a) S. He, L. Chen, Y.-N. Niu, L.-Y Wu, Y.-M. Liang, *Tetrahedron Lett.* **2009**, *50*, 2443; b) M. Kissane, S. E. Lawrence, A. R. Maguire, *Org. Biomol. Chem*. **2010**, *8*, 2735.
[206] D. Vuluga, J. Legros, B. Crousse, D. Bonnet-Delpon, *Green Chem.* **2009**, *11*, 156.
[207] D. Gladow, S. Doniz-Kettenmann, H.-U. Ressig, *Helv. Chim. Acta*, **2014**, *97*, 808.



Esquema 2.45. Síntesis de pirazoles trifluorometilados a través de una secuencia de cicloadición 1,3-dipolar y un reagrupamiento [1,5]-sigmatrópico.

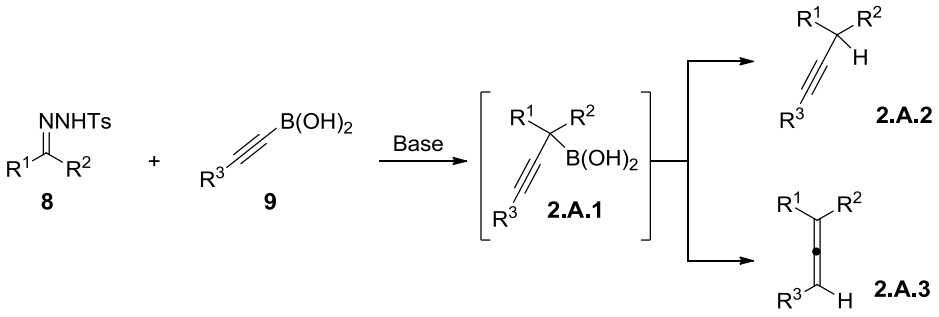
PARTE A: SÍNTESIS REGIOSELECTIVA DE PIRAZOLES A PARTIR DE ALQUINOS Y *N*-TOSILHIDRAZONAS A TRAVÉS DE UNA SECUENCIA DE CICLOADICIÓN 1,3-DIPOLAR Y UN REAGRUPAMIENTO [1,5]-SIGMATRÓPICO.

2.A.1. DISCUSIÓN DE RESULTADOS.

2.A.1.1. Objetivos y estudios preliminares.

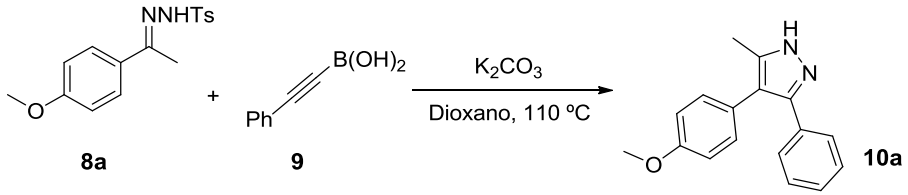
El desarrollo de esta Tesis Doctoral tiene como hilo conductor el empleo de *N*-tosilhidrazonas en diferentes procesos que transcurren en ausencia de un catalizador metálico. Con objeto de desarrollar nuevas aplicaciones sintéticas que involucren a estos reactivos tan versátiles, se inició la búsqueda de otros agentes de acoplamiento que se pudieran enfrentar a ellas.

En primer lugar, se decidió extender el estudio de la olefinación de compuestos carbonílicos descrita en el Capítulo 1 a otros nucleófilos, concretamente, a los ácidos alquinilborónicos. En base a nuestras anteriores experiencias, el resultado que esperábamos encontrar para esta reacción, era la formación de los productos que se muestra en el Esquema 2.A.1. De este modo, el alquino **2.A.2** provendría de la α-protodeboronación del intermedio **2.A.1**, mientras que el aleno **2.A.3** provendría de la γ-protodeboronación del intermedio y por tanto la migración del correspondiente enlace.



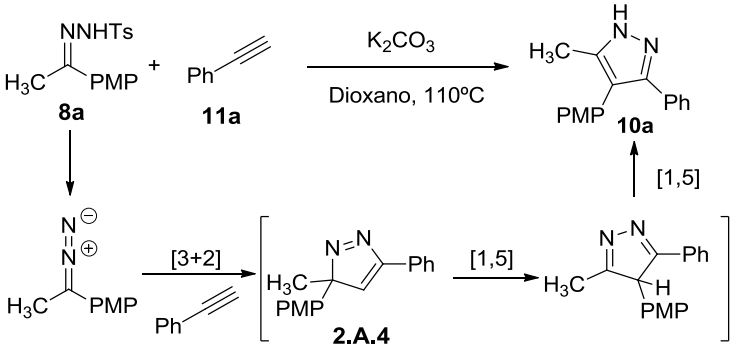
Esquema 2.A.1. Posibles caminos de reacción en el acoplamiento reductor entre ácidos alquinilborónicos **9** y *N*-tosilhidrazonas **8**.

Con este fin, se decidió escoger como reacción modelo la combinación de la *N*-tosilhidrazona derivada de la 4-metoxiacetofenona **8a** y el ácido 1-etinil-2-fenilborónico **9.** La transformación se llevó a cabo bajo las condiciones previamente descritas para la reacción de olefinación de compuestos carbonílicos, descrita en el Capítulo 1. Sin embargo, un análisis del crudo de este primer ensayo determinó que los productos esperados no se habían generado, y en su lugar, se observó la formación mayoritaria de otro compuesto totalmente diferente. Mediante experimentos de resonancia magnética nuclear y espectrometría de masas se pudo establecer que el producto formado se correspondía con la estructura de pirazol **10a** (Esquema 2.A.2).



Esquema 2.A.2. Reacción entre la tosilhidrazona **8a** y el ácido alquinilborónico **9**. La reacción se llevó a cabo empleando proporción 1:2 de tosilhidrazona y ácido alquinilborónico en presencia de 2 equivalentes de K_2CO_3 en dioxano a 110 ^{0}C.

Como ya se ha comentado en los antecedentes de este mismo capítulo (Sección 2.1.3.1, referencia 180), Aggarwal desarrolló la síntesis de pirazoles disustituidos a partir de las correspondientes tosilhidrazonas derivadas de aldehido y alquinos terminales sustituidos tanto con restos alquilos como arilos. El mecanismo propuesto para esta reacción involucra un intermedio de pirazol, el cual, mediante aromatización daría el 1*H*-pirazol. La formación de un intermedio similar, concretamente un anillo de 3*H*-pirazol **2.A.4**, tendría lugar si se emplea el correspondiente alquino terminal y la tosilhidrazona derivada de una cetona. Este intermedio es suceptible de evolucionar mediante un reagrupamiento [1,5]-sigmatrópico generando el anillo de pirazol trisustituido, que daría lugar al 1*H*-pirazol aromático tras la subsiguiente transposición de H. Por otro lado, el ácido alquinil borónico se descompone dando el alquino correspondiente. Para comprobar si en la síntesis del pirazol observado estaba implicado el ácido borónico o si por el contrario, la reacción se daba entre el producto de descomposición, en nuestro caso concreto, el fenilacetileno **11a**, decidimos enfrentarlo a la tosilhidrazona **8a** en las mismas condiciones de reacción (Esquema 2.A.3).



Esquema 2.A.3. Estudios preliminares para la reacción entre la *N*-tosilhidrazona derivada de la metoxiacetofenona **8a** y fenilacetileno **11a**.

De este modo, se obtuvo el pirazol **10a** con buen rendimiento (74%),[208] demostrando, en este caso, que en las condiciones elegidas, la descomposición del correspondiente ácido alquinilborónico se produce con anterioridad al propio acoplamiento con la hidrazona. Por tanto, la reacción que había tenido lugar en el experimento inicial era entre la tosilhidrazona y el alquino generado en el medio.

A la vista de este resultado y teniendo en cuenta los antecedentes expuestos en la introducción de este capítulo, pueden formularse las siguientes consideraciones:

1. La reacción entre una tosilhidrazona derivada de una acetofenona y un acetileno terminal podría transcurrir a través de una reacción de cicloadición 1,3-dipolar seguida de un reagrupamiento [1,5]-sigmatrópico, generando el pirazol trisustituido de forma totalmente regioselectiva y con buen rendimiento.

2. La síntesis de pirazoles a partir de tosilhidrazonas y acetilenos terminales fue descrita previamente por Aggarwal y colaboradores.[183] Sin embargo, esta reacción está restringida exclusivamente al empleo de tosilhidrazonas derivadas de aldehídos.

3. La secuencia de cicloadición 1,3-dipolar seguida de un reagrupamiento sigmatrópico había sido observada en reacciones entre diazocompuestos estabilizados y alquinos.[174] No obstante, los ejemplos en los cuales se empleen diazocompuestos no estabilizados, como a los que se puede acceder a partir de las tosilhidrazonas son muy escasos, lo que ha limitado en gran medida las aplicaciones sintéticas del proceso.

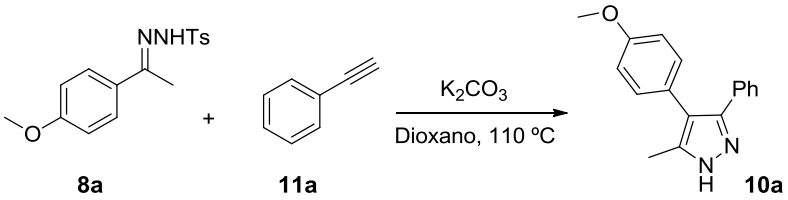
Debido al gran interés que suscita el descubrimiento de nuevas rutas para sintetizar pirazoles polisustituidos, se decidió explorar el potencial sintético de estas reacciones. A continuación, se mostrarán los estudios realizados en este campo.

2.A.1.2. Reacción entre las *N*-tosilhidrazonas 8 y los alquinos terminales 11.

2.A.1.2.1. Optimización.

Con el objetivo de optimizar las condiciones del proceso, se decidió escoger como reacción modelo la presentada anteriormente en el Esquema 2.A.3, la cual consiste en combinación de la *N*-tosilhidrazona derivada de 4-metoxiacetofenona **8a** y el fenilacetileno **11a** (Esquema 2.A.4).

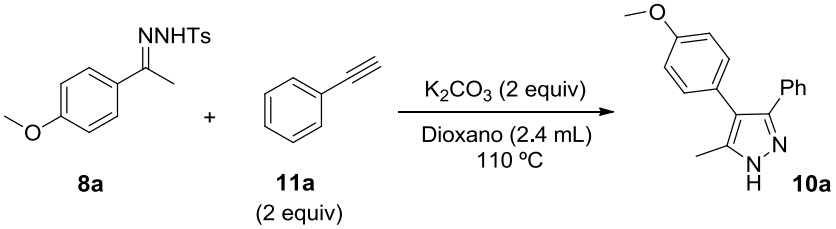
[208] La confirmación de la regioquímica fue determinada mediante el estudio de otros derivados.



Esquema 2.A.4. Reacción modelo para el estudio de las condiciones de reacción de la *N*-tosilhidrazona **8a** y el alquino terminal **11a**.

Basándonos en nuestra experiencia, las bases que mejor toleran las reacciones que transcurren en ausencia de metal son de tipo carbonato, en particular, el carbonato potasio. Además, para las transformaciones que involucran *N*-tosilhidrazonas, el dioxano se revela como el disolvente idóneo. De este modo, decidimos estudiar, en primer lugar, la influencia de la temperatura en el proceso (Tabla 2.A.1).

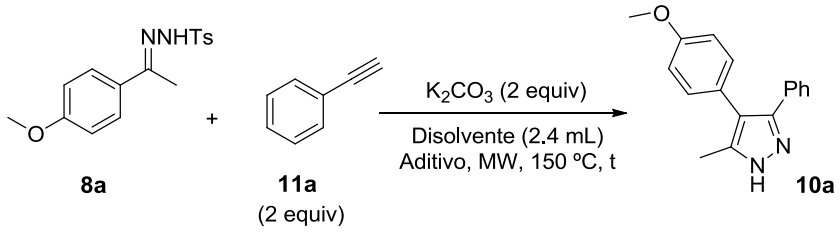
Tabla 2.A.1. Estudio de la influencia de la temperatura en la formación del pirazol **10a** a partir de la *N*-tosilhidrazona **8a** y el alquino terminal **11a.**



Entrada	Temperatura (^{0}C)	Rendimiento (%)
1	**70**	n.d
2	**85**	32
3	**110**	74

Como se puede observar en la Tabla 2.A.1, a medida que aumenta la temperatura del medio de reacción, la formación del pirazol **10a** se produce de una forma más efectiva. Esto sugiere que la transformación requiere elevadas temperaturas para poder llevarse a cabo. Una forma de poder alcanzar temperaturas de reacción altas de una forma segura, es empleando la radiación microondas (Tabla 2.A.2).

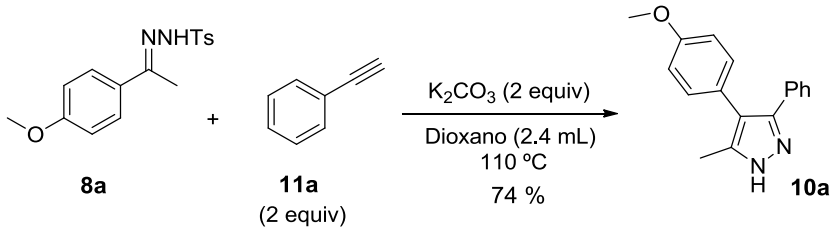
Tabla 2.A.2. Empleo de la radiación microondas en la formación del pirazol **10a** a partir de la *N*-tosilhidrazona **8a** y el alquino terminal **11a.**



Entrada	Disolvente	Aditivo	Tiempo (min)	Rendimiento (%)
1	**Dioxano**	-	30	36
2	**Dioxano**	10 µL H_2O	30	-
3	**C_6H_5F**	-	30	-
4	**CH_3CN**	-	30	-
5	**Dioxano**	10 µL H_2O	60	-

Sin embargo, el empleo de la radiación microondas condujo a un rendimiento muy pobre cuando se empleó dioxano como disolvente a 150 ^{0}C durante 30 minutos (Entrada **1**). En trabajos anteriores, se había observado que al añadir pequeñas cantidades de agua en el medio de reacción, se producía un aumento en la eficiencia de la misma. Sin embargo, en ninguno de los casos (Entrada **2** y **5**), se detectó el producto deseado, recuperándose los reactivos de partida sin reaccionar junto con los productos típicos procedentes de la descomposición de la hidrazona. Finalmente, la reacción no tuvo lugar cambiando el disolvente (Entradas **3** y **4**).

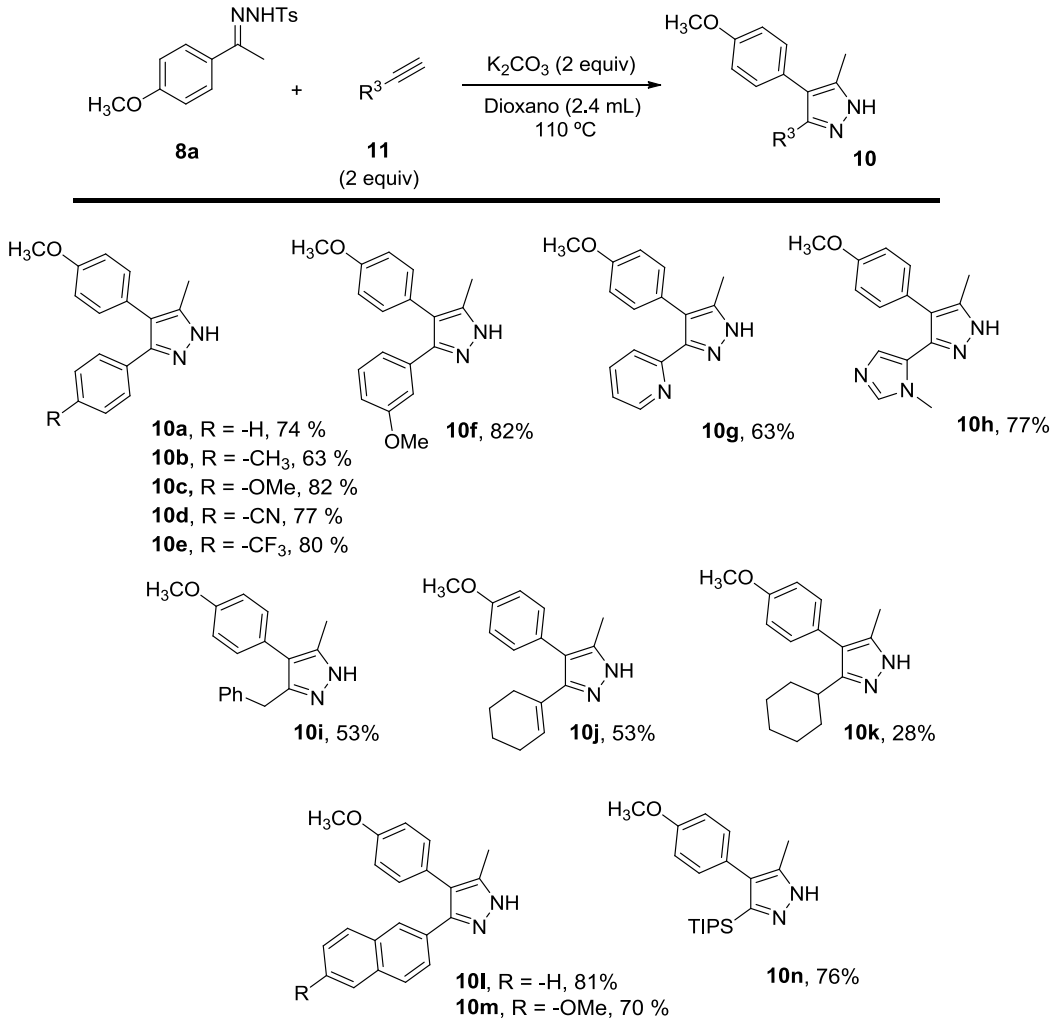
Por tanto, de acuerdo con los experimentos llevados a cabo, las mejores condiciones de esta transformación son, K_2CO_3 como base, dioxano como disolvente y 110 °C como la temperatura de reacción (Esquema 2.A.5).



Esquema 2.A.5. Condiciones optimizadas de reacción para la síntesis del pirazol trisustituido **10a** a partir de la *N*-tosilhidrazona **8a** y el alquino terminal **11a**.

2.A.1.2.2. Generalización de la síntesis de pirazoles 10 con respecto del alquino terminal empleado 11.

A continuación, se procedió a evaluar la generalidad del proceso. En primer lugar, se exploró el efecto de la naturaleza del alquino en el transcurso de la reacción, tal y como se muestra en Esquema 2.A.6. Así, la transformación se presenta muy general y totalmente regioselectiva, en las condiciones de reacción empleadas.



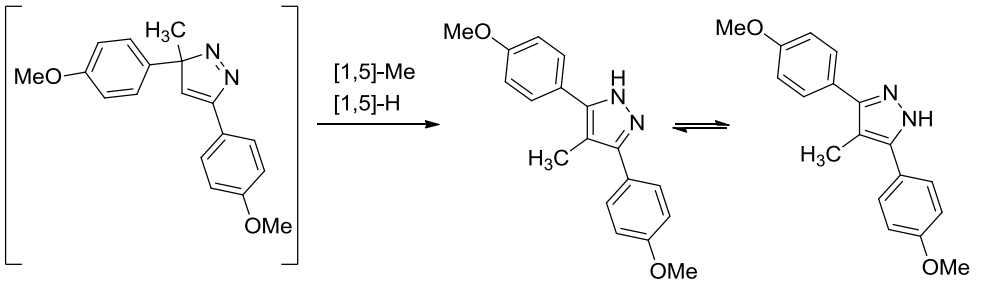
Esquema 2.A.6. Generalización de la reacción de la síntesis de pirazoles con respecto al alquino de partida **11**.

La reacción tolera el empleo de alquinos sustituidos con anillos aromáticos de muy diversa naturaleza (**10a**-**10h, 10l, 10m**), pudiendo presentar tanto sustituyentes dadores como aceptores de electrones (**10a**-**10d**) y además, ocupar diferentes

posiciones del anillo (**10f**). Es más, el proceso presenta una considerable tolerancia con respecto a los grupos funcionales presentes en el alquino. Además, el alquino puede presentar restos alifáticos, alquenicos y heteroaromáticos. En el caso del empleo de un grupo bencilo como representante de grupos alifáticos primarios, conduce a rendimientos moderados (**10i**). En cambio, se observa una disminución del rendimiento muy considerable cuando se emplean restos alifáticos secundarios (**10k**). También experimentan la reacción alquinos sustituidos con heterociclos π-excedentes como el imidazol (**10h**) y π-deficientes, como es la piridina (**10g**). Finalmente, la reacción empleando como alquino el triisopropilsililacetileno, conduce al pirazol sustituido con un grupo sililo, susceptible de posteriores derivatizaciones, en alto rendimiento (**10n**).

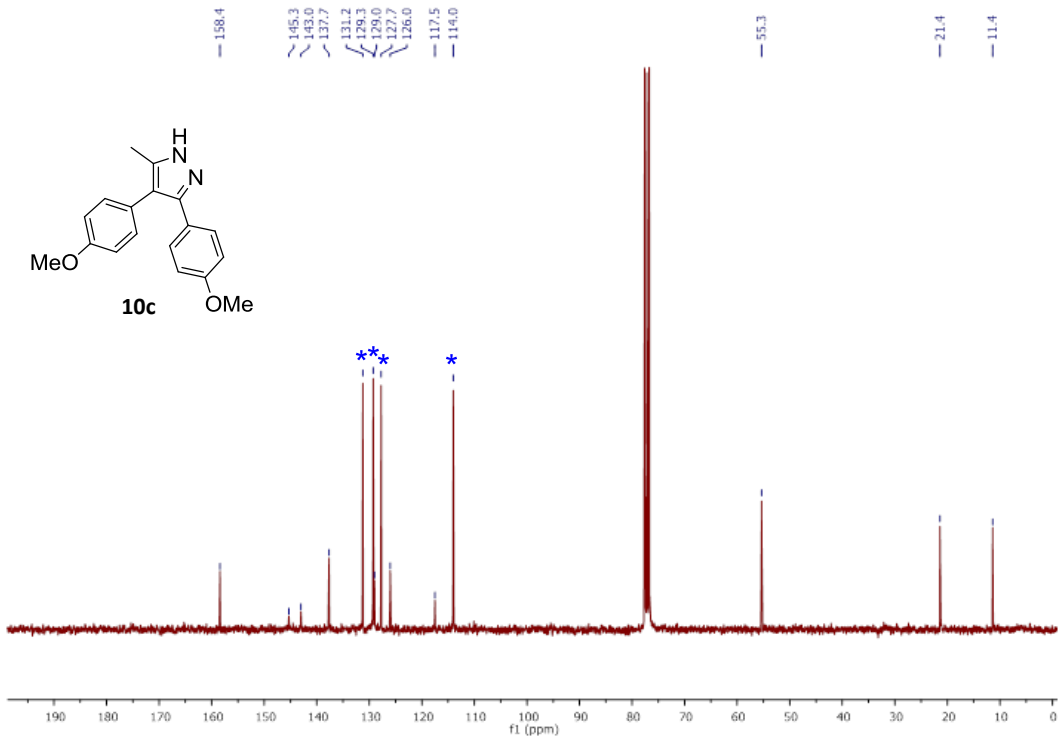
Determinación del regioisómero 10

La regioquímica del pirazol 3,4,5-trisustituido fue confirmada a través del estudio del derivado **10c**, en el cuál, en el caso de que la migración la hubiese experimentado el grupo metilo daría lugar a la formación de un pirazol simétrico (Esquema 2.A.7).



Esquema 2.A.7. Pirazol 3,4,5-trisustituido simétrico obtenido en el caso en el que migrara el grupo metilo.

Esta simetría, se traduciría en una superposición de señales correspondientes a los dos anillos del *p*-metoxifenilo en el experimento de ^{13}C-RMN. Sin embargo, se puede observar en el espectro realizado, los diferentes desplazamientos que poseen las diferentes señales aromáticas de estos anillos (Esquema 2.A.8). De esta manera, se confirma la migración exclusiva del grupo PMP, hecho que se encuentra de acuerdo con los estudios anteriores realizados y recogidos en la literatura.



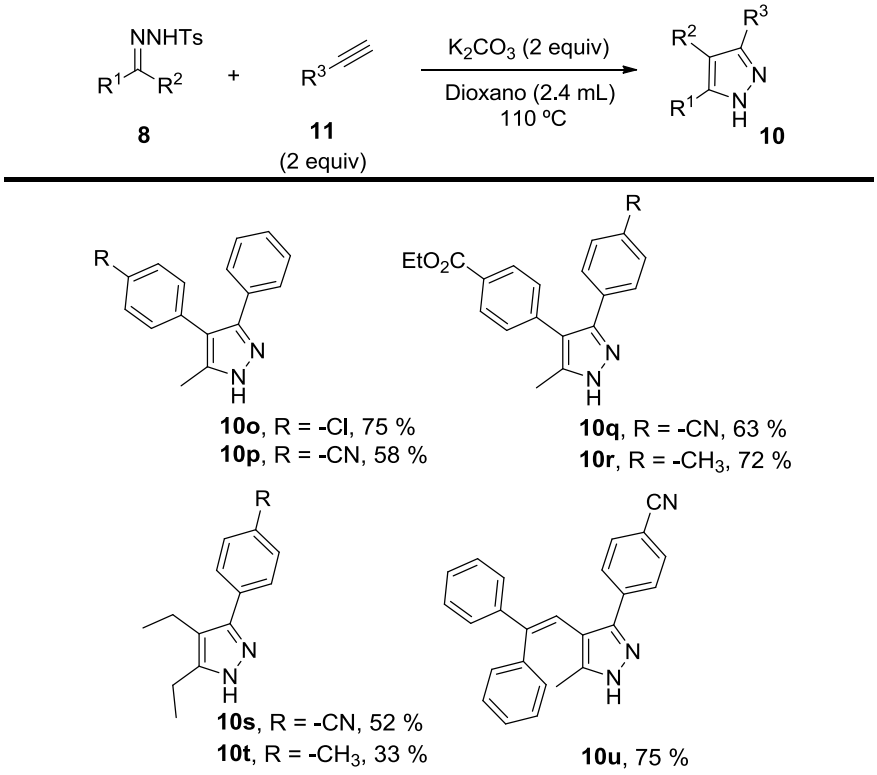
Esquema 2.A.8. Confirmación de la regioquímica de los pirazoles **10** a través del experimento ^{13}C-RMN del ejemplo **10c**.

2.A.1.2.3. Generalización de la síntesis de pirazoles 10 con respecto a la hidrazona 8.

También se examinó el alcance de la reacción con respecto a la estructura de la tosilhidrazona. Para ello, se enfrentaron diversas tosilhidrazonas provenientes de cetonas con diferentes alquinos (Esquema 2.A.9).

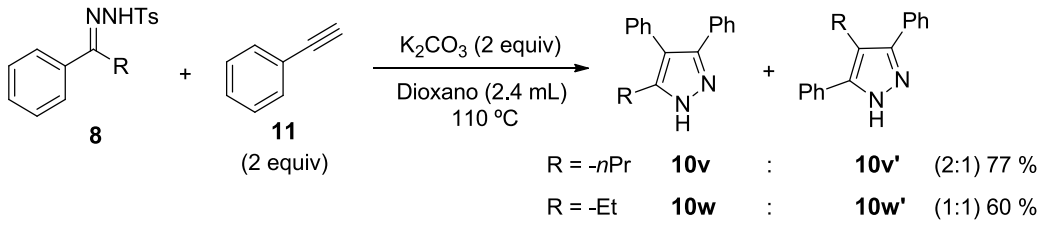
La transformación tiene lugar de forma regioselectiva con derivados de aril metil cetonas que poseen sustituyentes tanto aceptores (**10p**, **10q, 10r**) como dadores de electrones en el anillo aromático (**10o**). De nuevo, la reacción presenta una considerable tolerancia de grupos funcionales. Así, puede transcurrir en presencia de un grupo ester (**10q**, **10r**), obteniéndose buenos rendimientos en todos los casos. Además, el empleo de la 4,4-difenil-1,3-buten-2-ona conduce a la obtención del pirazol trisustituido con buenos rendimientos, en el cual, ha migrado un grupo alquenilo voluminoso (**10u**). Sin embargo, el empleo de la hidrazona derivada de la benzofenona como ejemplo de una diaril cetona, no condujo a la formación del pirazol deseado observándose mezclas

complejas perteneciente a la descomposición de la hidrazona. Finalmente, la utilización de hidrazonas simétricas sustituidas con restos alquilos, da lugar a los correspondientes pirazoles con rendimientos moderados (**10s**, **10t**).



Esquema 2.A.9. Generalización de la reacción de la síntesis de pirazoles con respecto a la hidrazona de partida **8.**

En cambio, el empleo de cadenas más largas en la hidrazona en lugar del grupo metilo, conduce a una disminución en la regioselectividad del proceso (Esquema 2.A.10). Así, cuando se emplean hidrazonas derivadas de propiofenona R= Et y butirofenona R= *n*Pr, se obtiene una mezcla de los isómeros del 1*H*-pirazol **10v**, **10v'** y **10w**, **10w'**, en los que se ha producido la transposición del grupo arilo y el grupo alquilo, respectivamente. Esto es debido a que los grupos alquilo más sustituidos poseen una capacidad migratoria superior que el propio grupo metilo empleado anteriormente. Por lo que existe una competencia entre los grupos alquilo y aromático en la reacción de transposición.



Esquema 2.A.10. Síntesis de los pirazoles **10v** y **10w** empleando tosilhidrazonas con grupos diferentes al metilo.

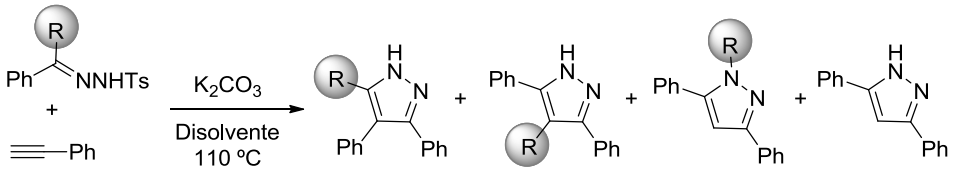
Este resultado se analizará posteriormente, ya que el estudio de la migración de diferentes restos nos ha guiado en la elucubración de cómo transcurre el reagrupamiento [1,5]-sigmatrópico en el mecanismo de reacción.

Como conclusión de esta parte inicial del capítulo, puede indicarse que los resultados obtenidos para esta reacción presentan un valor añadido, dado que es particularmente eficiente para la preparación de pirazoles sustituidos en las posiciones 3, 4 con grupos arilos (**10a-10g**, **10o-10r**, **10v**, **10w**). Es de destacar que se trata de una aproximación original en la que como resultado del proceso tiene lugar la formación de dos enlaces C-C en el carbono terminal del alquino. Por otra parte, también debe señalarse que la síntesis regioselectiva de pirazoles trisustituidos es un proceso no trivial, que habitualmente requiere de secuencias multipasos. Además, esta estructura ha adquirido gran interés en los últimos años debido a que representa un esqueleto que forma parte de numerosas familias de compuestos con actividad biológica.[209] Por ello, esta metodología presenta una ruta alternativa de acceso a estos pirazoles de forma muy atractiva, versátil y simple.

2.A.1.3. Influencia de la naturaleza de la sustitución de la hidrazona.

Como se ha comentado anteriormente, el empleo de grupos en la hidrazona diferentes al metilo, conduce a la formación de una mezcla de regioisómeros (**10v**, **10w**), derivados de la transposición de cada uno de los dos grupos. Así, con el objetivo de estudiar en más detalle la influencia de los sustituyentes, se procedió a la selección de hidrazonas de diferente naturaleza. (Esquema 2.A.11).

[209] a) B. W. Dymock, X. Barril, P. A. Brough, J. E. Cansfiel, A. Massey, E. Mcdonald, R. E. Hubbard, A. Surgenor, S. D. Roughley, P. Webb, P. Workman, L. Wright, M. J. Drysdale, *J. Med. Chem.* **2005**, *48*, 4212; b) K.-M. J. Cheung, T. P. Matthews, K. James, M. G. Rowlands, K. J. Boxall, S. Y. Sharp, A. Maloney, S. M. Roc, C. Prodromou, L. H. Pearl, G. W. Aherne, E. McDonald, P. Workman, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3338.

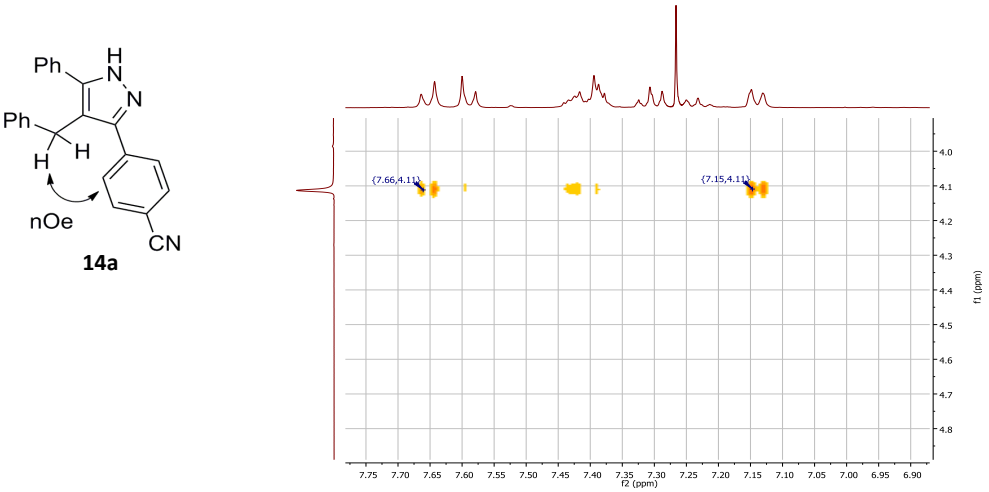


R	10	11	12	13
Me	100	-	-	-
Et	50	50	-	-
*n*Pr	35	65	-	-
*i*Pr	17	33	50	-
Bn	-	20	80	-
CH_2OCH_3	-	10	90	-
CH_2NMe_2	-	-	-	100

Esquema 2.A.11. Influencia del sustituyente de la hidrazona **8** en la regioselectividad del pirazol obtenido. La proporción entre los diferentes regioisómeros ha sido determinada mediante ^{1}H-RMN.

Como se puede observar en el Esquema 2.A.11, la obtención de un regioisómero u otro depende exclusivamente del resto *R* seleccionado. De este modo, cuando la hidrazona posee un resto primario como son los grupo etilo o propilo se obtiene mezcla de los pirazoles **10** y **11**. Cuando se trata de un resto secundario como el *i*Pr, además de los pirazoles **10** y **11**, aparece un nuevo regioisómero, resultado de la transposición del grupo *i*Pr a N1. Por otra parte, el empleo de un grupo bencilo, da lugar de forma mayoritaria al pirazol 1,3,5-trisustituido **12**, en el cual, el grupo bencilo ha migrado en el sentido de las agujas del reloj hacia el nitrógeno. De igual modo, el empleo de un grupo MOM conduce al mismo resultado, observándose una proporción aún mayor del pirazol **12.** Es interesante destacar que en estos dos ejemplos no se detecta la presencia del isómero derivado de la transposición del grupo Ar (**10**). Finalmente, la reacción de la hidrazona derivada de la dimetilaminoacetofenona conduce exclusivamente a la formación del pirazol **13**, en el cuál se ha perdido el grupo R.

La migración del grupo bencilo con respecto al grupo fenilo se determinó a partir de un experimento de RMN bidimensional NOESY sobre el derivado análogo **14a** (Esquema 2.A.12), en el que se observa puntos de cruce entre los hidrógenos bencílicos y los hidrógenos pertenecientes al anillo aromático proveniente del alquino, tal y como se muestra en la figura.



Esquema 2.A.12. Determinación de la regioquímica.

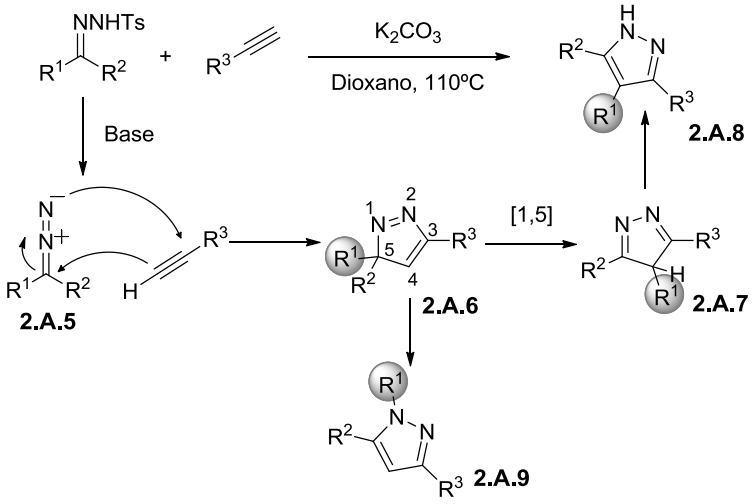
Una conclusión que se puede determinar a tenor de los resultados, es que el cambio de la naturaleza del sustituyente de la hidrazona no solo afecta a la regioselectividad de la reacción, sino al propio reagrupamiento [1,5]-sigmatrópico. Existen, por tanto, dos niveles de selectividad en el proceso:

1. Selectividad en el grupo que experimenta la transposición.

2. Selectividad en el sentido de la transposición (en contra de las agujas del reloj -C5 a C4 o a favor de las agujas del reloj -C5 a N1).

2.A.1.4. Consideraciones mecanísticas.

El mecanismo para esta transformación se puede explicar a través de un proceso en cascada, tal como se muestra en el Esquema 2.A.13.

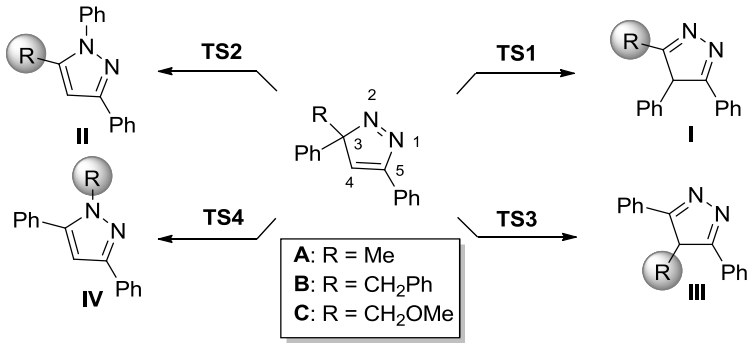


Esquema 2.A.13. Mecanismo propuesto para la reacción.

En primer lugar, la tosilhidrazona se descompone en presencia de la base para generar el diazocompuesto **2.A.5**, el cual, reacciona con el alquino a través de una cicloadición 1,3-dipolar generando el intermedio de 3*H*-pirazol **2.A.6**. Este pirazol intermedio puede evolucionar de dos maneras diferentes, a través de reagrupamientos [1,5]-sigmatrópicos. La migración se podría producir al átomo de carbono C-4 o al átomo de nitrógeno N-1, dando lugar a los pirazoles **2.A.8** y **2.A.9**, respectivamente. En la transposición de estos 3*H*-pirazoles, tal y como se ha comentado en la Sección 2.1.4.1, ya se había observado previamente la competencia entre la formación de los diferentes pirazoles finales (**2.A.8**, **2.A.9**).[210] Como se ha mostrado en la introducción de este capítulo, existen en la literatura algunos estudios sobre las reacciones de transposición [1,5] en 3*H*-pirazoles. Sin embargo, estos estudios se centran en pirazoles electrónicamente pobres, y los resultados difieren en cierta medida de nuestras observaciones. Por ello, se consideró interesante estudiar en más detalle el proceso de transposición sobre nuestros sistemas, que presentan sustituyentes con efectos electrónicos más moderados, para racionalizar los resultados obtenidos.

[210] a) E. A. Jefferson, J. Warkentin, *J. Am. Chem. Soc.* **1992**, *114*, 6318; b) P. Schiess, H. Stalder, *Tetrahedron Lett.* **1980**, *21*, 1417; c) E. A. Jefferson, J. Warkentin, *J. Org. Chem.* **1994**, *59*, 455; d) Y.-P. Yen, S.-F. Chen, Z.-C. Heng, J.-C. Huang, L.-C. Kao, C.-C. Lai, R. S. H. Liu, *Heterocycles* **2001**, *55*, 1859.

Para encontrar una explicación a los resultados experimentales, los cuales sugieren que la regioselectividad del proceso depende de la propia naturaleza del reagrupamiento [1,5]-sigmatrópico, se decidió estudiar la evolución el intermedio 3*H*-pirazol **2.A.6** a través de cálculos computacionales.[211] Para ello se eligieron tres sistemas diferentes **A**, **B** y **C**, los cuales poseían un sustituyente fenilo en C3, y metilo (**A**), bencilo (**B**) y metoximetilo, MOM (**C**) como sustitución en C5, respectivamente. Estos tres modelos, permiten el estudio tanto de la capacidad migratoria de los diferentes grupos, como las diferentes regioselectividades observadas para los ejemplos estudiados. Así, los estados de transición para los 12 caminos de reacción posibles para el reagrupamiento [1,5]-sigmatrópico fueron calculados al nivel b3lyp/6-31G* (Esquema 2.A.14).



Esquema 2.A.14. Sistemas modelo estudiados.

De este modo, como se muestra en la Tabla 2.A.3, para el sistema **A** (R = Me), la migración del grupo fenilo al C4 **TS1-A** (ΔG = 25.7 kcal·mol^{-1}) está favorecida en 5.2 kcal·mol^{-1} frente a la migración del grupo fenilo al N2 (**TS2-A**). Las migraciones del grupo metilo al C4 o al N2 (**TS3-A** y T**S4-A**, respectivamente) se encuentran claramente desfavorecidas debido a que presentan energías de activación muy elevadas (>30 kcal·mol^{-1}).

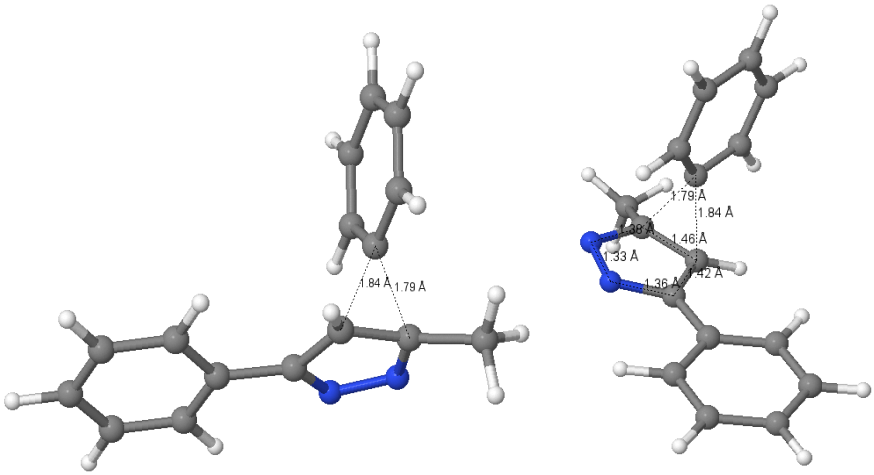
Los cuatro estados de transición presentan geometrías típicas para reacciones pericíclicas concertadas. Considerando los enlaces que están involucrados en la transposición, **TS1-A** y **TS4-A** poseen distancias CAr–C3 y Car-C4 alrededor de 1.8 Å (Esquema 2.A.15), mientras que **TS3-A** y **TS4-A** muestran distancias CH_3-C3 y CH_3-C4 que abarcan desde 1.93 Å a 2.03 Å. Estas distancias son típicas para reacciones pericíclicas concertadas y sincrónicas. Además, estos resultados están de acuerdo con la mayor habilidad migratoria ya conocida que posee el fenilo con respecto al metilo en los reagrupamientos sigmatrópicos. En el Esquema 2.A.16, se muestra a modo de resumen,

[211] Los cálculos teóricos presentados en esta Sección han sido realizados por el Profesor Carlos Valdés.

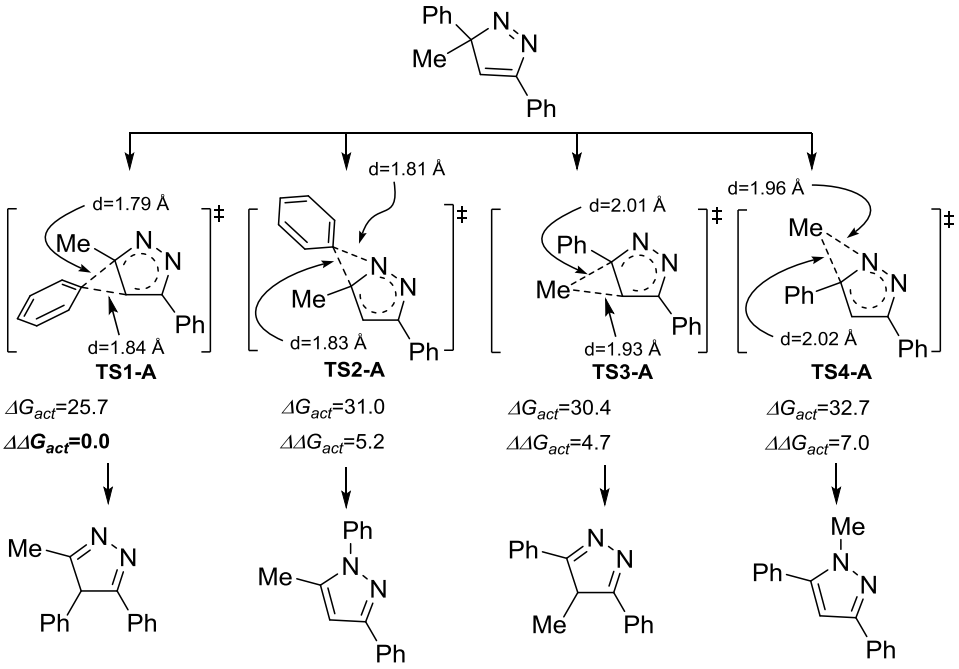
una representación gráfica de los diferentes estados de transición para cada camino de reacción.

Tabla 2.A.3. Energías libre de Gibbs y electrónicas obtenidas para el modelo A (b3lyp/6-31G*). Las energías de Gibbs incluyendo los efectos de solvatación están presentados entre paréntesis. Las energías están expresadas en kcal·mol^{-1}.

	ΔE_{elact}	$\Delta\Delta E_{el}$	ΔG_{act}	$\Delta\Delta G_{act}$
TS1-A	**29.1**	**0.0**	**29.3 (25.7)**	**0.0 (0.0)**
TS2-A	32.5	3.4	31.9 (31.0)	2.6 (5.2))
TS3-A	32.8	3.7	32.5 (30.4)	3.1 (4.7)
TS4-A	34.0	5.0	33.3 (32.7)	3.9 (7.0)



Esquema 2.A.15. Modelo molecular obtenido para **TS1-A**.



Esquema 2.A.16. Los diferentes estados de transición obtenidos para el reagrupamiento [1,5]-sigmatrópico (b3lyp/6-31G*) para el sistema **A**. Las energias relativas de Gibbs están expresadas en kcal·mol^{-1} e incluyen los efectos de solvatación considerando el tolueno como disolvente.

Por el contrario, para el sistema **C** (R = CH_2OCH_3), la migración del grupo metoximetilo al N2 a través de **TS4-C** posee la barrera energética más baja de todos los modelos estudiados, presentando una energía libre de activación de 17.5 kcal·mol^{-1}. Este estado de transición se encuentra claramente favorecido por 2.4 kcal·mol^{-1} con respecto a la migración de este grupo al C4 (**TS3-C**). Además, los estados de transición que representan la migración del grupo fenilo están fuertemente desfavorecidos (7.4 kcal·mol^{-1} frente a la migración al C1) (Tabla 2.A.4).

Tabla 2.A.4. Energías libre de activación y electrónicas obtenidas para el modelo **C** (b3lyp/6-31G*). Las energías vienen dadas en kcal·mol^{-1}.

	ΔE_{elact}	$\Delta\Delta E_{el}$	ΔG_{act}	$\Delta\Delta G_{act}$
TS1-C	28.3	9.4	28.3 (24.9)	9.3 (7.4)
TS2-C	33.0	7.4	32.3 (31.3)	13.3 (13.7)
TS3-C	22.4	3.4	21.9 (19.9)	3.6 (2.4)
TS4-C	**19.0**	**0.0**	**18.3 (17.5)**	**0.0**

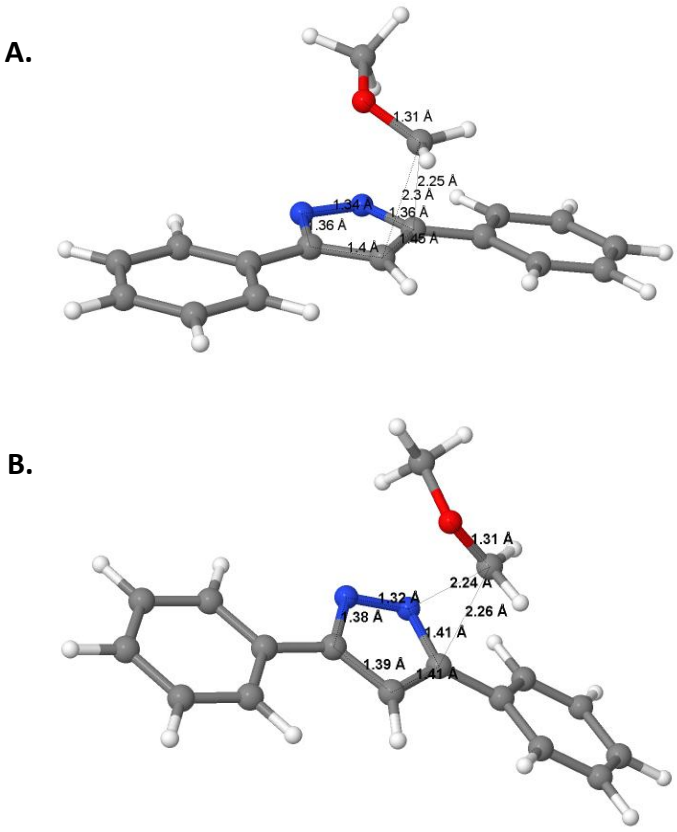
Un resultado muy interesante se deriva del análisis de las geometrías obtenidas para los estados de transición. Para el **TS4-C**, se obtienen distancias muy largas C-C5 (2.26 Å) y C-N2 (2.24 Å), tal y como se muestra en el Esquema 2.A.17. Además, el enlace C-O presenta una distancia muy corta de 1.31 Å debido al carácter parcial del doble enlace que adquiere por la estabilización de la carga positiva incipiente por parte del par de electrones del oxigeno. De hecho, aunque se sigue prediciendo un reagrupamiento [1,5]-sigmatrópico concertado, el estado de transición transcurre con una separación de carga neta.[212] De forma interesante, se pueden localizar tres puntos de silla diferentes para esta transformación en particular, los cuales, se diferencian en la disposición del grupo metoxi. En la conformación más favorable el grupo metoxi se encuentra en una posición endo relativa al anillo de pirazolilio. Esta disposición estaría estabilizada a través de interacciones electrostáticas entre la carga parcial positiva que se encuentra en el átomo de oxígeno y la carga parcial negativa del anillo de pirazolilo. De este modo el estado de transición esta favorecido por tres factores:

1. La estabilización del carbocatión incipiente por el átomo de oxígeno.

2. La naturaleza aromática del anión pirazolilo.

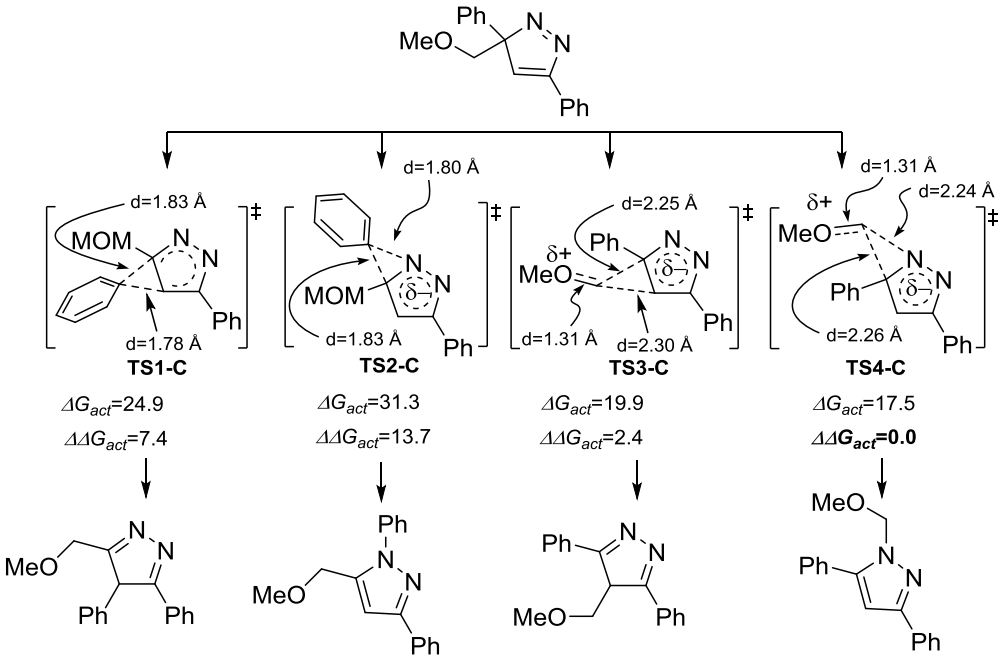
3. La migración del grupo MOM cargado positivamente al N1, el átomo que soporta mayor densidad electrónica dentro del anillo de pirazolilo.

[212] Cálculos de la Coordenada Intrínseca de Reacción (IRC) muestran que, efectivamente, **TS4-B** comunica el 3*H*-pirazol con el 1*H*-pirazol a través de un proceso concertado.



Esquema 2.A.17. Modelo molecular obtenido para **TS3-C** (a) y **TS4-C** (b).

De igual modo, se presenta un esquema resumen con los posibles estados de transición para la transposición del 3*H*-pirazol, las energías de activación para cada uno de ellos así como las distancias observadas en el estado de transición (Esquema 2.A.18).



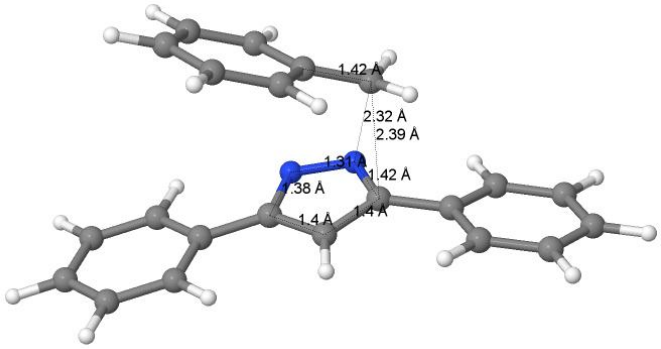
Esquema 2.A.18. Diferentes estados de transición obtenidos para el reagrupamiento [1,5]-sigmatrópico (b3lyp/6-31G*) del sistema **C**. Las energías de Gibbs relativas están expresadas en kcal·mol^{-1} e incluyen los efectos de solvatación considerando el tolueno como disolvente.

Para la serie del bencilo (Esquema 2.A.20), sistema **B**, la situación es muy similar a la descrita para el MOM. En este caso también se encontraron los cuatro posibles caminos de reacción, correspondientes a la migración de los grupos arilo y bencilo a C-4 y N2, respectivamente. La migración del grupo bencilo al N2 presenta el estado de transición más favorable, **TS4-B**, pero las energías de los diferentes estados de transición se encuentran más cercanas que en el sistema **C** (Tabla 2.A.5). Los estados de transición **TS1-B** y **TS2-B** se corresponden con las diferentes migraciones del grupo fenilo. Estos estados de transición poseen unas distancias relativamente cortas para los enlaces que se forman y se rompen (1,80-1,85 Å) típicas de una reacción pericíclica. Sin embargo, la migración del grupo Bn transcurriría a través de los estados de transición **TS3-B** y **TS4-B**, que aunque también son concertados, presentan distancias sustancialmente más largas para los enlaces implicados en la reacción de transposición (2,16-2,32 Å). Estas distancias mayores podrían sugerir que al igual que en el caso del MOM en el estado de transición existiría una separación de carga parcial entre el fragmento de pirazolilo y el bencilo.

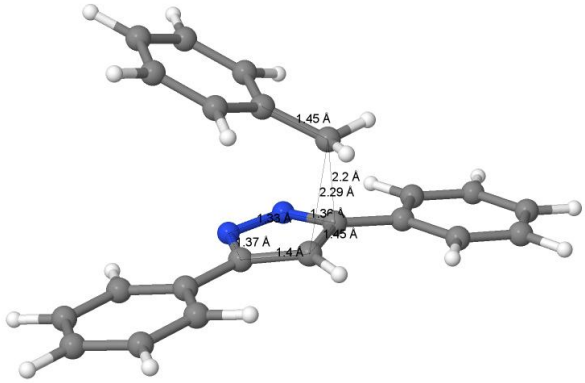
Tabla 2.A.5. Energías libre de activación y electrónicas obtenidas para el modelo **B** en el nivel b3lyp/6-31G* y b3lyp/6311++G**. Las energías están expresadas en kcal·mol^{-1}.

	ΔE_{elact}	$\Delta\Delta E_{el}$	ΔG_{act}	$\Delta\Delta G_{act}$
TS1-B	27.7	4.4	27.8 (24.4)	5.7 (3.2)
TS2-B	31.9	8.5	31.0 (30.1)	8.9 (8.9)
TS3-B	26.8	3.9	25.7 (23.5)	3.2 (2.3)
TS4-B	**23.8**	**0.0**	**22.6 (21.1)**	**0.0**
6-311++G**				
TS1-B	27.9	5.5	27.7	6.5 (3.6)
TS2-B	32.0	9.6	30.8	9.6 (13.4)
TS3-B	25.6	3.2	24.3	3.1 (2.1)
TS4-B	**22.4**	**0.0**	**21.2**	**0.0**

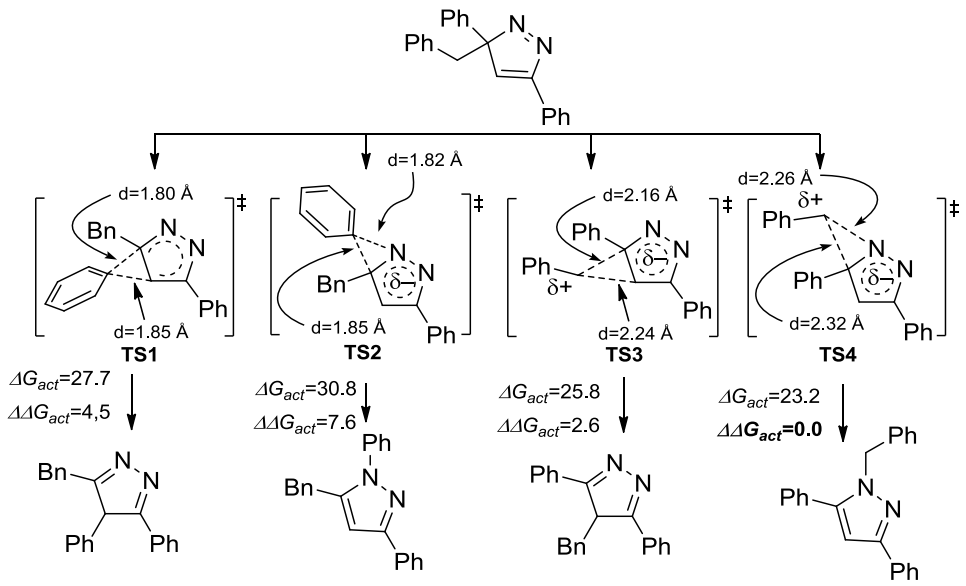
A.



B.



Esquema 2.A.19. Modelos moleculares obtenidos para **TS4-B** (a) y **TS3-B** (b).



Esquema 2.A.20. Diferentes estados de transición para el reagrupamiento [1,5]-sigmatrópico. (b3lyp/6-311++G**). Las energias de los estados de transición están expresadas en kcal·mol^{-1}.

Teniendo en cuenta las energías para cada estado de transición, se puede determinar que el estado de transición **TS4** se encuentra favorecido frente a los demás. De nuevo, esto puede justificarse atendiendo a tres razones:

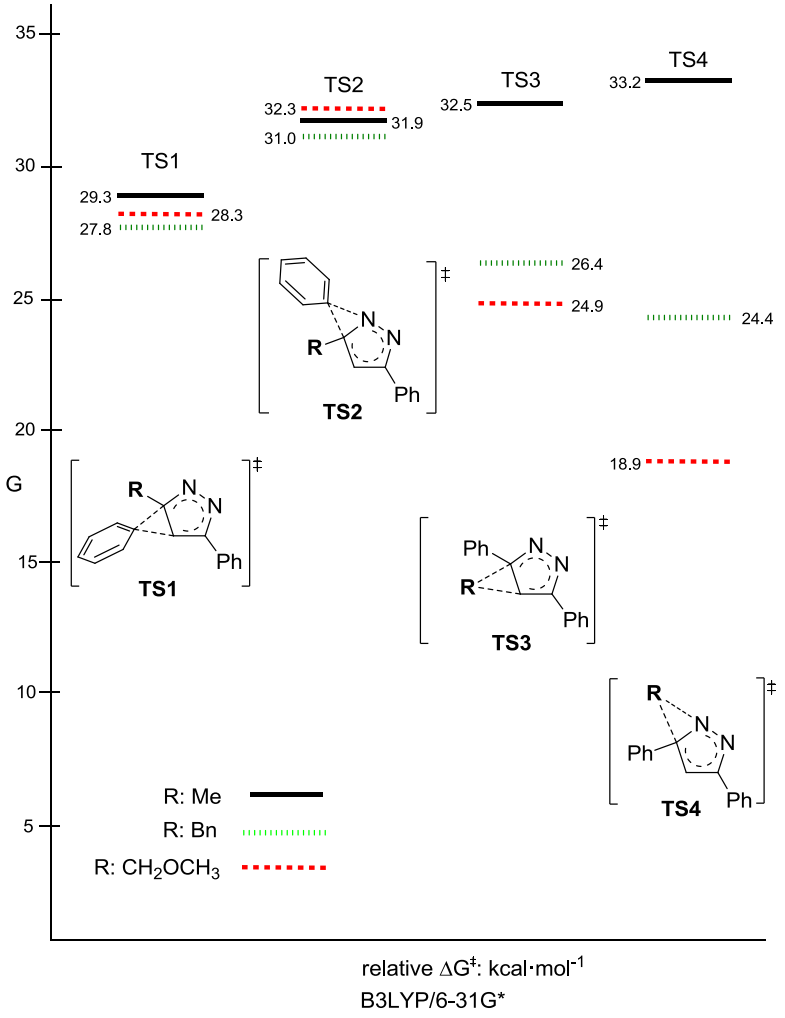
1. La carga parcial positiva generada durante el reagrupamiento se encuentra estabilizada ya que se encuentra en una posición bencílica.

2. El ión pirazolilo incipiente posee cierto carácter aromático.

3. De nuevo, la migración del grupo cargado positivamente ocurre al N, el átomo donde se concentra la mayor densidad electrónica del anillo de pirazolilo.

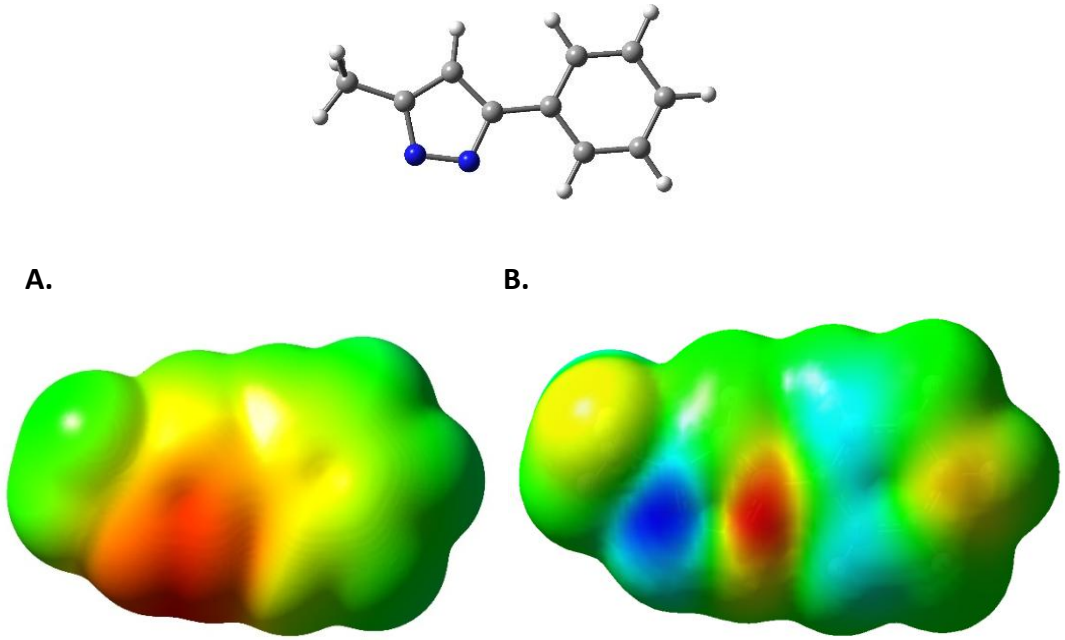
Este razonamiento se encuentra de acuerdo con los resultados observados experimentalmente en el Esquema 2.A.11. Los sustituyentes que contribuyen a la estabilización de la carga positiva generada como son el Bn o el MOM, favorecen el estado de transición en el cual se produce una separación de carga y la posterior migración al átomo de nitrógeno, el cual, soporta mayor carga parcial negativa que el C4 del anillo.

A continuación, se muestra un diagrama donde se compara de forma esquemática las energías de los estados de transición detectados para los diferentes modelos estudiados teóricamente. Así, las energías de activación para la migración del fenilo (**TS1** y **TS2**) no se encuentran afectadas por la sustitución en ninguno de los tres modelos representados (Esquema 2.A.21). También se puede observar la fuerte dependencia que poseen las energías de los estados de transición **TS3** y, principalmente, **TS4**, con la naturaleza del sustituyente. De hecho, la capacidad migratoria de los grupos que poseen C-sp^3 se mejora mediante sustituyentes que estabilizan la carga positiva que se genera en el estado de transición.



Esquema 2.A.21. Representación gráfica de las energías de activación obtenidas para los diferentes caminos de reacción. Los cálculos se llevaron a cabo en el nivel b3lyp/6-31G*.

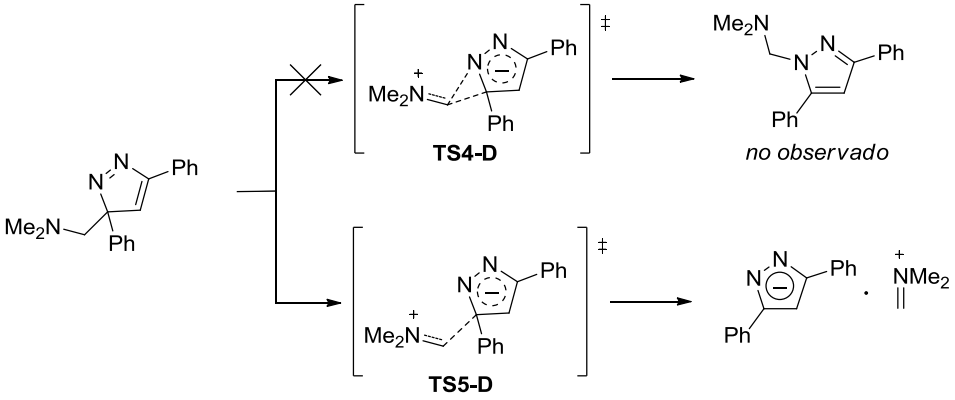
Además, para los sistemas **B** (R=Bn) y **C** (R=MOM), la migración ocurre de forma preferente hacia el átomo de N, el cual, soporta mayor densidad de carga negativa que el C4 (Esquema 2.A.22.**A**). Que la migración se produzca al átomo de nitrógeno también puede ser justificado a través de la Teoría de los Orbitales Frontera, ya que el HOMO para el anión pirazolilo posee mayores valores en las posiciones donde se encuentran los átomos de nitrógeno (Esquema 2.A.22.**B**).



Esquema 2.A.22. Anión pirazolilo: **A)** Representación del potencial electrostático sobre la superficie de isodensidad electrónica, la cual, muestra mayor densidad de carga negativa en las posiciones correspondientes a los átomos de nitrógeno; **B)** Representación del HOMO sobre la superficie de isodensidad electrónica, el cual, muestra valores mayores en los átomos de nitrógeno.

Sin embargo, el balance entre un estado de transición con separación de carga para la reacción de transposición concertada y la disociación de ambos fragmentos se encuentra determinado por la sustitución del grupo C-sp^3. En los resultados experimentales, como se ha comentado anteriormente, se ha observado que la reacción con la hidrazona derivada de la α-dimetilaminoacetofenona conduce exclusivamente a la formación del pirazol disustituido en las posiciones 3,5. Esto indica que se ha perdido el fragmento dimetilamino, en una secuencia que involucra una cicloadición 1,3-dipolar para dar el 3*H*-pirazol **D**, seguido de una reacción de tipo retro-Mannich. Los cálculos

computacionales también conducen a una explicación para este hecho, ya que en este caso, el estado de transición **TS4-D** para un reagrupamiento sigmatrópico concertado no se detecta. En su lugar se encontró **TS5-D**, el estado de transición a través del cual se rompe el enlace C-C y conduce a una especie de tipo par iónico (Esquema 2.A.23). En este caso, la mayor estabilidad del fragmento catiónico dimetilaminometilo hacen que la disociación sea el camino a través del cual transcurre la reacción.



Esquema 2.A.23. Estados de transición posibles para el 3*H*-pirazol proveniente de la cicloadición 1,3-dipolar cuando se emplea la hidrazona derivada de la α-dimetilaminoacetofenona.

A modo de resumen, se puede concluir que los cálculos computacionales sugieren que el reagrupamiento [1,5]-sigmatrópico sucede a través de procesos concertados. Además, se pueden encontrar dos tipos de estado de transición diferentes para este proceso:

1. Un estado de transición con separación de carga cuando el grupo que migra puede estabilizar la carga positiva incipiente generada.

2. Un estado de transición sin separación de carga cuando la estabilización de la carga positiva no es posible.

Finalmente, cabe destacar que estos datos se encuentran en consonancia con los estudios llevados a cabo previamente en la literatura y que se encuentran discutidos en la Sección 2.1.4. De este modo, cuanto mayor sea la capacidad que posea el resto para estabilizar esa carga positiva, más favorecido se encontrará ese estado de transición. En consecuencia, dependiendo de la hidrazona de partida escogida, se debería poder dirigir la regioselectividad hacia la síntesis de pirazoles trisustituidos con diferente patrón de sustitución. En este punto, decidimos aplicar estos conceptos para dirigir la reacción hacia la formación de pirazoles 1,3,5-trisustituidos, difíciles de sintetizar mediante otras rutas sintéticas.

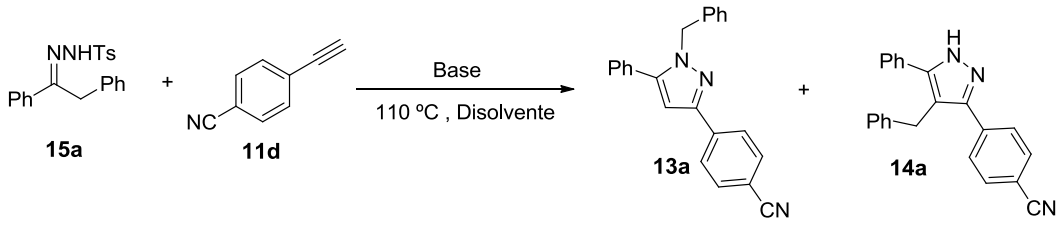
2.A.1.5. Reacción entre las *N*-tosilhidrazonas 15 y los alquinos terminales 11.

2.A.1.5.1. Optimización de la reacción.

Como punto de partida para la búsqueda de las condiciones adecuadas para sintetizar pirazoles 1,3,5-trisustituidos, se decidió escoger la hidrazona derivada de la 2-fenilacetofenona **15a** y el 4-etinilbenzonitrilo **11d**. La elección de la hidrazona permitiría verificar el razonamiento derivado de los cálculos teóricos. A su vez, evaluar también la dependencia de la proporción entre los diferentes pirazoles finales con las condiciones de reacción escogidas. Por todo ello, se desarrolló un estudio diversas variables que van a ser discutidas a lo largo de esta sección.

A continuación, se muestran los resultados más relevantes que se han obtenido en este proceso de optimización. Como se puede observar en la Tabla 2.A.6, la elección del disolvente es un parámetro que juega un papel fundamental. Concretamente, disolventes más polares como DMF (entrada **2**) y CH_3CN (entrada **3**) dirigen la reacción con total regioselectividad hacia el producto **13a** con rendimiento moderado. Este hecho, que había sido observado anteriormente,[202] podría justificarse teniendo en cuenta que los disolventes polares estabilizarán los estados de transición con separación de carga, aumentando la probabilidad que la migración se produzca hacia el nitrógeno. Además, entre las diversas bases estudiadas para esta transformación, de nuevo la más apropiada se corresponde con el K_2CO_3.

Tabla 2.A.6. Estudio de la influencia de la base y del disolvente en la proporción de los pirazoles **13a** y **14a** a partir de la *N*-tosilhidrazona **15a** y el alquino terminal **11d.**

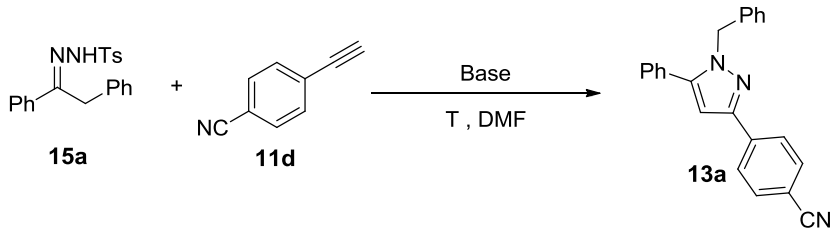


Entrada	Disolvente	Base	13a : 14a	R (13a:14a) (%)
1	**Dioxano**	**K_2CO_3**	2 : 1	34 : 11

2	**DMF**	**K_2CO_3**	1 : 0	43
3	**CH_3CN**	**K_2CO_3**	1 : 0	36
4	**Tolueno**	**K_2CO_3**	3 : 1	67 : 25
5	**THF**	**K_2CO_3**	1 : 0.7	37 : 18
6	**Dioxano**	**NaOH**	4 : 1	50 : 20
7	**DMF**	**NaOH**	1 : 0	18
8	**H_2O**	**NaOH**	1 : 1	34 : 32
9	**DMF**	**KOH**	-	-
10	**DMF**	**LiOH**	1 : 0	25

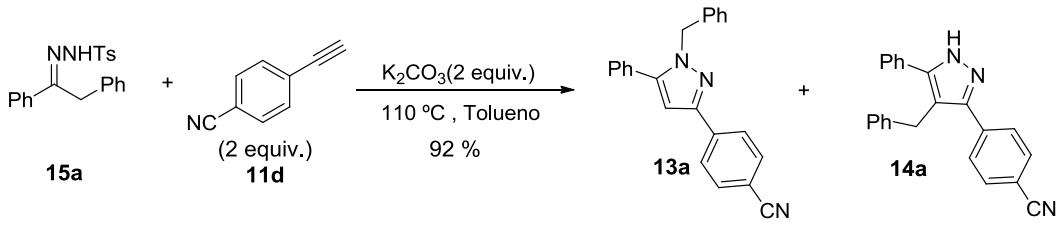
Tras haber quedado de manifiesto la importancia que posee el disolvente, se realizó un estudio con el objetivo de encontrar las condiciones adecuadas empleando DMF como disolvente. De este modo, fue analizada la influencia de la proporción empleada de los diferentes reactivos, el volumen y la temperatur. En cambio, aunque en todos los casos la reacción conduce al producto **13a** de forma regioselectiva, los rendimientos son muy pobres. Además, la adición de un ácido de Lewis, como el $BF_3.OEt_2$, no condujo en ningún caso a la formación del pirazol, observándose productos secundarios pertenecientes a la hidrazona.

Tabla 2.A.7. Estudio de la influencia de la proporción hidrazona **15a** con respecto al alquino **11d**, los equivalentes de base, volumen de disolvente y temperatura en la obtención del pirazol **13a** a partir de la *N*-tosilhidrazona **15a** y el alquino terminal **11d.** (a) El rendimiento correspondiente a la formación del producto **13a** ha sido determinado mediante la adición de un patrón interno en el crudo de reacción empleando ^{1}H-RMN.



Entrada	Base	Equiv. Base	Volumen Disolvente (mL)	Temperatura (^{0}C)	Proporción 15a:11d	*R* 13a (%)[(a)]
1	**K_2CO_3**	2	2.4	110	1 : 1	18
2	**K_2CO_3**	2	2.4	110	1 : 4	23
3	**K_2CO_3**	3	2.4	110	1 : 2	25
4	**K_2CO_3**	1	2.4	110	1 : 2	25
5	**K_2CO_3**	2	2.4	70	1 : 2	20
6	**K_2CO_3**	2	2.4	85	1 : 2	21
7	**K_2CO_3**	2	2.4	130	1 : 2	21
8	**K_2CO_3**	2	1.4	110	1 : 2	19
9	**K_2CO_3**	2	3	110	1 : 2	19

Por tanto, llegando a un término medio entre rendimiento y proporción entre los diferentes pirazoles finales **13a** y **14a**, los mejores resultados obtenidos para reacción entre la tosilhidrazona derivada de la 2-fenilacetofenona **15a** y el 4-etinilbenzonitrilo **11d,** se encontraron empleando K_2CO_3 como base en tolueno a 110 ^{0}C. De este modo, se obtuvo una proporción entre los pirazoles trisustituidos **13a**:**14a** de 3:1, con un rendimiento total del 92 %.



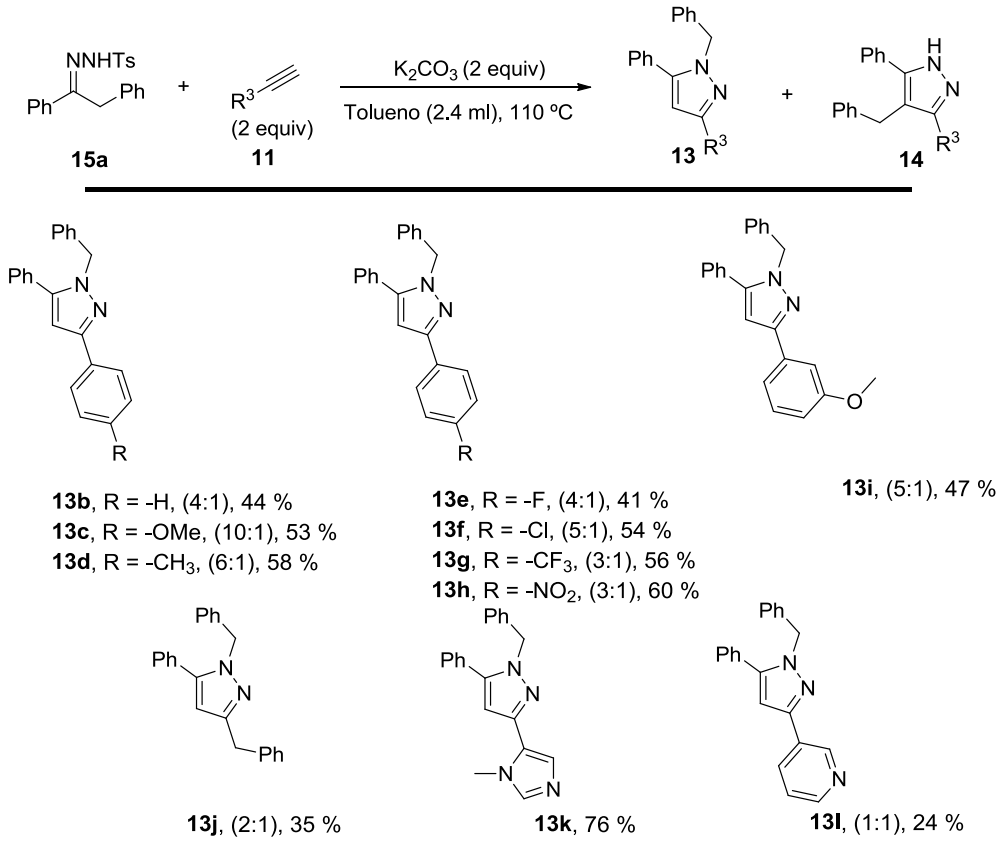
Esquema 2.A.24. Condiciones óptimas seleccionadas para la reacción entre la tosilhidrazona derivada de la 2-fenilacetofenona **15a** y el 4-etinilbenzonitrilo **11d.**

2.A.1.5.2. Generalización de la reacción con respecto al alquino terminal 11 empleado.

Una vez establecidas las condiciones de reacción apropiadas, se procedió inicialmente a abordar el estudio de cómo influye la naturaleza del alquino (Esquema 2.A.25).

La reacción transcurre en todos los casos con rendimientos que van desde buenos a moderados. Además, tolera el empleo de alquinos de muy diversa naturaleza, así, el proceso es compatible con acetilenos que presentan restos tanto deficientes como ricos en electrones (**13b** - **13h**), así como sustituyentes en diferentes posiciones del anillo (**13i**). También, se da lugar la reacción en presencia de heterociclos como el imidazol (**13k**) y la piridina (**13l**), y con el bencilo (**13j**) como representante de un resto alquilo primario. En la mayoría de los casos, se obtuvieron los correspondientes pirazoles 1,3,5-trisustituidos de forma mayoritaria. Es importante destacar que aunque las reacciones proporcionan mezclas de regioisómeros, el regioisómero mayoritario es muy fácilmente separable por cromatografía de columna debido a las diferentes propiedades eluotrópicas de ambos compuestos.

De los datos recogidos en el Esquema 2.A.25, se puede deducir una cuestión importante. El empleo de sustituyentes ricos en electrones en el alquino, así como anillos π-excedentes conducen de forma totalmente regioselectiva a la formación del pirazol 1,3,5-trisustituido. Esto indica que la naturaleza del alquino empleado afecta de forma directa a la reacción de transposición. Una posible explicación sería que los sustituyentes dadores de electrones contribuyen a aumentar la densidad de carga del fragmento pirazolilo en el estado de transición. De esta forma, se dota de mayor densidad electrónica al N del anillo y en consecuencia, se favorece la migración hacia ese núcleo generando el correspondiente pirazol 1,3,5-trisustituido como único producto.



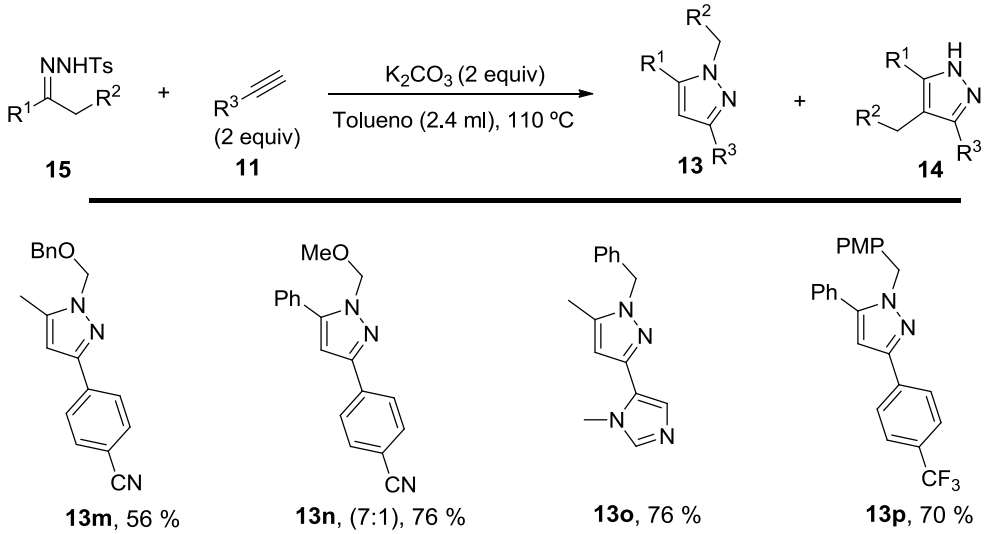
Esquema 2.A.25. Generalización de la reacción con respecto al alquino terminal empleado **11**. El rendimiento expresado corresponde con el obtenido para el regioisómero mayoritario puro aislado tras cromatografía de columna.

2.A.1.5.3. Generalización de la reacción con respecto a la hidrazona de partida 15 empleada.

Una vez examinada la influencia del alquino, se dispuso el estudio de la naturaleza de la hidrazona **15** empleada. En el Esquema 2.A.26 y Esquema 2.A.27, se recogen los resultados recopilados durante el proceso. Aunque la reacción se muestra muy general, requirió una optimización individualizada para cada uno de los sustratos de partida.

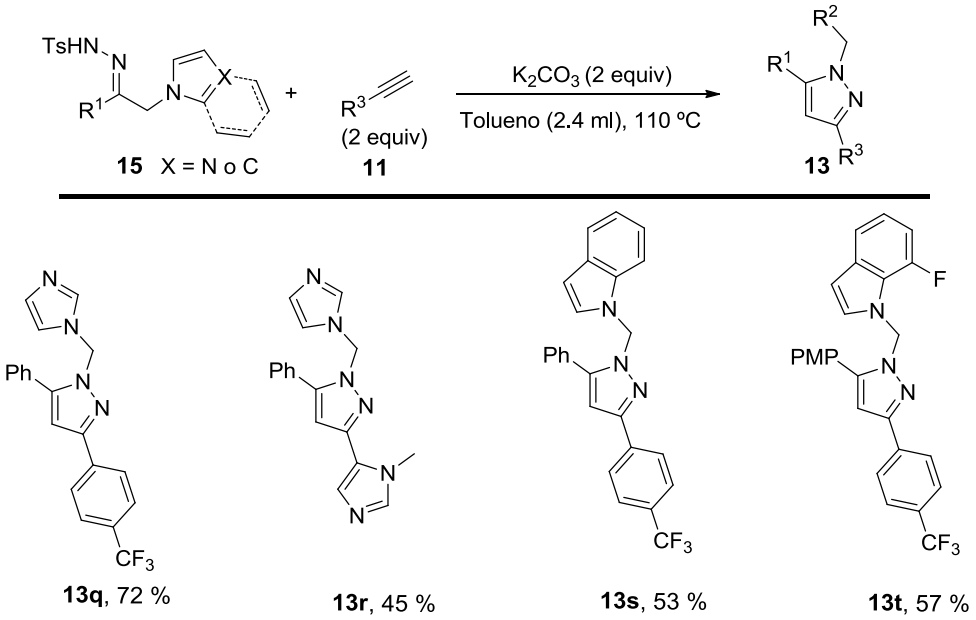
Como se puede observar (Esquema 2.A.26), la incorporación de grupos que sean capaces de estabilizar la carga positiva generada en el estado de transición conducen de forma totalmente regioselectiva a la formación del pirazol 1,3,5-trisustituido con rendimientos buenos. A modo de ejemplo, la introducción de un resto metoxi en el anillo (**13n**) o el empleo de un grupo benciloxi (**13m**) o alcoximetilo (**13p**) en el

fragmento que migra, da lugar a una elevada o completa regioselectividad obteniéndose de forma mayoritaria el producto correspondiente al pirazol **13**.



Esquema 2.A.26. Generalización con respecto a la hidrazona **15** empleada. (a) La reacción fue llevada a cabo empleando NaOH como base. (b) Empleo de dioxano como disolvente. (c) Empleo de 4 equivalentes del correspondiente alquino.

En este punto, y teniendo en cuenta los resultados de la hidrazona *N*-dimetilamino sustituida, se decidió emplear sustituyentes nidrogenados con menor capacidad π-dadora. Con esta idea, se emplearon hidrazonas derivadas de cetonas α-*N*-azol sustituidas (**13q**-**13t**). De forma satisfactoria, la reacción se mostró totalmente regioselectiva, demostrando la capacidad de estos sustituyentes para estabilizar el carbocatión incipiente generado de forma adecuada (Esquema 2.A.27). Desde el punto de vista sintético, se trata de una reacción muy atractiva, ya que en una única operación sintética se ensamblan pirazoles trisustituidos con gran diversidad estructural difícilmente accesibles por otros métodos. Como ejemplo, en un solo paso de reacción, se puede acceder al producto **13r**, el cual, contiene 3 heterociclos de cinco eslabones diferentes en su estructura.



Esquema 2.A.27. Generalización con respecto a la tosilhidrazona **15** derivada de cetonas α-*N*-azol sustituidas.

2.A.1.5.4. Influencia de los sustituyentes en la regioselectividad: Relación lineal de energía libre.

Como se ha visto en los apartados anteriores, el sentido de la reacción de transposición (a C4 o N1) viene determinado por las características electrónicas de los sustituyentes. La influencia del grupo que migra puede racionalizarse teniendo en cuenta la mayor estabilización del estado de transición con separación de carga por efecto de grupos electrón dadores. Sin embargo, el efecto del sustituyente en C3 es más difícil de justificar. En un intento de entender mejor este efecto, se llevo a cabo un estudio de la influencia de sustituyentes con diferentes propiedades electrónicas en la regioquímica de la reacción.

Un método clásico de racionalizar la influencia de los sustituyentes en reacciones en química orgánica es el estudio de la existencia de relaciones lineales de energía libre por aplicación de la ecuación de Hammett.

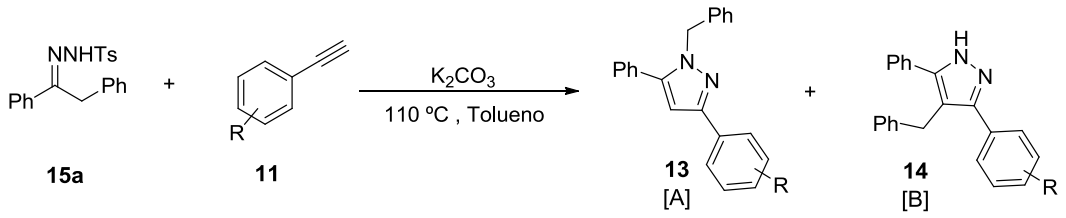
A partir de la ecuación de Hammett (Esquema 2.A.28)[213] se puede llevar a cabo una relación entre las constantes de equilibrio o velocidad y el efecto provocado por la propia naturaleza de los sustituyentes.

$$log\left(\frac{K}{K_0}\right) = \rho\sigma$$

Esquema 2.A.28. Ecuación de Hammett.

De forma breve, *K* se corresponde con la constante de equilibrio para la reacción a estudiar con el sustituyente apropiado y K_0, la constante de equilibrio de referencia donde el sustituyente es igual a un hidrógeno. El símbolo σ es la constante asociada al sustituyente, la cual se encuentra ya establecida para cada grupo y mide el efecto electrónico del mismo dependiendo de la posición en la que se encuentre. Finalmente, ρ mide la sensibilidad de la reacción a los efectos electrónicos del propio sustituyente y se corresponde con la pendiente de la línea una vez representados los datos en una gráfica.

Para completar este estudio, se escogió como reacción modelo la representada en el Esquema 2.A.29. De este modo, se enfrentó la hidrazona **15a** a arilacetilenos sustituidos con restos de diversa naturaleza electrónica y se estudió la proporción correspondiente para cada uno de los pirazoles **13** [A] y **14** [B]. Esta proporción fue medida en el espectro de resonancia magnética nuclear del crudo de la reacción. Así, al representar la relación de los dos pirazoles regioisómeros frente al valor del parámetro σ, se encuentra una cierta corelación lineal.

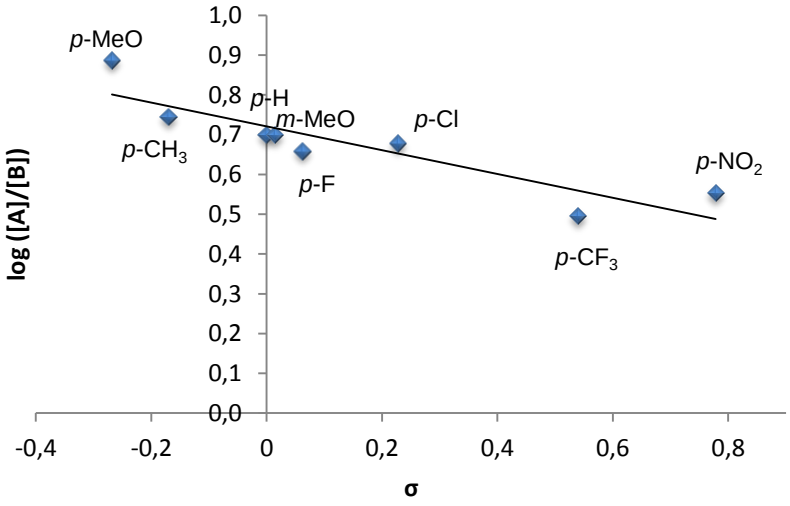


15a **11** **13** [A] **14** [B]

	[A]	[B]	Log[A]/[B]	σ
***p*F**	1,00	0,22	0,66	0,062
***p*Cl**	1,00	0,21	0,68	0,227
***p*CH_3**	1,00	0,18	0,74	-0,17
***p*NO_2**	1,00	0,28	0,55	0,778

[213] F. A. Carroll, *Perspectives on Structure and Mechanism in Organic Chemistry*, Brooks/Cole Publishing Company, **1998**.

***p*H**	1,00	0,20	0,70	0
***p*CF_3**	1,00	0,32	0,49	0,54
***p*MeO**	1,00	0,13	0,89	-0,268
***m*MeO**	1,00	0,20	0,70	0,015



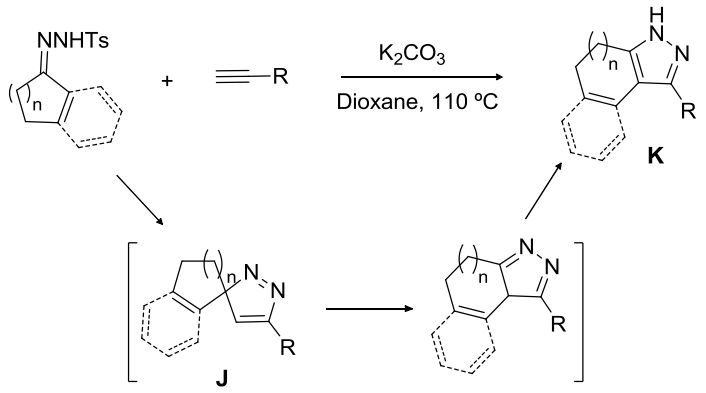
Esquema 2.A.29. Representación lineal del logaritmo de las concentraciones con respecto a σ.

Como se puede observar en la gráfica, se obtiene un valor negativo para ρ. Esto confirma que, efectivamente, los sustituyentes electróndadores favorecen la reacción de transposición hacia N2 frente a la migración a C4.

2.A.1.6. Reacción entre las *N*-Tosilhidrazonas 16 y los alquinos terminales 11.

2.A.1.6.1. Estudios preliminares y optimización.

Finalmente, nos dispusimos a estudiar reacciones con las hidrazonas cíclicas **16**. En este caso, se esperaba que una vez producida la cicloadición [3+2] se generaría un intermedio de pirazol espirocíclico **J**. Este intermedio evolucionaría mediante un reagrupamiento sigmatrópico, permitiendo el acceso a los pirazoles benzofusionados **K**, en los cuales se habría producido una expansión del carbociclo (Esquema 2.A.30).



Esquema 2.A.30. Predicción para la síntesis de pirazoles empleando las hidrazonas cíclicas **16**.

Se ha demostrado que este tipo de pirazoles fusionados presentan numerosas actividades biológicas.[214] En concreto, para los benzocicloheptapirazoles, se ha comprobado su actividad como antagonistas del receptor cannabinoide CB1. En este campo, se ha demostrado que la manipulación de este tipo de receptores inhibe ciertos trastornos alimenticios en humanos sin producir efectos colaterales en el sistema nervioso central.[215] Un ejemplo de este tipo de moléculas son los que se muestran en la Figura 2.A.1.

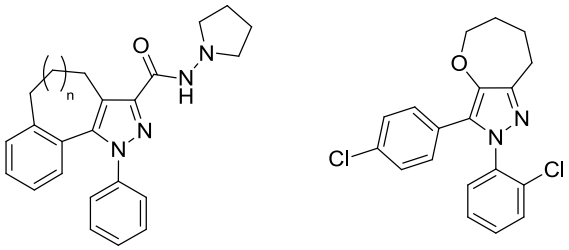


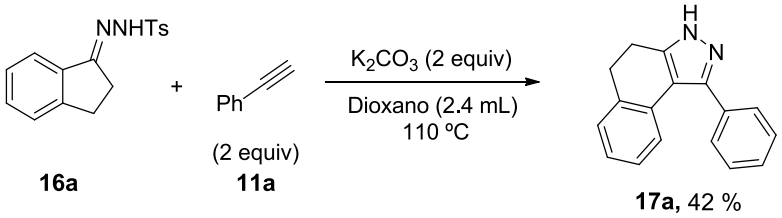
Figura 2.A.1. Ejemplos de pirazoles fusionados con actividad biológica.

De este modo, se decide poner a prueba las condiciones de reacción inicialmente empleadas en la síntesis de pirazoles 3,4,5-trisustituidos, con el objetivo de probar nuestra predicción. Para ello, se escogieron como sustratos modelo la hidrazona

[214] a) Z. Sui, J. Guan, M. P. Ferro, K. McCoy, M. P. Wachter, W. V. Murray, M. Singer, M. Steber, D. M. Ritchie, D. C. Argentieri, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 601; b) S. Löber, H. Hübner, P. Gmeiner, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2377.

[215] R. L. Dow, P. A. Carpino, D. Gautreau, J. R. Hadcock, P. A. Iredale, D. Kelly-Sullivan, J. S. Lizano, R. E. O'Connor, R. S. Scheneider, D. O. Scott, K. M. Ward, *ACS Med. Chem. Lett*. **2012**, *3*, 397.

derivada de la indanona **16a** y el fenilacetileno **11a** en presencia de K_2CO_3 como base y dioxano como disolvente a 110 °C (Esquema 2.A.31).

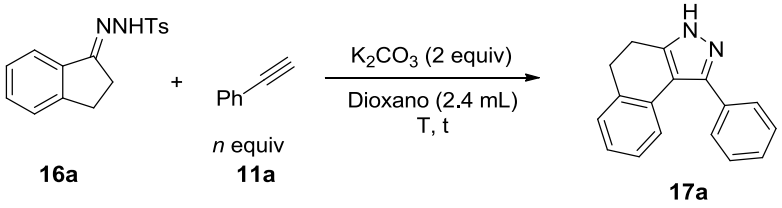


Esquema 2.A.31. Reacción de la tosilhidrazona **1a** y el alquino **11a** en presencia de K_2CO_3 como base en dioxano a 110 °C empleando calefacción clásica.

Satisfactoriamente, la reacción tiene lugar mediante el mecanismo propuesto. Así, aunque el rendimiento es moderado, la estrategia permite acceder al pirazol cíclico **17a** benzofusionado de forma completamente regioselectiva, donde el grupo arilo migra exclusivamente hacia el átomo de carbono C4 del anillo de pirazol.

En este punto, se llevó a cabo un estudio de diferentes variables con el fin de mejorar el rendimiento obtenido. En la Tabla 2.A.8, se recogen los resultados más representativos. Sin embargo, a pesar de la extensa exploración de bases, disolventes, temperatura y proporción de los reactivos de partida, no se consiguió mejorar el rendimiento inicial.

Tabla 2.A.8. Influencia de la fuente de calefacción y la proporción entre la hidrazona **16a** y el alquino **11a** de partida.



Entrada	Fuente de calefacción	T (°C)	t	16a:11a	Rendimiento (%)
1	CC	110	24 h	1 : 1	16 %
2	CC	110	24 h	2 : 1	-
3	CC	110	24 h	1 : 2	42 %

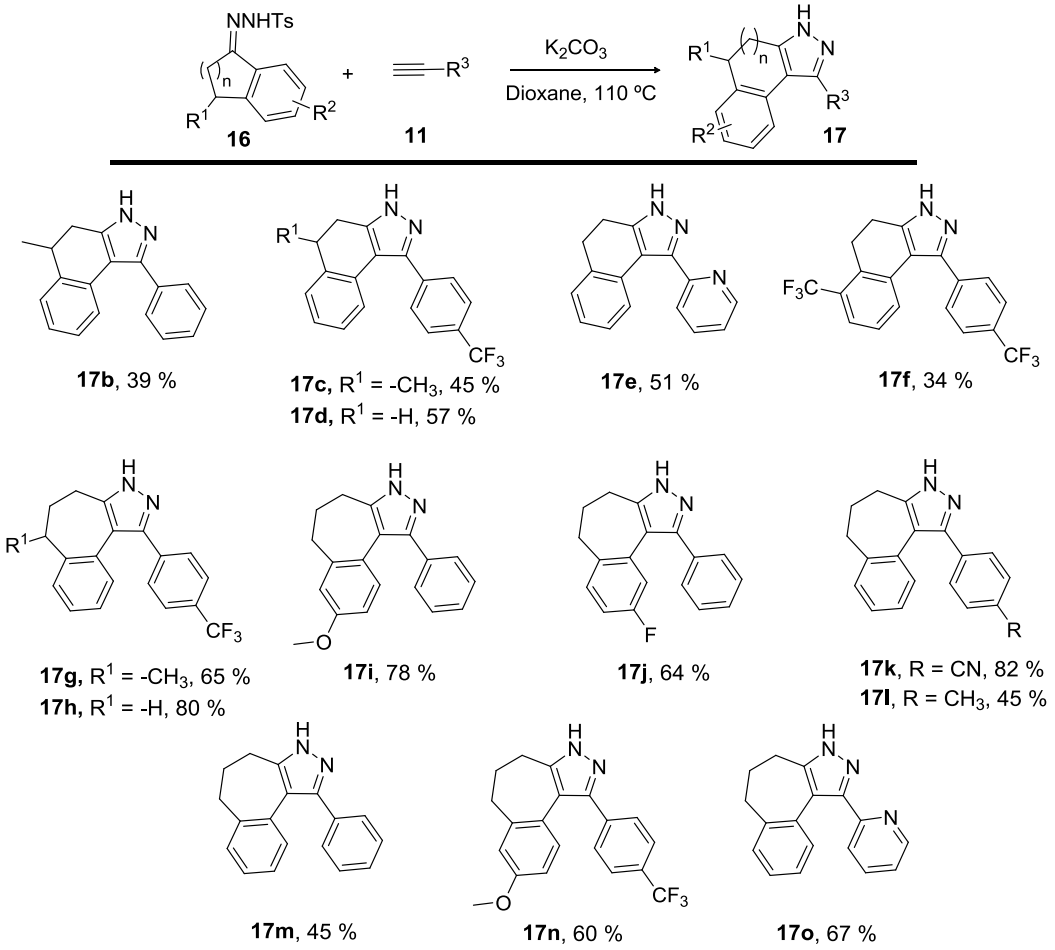
4	MW	150	30 min	1 : 2	12 %

CC=Calefacción Clásica

Por tanto, las condiciones óptimas para esta transformación consistirían en una proporción 1:2 de hidrazona:alquino para 0.3 mmol de tosilhidrazona de partida empleando 2 equivalentes de K_2CO_3 en 2.4 mL de dioxano a 110 °C durante 24 horas (Esquema 2.A.31).

2.A.1.6.2. Generalización de la reacción de síntesis de pirazoles 17 empleando tosilhidrazonas cíclicas 16 y alquinos terminales 11.

Seguidamente se llevo a cabo un estudio del alcance de la reacción. El proceso se presenta general, ya que transcurre con rendimientos que van desde buenos a moderados con hidrazonas **16** derivadas de la tetralona e indanona (**17a**-**17o**). Estas hidrazonas, a su vez, se pueden encontrar sustituidas con diferentes restos en diferentes posiciones, tanto del carbociclo como de la parte aromática. Además, la reacción se pudo llevar a cabo con éxito empleando sustratos **11** muy diversos desde el punto de vista electrónico (Esquema 2.A.32).



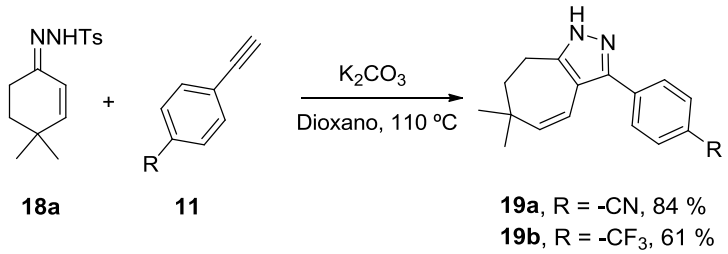
Esquema 2.A.32. Generalización de la reacción entre la tosilhidrazona cíclica **16** y el alquino terminal **11**.

Así, se accede a un método de síntesis de pirazoles fusionados a ciclos de seis y siete eslabones, difíciles de obtener mediante las rutas sínteticas convencionales.[216]

Adicionalmente, esta transformación pudo ser llevada a cabo con la hidrazona procedente de la ciclohexenona **18a**, dando lugar a los benzocicloheptapirazoles **19** con muy buenos rendimientos y de forma totalmente regioselectiva. Los productos

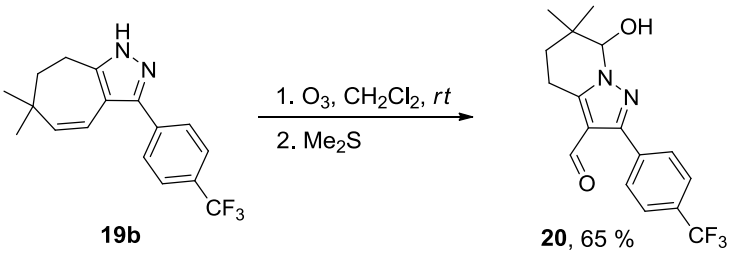
[216] Posteriormente a la publicación de nuestro trabajo de investigación, Allywood y colaboradores desarrollaron una extensión de esta reacción utilizando condiciones muy semejantes a las descritas en esta memoria. En ella, se generan diversos sistemas policíclicos a partir de hidrazonas cíclicas y alquinos terminales: R. R. Merchant, D. M. Allwood, D. C. Blakemore, S. V. Ley, *J. Org. Chem*. **2014**, *79*, 8800.

obtenidos se corresponde con la migración del carbono sp^2 al C-4 del anillo del pirazol (Esquema 2.A.33).[217]



Esquema 2.A.33. Síntesis de benzocicloheptapirazoles **19** a partir de la hidrazona derivada de la ciclohexenona **18** y el alquino terminal **11**.

Estos pirazoles pueden resultar muy útiles como intermedios ya que mediante protocolos muy simples, se puede funcionalizar u oxidar el doble enlace. A modo de ejemplo, la ozonolisis del compuesto **19b** da lugar al tetrahidropiridinopirazol **20** (Esquema 2.A.34).



Esquema 2.A.34. Reacción de ozonolisis del bencicloheptapirazol **19b** para generar el tetrahidropiridinopirazol **20**.

Un aspecto muy interesante de este nuevo pirazol tetrasustituido es la presencia de grupos suceptibles de una posterior derivatización. Por otra parte, el esqueleto de pirazolo-[1,5-a]isoquinolinas se encuentra presente en numerosos compuestos con actividad farmacológica, tales como antibióticos y anticonvulsivos (Figura 2.A.1)

[217] Esta migración fue comprobada mediante experimentos de RMN bidimensional NOESY. Ver apéndice de espectros.

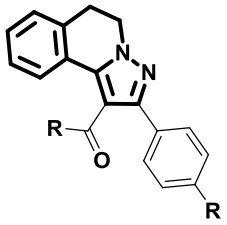
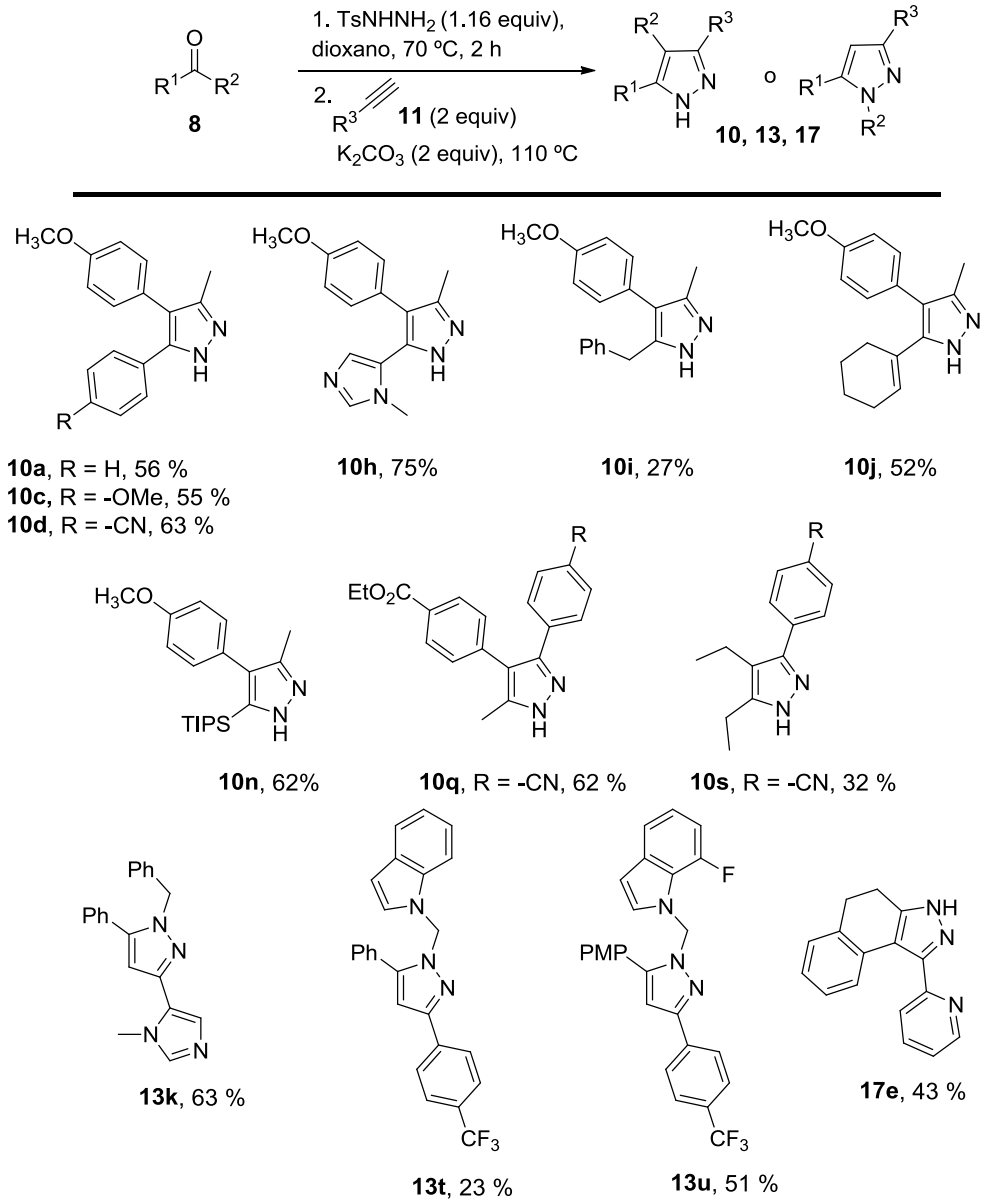


Figura 2.A.2

2.A.1.7. Variaciones en el procedimiento operativo: reacción *one-pot* y reacciones a escala gramo.

Una vez establecida la metodología para llevar a cabo la síntesis de una amplia familia de pirazoles trisustituidos, se valoró la posibilidad de llevar a cabo el proceso sin aislar la *N*-tosilhidrazona de partida. De este modo, al igual que fue comentado en el Capítulo 1 (Seccion 1.2.3.6), se desarrollaría un proceso *one-pot* en el cual se parte directamente del carbonilo y la tosilhidracida.

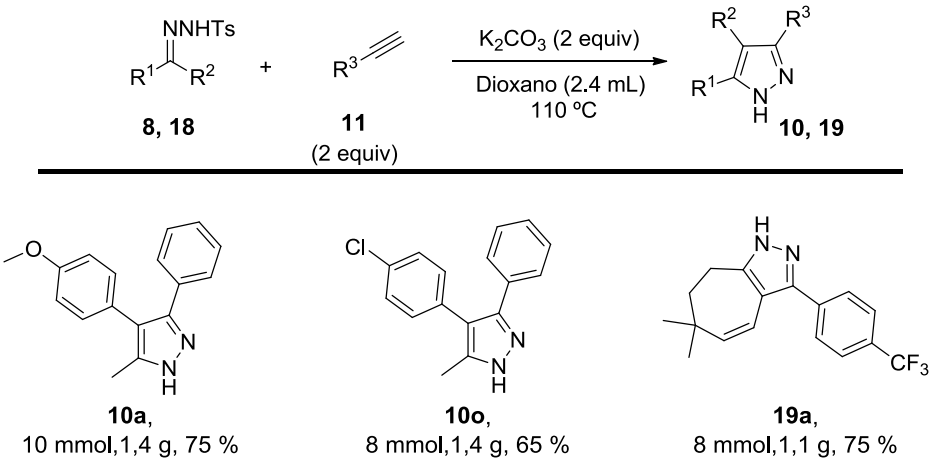
Para ello, la hidrazona se preforma *in situ* mediante calentamiento de la hidracida con los correspondientes compuestos carbonílicos en dioxano a 70 °C durante 2 horas. A continuación, se deja que alcance temperatura ambiente y se añade la base y el alquino y la mezcla se calienta a 110 °C durante 24 horas (Esquema 2.A.35). Siguiendo este protocolo es posible preparar los pirazoles 3,4,5- y 1,3,5-trisustituidos con idénticas regioselectividades. No obstante, los rendimientos son ligeramente inferiores a los obtenidos utilizando la hidrazona aislada.



Esquema 2.A.35. Reacción *one-pot* de síntesis de pirazoles a partir de compuestos carbonílicos **8** y alquinos terminales **11**.

Además, otro aspecto muy interesante es la posibilidad de desarrollar la reacción a gran escala. Así, siguiendo el protocolo establecido se ha podido sintetizar diferentes pirazoles en escala de gramo. En el Esquema 2.A.36, para cada producto se muestra la cantidad obtenida y los milimoles de partida de la hidrazona correspondiente.

Los rendimientos obtenidos resultaron ser semejantes a los proporcionados a una escala treinta veces inferior. Considerando la accesibilidad de los reactivos de partida y la simplicidad del proceso, este método se presenta como una alternativa óptima en términos de eficiencia y economía para la preparación de pirazoles trisustituidos.



Esquema 2.A.36. Ejemplos de la reacción de síntesis de pirazoles en escala de gramo.

2.A.1.8. Empleo de tosilhidrazonas trifluorometiladas 21: cambio en la reactividad.

Durante este capítulo se ha destacado la importancia de la estructura de pirazol en la industria farmacéutica y agroquímica.[143] En este contexto, concretamente, los pirazoles trifluorometilados en la posición 3 ha sido objeto de numerosos estudios, puesto que han demostrado poseer actividad biológica. De hecho, esta estructura se encuentra presente en numerosos fármacos así como en insecticidas. A modo de ejemplo se muestra en la Figura 2.A.3 el Mavacoxib[218] empleado para la artritis, Razaxaban[219] el cual se utiliza como anticoagulante y DP-23[220] que posee actividad como insecticida.

[218] S. R. Cox, S. P. Lesman, J. F. Boucher, M. J. Krautmann, B. D. Hummel, M. Savides, S. Marsh, A. Fielder, M. R. Stegemann, *J. Vet. Pharmacol. Ther.* **2010**, *33*, 461.
[219] J. G. Varnes, D. A. Wacker, D. J. P. Pinto, M. J. Orwat, J. P. Theroff, B. Wells, R. A. Galemo, J. M. Luettgen, R. M. Knabb, S. Bai, K. He, P. Y. S. Lam, R. R. Wexler, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 749.
[220] G. P. Lahm, T. P. Selby, J. H. Freudenberger, T. M. Stevenson, B. J. Myers, G. Seburyamo, B. K. Smith, L. Flexner, C. E. Clark, D. Cordova, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4898.

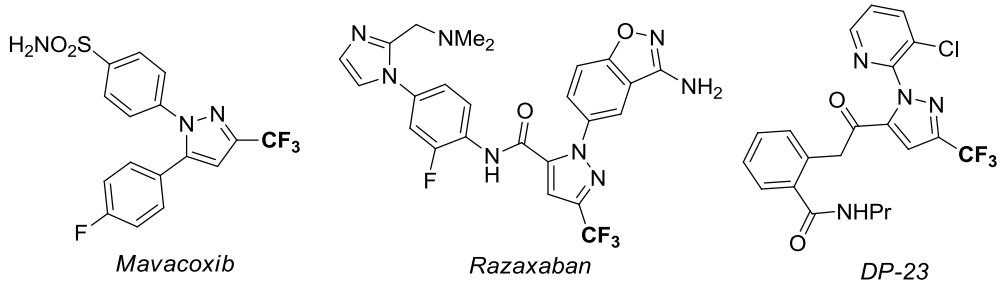
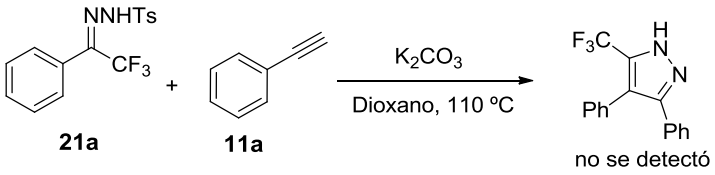


Figura 2.A.3. Ejemplos de pirazoles sustituidos en la posición 3 con actividad biológica.

Generalmente, la síntesis de estas estructuras se lleva a cabo a partir de ciclocondensaciones de la hidracina apropiada con el correspondiente compuesto 1,3-dicarbonílico, con las limitaciones en cuanto a regioselectividad se refiere que estos protocolos poseen.

En este contexto, nos propusimos abordar la síntesis de pirazoles trifluorometilados empleando nuestra metodología, puesto que, seleccionando la hidrazona apropiada, la ruta de acceso a estos pirazoles debería ser muy sencilla. Para ello, se seleccionó como ensayo modelo la reacción entre la hidrazona derivada de la 2,2,2-trifluoroacetofenona **21a** y el fenilacetileno **11a** empleando las condiciones descritas para la síntesis de los pirazoles 3,4,5-trisustituidos (Sección 2.A.1.2), tal y como se muestra en el Esquema 2.A.37.[221]



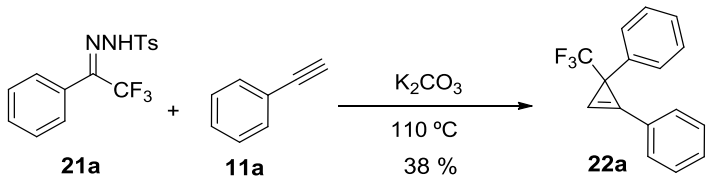
Esquema 2.A.37. Estudio inicial en la reacción entre la hidrazona derivada de la 2,2,2-trifluoroacetofenona **21a** y fenilacetileno **11a**.

Desafortunadamente, no se obtuvo el correspondiente pirazol trifluorometilado. Mediante un estudio exhaustivo del espectro del crudo de reacción, se observó una mezcla compleja, en la cual, señales típicas indicaban que probablemente el disolvente entraba en juego en algún punto del proceso. Si esto era así, la hidrazona reaccionaría antes con el propio disolvente que con el alquino, hecho sin precedentes en nuestro

[221] Síntesis de pirazoles trifluorometilados a partir de tosilhidrazonas o diazocompuestos: a) R. S. Foster, H. Jakobi, J. D. A. Harrity, *Org. Lett.* **2012**, *14*, 4858; b) F. Li, J. Nie, L. Sun, Y. Zheng, J.-A. Ma, *Angew. Chem. Int. Ed*. **2013**, *52*, 870; c) G. Ji, X. Wang, S. Zhang, Y. Xu, Y. Ye, M. Li, Y. Zhang, J. Wang, *Chem. Commun*. **2014**, *50*, 4361.

grupo de investigación y además, resultaría un comportamiento distinto de la hidrazona con respecto a las empleadas con anterioridad.

Así, para comprobar esta hipótesis, decidimos iniciar un estudio de la reactividad de estas hidrazonas frente al alquino en ausencia de disolvente. Para ello, se llevó a cabo la reacción usando un gran exceso de alquino (10 equiv), únicamente en presencia de base. De forma inesperada, en lugar del pirazol, se obtuvo la formación de un nuevo producto, el ciclopropeno **22a** (Esquema 2.A.38). Esta reacción involucra la formación de dos nuevos enlaces C-C entre el carbono hidrazónico y los carbonos del triple enlace, que conduce al ciclopropeno final **22a** con un rendimiento del 38%.[222]

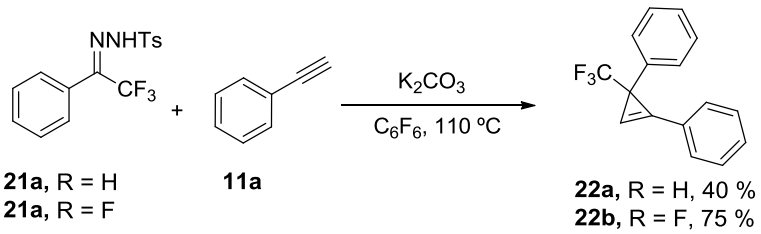


Esquema 2.A.38. Reacción entre la hidrazona derivada de la 2,2,2-trifluoroacetofenona **21a** y fenilacetileno **11a** en ausencia de disolvente.

Debido a este cambio de reactividad, resulta una reacción muy interesante y complementaria a lo estudiado hasta ahora en esta Memoria. A través de una exhaustiva optimización de la reacción de ciclopropenación, en la cual se estudió la influencia de la base y del disolvente, las condiciones óptimas para esta transformación corresponderían con el empleo de 2 equivalentes de alquino, K_2CO_3 como base, empleando hexafluorobenceno[223] como disolvente a 110 ^{0}C durante 12 horas (Esquema 2.A.39.).

[222] Síntesis de ciclopropenos triflurometilados a partir de diazocompuestos y alquinos, B. Morandi, B. Mariampillai, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 1101.

[223] La utilización de este disolvente fue esencial, puesto que se comporta como "mero observador" del proceso. El empleo de otros disolventes condujo a la formación de mezclas complejas en las que pudieron identificarse cantidades apreciables de compuestos derivados de la inserción del carbeno generado a partir de de la tosilhidrazona en enlaces C-H del disolvente.



21a, R = H
21a, R = F

11a

22a, R = H, 40 %
22b, R = F, 75 %

Esquema 2.A.40. Reacción de ciclopropenación entre hidrazonas derivada de la 2,2,2-trifluoroacetofenona **21a, 21b** y fenilacetileno **11a**.

Mediante este protocolo se ha podido acceder a los ciclopropenos **22a** y **22b**. Identificándose de este modo, una reactividad totalmente diferente a la desarrollada a lo largo de este Capítulo. Los resultados presentados en este apartado corresponden a los estudios preliminares, así, tanto la generalidad como el mecanismo de reacción siguen estudiándose en nuestro grupo.

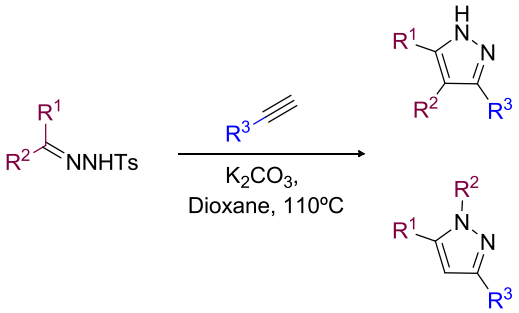
2.A.2. CONCLUSIONES

En la parte A de este Capítulo se ha presentado un nuevo método para sintetizar pirazoles con diferentes patrones de sustitución. A partir del protocolo descrito se puede acceder a estructuras de pirazoles trisustituidos de forma altamente regioselectiva. Este proceso transcurre a través de una reacción en cascada que implica una cicloadición [3+2] seguida de un reagrupamiento [1,5]-sigmatrópico, en el cual, se produce la migración del resto procedente de la hidrazona hacia el carbono C4 o hacia el nitrógeno N2.

Se ha mostrado que la naturaleza de los sustituyentes procedentes de la hidrazona son los que gobiernan la propia migración de la cadena, generando pirazoles 3,4,5- o 1,3,5-trisustituidos en un solo paso de reacción. Además, el empleo de hidrazonas cíclicas permite el acceso a pirazoles benzofusionados difíciles de preparar de otro modo. Es más, el proceso puede llevarse a cabo de forma *one-pot* generando la N-tosilhidrazona *in situ* a partir del correspondiente compuesto carbonílico. Finalmente, se ha mostrado los resultados iniciales observados en el empleo de tosilhidrazonas trifluorometiladas en la síntesis de ciclopropenos.

Los pirazoles son estructuras muy importantes en la industria farmacéutica y agroquímica. A lo largo de este capítulo se ha puesto de manifiesto el alto potencial sintético de esta transformación con respecto a los métodos de síntesis descritos en la literatura. Esto es debido a que la reacción transcurre en ausencia de un catalizador metálico y de forma regioselectiva, los reactivos de partida son comerciales o fácilmente accesibles, y la simplicidad operacional es destacable.

2.A.3. RESUMEN GRÁFICO



Único isómero....

R^1 = Me, R^2 = Arilo

R^1 = Me, R^2 = Alquenilo

Isómero mayoritario o o único isómero...

R^1 = Alquilo, Arilo

R^2 = Bn, CH_2X

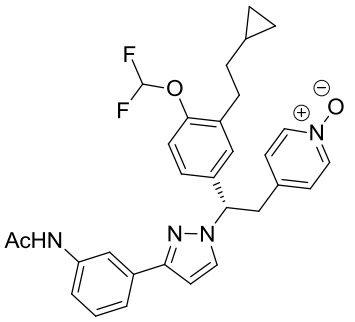
PARTE B:

SÍNTESIS DE PIRAZOLES QUIRALES A TRAVÉS DE UNA SECUENCIA DE CICLOADICIÓN 1,3-DIPOLAR Y UN REAGRUPAMIENTO [1,5]-SIGMATRÓPICO CON MIGRACIÓN DE UN GRUPO ESTEREOGÉNICO CON RETENCIÓN DE LA CONFIGURACIÓN.

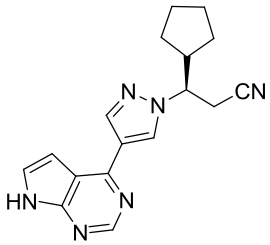
2.B.1. INTRODUCCIÓN.

2.B.1.1. Pirazoles quirales. Consideraciones generales.

Los compuestos heterocíclicos ópticamente activos son moléculas que se pueden encontrar comúnmente en productos naturales así como en numerosos medicamentos. Sin embargo, concretamente, moléculas con actividad biológica constituidas por un anillo de pirazol con un sustituyente quiral, son escasas. En el Esquema 2.B.1, se muestran algunos de estos productos.



2.B.1



2.B.2. *Ruxolitinib*

Esquema 2.B.1. Ejemplos de pirazoles quirales con actividad biológica.

Por ejemplo, la molécula **2.B.1** se presenta como un potente inhibidor de PDE4 (Fosfodiesterasa tipo 4) utilizado en el tratamiento de diversas enfermedades inflamatorias[224] o el ruxolitinib **2.B.2**, el cual, se encuentra muy extendido en el tratamiento de la mielofibrosis.[225]

Los limitados ejemplos que existen de estos pirazoles quirales es debido, principalmente, a la dificultad que presenta su propia síntesis de forma enantiopura. Una revisión de la bibliografía existente mostrada a continuación, revela la escasez de métododologías efectivas que permitan el acceso a estas estructuras.

[224] a) E. S. John, A. David, S. Carol, I*mmunopharmacology* **2000**, *47*, 127; b) D. H. Miles, S. Peter, Y. J. Z. Kam, *Drug Discovery Today* **2005**, *10*, 1503.
[225] R. A. Mesa, U, Yasothan, P. Kirkpatrick, *Nat. Rev. Drug Discovery* **2012**, *11*, 103.

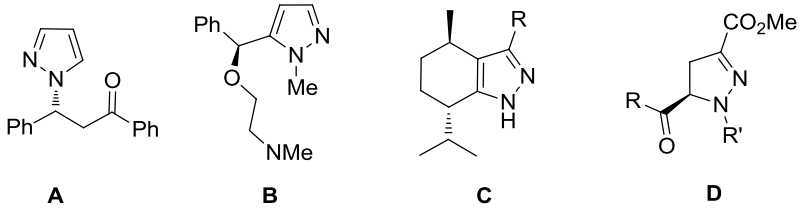
2.B.1.2. Síntesis de pirazoles quirales.

Los pirazoles quirales se pueden dividir en tres grupos bien diferenciados dependiendo donde se encuentre la quiralidad de la molécula:

- La quiralidad viene dada por el sustituyente, ya sea unido a uno de los átomos de carbono o de nitrógeno (Esquema 2.B.2.**A** y **B**).

- La quiralidad se encuentra en el anillo fusionado al esqueleto de pirazol, como ocurre en los tetrahidroindazoles procedentes de cetonas quirales (Esquema 2.B.2.**C**).

- La quiralidad pertenece al propio anillo, el cual, se encuentra parcialmente o totalmente saturado, como son las pirazolinas o las pirazolidinas respectivamente (Esquema 2.B.2.**C**).



Esquema 2.B.2. Diferentes posiciones de la quiralidad en el anillo de pirazol.

Debido a la similitud con los heterociclos sintetizados en este Capítulo, nos centraremos, exclusivamente, en aquellos pirazoles que poseen el centro estereogénico unido directamente al átomo de nitrógeno. A continuación, serán presentados los diferentes métodos descritos en la literatura para la construcción de estas moléculas.

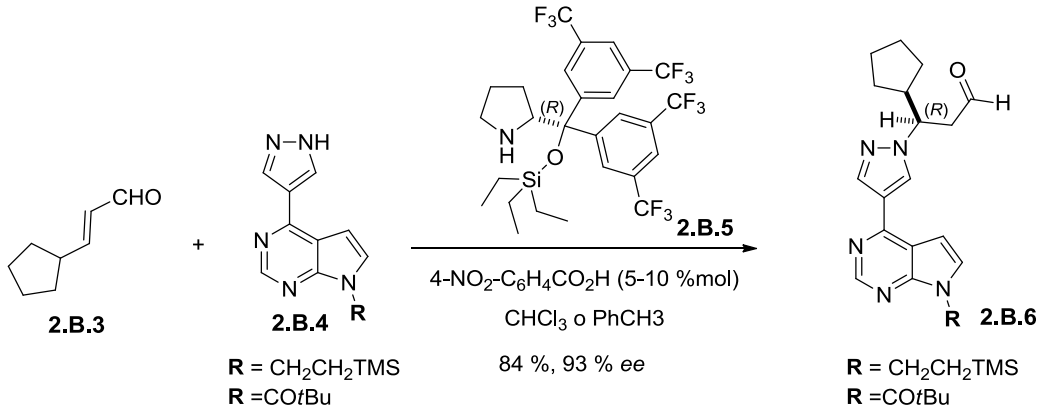
2.B.1.2.1. Adiciones conjugadas.

Esta estrategia ha sido la más empleada para la síntesis de heterociclos nitrogenados con un sustituyente quiral unido al áltomo de nitrogeno. Sin embargo, existe un número muy limitado de ejemplos donde se utilice el anillo de pirazol como nucleófilo y en las que además, el proceso transcurra con buena enantioselectividad. Este apartado se va a dividir en dos partes correspondientes a dos tipos de adición conjugada llevadas a cabo de forma asimétrica para la síntesis de pirazoles con un sustituyente quiral sobre el átomo de nitrógeno: la adición aza-Michael y la reacción de Hayashi-Miyaura.

2.B.1.2.1.1. Adición aza-Michael organocatalítica.

Dentro de las adiciones conjugadas, la adición asimétrica aza-Michael organocatalizada ha sido empleada en mayor medida. Esto ha sido así, puesto que posee una ventaja muy atractiva desde el punto de vista de producción a gran escala. Al transcurrir en ausencia del catalizador metálico no es necesario la etapa de retirar trazas metálicas de los productos finales.

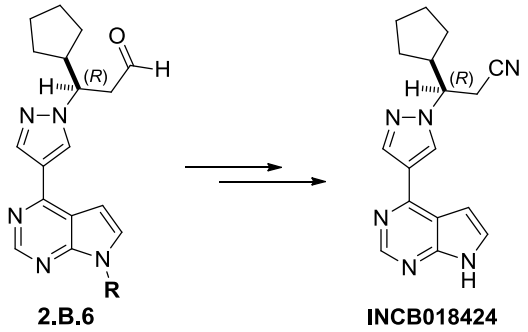
En este contexto, recientemente, se ha desarrollado una adición de aza-Michael asimétrica de diferentes pirazoles **2.B.4** a aldehídos α,β-insturados **2.B.3** usando diarilpropinol sililéter **2.B.5** como organocatalizador (Esquema 2.B.3).[226] Para llevar a cabo la reacción con buenos rendimientos, es necesario la presencia de un aditivo como el ácido benzoico o el ácido 4-nitrobenzoico que active el organocatalizador. También, es de destacar que el volumen estérico del catalizador es muy importante, así se obtienen mejores enantioselectividades cuanto más impedido se encuentra. A través de este protocolo, se puede acceder a los pirazoles quirales finales **2.B.6** con buenos rendimientos y altos excesos enantioméricos.



Esquema 2.B.3. Síntesis de pirazoles quirales **2.B.6** a partir de una reacción aza-Michael asimétrica organocatalizada.

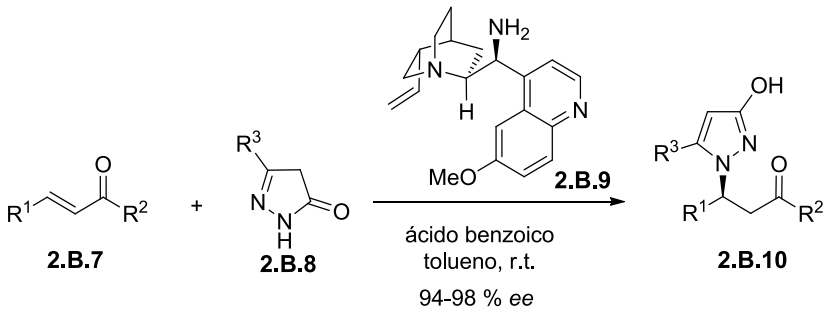
Para poner de manifiesto la utilidad que posee esta metodología, se lleva a cabo la síntesis de la molécula INCB018424, la cual, se encuentra en estudios clínicos para el tratamiento de enfermedades como la artritis reumatoide (Esquema 2.B.4).

[226] Q. Lin, D. Meloni, Y. Pan, M. Xia, J. Rodgers, S. Shepard, M. Li, L. Galya, B. Metcalf, T.-Y Yue, P. Liu, J. Zhou, *Org. Lett.* **2009**, *11*, 1999.



Esquema 2.B.4. Síntesis de INCB018424.

Simultáneamente a este trabajo, el profesor Zhao y colaboradores publicó la preparación de β-(3-hidroxipirazol-1-il)cetonas **2.B.10** siguiendo de nuevo una adición asimétrica aza-Michael organocatalizada.[227] Sin embargo, en este caso utilizan 2-pirazolin-5-ona **2.B.7** y cetonas α,β-insaturadas **2.B.8** usando 9-*epi*-9-amino-9-desoxiquinina **2.B.9** como catalizador y ácido benzoico como cocatalizador (Esquema 2.B.5).



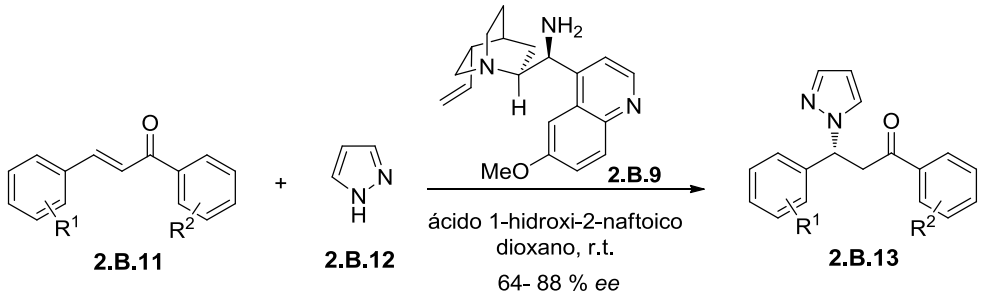
Esquema 2.B.5. Síntesis de β-(3-hidroxipirazol-1-il)cetonas a través de una adición aza-Michael organocatalizada.

Aunque la reacción transcurre con buenos rendimientos y buenos excesos enantioméricos, la generalidad que posee está limitada al empleo exclusivamente de grupos alquilo. De este modo, cuando R^1 o R^2 es un grupo fenilo se produce una mezcla compleja difícil de identificar.

Esta misma estrategia ha sido publicada recientemente para acceder a los pirazoles quirales monosustituidos **2.B.13** partiendo del pirazol **2.B.11** y calconas **2.B.12**

[227] S. Gogoi, C.-G Zhao, D. Ding, *Org. Lett*. **2009**, *11*, 2249.

(Esquema 2.B.6).[228] En este caso, se extiende la reacción a calconas aromáticas aunque el exceso enantiomérico es considerablemente menor al obtenido con restos alquilos.



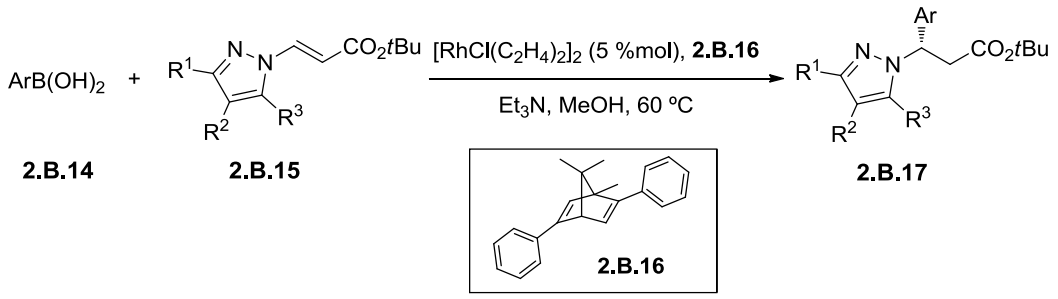
Esquema 2.B.6. Síntesis de pirazoles a partir de una adicón aza-Michael organocatalizada.

2.B.1.2.1.2. Reacción de Hayashi-Miyaura.

La reacción de Hayashi-Miyaura consiste en la adición de un ácido borónico a un compuesto carbonílico α,β-insaturado. Esta reacción posee ciertas ventajas con respecto a las adiciones conjugadas asimétricas de organocupratos puesto que no requieren baja temperatura, no son sensibles al aire o a la humedad, son catalíticas y además no requieren la preparación *in situ* de los correspondientes nucleófilos.

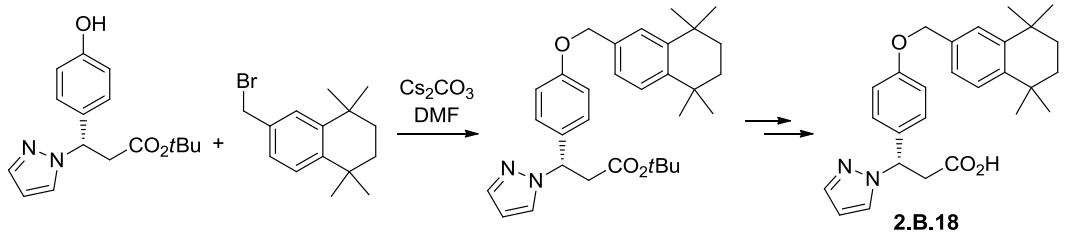
Recientemente, en el 2015, ha sido publicada por primera vez la síntesis de los β-aril-β-pirazol-1-il esteres **2.B.17** a través de una adición conjugada asimétrica de ácidos borónicos **2.B.14** a acrilatos **2.B.15** catalizada por rodio (Esquema 2.B.7).[229] En esta transformación, la especie catalítica de Rh(I) quiral, la cual es generada *in situ* a partir de $[RhCl(C_2H_4)_2]_2$ y el dieno quiral **2.B.16** como ligando, induce muy buenos excesos enantioméricos (99% *ee*), es general y además, transcurre con buenos rendimientos (44-90 %).

[228] P. Li, F. Fang, J. Chen, J. Wang, *Tetrahedon Asymm*. **2014**, *25*, 98.
[229] B. Gopula, Y.-F. Tsai, T.-S. Kuo, P.-Y. Wu, J. P. Henschke, H.-L. Wu, *Org. Lett*. **2015**,



Esquema 2.B.7. Síntesis de pirazoles quirales a través de la adición asimétrica de ácidos borónicos a acrilatos.

Una ventaja de esta síntesis con respecto a las adiciones aza-Michael es que los excesos enantioméricos obtenidos son mayores. Finalmente, para demostrar la utilidad sintética de esta estrategia, se ha diseñado la síntesis formal del compuesto **2.B.18**, inhibidor de la proteína G responsable de la generación de los ácidos grasos (Esquema 2.B.8).

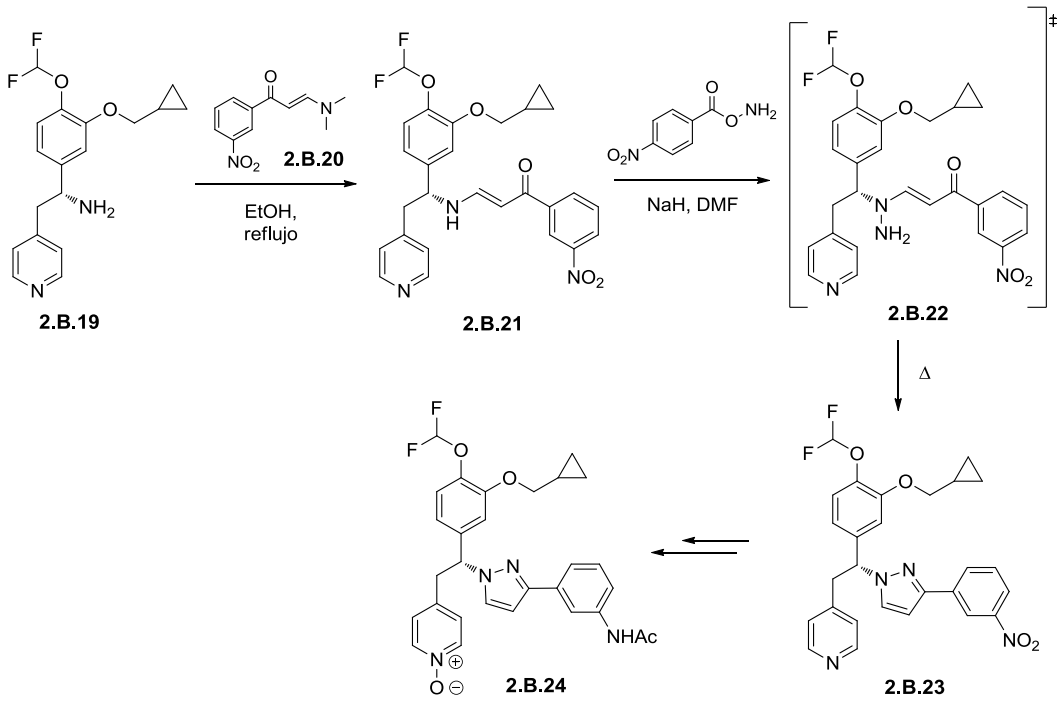


Esquema 2.B.8. Síntesis del pirazol **2.B.18**. biológicamente activo.

2.B.1.2.2. A partir de aminas quirales.

La síntesis asimétrica de pirazoles también se puede llevar a cabo empleando aminas quirales. Esta estrategia ha sido empleada en la síntesis de un potente inhibidor de las proteinas PDE4 **2.B.24** utilizado en enfermedades como el asma.[230] En rasgos generales, la construcción del esqueleto de este fármaco transcurre a través de la *N*-aminación de la enaminona quiral **2.B.21** de tipo *cis,* la cual, deriva de la adición de una enamina **2.B.19** a la correspondiente amina quiral **2.B.20**. La posterior deshidrociclación térmica del intermedio **2.B.22** generado en la aminación, daría lugar finalmente a la estructura de pirazol **2.B.23** (Esquema 2.B.9).

[230] C. M. Park, D. J. Jeon, *Org. Biomol. Chem.* **2012**, *10*, 2613.



Esquema 2.B.9. Síntesis de pirazoles quirales empleando aminas quirales.

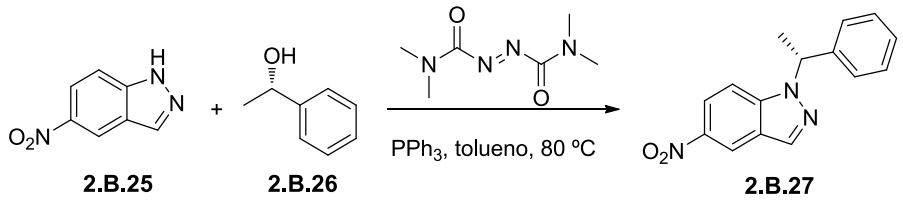
El inconveniente que posee esta metodología es el acceso a las propias aminas quirales, puesto que en algunas ocasiones, implican numerosos pasos de síntesis.

2.B.1.2.3. Reacción de Mitsunobu.

Una forma muy intuitiva de introducir grupos quirales directamente unidos al nitrógeno es precisamente la reacción de Mitsunobu.[231] A partir del 1*H*-pirazol apropiado y los correspondientes alcoholes quirales, se puede acceder a este tipo de estructuras, en principio, de un modo sencillo. Si bien es verdad, una revisión de la bibliografía condujo a un resultado sorprendente, ya que los ejemplos son verdaderamente escasos y la mayoría de ellos, se corresponden con patentes. En este apartado, a modo de ejemplo, se muestra la síntesis de un aminoindazol **2.B.27** a partir

[231] L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Burlington, **2005**, pag. 294.

del (*S*)-1-feniletanol **2.B.25** y el nitroindazol **2.B.26** (Esquema 2.B.10).[232] La reacción se da con completa inversión de la configuración del centro estereogénico y con un exceso enantiomérico superior al 99%. Sin embargo, se observa una proporción 2:1 de los diferentes regioisómeros correspondientes al nitrógeno.



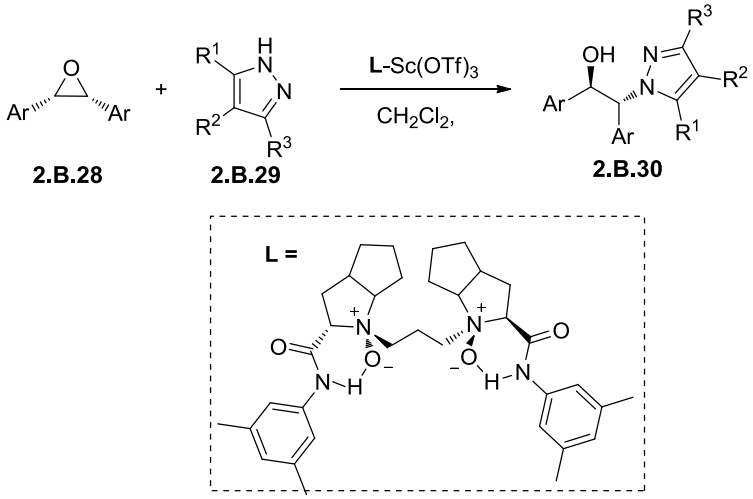
2.B.25 **2.B.26** **2.B.27**

Esquema 2.B.10. Síntesis de pirazoles quirales a través del empleo de la reacción de Mitsunobu.

2.B.1.2.4. Apertura asimétrica de epóxidosmeso.

La desimetrización de epóxidos se puede llevar a cabo a partir de la utilización de nucleófilos en presencia de complejos metálicos quirales.[233] Empleando pirazoles **2.B.29** como un aza-nucleófilo para esta reacción, se ha desarrollado la síntesis de una familia de pirazoles quirales **2.B.30** a partir de la apertura de asimétrica de *meso*-epóxidos **2.B.28**.[234] La transformación transcurre con excelentes diastereoselectividades, enantioselectividades y altos rendimientos empleando $Sc(OTf)_3$ como catalizador (Esquema 2.B.11).

[232] H. Mastalerz, M. Chang, P. Chen, P. Dextraze, B. E. Fink, A. Gavai, B. Goyal, W.-C. Han, W. Johnson, D. Langley, F. Y. Lee, P. Marathe, A. Mathur, S. Oppenheimer, E. Ruediger, J. Tarrant, J. S. Tokarski, G. D. Vite, D. M. Vyas, H. Wong, T. W. Wong, H. Zhang, G. Zhang, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2036.
[233] B. Gao, Y. H. Wen, Z. G. Yang, X. Huang, X. H. Liu, X. M. Feng, *Adv. Synth. Catal.* **2008**, *350*, 385.
[234] X. Hu, B. Gao, Y. Chu, W. Li, X. Liu, L. Lin, X. Feng, *Chem. Eur. J.* **2012**, *18*, 3473.



Esquema 2.B.11. Síntesis de pirazoles quirales a través de la desimetrización de epóxidos *meso*

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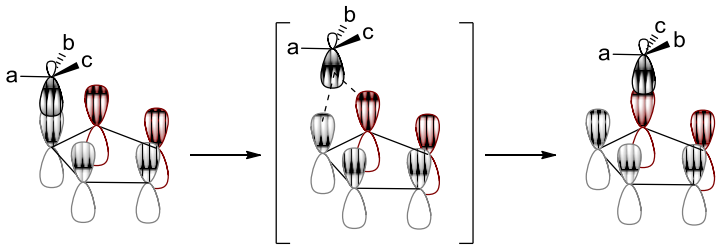
2.B.2. DISCUSIÓN DE RESULTADOS

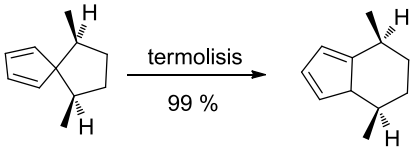
2.B.2.1. Introducción y objetivos.

En el Capítulo 2 se han mostrado una serie de estudios computacionales llevados a cabo en nuestro grupo de investigación que indican que la transposición [1,5] del intermedio 3*H*-pirazol formado, es en cualquier caso concertada y transcurre de manera suprafacial. Por tanto, siguiendo las reglas de selección de Woodward-Hoffman para los reagrupamientos [1*s*,5*s*]-sigmatrópicos, si el grupo que se traspone fuese un centro esterogénico la migración debería de proceder con la retención de configuración de ese centro (Esquema 2.B.12).



Esquema 2.B.12. Esquema correspondiente a la transposición [1,5] de un grupo al nitrógeno del anillo de pirazol con retención de la configuración.

Sin embargo, cabe destacar que aunque estas reglas predicen el transcurso de la transposición, los ejemplos basados en este principio son realmente escasos. Es más, hasta donde sabemos la transposición estereoespecífica de la spiro[4,4]nona-1,3-dieno, descrita en 1970, se trata del único ejemplo en el cual se produce el reagrupamiento [1,5]-sigmatrópico conservando la configuración del grupo que se transpone (Esquema 2.B.13).[235]

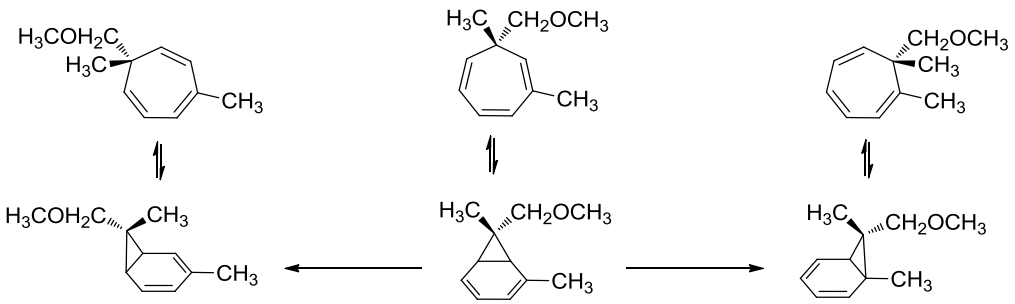


Esquema 2.B.13. Único ejemplo conocido en el cual se produce el reagrupamiento [1,5]-sigmatrópico de manera estereoespecífica y con retención de la configuración.

En cambio, un resultado totalmente distinto se encuentra para los reagrupamientos [1,5] de los derivados biciclo[2.1.0]heptadienilos. Estas transposiciones

[235] M. A. M. Boersma, J. W. de Haan, H. Kloosterziel, L. J. M. van de Ven, *J. Chem. Soc. Chem. Commun.* **1970**, 1168.

llamadas "*walk rearrangements*", aunque son mayoritariamente esteroselectivas, proceden con total inversión de la configuración en el carbono que migra (Esquema 2.B.14).[236] Este hecho se presenta totalmente contrario a las predicciones de las reglas de Woodward-Hoffmann. Para explicar esta inversión, se propuso que se daba la fomación de un intermedio diradical en el cual se ha producido la ruptura homolítica del enlace. Para el caso de estos grupos terciarios que sufren la migración, se había estudiado con anterioridad que la rotación para ese enlace es más rápida que el propio cierre de ciclo. De este modo, podría producirse la inversión de ese centro.

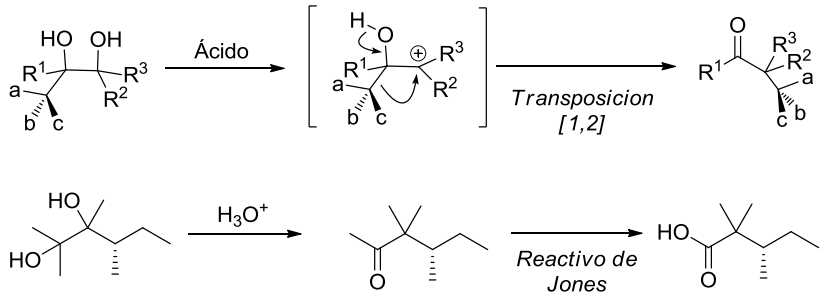


Esquema 2.B.14. Ejemplo de los "*walk rearrangements*" para 7-metoximetil-2,7-dimetilbiciclo[4.1.0]hepta-2,4-dieno.

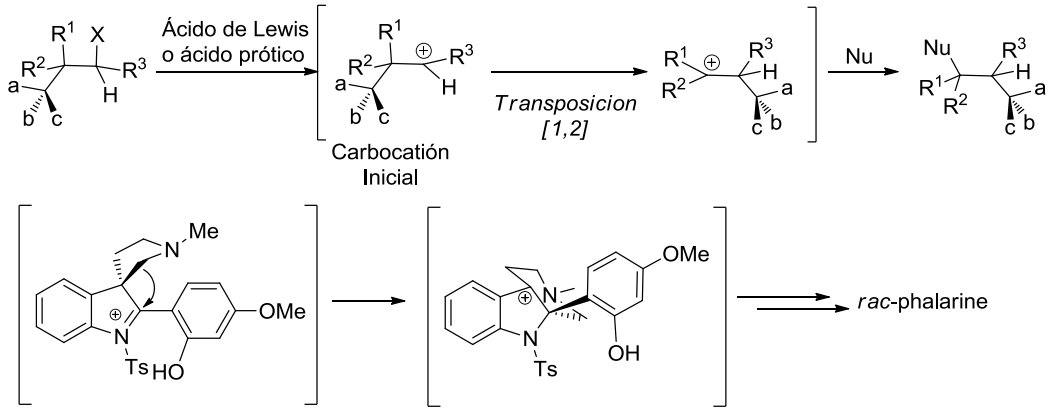
En contraste con la escasez de ejemplos para transposiciones [1,5], en las migraciones [1,2] se pueden encontrar en la literatura ejemplos en los cuales se produce la migración del grupo arilo con retención de la configuración. Así, el reagrupamiento pinacolínico (Esquema 2.B.15.**A**) se ha empleado para sintetizar diferentes ácidos carboxílicos ópticamente activos[237] o el de Wagner-Meerwein (Esquema 2.B.15.**B**) ha sido muy recurrente como paso clave en síntesis totales de moléculas complejas. [238]

[236] a) F.-G. Klärner, B. Brassel, *J. Am. Chem. Soc.* **1980**, *102*, 2469; b) W. T. Borden, J. G. Lee, S. D. Young, *J. Am. Chem. Soc.* **1980**, *102*, 4841.
[237] J. J. Beggs, M. B. Meyers, *J. Chem. Soc. B* **1970**, 930.
[238] a) T. Shono, K. Fujita, S. Kumai, *Tetrahedron Lett.* **1973**, *33*, 3123; b) J. D. Trzupek, D. Lee, B. M. Crowley, V. M. Marathias, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 8506; c) C. Zheng, Q,-F. Wu, S.-L. You, *J. Org. Chem.* **2013**, *78*, 4357.

A. Reagrupamiento pinacolínico:



B. Reagrupamiento de Wagner-Meerwein:

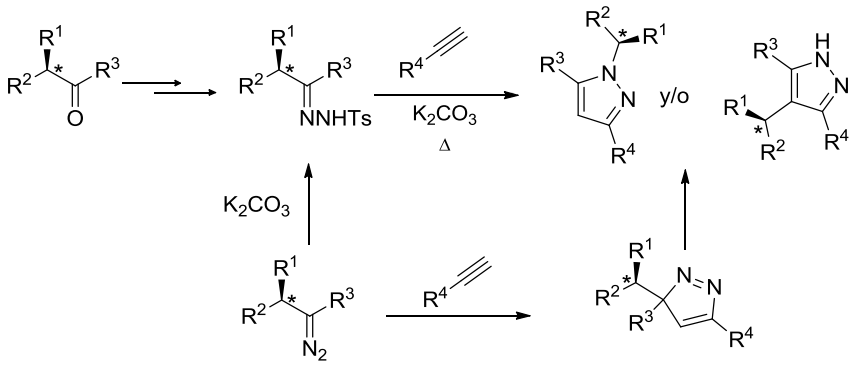


Esquema 2.B.15. **A**. Mecanismo del reagrupamiento pinacolínico. **B**. Mecanismo del reagrupamiento de Wagner Meerwein.

Además de los escasos ejemplos descritos donde se produce la migración con retención de configuración en reacciones de transposición [1,5], no se ha encontrado la utilización de este principio para la obtención de productos enantioméricamente enriquecidos. Por otra parte, en trabajos anteriores llevados a cabo en nuestro grupo de investigación, se han empleado tosilhidrazonas procedentes de cetonas quirales que poseen un grupo estereogénico en posición α, en los cuales, la configuración de ese átomo de carbono se ha preservado durante todo el proceso, tanto para reacciones catalizadas por paladio como para cicloadiciones [3+2].[79]

Con todo esto en nuestras manos, decidimos estudiar el empleo de tosilhidrazonas derivadas de cetonas quirales en la posición α en el proceso en cascada que implica una cicloadición 1,3-dipolar seguido de un reagrupamiento [1,5]-sigmatrópico descrito en la Parte A de este segundo capítulo. De este modo, si el

sistema sigue las reglas establecidas por Woodward-Hoffmann, el proceso transcurriría sin pérdida de la información quiral del reactivo de partida. Desde un punto de vista mecanístico, constituiría el primer ejemplo de una transposición sigmatrópica [1,5] con retención de configuración de un centro estereogénico en un sistema enantioméricamente puro. Además, la elección de estos sustratos nos serviría para estudiar cómo transcurre la transposición [1,5] de un resto que posee centro estereogénico en este tipo de sistema y al fin y al cabo, determinar si se cumple la reglas predichas por Woodward-Hoffmann se cumplen para nuestro sistema (Esquema 2.B.16).



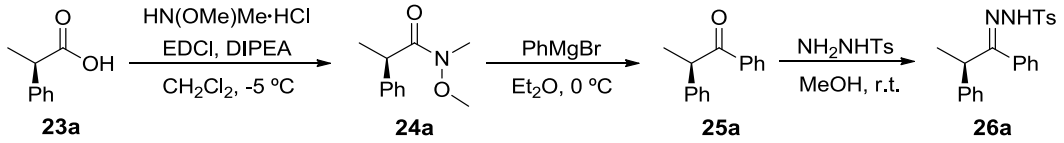
Esquema 2.B.16. Síntesis propuesta para la obtención de pirazoles quirales a través de un proceso en cascada que involucra una transposición [1,5] con retención en la configuración.

Por otra parte, desde un punto de vista sintético, se debe remarcar en este punto, que la síntesis de estos pirazoles enantioméricamente enriquecidos es importante debido a que se encuentran presentes en estructuras destacadas en la química farmacéutica para la que existen pocas alternativas sintéticas. Así, mediante esta estrategia sería un modo muy simple de acceder a ellas.

2.B.2.2. Resultados preliminares y condiciones óptimas.

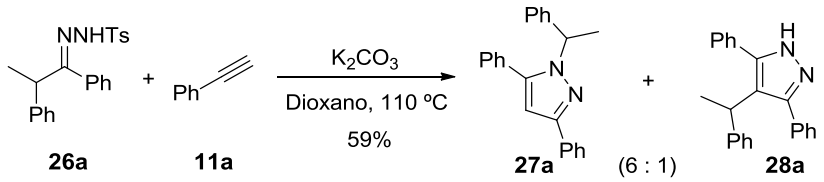
Para iniciar el estudio de esta transformación, se escogió la hidrazona derivada de (*R*)-3-fenil-2-butanona **26a,** la cual, puede ser sintetizada a partir del correspondiente carbonilo **25a**. Las diferentes cetonas **25** son obtenidas fácilmente a partir de los correspondientes ácidos carboxílicos comerciales **23** siguiendo una secuencia muy simple. En concreto para hidrazona **26a**, se transforma el ácido carboxílico en la amida de Weinreb **24** bajo condiciones estándar. La posterior reacción de la amida **24** con un

reactivo de Grignard da lugar a la cetona deseada. Los correspondientes carbonilos racémicos se sintetizan siguiendo la misma ruta sintética.[239]



Esquema 2.B.17. Secuencia sintética para la preparación de las correspondientes hidrazonas **26**.

En primer lugar, se llevo a cabo un estudio de la viabilidad de la secuencia de cicloadición y reagrupamiento con la hidrazona **26a** racémica. Para ello, se escogieron las condiciones estándar desarrolladas en el Capítulo 2. Así, se empleó una proporción hidrazona: alquino, 1:2 (para 0.3 mmol), 2 equivalentes de K_2CO_3 como base, 2.4 mL de dioxano a 110 °C. Como resultado se observó que la reacción en cascada transcurría con buenos rendimientos aunque con regioselectividades moderadas (6:1) (Esquema 2.B.18).[240]



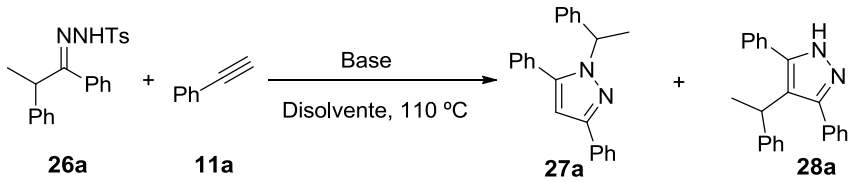
Esquema 2.B.18. Estudio preliminar para la reacción entre la tosilhidrazona **26a** y el alquino **11a**.

Es de destacar que aunque se obtiene una mezcla de los 1*H*-pirazoles isómeros **27a** y **28a,** éstos son fácilmente separables mediante cromatografía. Además, el regioisómero mayoritario se corresponde con el pirazol 1,3,5-trisustituido, en el cual, la migración se ha producido a favor de las agujas del reloj hacia el nitrógeno.

Un pequeño estudio para determinar las condiciones óptimas de reacción variando el disolvente (CH_3CN) y la base (Cs_2CO_3), condujeron a una leve disminución del rendimiento y a la misma proporción entre los diferentes regioisómeros (Esquema 2.B.19).

[239] Ver la sección *Parte Experimental* para mayor detalle.

[240] La proporción entre los diferentes regioisómeros fue determinada a partir del espectro ^{1}H-RMN del crudo.

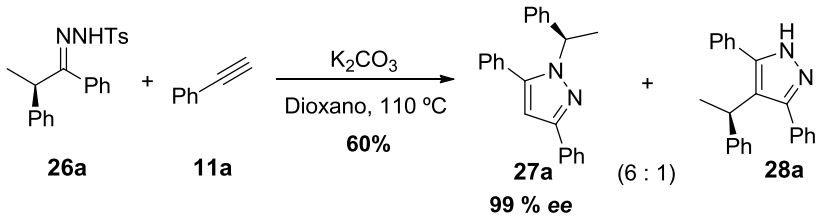


26a **11a** **27a** **28a**

Condiciones	Rendimiento	Proporción 27a:28a
Cs_2CO_3, Dioxano	56 %	6 : 1
K_2CO_3, CH_3CN	49 %	6 : 1

Esquema 2.B.19. Optimización de la reacción entre la tosilhidrazona **26a** y fenilacetileno **11a**.

Por tanto, las condiciones óptimas de reacción se establecen como K_2CO_3 como base y dioxano como disolvente, tal y como se ha visto en el Esquema 2.B.18. Una vez establecidas estas condiciones, se examinó la correspondiente cetona con un centro quiral en la posición α. Así, se llevó a cabo la secuencia de la reacción en cascada empleando la tosilhidrazona **26a** enantioméricamente enriquecida sintetizada a partir de la (*R*)-1,2-difenil-1-propanona **25a** (99 % *ee*). Para nuestra satisfacción, se obtuvo la misma mezcla de 1*H*-pirazoles, con rendimientos buenos y con un 99 % *ee* para el regioisómero mayoritario **27a** (Esquema 2.B.20).



26a **11a** **27a** (6 : 1) **28a**

99 % *ee*

Esquema 2.B.20. Síntesis de pirazoles **27a** y **28a** a partir de la hidrazona enantioméricamente enriquecida **26a**.

Esto indica que el centro estereogénico procedente de la cetona **25a** no presenta erosión en la quiralidad durante todo el proceso, el cual, involucra cuatro pasos: la formación de la tosilhidrazona **26a**, la descomposición de ésta para dar el correspondiente diazocompuesto, la cicloadición 1,3-dipolar y la transposición [1,5]-sigmatrópica.

En este punto, cabe destacar que en la literatura se encuentran muy pocos ejemplos mediante los cuales se puede acceder a pirazoles enantioméricamente enriquecidos. Además, en estas síntesis encontradas, por norma general, requieren siempre numerosos pasos de síntesis para los reactivos de partida, los cuales, en determinados casos, no son triviales. En concreto, para los pirazoles que poseen un

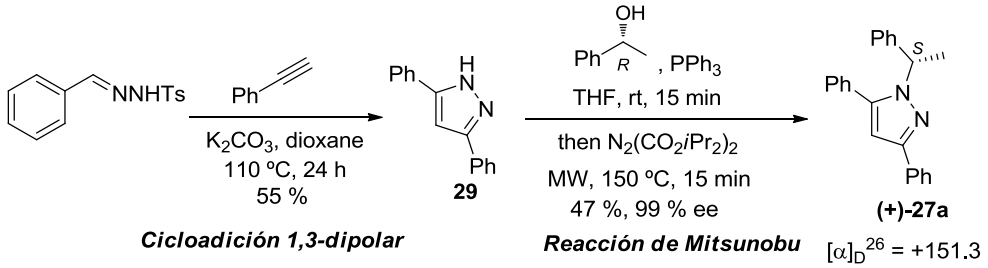
centro estereogéneo unido directamente al átomo de nitrógeno son difíciles de preparar de forma regioselectiva. El método más empleado es la alquilación directa del enlace N-H del pirazol, como por ejemplo, la reacción de Mitsunobu. Sin embargo estas reacciones son muy poco regioselectivas obteniéndose una mezcla de los dos posibles isómeros provenientes de la alquilación de cada nitrógeno.

A lo largo de esta Sección, se va a presentar una nueva metodología mediante la cual se pueden sintetizar estos pirazoles de forma muy simple a partir de reactivos como son las hidrazonas, fácilmente accesibles.

2.B.2.3. Determinación de la configuración absoluta del pirazol 27a

Llegados a este punto, una vez que se observó que el 1*H*-pirazol se ha obtenido con la misma pureza enantiomérica que el sustrato de partida, una cuestión importante era comprobar que efectivamente la transposición había transcurrido con retención de la configuración. Así, la configuración absoluta para el pirazol quiral **27a** fue determinada comparando la rotación óptica de este producto con el mismo pirazol sintetizado a través de una estrategia alternativa.

Para ello, en primer lugar se realizó la síntesis de 3,5-difenilpirazol **29** a través de una cicloadición 1,3-dipolar a partir de la correspondiente tosilhidrazona derivada del benzaldehído y el fenil acetileno. Seguidamente se llevó a cabo una reacción de Mitsunobu utilizando (*R*)-1-feniletanol. De estaforma, se accede al pirazol deseado **27a** con un rendimiento moderado y un excelente exceso enantiomérico (99 % *ee*) (Esquema 2.B.21).

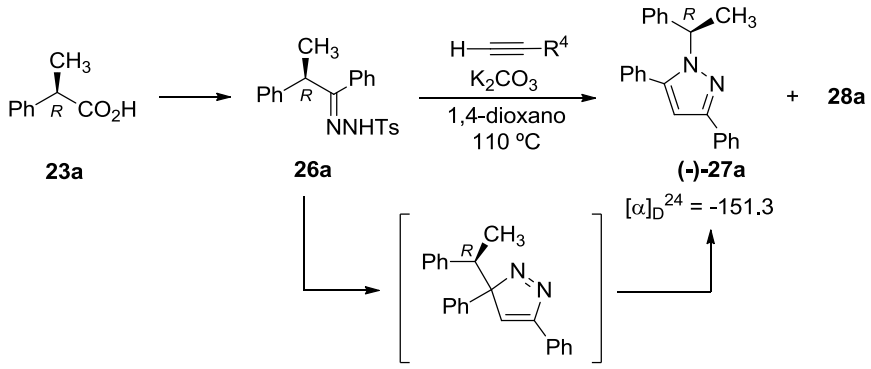


Esquema 2.B.21. Síntesis del pirazol **27a** empleando la estrategia que involucra una cicloadición 1,3-dipolar seguida de la reacción de Mitsunobu.

Este pirazol simétrico **29** con los mismos sustituyentes en las posiciones 3 y 5 del anillo, fue escogido en particular para evitar la formación de los diferentes regioisomeros correspondientes a la alquilación en cada uno de los nitrógenos. Estas

mezclas suelen obtenerse en reacciones de alquilación de N*H*-pirazoles 3,5-disustituidos no simétricos.

Como es de sobra conocido, la reacción de Mitsunobu procede con la inversión de la configuración del centro estereogénico, así, cuando el proceso se lleva a cabo con el (*R*)-1-feniletanol, el correspondiente centro estereogénico experimenta una inversión dando el pirazol con el centro estereogénico de configuración *S*.[241] Este enantiómero corresponde justamente con el contrario al obtenido mediante nuestro método, considerando que el reagrupamiento [1,5]-sigmatrópico procede con retención de la configuración en el grupo que migra (Esquema 2.B.22). Consecuentemente, la rotación óptica para los dos pirazoles debe ser la misma pero de signo contrario.



Esquema 2.B.22. Síntesis del enantiómero **(-)-27b** mediante nuestro método partiendo del ácido (*R*)-2-fenilpropanoico **23a**.

Para nuestra satisfacción, este fue el resultado que obtuvimos como se representa a continuación a través de los valores de rotación específica:

- Pirazol obtenido mediante nuestro método: **(-)-27a**, $[\alpha]_D^{24}$ = -149.3.
- Pirazol obtenido a través de la reacción de Mitsunobu **(+)-27a**, $[\alpha]_D^{26}$ = +151.3.

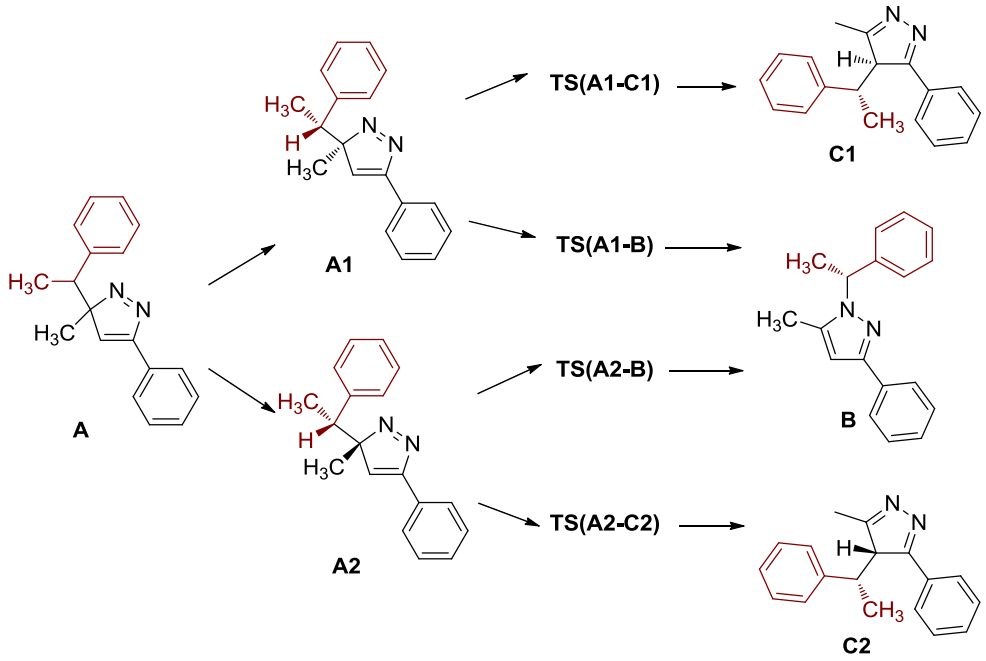
Así, a través de estos resultados se puede establecer que la configuración del centro estereogénico para el **(-)-27a** es *R* y confirma de hecho, que todo el proceso en cascada, incluyendo el reagrupamiento [1,5] sigmatrópico, ha tenido lugar con retención de la configuración del grupo que migra.

[241] H. Mastalerz, M. Chang, P. Chen, P. Dextraze, B. E. Fink, A. Gavai, B. Goyal, W.-C. Han, W. Johnson, D. Langley, F. Y. Lee, P. Marathe, A. Mathur, S. Oppenheimer, E. Ruediger, J. Tarrant, J. S. Tokarski, G. D. Vite, D. M. Vyas, H. Wong, T. W. Wong, H. Zhang, G. Zhang, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2036.

2.B.2.4. Estudios mecanísticos.

Para encontrar más argumentos que expliquen la naturaleza concertada de las transposiciones [1,5] de los 3*H*-pirazoles, se llevó a cabo un estudio computacional muy simple.[242] Para ello, se escogió como modelo el 3*H*-pirazol **A** intermedio generado en la reacción entre la tosilhidrazona **26a** y el fenilacetileno **11a**.

La cicloadición del correspondiente diazocompuesto generado a partir de la tosilhidrazona **26a** al alquino terminal **11a** da lugar a dos intermedios diastereoisómeros del 3*H*-pirazol, **A1** y **A2**. Además para los dos intermedios, hay dos posibles caminos de reacción, aquel en el que la transposición se produce en el sentido de las agujas del reloj para dar el 1*H*-pirazol **B**, y el que se produce en el sentido contrario para dar lugar de nuevo a una mezcla de diastereoisómeros 4*H*-pirazol, **C1** y **C2** respectivamente (Esquema 2.B.23).



Esquema 2.B.23. Diferentes pirazoles posibles que se pueden obtener a partir del 3*H*-pirazol **A**.

Los cálculos llevados a cabo para los diferentes estados de transición de los 3*H*-pirazoles diastereoisoméricos **A1** y **A2** se realizaron al nivel B3lyp/6-31G*. Estos cálculos revelan que ambos caminos de reacción conducentes al 1*H*-pirazol **B**, poseen un estado de transición de menos energía que aquellos que generan los 4*H*-pirazol **C1** y **C2** (Tabla

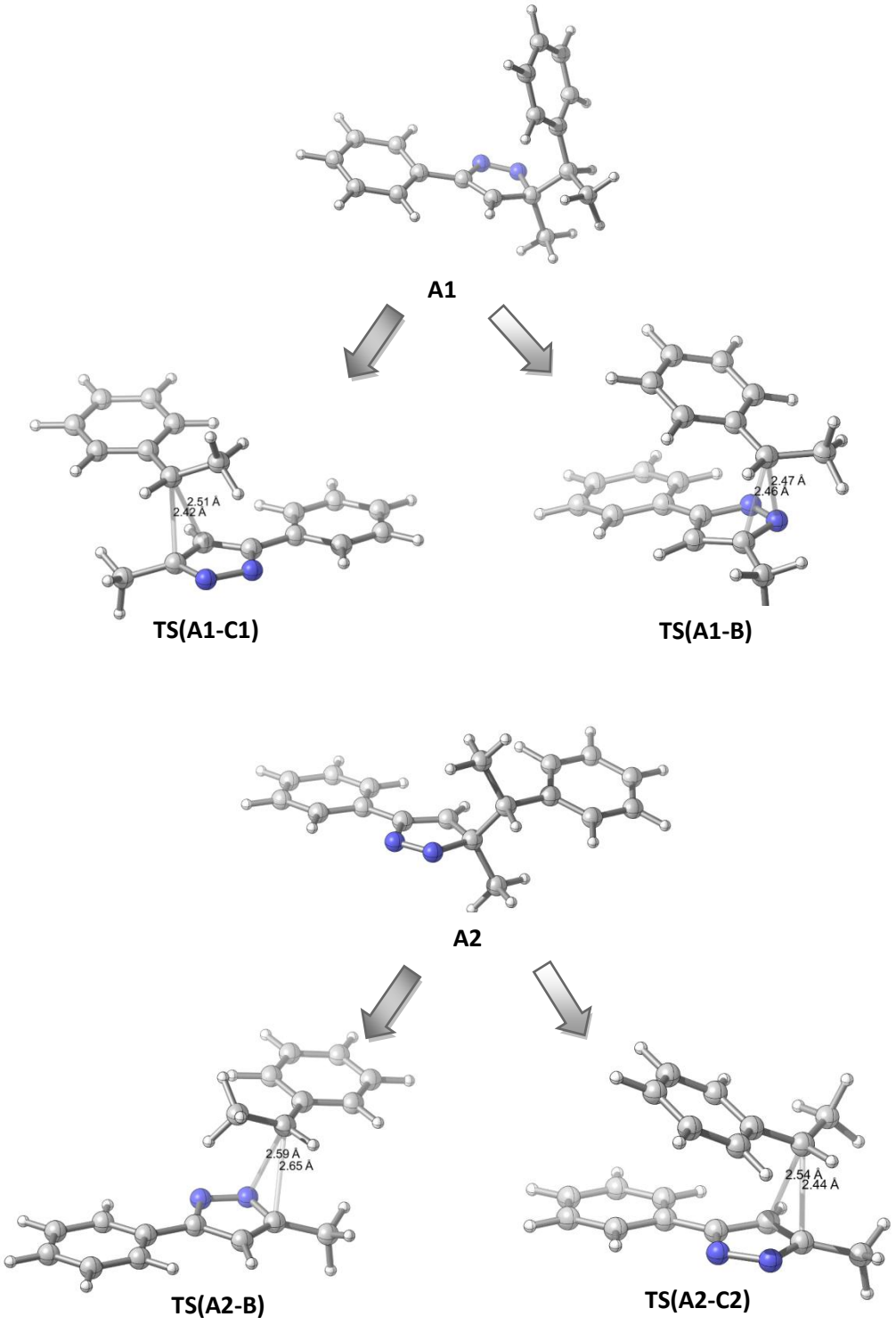
[242] Los cálculos computacionales se han realizado por el Profesor Carlos Valdés.

2.B.1). Por tanto, siendo esto así, la migración al nitrógeno se encuentra favorecida, hecho que está en concordancia con lo observado experimentalmente.

Tabla 2.B.1. Energías calculadas en el nivel b3lyp/6-31G* en fase gaseosa. Se encuentran expresadas en kcal·mol^{-1}

	ΔG_{act}	$\Delta\Delta G_{act}$
TS(A1-B)	30.6	0.0
TS(A1-C1)	34.3	3.7
TS(A2-B)	26.3	0.0
TS(A2-C2)	29.9	3.58

Las estructuras obtenidas para los estados de transición se corresponden a las esperadas para transposiciones [1*s*,5*s*] suprafaciales, concertadas y sincrónicas, tal y como revelan la similitud entre las distancias tanto para los enlaces que se forman como los que se rompen durante el proceso. Estas distancias son un poco más largas que para un reagrupamiento sigmatrópico clásico (alrededor de 2.3-2.5 Å). Esto es debido a la separación de carga que se produce en el estado de transición. Es más, para el estado de transición de mínima energía correspondiente a cada camino de reacción, el resto que migra, concretamente el 1-fenetilo, se ordena de tal manera que las interacciones estéricas con el metilo que se encuentra en el C5 del resto pirazolilo son mínimas. Para obtener cálculos más precisos en las energías de activación para los diastereoisómeros **A1** y **A2**, se llevaron a cabo en el nivel b3lyp/6-311++G**, incluyendo los efectos de solvatación a través del SCRF-PCM (Esquema 2.B.24).



Esquema 2.B.24. Estados de transición calculados usando el nivel b3lyp/6-311G**.

Los estados de transición encontrados mostraron distancias ligeramente mayores a los enlaces rotos y formados en el reagrupamiento, pero aun así, siguen siendo un proceso concertado. Adicionalmente, a este nivel, las energías de activación para el pirazol sustituido en el átomo de N se encuentra claramente favorecida. Así, las energías de activación libre de Gibss de 21.6 y 22.5 kcal·mol^{-1} obtenidas para la migración al C5-N1 a partir de los diastereoisómeros **A1** y **A2**, respectivamente, son estados muy accesibles (Tabla 2.B.2). Este hecho se encuentra de nuevo en concordancia con el hecho de que los 3*H*-pirazoles nunca se han observado a una temperatura de 110 °C.

Tabla 2.B.2. Energías calculadas para el nivle b3lyp/6-311++G** teniendo en cuenta el efecto de solvatación del disolvente, en este caso el dioxano. Las energías están expresadas en kcal·mol^{-1}.

	ΔG_{act}	$\Delta\Delta G_{act}$
TS(A1-B)	21.6	0.0
TS(A1-C1)	26.7	5.1
TS(A2-B)	22.5	0.0
TS(A2-C2)	25.2	2.7

Como resumen, los cálculos de DFT son consistentes con respecto a lo observado experimentalmente, puesto que predicen la migración del resto al átomo de nitrógeno. Además, son también predichos mecanismos típicos concertados para los cuales se daría la migración preservándose la estereoquímica del grupo que migra.

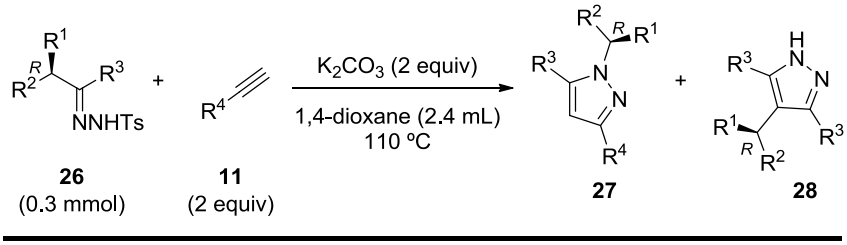
2.B.2.5. Generalización de la reacción entre las tosilhidrazonas 26 y los alquinos terminales 11.

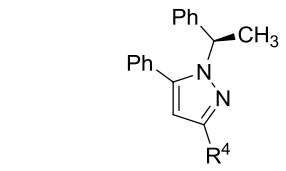
Siendo conscientes del potencial que posee este procedimiento para sintetizar pirazoles 1,3,5-trisustituidos de forma enantiopura, nos propusimos estudiar la generalidad del proceso en cascada entre la tosilhidrazona **26** y el alquino terminal **11** tanto desde el punto de vista de la hidrazona como del alquino. Como se muestra en el Esquema 2.B.25, en todos los casos, se obtienen regioselectividades moderadas o altas y excelentes excesos enantioméricos (**27a**-**27k**).[243] La reacción además es compatible con diferentes alquinos terminales de diferente naturaleza, así, se pueden emplear alquinos

[243] Se observa una epimerización parcial con el tiempo para algunos pirazoles (**27**, **30**). Por ello, es necesario la medición de los excesos enantioméricos justamente después de haber aislado el pirazol final.

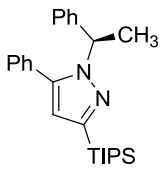
aromáticos sustituidos con grupos con diferentes propiedades electrónicas (**27a**-**27d**, **27h**-**27k**), heteroarenos (**27g**), un sustituyente bencilo (**27e**) e incluso con un grupo sililo (**27f**). Desde el punto de vista del resto que no migra de la hidrazona R^1, tolera grupos alquilos primarios (**27h**-**27k**) y arilos (**27a**-**27g**).

En cualquier caso, no se pudo desarrollar la metodología *one-pot* debido a la pérdida total en la información quiral de la hidrazona ya que se obtenía la mezcla racémica de los productos finales.[244]

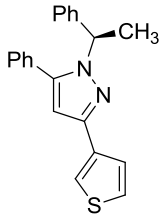




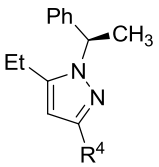
27a, R^4 = Ph, 51%, (86:14), 99 % *ee*
27b, R^4 = 4-$CH_3C_6H_4$, 54%, (85:15), 99 % *ee*
27c, R^4 = 4-$OMeC_6H_4$, 65%, (93:7), 93 % *ee*
27d, R^4 = 4-CNC_6H_4,71%, (82:18), 98 % *ee*
27e, R^4 = Bn, 33%, (85:15), 97 % *ee*



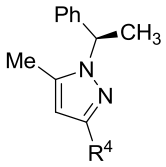
27f, 57%, (73:27), 99 % *ee*



27g, 57%, (88:12), 98 % *ee*



27h, R^4 = Ph, 51%, (68:32), 92 % *ee*
27i, R^4 = 4-FC_6H_4, 58%, (64:36), 99 % *ee*



27j, R^4 = 4-CNC_6H_4, 43%, (70:30), 97 % *ee*
27k, R^4 = 4-$OMeC_6H_4$, 40%

Esquema 2.B.25. Generalización de la síntesis de pirazoles trisustituidos **27** enantioenriquecidos a partir de las tosilhidrazonas **26** y los alquinos terminales **11**. Se muestra el rendimiento y el exceso enantiomérico correspondiente para el isómero mayoritario. Entre paréntesis se muestra la proporción determinada por ^{1}H-RMN para cada uno de los regioisómeros.

[244] El empleo de la hidrazona recién preparada es de vital importancia para acceder a los pirazoles con un exceso enantiomérico alto y reproducible. Se ha observado que a partir de tosilhidrazonas **26** almacenadas se obtienen los pirazoles **27** con menor pureza enantiomérica.

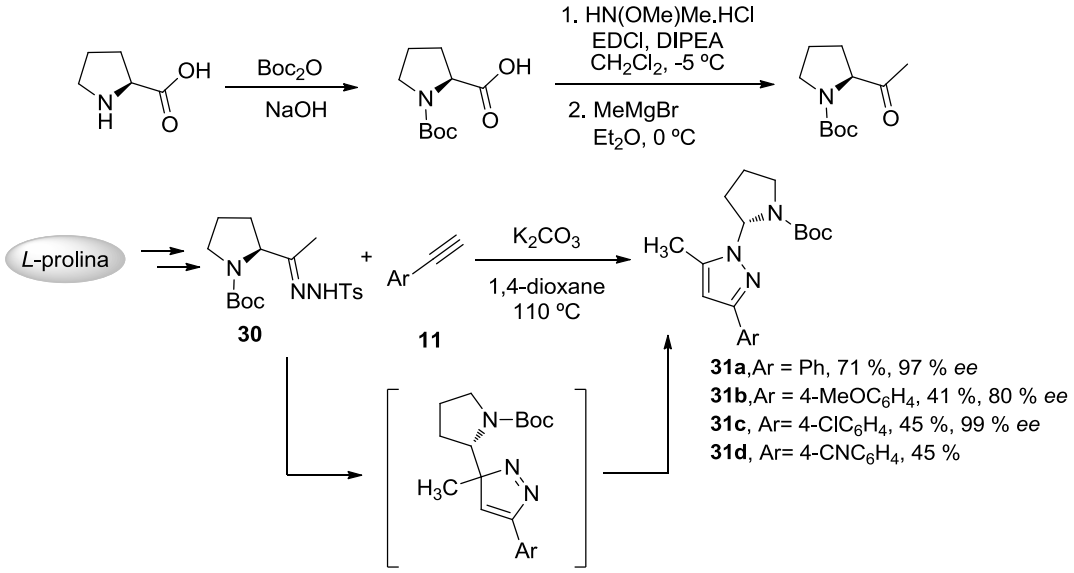
A tenor de los resultados recogidos en el Esquema 2.B.25, se observa que el empleo de restos de diferente naturaleza en el alquino, afecta directamente a la proporción de regioisómeros. Al emplear sustituyentes ricos en electrones, como por ejemplo el grupo metoxi (**27c**, **27k**), la regioselectividad se mejora obteniéndose incluso de forma regioselectiva la migración al nitrógeno (**27k**). Este hecho ya se había tratado anteriormente en la Parte A de este Capítulo. Desafortunadamente, en este último ejemplo no pudo ser determinado el exceso enantiomérico debido a su descomposición en las condiciones requeridas para el HPLC.

2.B.2.6. Síntesis de pirazoles 1,3,5-trisustituidos de forma enantiopura a partir de α-aminoácidos.

Una fuente muy asequible y barata para generar diferentes carbonilos que poseen quiralidad en la posición α, son los α-aminoácidos. Con el objetivo de extender el alcance de esta síntesis de pirazoles enantiomericamente enriquecidos al empleo de otras cetonas quirales, se decidió emplear tosilhidrazonas derivadas de α-aminocetonas, las cuales, se obtienen fácilmente a partir de los correspondientes aminoácidos siguiendo la estrategia descrita anteriormente (Esquema 2.B.17).

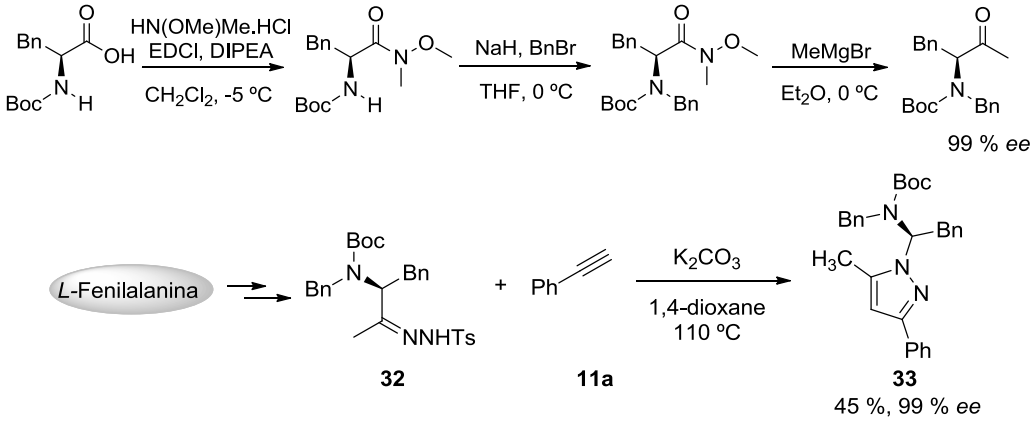
En primer lugar, se enfrentó la tosilhidrazona **30** derivada de la *L*-prolina a diferentes alquinos terminales. El carbonilo fue sintetizado a partir de la estrategia descrita de protección con el grupo Boc, amida de Weinreb y poterior alquilación. Las condiciones empleadas para llevar a cabo la transformación fueron las ya establecidas para la síntesis de los pirazoles **27**. Como se muestra en el Esquema 2.B.26, la reacción en estas condiciones permitieron el acceso al pirazol sustituido en el átomo de nitrógeno de forma totalmente regioselectiva. De hecho, cabe remarcar, que en ningún caso se observó el producto derivado de la migración al átomo de carbono. La reacción tiene lugar con rendimientos que van de moderados a buenos y casi con la completa retención de la configuración.[245]

[245] Únicamente no pudo medirse el exceso enantiomérico correspondiente al pirazol **31d** debido a su descomposición en las condiciones empleadas para la separación de los diferentes enantiómeros en el HPLC. Se intentó modificar el resto -Boc por un grupo -Ts con el objetivo de solventar este problema. Sin embargo, este nuevo compuesto también experimentaba la descomposición en las condiciones estudiadas.



Esquema 2.B.26. Síntesis regioselectiva de los pirazoles 1,3,5-trisustituidos enantioméricamente enriquecidos a partir de la tosilhidrazona derivada de la prolina **30** y los alquinos terminales **11**.

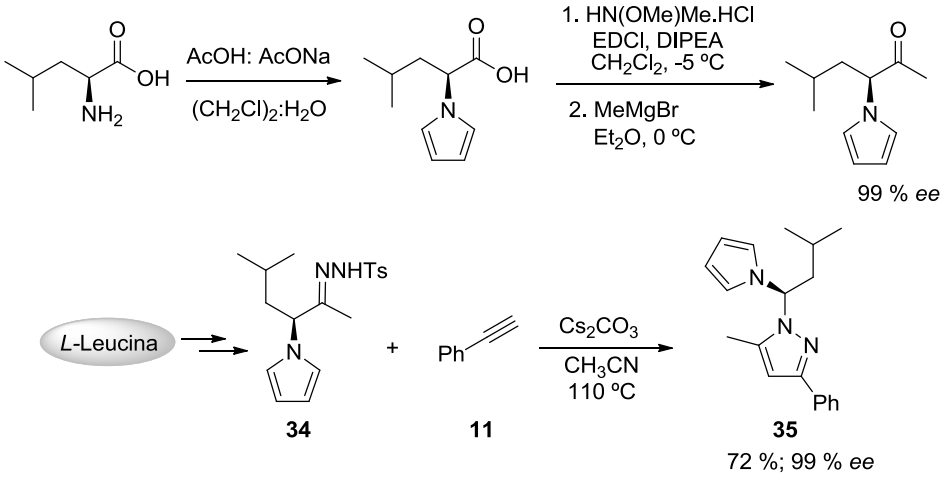
Animados por el resultado obtenido nos propusimos extender esta metodología a otro tipo de aminoácidos con diferentes sustituyentes en la posición α. Como modelo, se seleccionó la hidrazona del carbonilo derivado de la *L*-fenilalanina **32**, como representante de un aminoácido lineal. El carbonilo correspondiente fue generado a partir de la secuencia de creación de la amida de Weinreb, la protección de la amina con un grupo bencilo seguido de la correspondiente alquilación. Al llevar a cabo la reacción, se observó que la secuencia de cicloadición y transposición transcurrían con un rendimiento moderado pero con la completa retención en la configuración del grupo que migra (99 % *ee*). Además, la reacción es completamente regioselectiva, generándose únicamente los pirazoles 1,3,5-trisustituidos **33** (Esquema 2.B.27).



Esquema 2.B.27. Síntesis regioselectiva y enantioespecífica del pirazol trisustituido **33** a partir de la tosilhidrazona derivada de la *N*-Bn-*N*-Boc-(*L*)-fenilalanina **32** y el fenilacetileno **11a**.

En la Sección 2.A.1.5.2 de la Parte A de este Capítulo, empleando tosilhidrazonas derivadas de cetonas α-*N*-azol sustituidas se aislaba únicamente los pirazoles 1,3,5-trisustituidos con altos rendimientos y total regioselectividad. Teniendo en cuenta esta experiencia, se decidió estudiar sus análogos quirales. Para este fin, se eligió como modelo la hidrazona quiral **34**, la cual, se sintetiza de manera enantiopura a partir de la *L*-Leucina.[246] El carbonilo correspondiente fue obtenido a partir de la formación del derivado de pirrol seguido de la estrategia empleada para el resto de derivados. Después de un ajuste de las condiciones de reacción, se obtuvo el correspondiente pirazol **35** con un buen rendimiento, total regioselectividad y total retención de la configuración (99 % *ee*) (Esquema 2.B.28).

[246] Para la síntesis completa de la hidrazona quiral **34**, mirar la parte experimental.

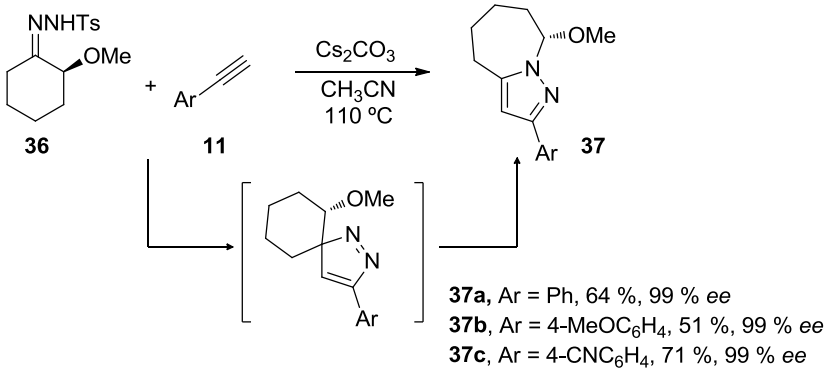


Esquema 2.B.28. Síntesis regioselectiva y enantioespecífica del pirazol trisustituido **35** a partir de la tosilhidrazona **34** y el fenilacetileno **11a**.

2.B.2.7. Síntesis de pirazoles cíclicos benzofusionados de forma enantiopura a partir de las tosilhidrazonas cíclicas 36 y el fenilacetileno 11a.

Finalmente, siguiendo con el estudio del alcance de la reacción, la metodología fue ampliada a tosilhidrazonas cíclicas **36**, en concreto, a la hidrazona derivada de la 2-metoxiciclohexanona.

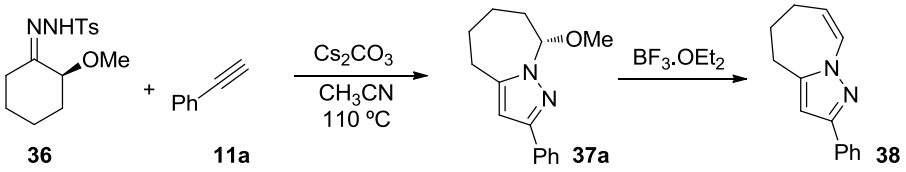
Para llevar a cabo este proceso fue necesario realizar una reoptimización de las condiciones de reacción, determinándose que las idóneas se correspondían con la utilización de proporciones 1:2 de hidrazona: alquino, el empleo de Cs_2CO_3 (2 equivalentes) como base y 2.4 mL de dioxano como disolvente. Como resultado de esta reacción, se encontró que la secuencia de cicloadición y reagrupamiento [1,5]-sigmatrópico transcurría con total regioselectividad, dándose la migración hacia el átomo de nitrógeno y obteniéndose, en consecuencia, los pirazoles cíclicos benzofusionados 1,3,5-trisustituidos **37** (Esquema 2.B.29).



Esquema 2.B.29. Síntesis regioselectiva y enantioespecífica de pirazoles cíclicos benzofuisonados **37** a partir de las tosilhidrazonas cíclicas **36** y el fenilacetileno **11a**.

Teniendo en cuenta trabajos anteriores llevados a cabo con tosilhidrazonas cíclicas implicadas en una cicloadición seguida de la transposición [1,5],[247] y nuestra propia experiencia, el pirazol esperado sería aquel en el cual el resto ha migrado hacia el el átomo de carbono en lugar de hacia el nitrógeno. Por tanto, la presencia del grupo metoxi es esencial para dirigir la reacción hacia la formación de los pirazoles **37**. Además, después de llevar a cabo la síntesis análoga con la correspondiente cetona racémica, se pudo comprobar que los pirazoles cíclicos benzofusionados se obtienen de forma enantioméricamente pura (99 % *ee*). Por tanto, se puede determinar que el proceso transcurre de nuevo con la completa preservación de la información quiral.

De forma interesante, el tratamiento de la mezcla de la reacción con $BF_3.OEt_2$ obtiene de forma cuantitativa un nuevo pirazol **38**, en el cual, se ha perdido una molécula de metanol (Esquema 2.B.30).



Esquema 2.B.30. Síntesis del pirazol **38** añadiendo en el medio de reacción $BF_3.OEt_2$.

[247] R. R. Merchant, D. M. Allwood, D. C. Blakemore, S. V. Ley, *J. Org. Chem.* **2014**, *79*, 8800.

2.B.3. CONCLUSIONES.

Durante esta segunda parte, se ha desarrollado una síntesis sin precedentes para la síntesis de pirazoles enantioenriquecidos a partir de alquinos terminales y las correspondientes tosilhidrazonas sustituidas con grupos quirales en la posición α. El acceso de esta estructura se lleva a cabo a través de una secuencia en cascada que implica una cicloadición 1,3-dipolar seguida de un reagrupamiento [1,5]-sigmatrópico.

Es importante destacar que la selección apropiada de los sustituyentes de las tosilhidrazonas conduce a una alta selectividad en tres niveles:

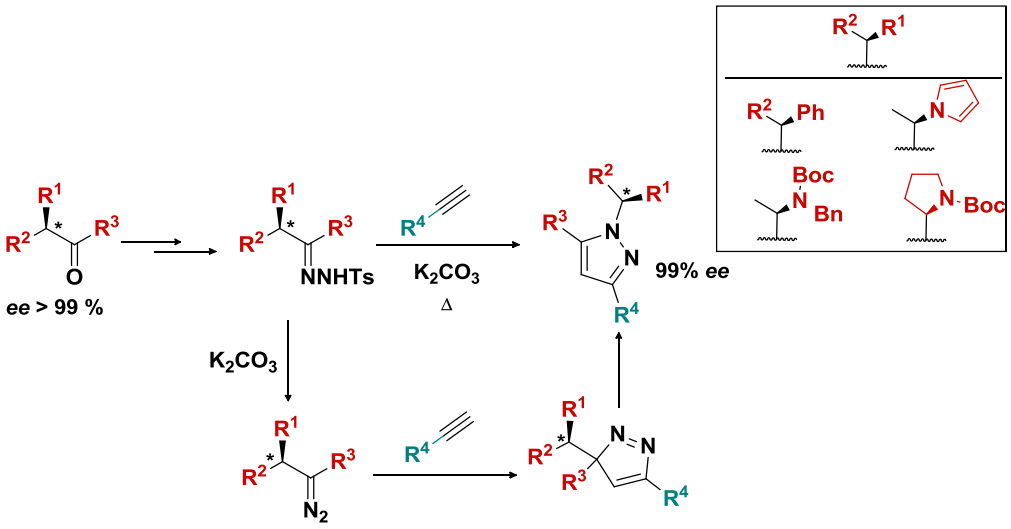
1- *Quimioselectividad*, ya que de los dos posibles grupo que pueden migrar sólo uno es el que experimenta esta migración.

2-*Regioselectividad*, la migración tiene lugar de forma preferente hacia una de las posiciones de las dos posibles, en este caso, hacia el átomo de nitrógeno.

3- *Estereoespecífica*, ya que la migración del grupo estereogénico ocurre con total retención de la configuración.

Esta estrategia además, desde el punto de vista mecanístico, supone la primera transposición [1,5] con retención de configuración del grupo que migra y que no sea un sistema espirocíclico.

2.B.4. RESUMEN GRÁFICO



Conclusions

The tosylhydrazones are very versatile intermediates to carry out different transformations of carbonyl compounds in an alternative way. They allow the development of new processes in a simple manner without the need of a transition metal catalyst.

In Chapter 1 of this dissertation, it has been demonstrated the aptitude of alkenyl boronic acids as nucleophilic coupling partner in metal-free reductive alkenylations of carbonyl compounds. These processes allow the synthesis of different olefinic compounds in a general way and with a remarkable operational simplicity. Moreover, the reaction is completely predictable and it is possible to choose the appropriate substrate to obtained the desired isomer.

In Chapter 2, a cascade reaction that involve a 1,3-dipolar cycloaddition followed by a [1,5]-sigmatropic rearrangement to synthesize trisubstituted pyrazols has been studied. This processes evolve through a migration of the rest of the tosylhydrazone to the C4 or N2, allowing the access to different 1,3,5- or 3,4,5-trisubstituted pyrazoles in a regioselective way, in one step process and in good yields. Furthermore, this migration depends on the nature of the migrating rest. When the rest accommodates the incipient positive charge generated, the migration takes place to N2, otherwise to de C4. This is indeed a quite intriguing case of double selectivity, i) chemoselectivity on the migrating group, ii) regioselectivity on the sense of the migration.

In Part B of the Chapter, it has been described a new methodology to synthesize enantioenriched trisubstituted pyrazoles from terminal alkynes and α-chiral-*N*-tosylhydrazones through a sequence of 1,3-dipolar cycloaddition followed by a [1,5]-sigmatropic rearrangement. This reaction is regioselective, again, depending on the nature of the substituent. Moreover, the process occurs with retention of the configuration in the migrating rest. This reaction constitutes a unique example of [1,5]-sigmatropic rearrangement with preservation of the configuration of the migrating group. In this way, it is possible to access to different structures that otherwise would be very difficult. Particularly, these reactions are highly selective in three different levels: i) chemoselectivity: one of the two possible groups undergoes migration; ii) regioselectivity: the migration takes place preferentially to one of the two possible positions; iii) stereospecificity: the migration of stereogenic groups occurs with retention of configuration.

Considering the importance of pyrazoles in pharmaceutical and agrochemical industries, the utility of the presented methods is revealed as an important strategy to acces to this heterocyclic molecules in a straightforward manner.

Conclusiones

(*En español*)

Las tosilhidrazonas son intermedios muy versátiles a la hora de llevar a cabo de forma alternativa las transformaciones típicas que experimentan los compuestos carbonílicos. De esta manera, permiten el desarrollo de nuevos procesos en los cuales no sea necesario el empleo de catalizadores metálicos.

En el Capítulo 1 de esta Tesis, se ha demostrado la aptitud de los ácidos alquenilborónicos como agente nucleófilo en las reacciones de acoplamiento reductor llevadas a cabo en ausencia de metal. Estos procesos permiten la síntesis de diferentes compuestos olefínicos de una forma general y con una simplicidad operacional destacable. Además, si se eligen los sustratos apropiados se puede obtener el isómero deseado haciendo a la reacción completamente predecible.

En el Capítulo 2, se ha estudiado una reacción en cascada para sintetizar pirazoles trisustituidos que involucra una cicloadición 1,3-dipolar seguida de un reagrupamiento [1,5]-sigmatrópico. Estos procesos transcurren con una migración del resto procedente de la hidrazona al C4 o al N2 permitiendo el acceso a diferentes pirazoles 1,3,5- o 3,4,5-trisustituidos de forma regioselectiva, en un solo paso de reacción y con buenos rendimientos. Además, la migración depende de la naturaleza propia del resto que migra. Cuando este resto acomoda la carga incipiente positiva generada, la migración tiene lugar al N2, si esto no es así, se produce hacia el C4. De esta forma, se accede a una doble regioselectividad: i) quimioselectividad del grupo que migra, ii) regioselectividad en el sentido de la migración.

En la Parte B de este Capítulo, ha sido descrita una nueva metodología para sintetizar pirazoles trisustituidos de forma enantioenriquecida a partir de alquinos terminales y tosilhidrazonas que poseen un centro estereogénico en posición α. La secuencia de la reacción implica de nuevo una cicloadición 1,3-dipolar seguida de un reagrupamiento [1,5]-sigmatrópico, la cual, se da de forma regioselectiva dependiendo de la naturaleza del sustituyente. Además, es de destacar que el proceso transcurre con retención de la configuración del centro estereogénico. Esta reacción constituye el primer ejemplo de transposición [1,5] en el cual se conserva la configuración del grupo que migra. De este modo, se puede sintetizar estructuras difícilmente accesible por otras vías. Estas reacciones son altamente selectivas por tres razones: i) quimioselectiva, uno de los posibles dos grupos migra ii) regioslectiva, la migración tiene lugar a uno de los dos posibles centrosy iii) estereoespecíficas, la migración del centro estereogénico transcurre con retención de la configuración

Considerando la importancia de los pirazoles en la industria farmacéutica, se pone de manifiesto la utilidad que poseen los métodos presentados en esta Tesis. Puesto que representan una forma muy sencilla de acceder a ellos.

Experimental Part

E.1. General information

E.1.1. Reactions

Reactions performed by conventional heating were carried out in a RR98030 12 place *Carousel Reaction Station™* from Radleys Discovery Technologies, equipped with gastight threaded caps with a valve, cooling reflux head system, and digital temperature controller. High temperature reactions were also performed using hot plate/oil bath apparatus with internal temperature control.

The microwave-assisted reactions were conducted using a focused microwave unit (*Biotage Initiator 2.0™*). The temperature was monitored with an infrared temperature sensor. In all experiments the microwave temperature was held constant. Reactions were performed in 0.5-2 mL glass vessels, which were sealed with a cap with septum. The specific reaction time corresponds to the total irradiation time.

Low temperature reactions were performed using Dewar flask with a chilled mixture of liquid nitrogen and acetone.

E.1.2. Solvents

All anhydrous solvents were dried and deoxygenated with a PureSolv® columm before use except for the case of 1,4-dioxane that was dried by standard techniques and freshly distilled from sodium metal.[246]

E.1.3. Reagents

Commercially available starting materials and reagents were purchased at the highest commercial quality and used without further purification. Those that required chemical manipulation were prepared according to the methods reported in the literature and purified by standard procedures.[248] Tosylhydrazones were prepared following the procedure described in literature.[249]

[248] D. D. Perrín, W.L.F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, **1997**.
[249] 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

K_2CO_3 and CsF were purchased from Fluka and Alfa Aesar Chemical co. respectively, stored in a flask purged with nitrogen and weight in the air. MeOH were purchased from Scharlau and stored in air. All alkenyl boronic acids and acetylenes are commercially available from Aldrich Chemical co., Acros Organics Chemical co. and Alfa Aesar Chemical co.

E.1.4. Chromatography

All flash chromatography were carried out using dry packed 60 silica gel (230-240-mesh, Merck, Scharlau) under a positive pressure of air.

Thin layer chromatography (TLC) was carried our on Merck Kieselgel 60 PF254 0.2 mm plates. Visualisation was accomplished using ultra violet light (λ=254 nm) and chemical staining with solutions of vanilline in ethanol containing sulfuric acid, Ce/Mo or acidic potassium permanganate as appropriate heating the TLC after the immersion.

E.1.5. Data Collection

GCMS (Gas chromatography-Mass spectrometry)

The reactions were monitored by GC-MS employing a combination of a gas chromatography to separates mixtures an mass spectrometry to identify the various components from their mass spectra. The CGMS is from Shimadzu Corporation GCMS-QP2010 with autoinjector AOC-20i.

Nuclear Magnetic Resonance (NMR)

NMR spectra were recorded in $CDCl_3$ at 600, 400, 300 MHz for ^{1}H and 100 or 75 MHz for ^{13}C, with tetramethylsilane as internal standard for ^{1}H and the residual solvent signals as standard for ^{13}C.

The temperature of the acquisition of the NMR spectra was 298 ± 3K unless otherwise stated.

Coupling constants (*J*) are corrected and quoted to the nearest 0.1 Hz. The data is being reported as bs = broad singlet, s = singlet, d = doublet, dd = double doblet, t = triplet, dt = double triplet, ddt = double double triplet, tt = triple triplet, q = quatriplet, qd = quadruple doblet, quint = quintuplet and m = multiplet or unresolved, chemical shifts in ppm and coupling constant(s) in Hz.

Data are reported as follows: ^{1}H-NMR : chemical shift (multiplicity, coupling, constant *J* in Hz, number of protons); ^{13}C-NMR: chemical shift (for fluorine-containing molecules: multiplicity, coupling constant J in Hz) and ^{19}F-NMR: chemical shift.

High-Resolution Mass Spectrometry (HRMS)

High-resolution mass spectrometry was carried out on a Finnigan-Mat 95 spectrometer at the Mass Spectrometry Service at the University of Burgos (Spain). Mass spectra were obtained by EI (70 eV).

High-Performance Liquid Chromatrography (HPLC)

Enantiomer ratios were determined by chiral HPLC analyses (Waters 2695 with a VUV 2996 or 996 photodiode Array detector) in comparison with the authentic racemic products, which were synthesized employing the same route from the racemic starting materials. The specific rotation was determined with an automatic polarimeter (Autopol® IV Rudolph Research Analytical) with a sodium lamp CH2Cl2 as solvent (c, g/100 mL).

Optical Rotation and Melting Point

Optical rotations were measured using a 2 mL cell with a 1 dm path length on an Autopol IV Rudolph Research Analytical polarimeter at 589 nm, and are reported as $[\alpha^{T}_{D}]$ (Concentration in grams/mL solvent).

Melting points (m.p.) are uncorrected and were measured in a Gallenkamp melting point apparatus.

Chapter 1: Olefination of Carbonyl Compounds through Reductive Couplings of Alkenyl Boronic Acids with Tosylhydrazones

E.2. General procedures for the reductive coupling

E.2.1. General procedure for the reductive coupling of tosylhydrazones 1 and alkenyl boronic acids 2 using conventional heating (*Method A*)

A reaction tube was charged with the tosylhydrazone **1** (0.5 mmol), the alkenyl boronic acid **2** (1 mmol), potassium carbonate (138.2 mg, 1 mmol), cesium fluoride (151.9 mg, 1 mmol) and dioxane (2.3 mL). The system was heated at 110 °C with stirring and reflux. The reaction was monitored by GCMS. When the reaction was completed, the crude reaction was cooled down to room temperature, the solvent was eliminated and a saturated solution of $NaHCO_3$ and dichloromethane were added and the lawyers were separated. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with $NaHCO_3$, brine, dried over $MgSO_4$ and filtered. Solvent was removed under reduced pressure. Finally, products were purified by flash chromatography on silica gel.

E.2.2. General procedure for the reductive coupling of tosylhydrazones 1 and alkenyl boronic acids 2 under microwave irradiation (*Methods B and C*)

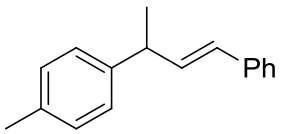
A 0.5-2 mL microwave vial was charged with the tosylhidrazone 1 (0.3 mmol), the alkenyl boronic acid (0.6 mmol), K_2CO_3 (82.9 mg, 0.6 mmol), cesium fluoride (91.1 mg, 0.6 mmol) in the case of *Method B* or MeOH (1mL) for *Method C*, dioxane (2 mL *Method B* or 1 mL *Method C*) and a triangular stir bar. The vessel was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction crude at the desire temperature (150 °C) during the reaction time (30 min) in a Biotage Initiator microwave apparatus. When the reaction was finished was allowed to reach room temperature, the solvent was eliminated and a saturated solution of $NaHCO_3$ and dichloromethane were added and the lawyers were separated. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with $NaHCO_3$, brine, dried over $MgSO_4$ and filtered. Solvent was removed under reduced pressure. Finally, products were purified by flash chromatography on silica gel.

E.2.3. General procedure for the one pot reductive coupling of tosylhydrazones 1 and alkenyl boronic acids 2 under microwave irradiation.

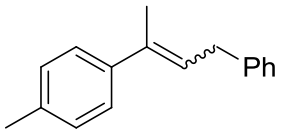
A 0.5-2 mL microwave vial was charged with the carbonyl compound (0.3 mmol) and tosylhydrazine (1.16 equiv) and dioxane (2 mL). The vessel was irradiated 30 min at 46 °C. Then, potassium carbonate (82.9 mg, 0.3 mmol), the alkenyl boronic acid (0.6 mmol) and cesium fluoride were added to the reaction mixture and the system was heated up to 150 °C for 30 min. At this point, the general procedure was followed.

E.3. Characterization data for compounds 5

(*E*)-1-methyl-4-(4-phenylbut-3-en-2-yl)benzene (3a) (*E/Z*)-1-methyl-4-(4-phenylbut-2-en-2-yl)benzene (4a, 4'a)



3a



4a, 4a'

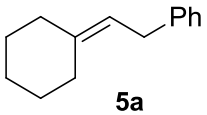
From 4-methyl-*N*'-(1-*p*-tolylethylidene)benzenesulfonohydrazide (151.2 mg, 0.5 mmol) and phenylvinylboronic acid (147.9 mg, 1mmol) was obtained 92% isolated yield following *General procedure A* as a colourless oil. **3a, 4a, 4'a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. Rf (hexanes/ethyl acetate) = 0.55

HRMS (EI): calcd. for $C_{17}H_{18}$: 222,1409; found 222.1410

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 – 7.00 (m, 11.9H, **3a+4a+4'a**), 6.38 – 6.23 (m, 0.2H, **3a**), 5.86 (tq, ^{3}J = 7.3, 1.3 Hz, 1H, **4a**), 5.55 (td, ^{3}J = 7.5, 1.5 Hz, 0.2H, **4'a**), 3.60 – 3.51 (m, 0.2H, **3a**), 3.48 (d, ^{3}J = 7.4 Hz, 2H, **4a**), 3.25 (d, ^{3}J = 7.4 Hz, 0.44H, **4'a**), 2.27 (s, 0.6H, **4'a**), 2.25 (s, 3H, **5a**), 2.05-2.04 (m, 3H, **4a**), 1.99 (app. dd, ^{3}J = 2.6, 1.2 Hz, 0.6H, **4'a**), 1.42 (s, 0.3H, **3a**), 1.37 (d, ^{3}J = 7.0 Hz, 0.3H, **3a**). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 141.3, 140.9, 136.5, 135.6, 129.3, 129.0, 128.6, 128.5, 128.0, 127.3, 126.3, 126.0, 125.7, 125.6, 35.5, 35.1, 25.8, 21.2, 16.1.

Spectroscopic data in agreement with those reported in *Org. Lett.* **2011**, *13*, 2208.

(2-cyclohexylideneethyl)benzene (5a)



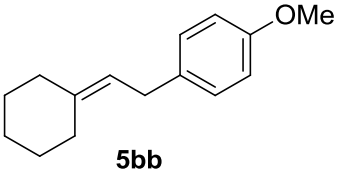
5a

From *N*'-cyclohexylidene-4-methylbenzenesulfonohydrazide (79.9 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 88% isolated yield following *General procedure B* as a colourless oil. **5a** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.46.

HRMS (EI): calcd. for $C_{14}H_{18}$: 186,1409; found 186,1404

^{1} H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.27 (m, 2H), 7.21-7.18 (m, 3H), 5.28 (t, ^{3}J = 7.5, 1H), 3.37 (d, ^{3}J = 7.5, 2H), 2.26 (m, 2H), 2.13 (m, 2H), 1.58 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 142.1 (C), 140.7 (C), 128.50 (4xCH), 125.8 (CH), 119.9 (CH), 37.3 (CH_2), 33.5 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 27.1 (CH_2).

1-(2-cyclohexylideneethyl)-4-methoxybenzene (5bb)



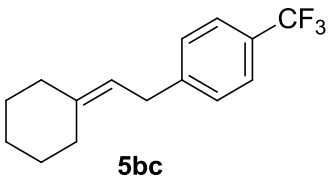
5bb

From N'-cyclohexylidene-4-methylbenzenesulfonohydrazide (79.9 mg, 0.3 mmol) and *trans*-2-(4-methoxyphenyl)vinylboronic acid (106.8 mg, 0.6 mmol) was obtained 92% isolated yield following *General procedure B* as a colourless oil. **5bb** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. Rf (hexanes/ethyl acetate 15:1) = 0.46.

HRMS (EI): calcd. for $C_{15}H_{20}O$: 216.1514; found 216.1516.

^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.10 (d, ^{3}J = 6.9 Hz, 2H), 6.83 (d, ^{3}J = 6.9 Hz, 2H), 5.25 (t, ^{3}J = 7.5 Hz, 1H), 3.79 (s, 3H), 3.30 (d, ^{3}J = 7.5 Hz, 1H), 2.27-2.21 (m, 2H), 2.15-2.09 (m, 2H), 1.59-1.53 (m, 6H). **^{13}C NMR** (75 MHz, CD_2Cl_2) δ 158.4 (C), 140.8 (C), 134.6(C), 129.7 (2xCH), 120.8 (CH), 114.2 (2xCH), 55.7 (CH_3), 37.7 (CH_2), 32.9 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.5 (CH_2), 27.5 (CH_2).

1-(2-cyclohexylideneethyl)-4-(trifluoromethyl)benzene (5bc)



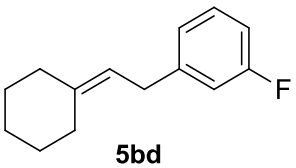
5bc

From N'-cyclohexylidene-4-methylbenzenesulfonohydrazide (79.9 mg, 0.3 mmol) and *trans*-2-[4-(trifluoromethyl)phenyl]vinylboronic acid (152.6 mg, 0.6 mmol) was obtained 52% isolated yield following *General procedure B* as a colourless solid. **5bc** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.65.

HRMS (EI): calcd. for $C_{15}H_{17}F_3$: 254,1282; found 254,1295.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, ^3J = 8.1 Hz, 1H), 7.29 (d, ^3J = 8.0 Hz, 1H), 5.25 (t, ^3J = 7.4 Hz, 1H), 3.41 (d, ^3J = 7.4 Hz, 1H), 2.24 (m, 2H), 2.14 (m, 2H), 1.58 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 146.1 (C), 141.7 (C), 128.6 (2xCH), 128.2 (q, ^2J=32.2 Hz, C), 125.2 (q, ^3J=3.7 Hz, 2xCH), 124.6 (q, ^1J=271.7 Hz, C)118.6 (CH), 37.2 (CH_2), 33.2 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 26.85 (CH_2). **^{19}F-NMR** (282 Hz, $CDCl_3$): δ = -62.28.

1-(2-cyclohexylideneethyl)-3-fluorobenzene (5bd)



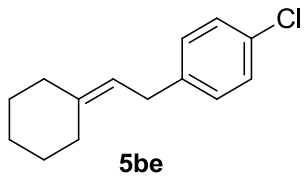
5bd

From N'-cyclohexylidene-4-methylbenzenesulfonohydrazide (79.9 mg, 0.3 mmol) and *trans*-2-(3-fluorophenyl)vinylboronic acid (99.6 mg, 0.6 mmol) was obtained 89% isolated yield following *General procedure B* as a colourless oil. **5bd** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 30:1 as eluent. Rf (hexanes/ethyl acetate 30:1) = 0.7.

HRMS (EI): calcd. for $C_{14}H_{17}F$: 204,1314; found 204,1219.

^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.25 (dt, ^{3}J =6.2, 7.7 Hz, 1H), 6.99 (d, ^{3}J = 7.7 Hz, 1H), 6.94-6.83 (m, 2H), 5.25 (t, ^{3}J = 7.5 Hz, 1H), 3.36 (d, ^{3}J = 7.5 Hz, 2H), 2.25 (m, 2H), 2.14 (m, 2H), 1.58 (m, 6H). **^{13}C NMR** (75 MHz, CD_2Cl_2): δ = 163.3 (d, ^{1}J = 244.5 Hz, C), 145.3 (d, ^{3}J = 7.0 Hz,C), 141.8 (C), 130.0 (d, ^{3}J = 8.3 Hz, CH), 124.4 (CH), 119.2 (CH), 115.4 (d, ^{2}J = 21.0 Hz, CH), 112.7 (d,^{2}J = 21.1 Hz,CH), 37.52 (CH_2), 33.4 (CH_2), 29.1 (CH_2), 28.26 (CH_2), 27.8 (CH_2). **^{19}F-NMR** (282 Hz, CD_2Cl_2); δ = -114.66.

1-chloro-4-(2-cyclohexylideneethyl)benzene (5be)



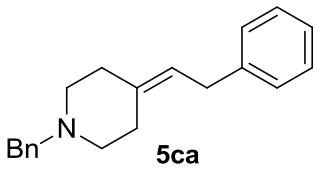
5be

Following the *Method B* from *N'*-cyclohexylidene-4 methylbenzenesulfonohydrazide (79.9 mg, 0.3 mmol) and *trans*-2-(4 chlorophenyl)vinylboronic acid (109.5 mg, 0.6 mmol) were obtained 66 mg of **5be** (76% isolated yield) as a colourless oil. **5be** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 50:1 as eluent. *Rf* (hexanes/ethyl acetate 50:1) = 0.74.

HRMS (EI): calcd. for $C_{14}H_{17}Cl$: 220,1019; found 220,1018.

1H NMR (300 MHz, CDCl3): δ = 7.16 (d, ^{3}J = 8.4 Hz, 2H), 7.03 (d, ^{3}J = 8.3 Hz, 2H), 5.14 (t, $_{3}J$ = 7.4 Hz, 1H), 3.24 (d, ^{3}J = 7.5 Hz, 2H), 2.16-2.14 (m, 2H), 2.06-2.04 (m, 2H), 1.49 (bs, 6H). **13C NMR** (75 MHz, CDCl3): δ = 141.3 (C), 140.5 (C), 131.4 (C), 129.8 (2xCH), 128.5 (2xCH), 119.2(CH), 37.3 (CH_2), 32.8 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 27.00 (CH_2).

1-benzyl-4-(2-phenylethylidene)piperidine (5ca)



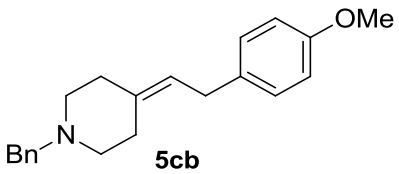
5ca

From *N'*-(1-benzylpiperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (107.2 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 82% isolated yield following *General procedure B* as a light brown oil. **5ca** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 4:1 as eluent. Rf (hexanes/ethyl acetate 4:1) = 0.3.

HRMS (EI): calcd. for $C_{20}H_{23}N$: 277,1830; found 277,1830.

^{1}H NMR (401 MHz, $CDCl_3$): δ = 7.39-7.27 (m, 7H), 7.21 (m, 3H), 5.36 (t, ^3J = 7.4 Hz, 1H), 3.57 (s, 2H), 3.39 (d, ^3J = 7.4 Hz, 2H), 2.50 (t, ^3J = 5.4 Hz, 4H), 2.41 (t, ^3J=5.4 Hz, 2H), 2.29 (t, ^3J = 5.4 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 141.7 (C), 138.66 (C), 137.22 (C), 129.9 (2xCH), 128.5 (2xCH), 128.4 (2xCH), 128.3 (2xCH), 127.1 (CH), 125.9 (CH), 121.1 (CH), 63.2 (CH_2), 55.4 (CH_2), 54.7 (CH_2), 36.2 (CH_2), 33.5 (CH_2), 28.5 (CH_2).

1-benzyl-4-(2-(4-methoxyphenyl)ethylidene)piperidine (5cb)



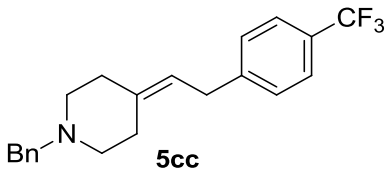
5cb

From *N'*-(1-benzylpiperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (178.7 mg, 0.5 mmol) and *trans*-2-(4-methoxyphenyl)vinylboronic acid (178.0 mg, 0.6 mmol) was obtained 57% isolated yield following *General procedure A* as a yellow oil. **5cb** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. Rf (hexanes/ethyl acetate 2:1) = 0.42.

HRMS (EI): calcd. for $C_{21}H_{25}NO$: 307,1936; found 307,1936.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.33 (m, 5H), 7.10 (d, ^3J = 8.7 Hz, 1H), 6.84 (d, ^3J = 8.7 Hz, 1H), 5.32 (t, ^3J = 7.5 Hz, 1H), 3.79 (s, 2H), 3.55 (s, 1H), 3.30 (d, ^3J = 7.5 Hz, 1H), 2.48 (t, ^3J = 5.5 Hz, 2H), 2.39 (t, ^3J = 5.1 Hz, 1H), 2.26 (t, ^3J = 5.4 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.8 (C), 138.2 (C), 136.6 (C), 133.58 (C), 129.3 (2xCH), 129.2 (2xCH), 128.2 (2xCH), 127.1 (CH), 121.6 (CH), 113.9 (2xCH), 63.0 (CH_2), 55.3 (CH_3), 55.2 (CH_2), 54.6 (CH_2), 35.9 (CH_2), 32.5 (CH_2), 28.2 (CH_2).

1-benzyl-4-(2-(4-(trifluoromethyl)phenyl)ethylidene)piperidine (5cc)



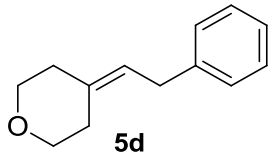
5cc

From *N'*-(1-benzylpiperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (107.2 mg, 0.3 mmol) and *trans*-2-[4-(trifluoromethyl)phenyl]vinylboronic acid (152.6 mg, 0.6 mmol) was obtained 68% isolated yield following *General procedure B* as a light brown oil. **5cc** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. Rf (hexanes/ethyl acetate 5:1) = 0.23.

HRMS (EI): calcd. for $C_{21}H_{22}F_3N$: 345,1704; found 345,1692.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, ^3J = 8.1 Hz, 2H), 7.29-7.11 (m, 7H), 5.21 (t, ^3J = 7.4 Hz, 1H), 3.45 (s, 2H), 3.32 (d, ^3J = 7.4 Hz, 2H), 2.47-2.34 (m, 4H), 2.31-2.24 (m, 2H), 2.20-2.17 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 145.8 (C), 138.4 (C), 138.2 (C), 129.3 (2xCH), 128.7 (2xCH), 128.4 (2xCH), 128.2 (^2J = 32.2 Hz, C), 127.2 (CH), 125.3 (q, ^3J = 3.7 Hz, 2xCH), 124.4 (J=271.7 Hz, C), 120.1 (CH), 63.1 (CH_2), 55.3 (CH_2), 54.6 (CH_2), 36.1 (CH_2), 33.4 (CH_2), 28.4 (CH_2).

4-(2-phenylethylidene)tetrahydro-2*H*-pyrane (5d)



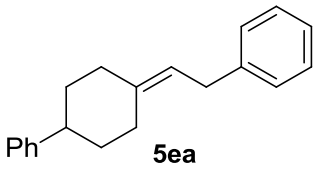
5d

From *N'*-(dihydro-2H-pyran-4(3*H*)-ylidene)-4-methylbenzenesulfonohydrazide (80.5 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 82% isolated yield following *General procedure B* as a colourless oil. **5d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. Rf (hexanes/ethyl acetate 10:1) = 0.32.

HRMS (EI): calcd. for $C_{13}H_{16}O$: 188,1201; found 188,1201.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.26 (m, 2H), 7.21-7.17 (m, 3H), 5.40 (t, ^{3}J = 7.5 Hz, 1H), 3.78-3.62 (m, 4H), 3.38 (d, ^{3}J = 7.4 Hz, 2H), 2.41-2.38 (m, 2H), 2.28-2.25 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 141.4 (C), 135.4 (C), 128.6 (2xCH), 128.4 (2xCH), 126.0(CH), 121.9 (CH), 69.8 (CH_2), 68.9 (CH_2), 37.1 (CH_2), 33.3 (CH_2), 29.9 (CH_2).

(2-(4-phenylcyclohexylidene)ethyl)benzene (5ea)



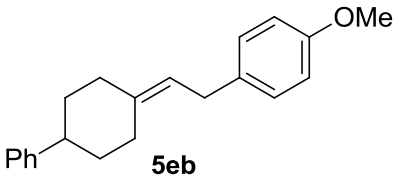
5ea

From 4-methyl-*N'*-(4-phenylcyclohexylidene)benzenesulfonohydrazide (102.6 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 81% isolated yield following *General procedure C* as a white solid. **5ea** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 80:1 as eluent. Rf (hexanes/ethyl acetate 80:1) = 0.3.

HRMS (EI): calcd. for $C_{20}H_{22}$: 262,1722 found 262,1709.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29-7.19 (m, 4H), 7.16-7.10 (m, 6H), 5.30 (t, ^{3}J = 7.5 Hz, 1H), 3.34 (d, ^{3}J = 7.4 Hz, 2H), 2.92-2.71 (m, 1H), 2.66 (tt, ^{3}J = 12.2, 3.2 Hz, 1H), 2.33-2.11 (m, 2H), 2.01-1.83 (m, 3H), 1.60-1.37 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.0 (C), 141.8 (C), 139.2 (C), 128.4 (6xCH), 126.9 (2xCH), 126.0 (CH), 125.8 (CH), 120.7 (CH), 44.8 (CH), 36.9 (CH_2), 35.8 (CH_2), 35.2 (CH_2), 33.6 (CH_2), 28.5 (CH_2).

1-methoxy-4-(2-(4-phenylcyclohexylidene)ethyl)benzene (5eb)



5eb

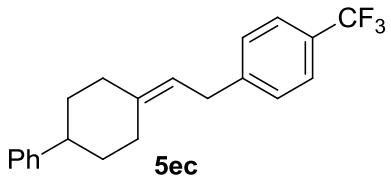
From 4-methyl-*N'*-(4-phenylcyclohexylidene)benzenesulfonohydrazide (102.6 mg, 0.3 mmol) and *trans*-2-(4-methoxyphenyl)vinylboronic acid (178.0 mg, 0.6 mmol) was

obtained 70% isolated yield following *General procedure C* as a colourless solid. **5eb** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 30:1 as eluent. Rf (hexanes/ethyl acetate 30:1) = 0.24.

HRMS (EI): calcd. for $C_{21}H_{24}O$: 292,1827; found 292,1819.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.17 (m, 5H), 7.15 (d, ^{3}J = 7.9 Hz, 2H), 6.87 (d, ^{3}J = 8.0 Hz, 2H), 5.36 (t, ^{3}J = 7.4 Hz, 1H), 3.82 (s, 3H), 3.36 (d, ^{3}J = 7.3 Hz, 2H), 2.89 (d, ^{3}J = 13.7 Hz, 1H), 2.75 (t, ^{3}J = 11.7 Hz, 1H), 2.45-2.17 (m, 3H), 2.11-1.87 (m, 2H), 1.69-1.46 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 157.9 (C), 147.1 (C), 139.0 (C), 134.0 (C), 129.3 (2xCH), 128.5 (2xCH), 127.0 (2xCH), 126.1 (CH), 121.2 (CH), 114.0 (2xCH), 55.4 (CH_3), 44.9 (CH), 37.0 (CH_2), 35.9 (CH_2), 35.3 (CH_2), 32.8 (CH_2), 28.6 (CH_2).

1-(2-(4-phenylcyclohexylidene)ethyl)-4-(trifluoromethyl)benzene (5ec)



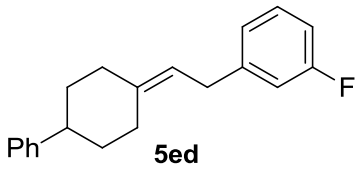
5ec

From 4-methyl-*N*′-(4-phenylcyclohexylidene)benzenesulfonohydrazide (102.6 mg, 0.3 mmol) and *trans*-2-[4-(trifluoromethyl)phenyl]vinylboronic acid (152.6 mg, 0.6 mmol) was obtained 83% isolated yield following *General procedure C* as a white solid. **5ec** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 30:1 as eluent. Rf (hexanes/ethyl acetate 30:1) = 0.37.

HRMS (EI): calcd. for $C_{21}H_{21}F_3$: 330,1595; found 330,1591.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, ^{3}J = 8.0 Hz, 2H), 7.33-7.30 (m, 4H), 7.24-7.19 (m, 3H), 5.35 (t, ^{3}J = 7.4 Hz, 1H), 3.46 (d, ^{3}J = 7.5 Hz, 2H), 2.85 (app. d, ^{3}J = 15.7 Hz, 1H), 2.74 (tt, ^{3}J = 12, 3.3 Hz, 1H), 2.37 (d, ^{3}J = 13.5 Hz, 1H), 2.27 (t, ^{3}J = 12.8 Hz, 1H), 2.13-1.92 (m, 3H), 1.67-1.40 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 146.9 (C), 146.1 (C), 140.4 (C), 128.8 (2xCH), 128.5 (2xCH), 127.0 (2xCH), 126.2 (CH), 125.4 (2xCH), 119.6 (CH), 44.8 (CH), 37.0 (CH_2), 35.9 (CH_2), 35.2 (CH_2), 33.6 (CH_2), 28.7 (CH_2).

1-fluoro-3-(2-(4-phenylcyclohexylidene)ethyl)benzene (5ed)



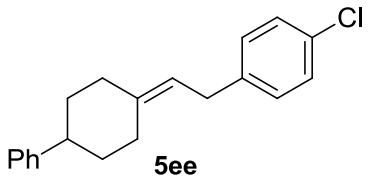
5ed

From 4-methyl-*N'*-(4-phenylcyclohexylidene)benzenesulfonohydrazide (102.6 mg, 0.3 mmol) and *trans*-2-(3-fluorophenyl)vinylboronic acid (99.6 mg, 0.6 mmol) was obtained 93% isolated yield following *General procedure C* as a colourless oil. **5ed** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 30:1 as eluent. Rf (hexanes/ethyl acetate 30:1) = 0.42.

HRMS (EI): calcd. for $C_{20}H_{21}F$: 280,1627; found 280,1620.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26-7.01 (m, 1H), 6.91 – 6.71 (m, 1H), 5.24 (t, ^{3}J = 7.4 Hz, 1H), 3.29 (d, ^{3}J = 7.4 Hz, 1H), 2.75-2.70 (m, 1H), 2.63 (tt, ^{3}J = 12.2, 3.2 Hz, 1H), 2.32 – 2.07 (m, 1H), 2.01 – 1.76 (m, 1H), 1.57 – 1.23 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 163.1 (d, ^{1}J = 245.2 Hz, C), 146.9 (C), 144.5 (d,^{3} J = 7.1 Hz, C), 140.1 (C), 129.8 (d, ^{3}J = 8.3 Hz, CH), 128.5 (CH), 127.0 (2xCH), 126.2 (2xCH), 124.1 (d, ^{4}J = 2.6 Hz, CH), 119.90 (CH), 115.3 (d, ^{2}J = 21.0 Hz, CH), 112.3 (d, ^{2}J = 21.1 Hz, CH), 44.8 (CH_2), 37.0 (CH_2), 35.9 (CH_2), 35.2 (CH_2), 33.4 (CH_2), 28.6 (CH_2).

1-chloro-4-(2-(4-phenylcyclohexylidene)ethyl)benzene (5ee)



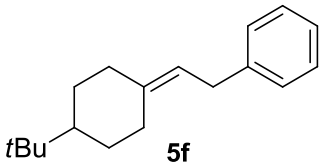
5ee

From 4-methyl-*N'*-(4-phenylcyclohexylidene)benzenesulfonohydrazide (102.6 mg, 0.3 mmol) and *trans*-2-(4-chlorophenyl)vinylboronic acid (109.5 mg, 0.6 mmol) was obtained 93% isolated yield following *General procedure C* as a white solid. **5ee** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 50:1 as eluent. Rf (hexanes/ethyl acetate 50:1) = 0.34.

HRMS (EI): calcd. for $C_{20}H_{21}Cl$: 296,1332; found 296,1326 .

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 – 7.07 (m, 7H), 7.04 (d, ^3J = 8.3 Hz, 2H), 5.23 (t, ^3J = 7.4 Hz, 1H), 3.27 (d, ^3J = 7.4 Hz, 2H), 2.74 (d, ^3J = 14.9 Hz, 1H), 2.64 (tt, ^3J = 12.2, 3.1 Hz, 1H), 2.33 – 2.09 (m, 2H), 1.99 – 1.81 (m, 3H), 1.59 – 1.29 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.0 (C), 140.4 (C), 139.9 (C), 131.6 (C), 129.8 (2xCH), 128.6 (2xCH), 128.5 (2xCH), 127.0 (2xCH), 126.2 (CH), 120.2 (CH), 44.9 (CH), 37.0 (CH_2), 35.9 (CH_2), 35.2 (CH_2), 33.0 (CH_2), 28.6 (CH_2).

(2-(4-(tert-butyl)cyclohexylidene)ethyl)benzene (5f)



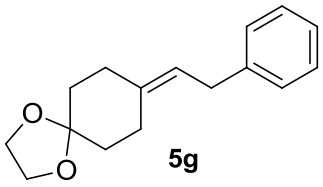
5f

From *N'*-(4-(*tert*-butyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (96.7 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 86% isolated yield following *General procedure B* as a white solid. **5f** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.53.

HRMS (EI): calcd. for $C_{18}H_{26}$: 242,2035; found 242.2034.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38-7.30 (m, 2H), 7.26-7.21 (m, 3H), 5.33 (t, ^3J = 7.4, 1H), 3.43 (d, ^3J = 7.4 Hz, 2H), 2.68-2.64 (m, 1H), 2.16-2.11 (m,1H), 1.97-1.93 (m,1H), 1.80-1.61 (m,3H), 1.09-1.03 (m,3H), 0.75 (s,9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 142.1 (C), 140.6 (C), 128.5 (4xCH), 125.8 (CH), 119.6 (CH), 48.7 (CH), 37.2 (CH_2), 33.7 (CH_2), 32.6 (C), 29.4 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 27.8 (3xCH_3).

8-(2-phenylethylidene)-1,4-dioxaspiro[4.5]decane (5g)



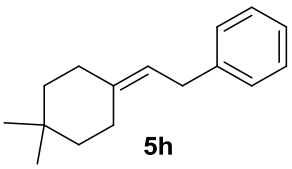
5g

From 4-methyl-*N'*-(1,4-dioxaspiro[4.5]decan-8-ylidene)benzenesulfonohydrazide (97.3 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 77% isolated yield following *General procedure B* as a colourless oil. **5g** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. Rf (hexanes/ethyl acetate 5:1) = 0.38.

HRMS (EI): calcd. for $C_{16}H_{20}O_2$: 244,1463; found 244,1468.

^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.35-7.28 (m, 2H), 7.25-7.18 (m, 3H), 5.38 (t, ^3J = 7.5 Hz, 1H), 3.99 (s, 4H), 3.41 (d, ^3J = 7.5 Hz, 2H), 2.49-2.40 (m, 2H), 2.35-2.25 (m, 2H), 1.79-1.68 (m, 4H). **^{13}C NMR** (75 MHz, CD_2Cl_2): δ = 142.3 (C), 138.6 (C), 128.9 (4xCH), 126.3 (CH), 121.8 (CH), 109.3 (C), 64.9 (2xCH_2), 36.8 (CH_2), 36.1 (CH_2), 34.2 (CH_2), 34.2 (CH_2), 25.7 (CH_2).

(2-(4,4-dimethylcyclohexylidene)ethyl)benzene (5h)



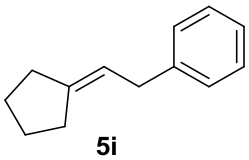
5h

From *N'*-(4,4-dimethylcyclohexylidene)-4-methylbenzenesulfonohydrazide (88.3 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 80% isolated yield following *General procedure C* as a colourless oil. **5h** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.54.

HRMS (EI): calcd. for $C_{16}H_{22}$: 214,1722; found 214,1722.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36-7.28 (m, 2H), 7.22-7.17 (m, 3H), 5.30 (t, ^3J = 7.4 Hz, 1H), 3.38 (d, ^3J = 7.4 Hz, 2H), 2.33 – 2.23 (m, 2H), 2.20 – 2.09 (m, 2H), 1.46 – 1.28 (m, 4H), 0.99 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 142.1 (C), 140.5 (C), 128.5 (4xCH), 125.8 (CH), 119.9 (CH), 41.1 (CH_2), 40.4 (CH_2), 33.7 (CH_2), 33.1 (CH_2), 30.8 (C), 28.4 (2xCH_3), 24.7 (CH_2).

(2-cyclopentylideneethyl)benzene (5i)



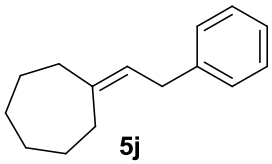
5i

From *N'*-cyclopentylidene-4-methylbenzenesulfonohydrazide (75.7 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 78% isolated yield following *General procedure C* as a colourless oil. **5i** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.5.

HRMS (EI): calcd. for $C_{13}H_{16}$: 172,1252 found 172,1257.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.28 (m, 2H), 7.23-7.17 (m, 3H), 5.50 (m, 1H), 3.38 (d, ^{3}J = 7.3 Hz, 2H), 2.45-2.22 (m, 4H), 1.84-1.59 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 144.6 (C), 141.9 (C), 128.5 (2xCH), 128.4 (2xCH), 125.8 (CH), 118.8 (CH), 36.1 (CH_2), 33.8 (CH_2), 29.0 (CH_2), 26.6 (CH_2), 26.5 (CH_2).

(2-phenylethylidene)cycloheptane (5j)



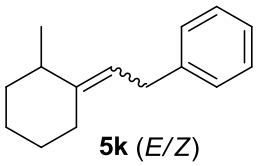
5j

From *N'*-cycloheptylidene-4-methylbenzenesulfonohydrazide (84.1 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 89% isolated yield following *General procedure C* as a colourless oil. **5j** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.57.

HRMS (EI): calcd. for $C_{15}H_{20}$: 200,1565 found 200,1566.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28-7.15 (m, 2H), 7.15-6.87 (m, 3H), 5.26 (t, ^{3}J = 7.2, 1.1 Hz, 1H), 3.26 (d, ^{3}J = 7.2 Hz, 2H), 2.34-2.20 (m, 2H), 2.20-2.10 (m, 2H), 1.64-1.37 (m, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 142.4 (C), 142.0 (C), 128.5 (4xCH), 125.8 (CH), 123.6 (CH), 38.0 (CH_2), 34.1 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.3 (CH_2).

(*E/Z*)-(2-(2-methylcyclohexylidene)ethyl)benzene (5k)



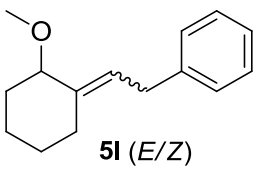
5k (*E/Z*)

From 4-methyl-*N'*-(2-methylcyclohexylidene)benzenesulfonohydrazide (140.2 mg, 0.5 mmol) and *trans*-2-phenylvinylboronic acid (147.8 mg, 1 mmol) was obtained 93% (*E/Z*, 10:1) isolated yield following *General procedure A* as a colourless oil. **5k** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.5.

HRMS (EI): calcd. for $C_{15}H_{20}$: 200,1565; found 200,1565.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.27 (m, 2.21H, isomers ***E+Z***), 7.21-7.17 (m, 3.3H, isomers ***E+Z***), 7.26 (t, ^{3}J = 7.6 Hz, 1.15H, isomers ***E+Z***), 3.40 (d, ^{3}J = 7.4 Hz, 2.37 H, isomers ***E+Z***), 2.63 (dt, ^{3}J = 13.3, 4.6 Hz, 1H, isomer ***E***), 2.29 (m, 0.22H, isomer ***Z***), 2.16 (m, 1H, isomer ***E***), 2.03 (m, 0.2H, isomer ***Z***) 1.81-1.56 (m, 4.15H, isomers ***E+Z***), 1.53-1.14 (m, 3.44H, isomers ***E+Z***), 1.12 (d, ^{3}J = 7.2 Hz, 0.70H, isomer ***Z***), 1.05 (d, ^{3}J = 6.8 Hz, 3H, isomer ***E***) **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 144.8 (C, isomer ***E***), 144.2 (C, isomer ***Z***), 142.3 (C, isomer ***E***), 142.1 (C, isomer ***Z***), 128.5 (2xCH, isomer ***E***), 128.4 (2xCH, isomer ***E***), 125.8 (CH, isomer ***E***), 119.9 (CH, isomer ***Z***), 117.3 (CH, isomer ***E***), 38.7 (CH, isomer ***E***), 36.9 (CH_2, isomer ***E***), 33.5 (CH_2, isomer ***E***), 33.3 (CH_2, isomer ***Z***), 32.7 (CH_2, isomer ***Z***), 30.4 (CH, isomer ***Z***), 28.7 (CH_2, isomer ***Z***), 28.5 (CH_2, isomer ***E***), 28.3 (CH_2, isomer ***E***), 25.7 (CH_2, isomer ***E***), 21.2 (CH_2, isomer ***Z***), 18.9 (CH_3, isomer ***E***), 18.4 (CH_3, isomer ***Z***).

(*E/Z*)-(2-(2-methoxycyclohexylidene)ethyl)benzene (5l)



5l (*E/Z*)

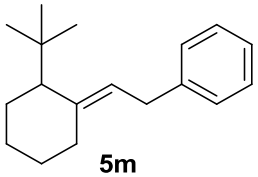
From *N'*-(2-methoxycyclohexylidene)-4-methylbenzenesulfonohydrazide (148.2 mg, 0.5 mmol) and *trans*-2-phenylvinylboronic acid (147.8 mg, 1 mmol) was obtained

50% (*E/Z*, 4:1) isolated yield following *General procedure A* as a light yellow oil. **5l** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. Rf (hexanes/ethyl acetate 10:1) = 0.34.

HRMS (EI): calcd. for $C_{15}H_{20}O$: 216,1514; found 216,1520.

^{1}H RMN (400 MHz, $CDCl_3$): δ = 7.32-7.28 (m, 2.8H, isomers ***E+Z***), 7.21-7.19 (m, 4H, isomers ***E+Z***), 5.56 (td, ^3J = 7.5, 1.5 MHz, 0.25H, isomer ***Z***), 5.52 (t, ^3J = 7.6 Hz, 1H, isomer ***E***), 3.60 (app. t, ^3J = 3.7 Hz, 1.14, isomers ***E+Z***), 3.43 (d, ^3J = 7.5 Hz, 2.8H, isomers ***E+Z***), 3.26 (s, 0.92 H, isomer ***Z***), 3.24 (s, 3H, isomer ***E***), 2.38 (dt, ^3J = 13.3, 4.3 Hz, 1.28H, isomers ***E+Z***), 2.19 (app. td, ^3J = 12.5, 4 Hz, 1.28H, isomers ***E+Z***), 1.91-1.66 (m, 5.8H, isomers ***E+Z***), 1.54 (dt, ^3J = 12.5, 4 Hz, 1.4H, isomers ***E+Z***), 1.44-1.35 (m, 2.21H, isomers ***E+Z***). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 141.5 (C), 139.2 (C), 128.5 (2xCH), 128.4 (2xCH), 126.0 (CH), 123.3 (CH), 83.1 (CH_3), 55.7 (CH), 33.9 (CH_2), 33.4 (CH_2), 27.5 (CH_2), 25.2 (CH_2), 22.0 (CH_2).

(2-(2-tertbutylcyclohexylidene)ethyl)benzene (5m)



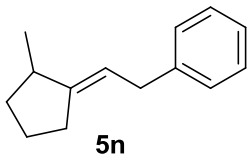
5m

From *N'*-(2-(tert-butyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (148.2 mg, 0.5 mmol) and *trans*-2-phenylvinylboronic acid (161.2 mg, 1 mmol) was obtained 49% isolated yield following *General procedure A* as a colourless oil. **5m** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.5.

HRMS (EI): calcd. for $C_{18}H_{26}$: 242,2035; found 242,2039.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.28 (m, 2H), 7.28-7.16 (m, 3H), 5.39 (t, ^3J = 7.4 Hz, 1H), 3.46 (d, ^3J = 7.4 Hz, 2H), 2.56 (dt, ^3J = 8.5, 4.0 Hz, 1H), 2.15-1.97 (m, 2H), 1.90-1.42 (m, 6H), 1.01 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 142 .3 (C), 141.3 (C), 128.5 (2xCH), 128.4 (2xCH), 125.7 (CH), 124.3 (CH), 53.8 (CH), 34.4 (C), 33.8 (CH_2), 30.0 (CH_3), 27.7 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 23.6 (CH_2).

(E)-(2-(2-methylcyclopentylidene)ethyl)benzene (5n)



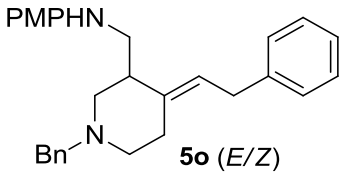
5n

From 4-methyl-*N'-(*2-methylcyclopentylidene)benzenesulfonohydrazide (79.9 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 86% isolated yield following *General procedure C* as a colourless oil. **5n** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.53.

HRMS (EI): calcd. for $C_{14}H_{18}$: 186,1409; found 186.1367.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24-7.17 (m, 2H), 7.15-7.06 (m, 3H), 5.26 (app. td, ^{3}J = 7.2, 5, 2.5 Hz, 1H), 3.27 (d, ^{3}J = 7.2 Hz, 2H), 2.32-2.28 (m, 3H), 1.91-1.61 (m, 2H), 1.54-1.46 (m, 1H), 1.26-1.02 (m, 1H), 0.99 (d, ^{3}J = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 149.3 (C), 142.0 (C), 128.5 (4xCH), 125.8 (CH), 118.0 (CH), 39.2 (CH), 35.8 (CH_2), 35.7 (CH_2), 29.4 (CH_2), 24.1 (CH_2), 19.2 (CH_3).

(*E/Z*)-*N*-((1-benzyl-4-(2-phenylethylidene)piperidin-3-yl)methyl)-4-methoxyaniline (5o)



5o (*E/Z*)

From *N'*-(1-benzyl-3-(((4-methoxyphenyl)amino)methyl)piperidin-4-ylidene)-4-methyl benzene sulfonohydrazide (102.6 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 78% (*E/Z* 4:1) isolated yield following *General procedure B* as a light brown oil. **5o** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. Rf (hexanes/ethyl acetate 5:1) = 0.18 (isomer ***E***) 0.27 (isomer ***Z***).

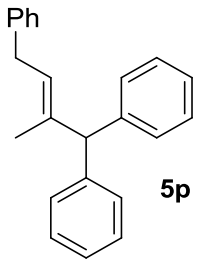
HRMS (EI): calcd. for $C_{28}H_{32}N_2O$: 412,2516 found 412,2515.

Isomer *E*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43-7.29 (m, 7H), 7.24-7.14 (m, 3H), 6.75 (d, ^{3}J = 8.8 Hz, 2H), 6.46 (d, ^{3}J = 8.8 Hz, 2H), 5.47 (t, ^{3}J = 7.5 Hz, 1H), 3.75 (s, 3H), 3.62 (d, ^{3}J = 13.2 Hz, 1H), 3.48 (d, ^{3}J = 13.3 Hz, 1H), 3.45-3.34 (m, 3H), 3.30 (dd, ^{3}J = 11.7, 6.5 Hz, 1H), 2.93-2.91 (m, 1H), 2.80 (d, ^{3}J = 10.9 Hz, 1H), 2.57-2.50 (m, 2H), 2.41 (t, ^{3}J = 10.9 Hz, 1H), 2.33 (d, ^{3}J = 9.6 Hz, 1H), 2.17 (t, ^{3}J = 10.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 151.8(C), 142.5(C), 141.2 (C), 137.2 (C), 129.0 (C), 128.5 (2xCH), 128.4(2xCH), 128.3 (4xCH), 128.2 (CH), 127.2 (CH), 126.0 (CH), 123.7 (2xCH), 114.9 (CH_2), 114.1 (2xCH), 62.7 (CH_2), 57.0 (CH_2), 55.9 (CH_3), 54.6 (CH_2), 46.9 (CH_2), 43.8 (CH), 33.5 (CH_2), 25.7 (CH_2).

Isomer *Z*

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.19 (m, 7H), 7.15-7.09 (m, 3H), 6.65 (d, ^{3}J = 8.8 Hz, 2H), 6.33 (d, ^{3}J = 8.8 Hz, 2H), 5.42 (t, ^{3}J = 6.9 Hz, 1H), 3.65 (s, 3H), 3.49 (d, ^{3}J = 13.2 Hz, 2H), 3.38-3.28 (m, 4H), 3.22 (dd, ^{3}J = 15.4, 7.5 Hz, 1H), 2.98-2.72 (m, 3H), 2.53 (app.t, ^{3}J = 13.6 Hz, 1H), 2.07-1.90 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 151.9 (C), 142.6 (C), 141.4 (C), 139.3 (C), 137.7 (C), 129.0 (2xCH), 128.6 (2xCH), 128.5 (4xCH), 127.2 (CH), 126.1 (CH), 124.1 (CH), 115.0 (2xCH), 114.1 (2xCH), 62.9 (CH_2), 56.1 (CH_2), 56.0 (CH_3), 55.7 (CH_2), 46.0 (CH_2), 36.4 (CH), 33.4(CH_2), 33.3(CH_2).

(2-methylbut-2-ene-1,1,4-triyl)tribenzene (5p)



5p

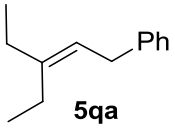
From *N'*-(1,1-diphenylpropan-2-ylidene)-4-methylbenzenesulfonohydrazide (189.1 mg, 0.5 mmol) and *trans*-2-phenylvinylboronic acid (161.2 mg, 1 mmol) was obtained 96% isolated yield following *General procedure A* as a colourless oil. **5p** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 50:1 as eluent. Rf (hexanes/ethyl acetate 50:1) = 0.26.

HRMS (EI): calcd. for $C_{23}H_{21}$: 298,1722; found.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.79-6.75 (m, 6H), 6.75-6.63 (m, 9H), 5.58 (t, ^{3}J = 4.3 Hz, 1H), 5.31 (s, 1H), 4.52 (d, ^{3}J = 4.3 Hz, 2H), 3.53 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ =

142.8 (2xC), 141.5 (C), 138.7 (C), 129.5 (4xCH), 128.5 (2xCH), 128.4 (2xCH), 128.3 (4xCH), 127.3 (CH), 126.3 (2xCH), 125.9 (CH), 60.2 (CH), 34.4 (CH_2), 17.3 (CH_3).

3-ethyl-1-phenyl-2-pentene (5qa)



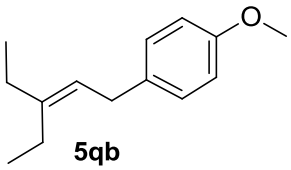
5qa

From 4-methyl-*N'*-(pentan-3-ylidene)benzenesulfonohydrazide (76.3 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 88% isolated yield following *General procedure B* as a colourless oil. **5qa** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. Rf (hexanes/ethyl acetate 10:1) = 0.51.

HRMS (EI): calcd. for $C_{13}H_{18}$: 174,1409; found 174,1409.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.28 (m,2H), 7.22-7.20 (m,3H), 5.30 (t, ^{3}J = 7.3 Hz, 1H), 3.40 (d, ^{3}J = 7.3 Hz, 1H), 2.18 (q, ^{3}J = 7.4 Hz, 2H), 2.09 (q, ^{3}J = 7.4 2H), 1.04 (t, ^{3}J = 7.4 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 144.1 (C), 142.2 (C), 128.5 (4xCH), 125.9 (CH), 121.3 (CH), 34.0 (CH_2), 29.4 (CH_2), 23.5 (CH_2), 13.5 (CH_3), 13.1 (CH_3).

1-(3-ethylpent-2-en-1-yl)-4-methoxybenzene (5qb)



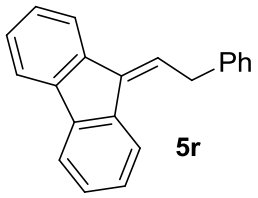
5qb

Following the *Method A* from 4-methyl-*N'*-(pentan-3 ylidene)benzenesulfonohydrazide (127.2 mg, 0.3 mmol) and -2-(4 methoxyphenyl)vinylboronic acid (178.0 mg, 1 mmol) were obtained 55 mg of **5qb** (87% isolated yield) as a colourless oil. **5qb** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 50:1 as eluent. Rf (hexanes/ethyl acetate 50:1) = 0.15.

HRMS (EI): calcd. for $C_{14}H_{20}O$: 204,1514; found 204,1518.

1H NMR (300 MHz, CDCl3): δ = 7.12 (d, ^{3}J = 8.7 Hz, 1H), 6.84 (d, ^{3}J = 8.7 Hz, 1H), 5.26 (t, ^{3}J = 7.3 Hz, 1H), 3.80 (s, 2H), 3.32 (d, ^{3}J = 7.3 Hz, 1H), 2.16 (q, ^{3}J = 7.6 Hz, 1H), 2.07 (qd, ^{3}J = 7.4 Hz, 2H), 1.02 (t, ^{3}J = 7.4 Hz, 3H). **13C NMR** (75 MHz, CDCl3): δ = 157.9 (C), 143.7 (C), 134.2 (C), 129.3 (2xCH), 121.7 (CH), 113.9 (2xCH), 55.4 (CH_3), 33.0 (CH_2), 29.3 (CH_2), 23.4 (CH_2), 13.4 (CH_3), 13.0 (CH_3).

9-(2-phenylethylidene)-9H-fluorene (5r)



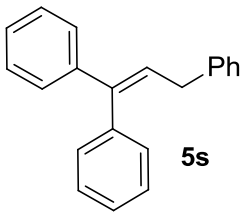
5r

From *N'*-(9H-fluoren-9-ylidene)-4-methylbenzenesulfonohydrazide (104.5 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 63% isolated yield following *General procedure B* as a yellow/orange solid. **5r** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 20:1 as eluent. Rf (hexanes/ethyl acetate 20:1) = 0.47.

HRMS (EI): calcd. for $C_{21}H_{16}$: 268,1252; found 268,1251.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, ^{3}J = 7.6 Hz, 1H), 7.69 (d, ^{3}J = 7.4 Hz, 1H), 7.63 (d, ^{3}J = 7.4 Hz, 1H), 7.55 (d, ^{3}J = 7.6 Hz, 1H), 7.40-7.08 (m, 9H), 6.77 (t, ^{3}J = 7.5 Hz, 1H), 4.12 (d, ^{3}J = 7.5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 141.2 (C), 139.9 (C), 139.3 (C), 138.8 (C), 137.4 (C), 136.1 (C), 128.8 (CH), 128.7 (4xCH), 128.1 (CH), 127.7 (CH), 127.1 (CH), 127.0 (CH), 126.6 (CH), 124.9 (CH), 120.0 (CH), 119.9 (2xCH), 119.6 (CH), 35.7 (CH_2).

prop-1-ene-1,1,3-triyltribenzene (5s)



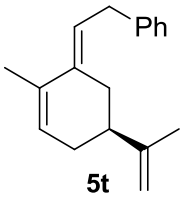
5s

From *N'*-(1,1-diphenylpropan-2-ylidene)-4-methylbenzenesulfonohydrazide (189.1 mg, 0.5 mmol) and *trans*-2-phenylvinylboronic acid (161.2 mg, 1 mmol) was obtained 55% isolated yield following *General procedure A* as a colourless oil. **5s** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 50:1 as eluent. Rf (hexanes/ethyl acetate 50:1) = 0.67.

HRMS (EI): calcd. for $C_{21}H_{18}$: 270,1409; found 270,1405.

^{1}H RMN (300 MHz, $CDCl_3$): δ = 7.38-7.22 (m, 15H), 6.28 (t, ^{3}J = 7.5 Hz, 1H),3.48 (d, ^{3}J = 7.5 Hz, 2H). **^{13}C RMN** (75 MHz, $CDCl_3$) δ = 142.9 (2xC),141.4 (C), 140.2 (C),130.3 (2xCH), 128.9 (2xCH), 128.8 (2xCH),128.7 (2xCH), 128.5 (2xCH), 128.2 (CH), 127.7 (2xCH), 127.6 (CH), 127.5(CH), 126.4(CH), 36.3(CH_2),

(*S,E*)-(2-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)ethyl)benzene (5t)



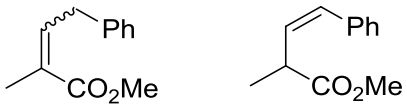
5t

From *(S)*-4-methyl-*N'*-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-ylidene)benzene sulfonohydrazide (95.5 mg, 0.3 mmol) and *trans*-2-phenylvinylboronic acid (88.7 mg, 0.6 mmol) was obtained 70% isolated yield following *General procedure B* as a colourless oil. **5t** was purified by flash chromatography on desactived silica gel using a mixture of hexanes/ethyl acetate 50:1 as eluent. Rf (hexanes/ethyl acetate 50:1) = 0.51.

HRMS (EI): calcd. for $C_{18}H_{22}$: 238,1722; found 238,1719.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.25 (m, 2H), 7.25-7.17 (m, 3H), 5.68 (s, 1H), 5.62 (t, ^{3}J = 6.9 Hz, 1H), 4.79 (s, 2H), 3.52 (dd, ^{3}J = 6.8 Hz, 2H), 2.82 (d, ^{3}J = 14.3 Hz, 1H), 2.43-2.02 (m, 4H), 1.83 (s, 3H), 1.79 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ =149.6 (C), 141.6 (C), 136.9 (C), 133.2 (C), 128.6 (CH), 126.3 (CH), 126.0 (CH), 122.5 (CH), 109.2 (CH_2), 41.8 (CH), 34.0 (CH_2), 31.5 (CH_2), 31.2 (CH_2), 20.9 (CH_3), 19.9 (CH_3).

Ethyl 2-methyl-4-phenylbut-2-enoate (5v)
(E)-ethyl 2-methyl-4-phenylbut-3-enoate (4v)



5v **4v**

From ethyl 2-(2-tosylhydrazono)propanoate (142.2 mg, 0.5 mmol) and *trans*-2-phenylvinylboronic acid (161.2 mg, 1 mmol) was obtained 73% (5u:4u 1:1) isolated yield following *General procedure A* as a light yellow oil. **5v, 4v** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. Rf (hexanes/ethyl acetate 5:1) = 0.23.

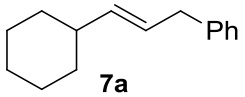
HRMS (EI): calcd. for $C_{13}H_{16}O_2$: 204,1150; found 204,1146.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32-8.27 (m, 2H, isomers **5v**+**4v**), 8.24-8.21 (m, 4H, isomers **5v**+**4v**), 8.18-8.07 (m, 4H, isomers **5v**+**4v**), 7.84 (td, ^3J = 7.6, 1.4 Hz, 1H, isomer **5v**), 7.40 (d, ^3J = 15.9 Hz, 1H, isomer **4v**), 7.21 (dd, ^3J = 15.9, 7.9 Hz, 1H, isomer **4v**), 5.11 (q, ^3J = 7.1 Hz, 2H, isomer **5v**), 5.08 (q, ^3J = 7.1 Hz, 2H, isomer **4v**), 4.45 (d, ^3J = 7.6 Hz, 2H, isomer **5v**), 4.22 (p, ^3J = 7.1 Hz, 1H, isomer **4v**), 2.88 (s, 3H, isomer **5v**), 2.29 (d, ^3J = 7.0 Hz, 3H, isomer **4v**), 2.20 (m, 6H, isomers **5v**+**4v**) **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 174.9 (C), 174.7 (C), 140.1 (CH), 139.2 (C), 137.0 (C), 131.1 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 127.6 (CH), 126.5 (CH), 126.4 (CH), 60.8 (CH_2), 60.7 (CH_2), 43.4 (CH), 35.0 (CH_2), 17.5 (CH_3), 14.4 (CH_3), 14.3 (CH_3), 12.7 (CH_3).

Spectroscopic data in agreement with those reported in *J. Org. Chem.* **1967**, *32*, 3481.

E.4. Characterization data for compounds 7

(*E*)-1-Cyclohexyl-3-phenylpropene (7a)



7a

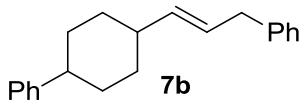
From *N'*-cyclohexylidene-4-methylbenzenesulfonohydrazide (79.9 mg, 0.3 mmol) and (*E*)-(3-phenylprop-1-en-1-yl)boronic acid (97.2 mg, 0.6 mmol) was obtained 57% (ratio of double bond regioisomers 15:1) isolated yield following *General procedure B* as a colourless oil. **7a** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.46.

HRMS (EI): calcd. for $C_{15}H_{20}$: 200,1565; found 200,1542.

^{1}H RMN (300 MHz, $CDCl_3$): δ = 7.30-7.26 (m,3H), 7.20-7.17 (m,2H), 5.53 (dt,^3J = 15.4, 5.6 Hz, 1H), 5.47(dd,^3J = 15.4, 5.4 Hz, 1H), 3.32 (d, ^3J = 5.6 Hz, 2H), 1.98-1.91 (m,1H),1.73-1.56 (m, 5H), 1.28-1.06 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 141.4 (C), 138.3 (CH), 128.6 (CH), 128.4 (CH), 126.3 (CH), 126.0 (CH), 40.8 (CH), 39.24 (CH), 33.27 (CH_2), 26.37 (2xCH_2), 26.24 (2xCH_2).

Spectroscopic data in agreement with those reported in *J. Organometallic Chem*. **2010**, *695*, 1518.

(*E*)-(3-(4-phenylcyclohexyl)allyl)benzene (7b)



7b

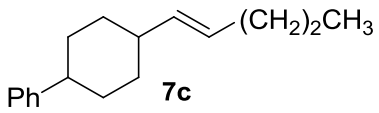
From 4-methyl-*N'*-(4-phenylcyclohexylidene)benzenesulfonohydrazide (102.6 mg, 0.3 mmol) and (*E*)-(3-phenylprop-1-en-1-yl)boronic acid (97.2 mg, 0.6 mmol) was obtained 69% (ratio of double bond regioisomers 15:1) isolated yield following *General procedure B* as a colourless oil. **7b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 100:1 as eluent. Rf (hexanes/ethyl acetate 100:1) = 0.37.

HRMS (EI): calcd. for $C_{21}H_{24}$: 276,1878; found276,1879.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23-7.18 (m, 4.4H, regioisomer may+min), 7.15-7.10 (m, 6.9H, regioisomer may+min), 5.53 (dt, ^3J = 15.4, 6 Hz, 1H, regioisomer may), 5.43 (dd, ^3J = 15.4, 5.5 Hz,1H, regioisomer may), 5.12 (t, ^3J = 7 Hz, 0.13H, regioisomer min), 3.27 (d, ^3J = 5.5 Hz, 2H, regioisomer may), 2.60-2.52 (m, 0.7H, regioisomer min), 2.39 (tt, ^3J = 12.3 Hz, 1.11H, regioisomer may+min), 2.02-1.89 (m, 0.97H, regioisomer min), 1.83-1.75 (m,

4H, regioisomer may), 1.51-1.33 (m, 0.93H, regioisomer min), 1.49-1.35 (m, 2H, regioisomer may), 1.27-1.09 (m, 2H, regioisomer may). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.8 (C), 141.3 (C), 137.7 (CH), 128.6 (3xCH) , 128.5 (2xCH), 128.4 (3xCH), 126.9 (CH), 126.7 (CH), 126.0 (CH), 44.2 (CH), 40.5 (CH), 39.2 (CH_2), 34.1 (2xCH_2), 33.5 (2xCH_2).

(*E*)-(4-(pent-1-en-1-yl)cyclohexyl)benzene (7c)



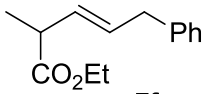
7c

From 4-methyl-*N*′-(4-phenylcyclohexylidene)benzenesulfonohydrazide (102.6 mg, 0.3 mmol) and (*E*)-pent-1-en-1-ylboronic acid (68.4 mg, 0.6 mmol) was obtained 62% (ratio of double bond regioisomers 10:1) isolated yield following *General procedure B* as a colourless oil. **7c** was purified by flash chromatography on silica gel using hexanes as eluent. Rf (hexanes) = 0.41.

HRMS (EI): calcd. for $C_{17}H_{24}$: 228,1878; found 228,1877.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.29 (t, ^{3}J = 7.6 Hz, 2H), 7.22 (d, ^{3}J = 7.0 Hz, 2H), 7.20-7.16 (m, 1H), 5.45-5.34 (m, 2H), 5.16 (t, ^{3}J = 7.3 Hz, 0.08H, regioisomer min), 2.46 (tt, ^{3}J = 12.2, 3.4 Hz, 1H), 2.01-1.95 (m, 3H), 1.95-1.90 (m, 2H), 1.89-1.82 (m, 2H), 1.50 (qd, ^{3}J = 12.9, 3.2 Hz, 2H), 1.42-1.35 (m, 2H), 1.24 (qd, ^{3}J = 13.0, 3.3 Hz, 2H), 0.90 (t, ^{3}J = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 147.9 (C), 136.6 (CH), 128.7 (2xCH), 128.4 (CH), 127.2 (2xCH), 126.3 (CH), 44.5 (CH), 40.9 (CH), 35.2 (CH_2), 34.5 (2xCH_2), 33.9 (2xCH_2), 23.2 (CH_2), 14.1 (CH_3).

(*E*)-ethyl 2-methyl-5-phenyl-3-pentenoate (7f)



7f

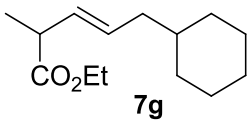
From ethyl 2-(2-tosylhydrazono)propanoate (85.3 mg, 0.3 mmol) and (*E*)-(3-phenylprop-1-en-1-yl)boronic acid (97.2 mg, 0.6 mmol) was obtained 61% isolated yield following *General procedure B* as a colourless oil. **7f** was purified by flash

chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. Rf (hexanes/ethyl acetate 15:1) = 0.34.

HRMS (EI): calcd. for $C_{14}H_{18}O_2$: 218,1307; found 218,1304.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.26 (m, 2H), 7.22-7.17 (m, 3H), 5.71 (dt, ^3J = 15.3, 6.4 Hz, 1H), 5.63 (dd, ^3J = 15.4, 7.3 Hz, 1H), 4.15 (q, ^3J = 7.1 Hz, 2H), 3.37 (d, ^3J = 6.3 Hz, 2H), 3.14 (quint, ^3J = 7.1 Hz, 1H), 1.28-1.24 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 174.9 (C), 140.3 (C), 130.6 (CH), 130.5 (4xCH), 128.5 (CH), 128.4 (CH), 126.0 (CH), 60.5 (CH_2), 42.8 (CH), 38.8 (CH_2), 17.4 (CH_3), 14.2 (CH_3).

_(E)_-Ethyl 4-cyclohexyl-2-methylbut-3-enoate (7g)



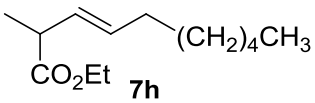
7g

Following the *Method B* from ethyl 2-(2-tosylhydrazono)propanoate (85.3 mg, 0.3 mmol) a **7g** (35% isolated yield) as a colourless oil. **7g** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 50:1 as eluent. *Rf* (hexanes/ethyl acetate 50:1) = 0.17.

HRMS (EI): calcd. for C13H22O2: 210,1620; found 210,1594.

1H NMR (300 MHz, CDCl3): δ = 5.58 – 5.31 (m, 2H), 4.12 (q, *3J* = 7.1 Hz, 2H), 3.14 – 2.94 (m, 1H), 1.70-1.61 (m, 5H), 1.36 – 1.16 (m, 9H). **13C NMR** (75 MHz, CDCl3): δ = 175.4 (C), 138.1 (CH), 126.5 (CH), 60.5, 43.1 (CH), 40.6 (CH3), 33.0 (CH2), 26.3 (CH3), 26.1 (2xCH2), 17.7 (CH2), 14.3 (CH2).

(*E*)-Ethyl 2-methyldec-3-enoate (7h)



7h

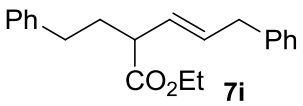
From ethyl 2-(2-tosylhydrazono)propanoate (85.3 mg, 0.3 mmol) and (*E*)-oct-1-en-1-ylboronic acid (93.6 mg, 0.6 mmol) was obtained 49% isolated yield following *General procedure B* as a colourless oil. **7h** was purified by flash chromatography on 240

silica gel using a mixture of hexanes/ethyl acetate 30:1 as eluent. Rf (hexanes/ethyl acetate 30:1) = 0.33.

HRMS (EI): calcd. for $C_{13}H_{24}O_2$: 212,1776; found 212.1729.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.61-5.39 (m, 2H), 4.11 (q, ^3J = 7.1 Hz, 2H), 3.14-2.94 (quint, ^3J = 7 Hz, 1H), 1.99 (dt, ^3J = 7.2, 6.7 Hz, 2H), 1.42-1.17 (m, 14H), 0.86 (t, ^3J = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 175.3 (C), 132.4 (CH), 129.0 (CH), 60.51, 43.0 (CH_3), 32.5 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 22.7 (CH_2), 17.6 (CH_2), 14.3 (CH_3), 14.2 (CH_3).

Ethyl 2-phenethyl-5-phenylpent-3-enoate (7i)



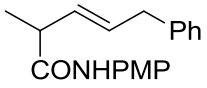
7i

From ethyl 4-phenyl-2-(2-tosylhydrazono)butanoate (112.3 mg, 0.3 mmol) and (*E*)-(3-phenylprop-1-en-1-yl)boronic acid (97.2 mg, 0.6 mmol) was obtained 61% isolated yield following *General procedure B* as a colourless oil. **7i** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. Rf (hexanes/ethyl acetate 15:1) = 0.33.

HRMS (EI): calcd. for $C_{14}H_{18}O_2$: 218,1307; found 218,1304.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27-7.02 (m, 10H), 5.64 (dt, ^3J = 15.2, 6.7 Hz, 1H), 5.49 (dd, ^3J = 15.3, 8.5 Hz, 1H), 4.07 (q, ^3J = 7.1 Hz, 2H), 3.31 (d, ^3J = 6.6 Hz, 2H), 2.95 (dd, ^3J = 15.5, 7.6 Hz, 1H), 2.64-2.41 (m, 2H), 2.02 (ddt, *J* = 13.6, 9.5, 6.8 Hz, 1H), 1.77 (ddt, *J* = 13.7, 9.5, 6.9 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3 (C), 141.6 (C), 140.3 (C), 132.4 (CH), 129.2 (CH), 128.6 (4xCH), 128.5 (4xCH), 126.2 (CH), 126.1 (CH), 60.7 (CH_2), 48.8 (CH), 39.1 (CH_2), 34.2 (CH_2), 33.5 (CH_2), 14.4 (CH_3).

***N*-(4-methoxyphenyl)-2-methyl-5-phenylpent-3-enamide (7j)**



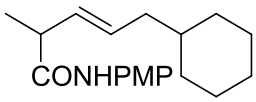
7j

From *N*-(4-methoxyphenyl)-2-(2-tosylhydrazono)propanamide (108.4 mg, 0.3 mmol) and (*E*)-(3-phenylprop-1-en-1-yl)boronic acid (97.2 mg, 0.6 mmol) was obtained 63% isolated yield following *General procedure B* as a light yellow solid. **7fa** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 3:1 as eluent. Rf (hexanes/ethyl acetate 3:1) = 0.29.

HRMS (EI): calcd. for $C_{19}H_{21}NO_2$: 295,1572; found 295,1575.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30-7.20 (m, 4H), 7.18-7.10 (m, 3H), 6.76 (d, ^3J = 9.0 Hz, 2H), 5.80 (dt, ^3J = 15.3, 6.7 Hz, 1H), 5.60 (dd, ^3J = 15.3, 8.1 Hz, 1H), 3.71 (s, 3H), 3.35 (d, ^3J = 6.7 Hz, 2H), 3.04 (quint, ^3J = 7.3 Hz, 1H), 1.27 (d, ^3J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 172.2 (C), 156.4 (C), 140.1 (C), 132.9 (CH), 131.4 (CH), 131.2 (C), 128.8 (2xCH), 128.6 (2xCH), 126.4 (CH), 121.5 (2xCH), 114.2 (2xCH), 55.6 (CH), 45.4 (CH), 39.1 (CH_2), 17.3 (CH_3).

4-cyclohexyl-*N*-(4-methoxyphenyl)-2-methylbut-3-enamide (7k)



7k

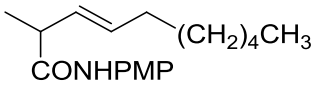
From *N*-(4-methoxyphenyl)-2-(2-tosylhydrazono)propanamide (108.4 mg, 0.3 mmol) and (*E*)-(2-cyclohexylvinyl)boronic acid (92.4 mg, 0.6 mmol) was obtained 40% isolated yield following *General procedure B* as a yellow solid. **7k** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. Rf (hexanes/ethyl acetate 5:1) = 0.14.

HRMS (EI): calcd. for $C_{18}H_{25}NO_2$: 287,1885; found 287,1882.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, ^3J = 9.0 Hz, 2H), 6.84 (d, ^3J = 9.0 Hz, 2H), 5.65 (dd, ^3J = 15.6, 6.5 Hz, 1H), 5.51 (dd, ^3J = 15.6, 7.8 Hz, 1H), 3.78 (s, 3H), 3.05 (quint, ^3J = 7.1 Hz, 1H), 1.83-1.58 (m, 7H), 1.31 (d, ^3J = 7.0 Hz, 3H), 1.29-0.89 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 172.6 (C), 156.4 (C), 140.4 (CH), 131.3 (C), 127.6 (CH), 121.8 (2xCH), 114.3

(2xCH), 55.6 (CH), 45.4 (CH), 40.8 (CH_3), 33.3 (CH_2), 33.1 (CH_2), 33.1 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 17.3 (CH_3).

_N_-(4-methoxyphenyl)-2-methyldec-3-enamide (7m)



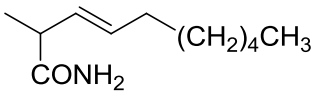
7m

From *N*-(4-methoxyphenyl)-2-(2-tosylhydrazono)propanamide (108.4 mg, 0.3 mmol) and (*E*)-oct-1-en-1-ylboronic acid (93.6 mg, 0.6 mmol) was obtained 58% isolated yield following *General procedure B* as a yellow solid. **7m** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. Rf (hexanes/ethyl acetate 5:1) = 0.23.

HRMS (EI): calcd. for $C_{18}H_{27}NO_2$: 289,2038; found 289,2042.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, ^3J = 8.8 Hz, 3H), 6.83 (d, ^3J = 8.9 Hz, 2H), 5.69 (dt, ^3J = 15.6, 6.5 Hz, 1H), 5.55 (app. dd, ^3J = 15.6, 7.8 Hz, 1H), 3.77 (s, 3H), 3.07 (quint, ^3J = 7.1 Hz, 1H), 2.07 (app. dd, ^3J = 13.7, 6.8 Hz, 2H), 1.45-1.19 (m, 12H), 0.88 (t, ^3J = 6.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 172.6 (C), 156.4 (C), 134.5 (CH), 131.3 (C), 129.9 (CH), 121.5 (2xCH), 114.2 (2xCH), 55.58 (CH), 45.4 (CH_3), 32.6 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 22.7 (CH_2), 17.4 (CH_3), 14.2 (CH_2).

(*E*)-2-methyldec-3-enamide (7n)



7n

From 2-(2-tosylhydrazono)propanamide (76.6 mg, 0.3 mmol) and (*E*)-oct-1-en-1-ylboronic acid (93.6 mg, 0.6 mmol) was obtained 35% isolated yield following *General*

procedure B as a white solid. **7n** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 3:1 as eluent. Rf (hexanes/ethyl acetate 3:1) = 0.12.

HRMS (EI): calcd. for $C_{11}H_{21}NO$: 183,1623; found 183,1623.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.62 (dt, ^{3}J = 15.4, 6.5 Hz, 1H), 5.53-5.37 (m, 1H), 2.97 (quint, ^{3}J = 7.2 Hz, 1H), 2.02 (q, ^{3}J = 6.7 Hz, 2H), 1.41-1.07 (m, 12H), 0.87 (t, ^{3}J = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.5 (C), 133.8 (CH), 129.8 (CH), 44.2 (CH), 32.6 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 22.7 (CH_2), 17.4 (CH_3), 14.2 (CH_3).

Chapter 2: Synthesis of polysubstituted pyrazols

Part A: Regioselective one step synthesis of pyrazoles from alkynes and N-tosylhydrazones through a [3+2]-dipolar cycloaddition/substituent controlled-[1,5]-sigmatropic rearrangement cascades.

E.5. Experimental procedures

E.5.1. General procedure for regioselective synthesis of pirazoles from tosylhydrazones 8, 15, 18 and terminal alkynes 11 using conventional heating.

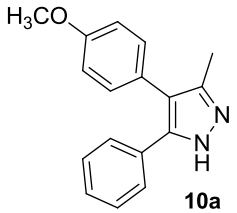
A reaction tube was charged with the tosylhydrazone **1** (0.3 mmol), the terminal alkynes **2** (0.6 mmol), potassium carbonate (83 mg, 0.6 mmol), dioxane or toluene (2.4 ml). The system was heated at 110 °C with stirring and reflux for 24 hours. The reaction was monitored by GCMS. When the reaction was completed, the crude reaction was cooled down to room temperature, the solvent was eliminated and a saturated solution of $NaHCO_3$ and dichloromethane were added and the layers were separated. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with $NaHCO_3$, brine, dried over $MgSO_4$ and filtered. Solvent was removed under reduced pressure. Finally, products were purified by flash chromatography on silica gel.

E.5.2. General procedure for regioselective *one pot* synthesis of pirazoles from tosylhydrazones 8, 18 and terminal alkynes 11 using conventional heating.

A reaction tube was charged with the carbonyl compound (0.3 mmol) and tosylhydrazide (1.1 equiv.) in dioxane (2.4 ml) or toluene at 70 °C for 2h. Then, potassium carbonate (82.9 mg, 0.6 mmol) and the terminal alkyne (0.6 mmol) were added to the reaction mixture and the system was heated up to 110 °C for 24h. At this point, the general procedure was followed.

E.6. Characterization data for compounds 10

4-(4-methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazole (10a)



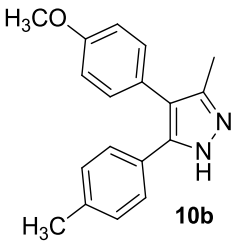
10a

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and phenylacetylene (67 µL, 0.6 mmol) were obtained 58.7 mg of **10a** (74 % isolated yield, 56 % following *one pot* procedure) as a white solid, m.p.= 160-164 °C. **10a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate, 2:1) = 0.17.

HRMS (EI): calcd. for $C_{17}H_{16}N_2O$: 264,1263; found 264,1262.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.58 (bs, 1H), 7.53 – 7.31 (m, 2H), 7.36 – 7.20 (m, 3H), 7.14 (d, ^3J = 8.7 Hz, 2H), 6.90 (d, ^3J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.16 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4 (C), 146.2 (C), 141.9 (C), 132.5 (C), 131.2 (2xCH), 128.4 (2xCH), 128.0 (2xCH), 127.7 (CH), 126.0 (C), 117.6 (C), 114.0 (2xCH), 55.3 (CH_3), 10.9 (CH_3).

4-(4-methoxyphenyl)-5-methyl-3-(*p*-tolyl)-1*H*-pyrazole (10b)

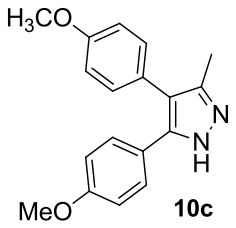


10b

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and *p*-tolylacetylene (78 µL, 0.6 mmol) were obtained 52.6 mg of **10b** (63 % isolated yield) as a white solid, m.p.= 182-

185 °C. **10b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate, 1:1) = 0.5.
HRMS (EI): calcd. for $C_{18}H_{18}N_2O$: 278,1419; found 278,1410.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, ^3J = 8.1 Hz, 2H), 7.13 (d, ^3J = 8.8 Hz, 2H), 7.06 (d, ^3J = 8.1 Hz, 2H), 6.88 (d, ^3J = 8.8 Hz, 2H), 3.83 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4 (C), 145.3 (C), 143.0 (C), 137.7 (C), 131.2 (2xCH), 129.3 (2xCH), 129.0 (C), 127.7 (2xCH), 126.0 (C), 117.5 (C), 114.0 (2xCH), 55.3 (CH_3), 21.4 (CH_3), 11.4 (CH_3)

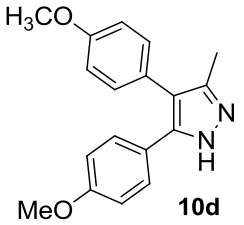
3,4-bis(4-methoxyphenyl)-5-methyl-1*H*-pyrazole (10c)



10c

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and 1-ethynyl-4-methoxybenzene (79 µL, 0.6 mmol) were obtained 72.4 mg of **10c** (82 % isolated yield, 55 % following *one pot* procedure) as a white solid, m.p.= 153-156 °C. **10c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate, 1:1) = 0.22.
HRMS (EI): calcd. for $C_{18}H_{18}N_2O_2$: 294,1368; found 294,1364.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (bs, 1H), 7.30 (d, ^3J = 8.8 Hz, 1H), 7.12 (d, ^3J = 8.7 Hz, 1H), 6.88 (d, ^3J = 8.7 Hz, 1H), 6.75 (d, ^3J = 8.8 Hz, 1H), 3.82 (s, 1H), 3.76 (s, 1H), 2.19 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.3 (C), 158.3 (C), 145.4 (C), 142.4 (C), 131.2 (2xCH), 129.2 (2xCH), 126.0 (C), 124.5 (C), 117.2 (C), 113.9 (2xCH), 113.9 (2xCH), 55.3 (CH_3), 55.3 (CH_3), 11.2 (CH_3).

4-(4-(4-methoxyphenyl)-5-methyl-1H-pyrazol-3-yl)benzonitrile (10d)



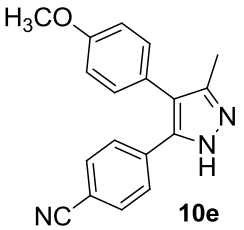
10d

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6 mg, 0.6 mmol) were obtained 66.8 mg of **10d** (77 % isolated yield, 63 % following *one pot* procedure) as a light yellow solid, m.p.= 146-148 °C. **10d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate, 1:1) = 0.25.

HRMS (EI): calcd. for $C_{18}H_{15}N_3O$: 289,1215; found 289,1211.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (bs, 1H), 7.42 (d, ^3J = 5.2 Hz, 2H), 7.40 (d, ^3J = 5.2 Hz, 2H), 7.15 (d, ^3J = 5.1 Hz, 2H), 7.05 (d, ^3J = 5.1 Hz, 2H), 5.26 (s, 3H), 4.26 (s, 3H)**. ^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.8 (C), 146.3 (C), 140.4 (C), 137.7 (C), 132.2 (2xCH), 131.1 (2xCH), 128.3 (2xCH), 124.9 (C), 119.0 (C), 118.5 (C), 114.3 (2xCH), 111.0 (C), 55.4 (CH_3), 10.4 (CH_3).

4-(4-methoxyphenyl)-5-methyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (10e)



10e

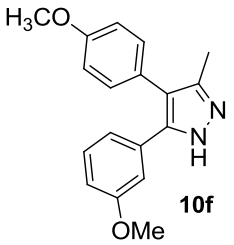
Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 79.8 mg of **10e** (80 % isolated yield) as a white solid, m.p.= 132-136 °C. **10e** was purified by flash

chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate, 2:1) = 0.32.

HRMS (EI): calcd. for $C_{18}H_{15}F_3N_2O$: 332,1136; found 332,1131.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (bs, 1H), 6.90 (d, ^3J = 4.9 Hz, 2H), 6.86 (d, ^3J = 5.0 Hz, 2H), 6.65 (d, ^3J = 5.1 Hz, 2H), 6.54 (d, ^3J = 5.1 Hz, 2H), 4.75 (s, 3H), 3.75 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.7 (C), 146.2 (C), 141.0 (C), 136.4 (C), 131.2 (2xCH), 129.5 (q, ^2J = 32.4 Hz, C), 128.1 (2xCH), 126.4 (q, ^1J = 201.7 Hz, C), 126.0 (C), 125.4 (q, ^3J = 3.5Hz, CH), 118.3 (C), 114.2 (2xCH), 55.4 (CH_3), 10.6 (CH_3).

3-(3-methoxyphenyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-pyrazole (10f)



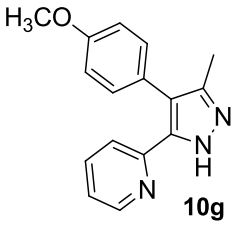
10f

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (, 0.6 mmol) were obtained 72.4 mg of **10f** (82 % isolated yield) as a yellow solid, m.p.= 108-110 °C. **10f** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate, 1:1) = 0.15.

HRMS (EI): calcd. for $C_{18}H_{18}N_2O_2$: 294,1368; found 294,1378.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (bs, 1H), 7.16 – 7.08 (m, 3H), 6.99- 6.95 (m, 2H), 6.89 (d, ^3J = 8.9 Hz, 2H), 6.79 (ddd, ^3J = 8.2, 2.4, 1.2 Hz, 1H), 3.82 (s, 3H), 3.62 (s, 3H), 2.19 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.6 (C), 158.5 (C), 145.9 (C), 142.2 (C), 133.4 (C), 131.3 (2xCH), 129.5 (CH), 125.9 (C), 120.4 (CH), 117.8 (C), 114.1 (CH), 114.0 (2xCH), 112.9 (CH), 55.4 (CH_3), 55.2 (CH_3), 11.0 (CH_3).

2-(4-(4-methoxyphenyl)-5-methyl-1*H*-pyrazol-3-yl)pyridine (10g)



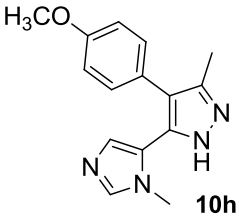
10g

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and 2-ethynylpyridine (, 0.6 mmol) were obtained 50.1 mg of **10g** (63 % isolated yield) as a yellow solid, m.p.= 123-126 °C. **10g** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:2 as eluent. *Rf* (hexanes/ethyl acetate, 1:2) = 0.11.

HRMS (EI): calcd. for $C_{16}H_{15}N_3O$: 265,1215; found 265,1216.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (d, ^3J = 4.7 Hz, 1H), 7.73 (td, ^3J = 8.5, 1.9 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.39 - 7.34 (m, 2H), 7.19 – 7.16 (m, 2H), 3.80 (s, 3H), 2.03 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.0 (C), 149.3 (CH), 148.8 (C), 148.1 (C), 139.1 (C), 136.9 (CH), 131.4 (2xCH), 125.9 (C), 122.7 (CH), 120.9 (CH), 118.8 (C), 114.4 (2xCH), 55.4 (CH_3), 12.2 (CH_3).

4-(4-methoxyphenyl)-5-methyl-3-(1-methyl-*1H*-imidazol-5-yl)-*1H*-pyrazole (10h)



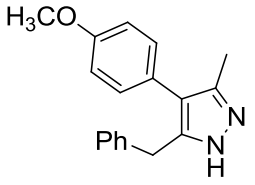
10h

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and 5-ethynyl-1-methyl-1*H*-imidazole (63 µL, 0.6 mmol) were obtained 55.0 mg of **10h** (77 % isolated yield, 75 % following *one pot* procedure) as a yellow solid, m.p.= 218-221 °C. **10h** was purified by flash chromatography on silica gel using a mixture of dichloromethane/methanol 10:1 as eluent. *Rf* (dichloromethane/methanol, 10:1) = 0.34.

HRMS (EI): calcd. for $C_{15}H_{16}N_4O$: 268,1324; found 268.1331.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (bs, 1H), 7.09 (d, ^{3}J = 8.6 Hz, 2H), 6.99 (bs, 1H), 6.87 (d, ^{3}J = 8.6 Hz, 2H), 3.81 (s, 3H), 3.39 (s, 3H), 2.31 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5 (C), 138.8 (CH), 130.3 (2xCH), 129.7 (CH), 125.1 (C), 119.1 (C), 114.1 (2xCH), 55.2 (CH_3), 32.6 (CH_3), 10.8 (CH_3).

3-benzyl-4-(4-methoxyphenyl)-5-methyl-1H-pyrazole (10i)



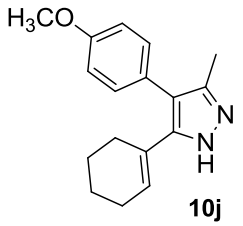
10i

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and prop-2-yn-1-ylbenzene (77 µL, 0.6 mmol) were obtained 44.3 mg of **10i** (53 % isolated yield, 27 % following *one pot* procedure) as a white solid, m.p.= 114-116 °C. **10i** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate, 2:1) = 0.2.

HRMS (EI): calcd. for $C_{18}H_{18}N_2O$: 278,1419; found 278,1431.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 3H), 7.17-7.15 (m, 4H), 6.94 (d, ^{3}J = 8.7 Hz, 2H), 3.99 (s, 2H), 3.85 (s, 3H), 2.27 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4 (C), 144.3 (C), 142.3 (C), 139.2 (C), 130.8 (2xCH), 128.7 (2xCH), 128.6 (2xCH), 126.4 (CH), 125.8 (C), 118.6 (C), 114.0 (2xCH), 55.4 (CH_3), 32.0 (CH_2), 11.6 (CH_3).

3-(cyclohex-1-en-1-yl)-4-(4-methoxyphenyl)-5-methyl-1*H*-pyrazole (10j)

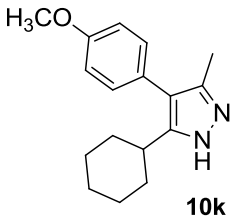


10j

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and 1-ethynylcyclohex-1-ene (142

µL, 1.2 mmol) were obtained 42.7 mg of **10j** (53 % isolated yield, 52 % following *one pot* procedure) as a yellow oil. **10j** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate, 1:1) = 0.16.
HRMS (EI): calcd. for $C_{17}H_{20}N_2O$: 268,1576; found 268,1569.
^{1}H NMR (401 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.19 (d, ^3J = 8.6 Hz, 2H), 6.92 (d, ^3J = 8.7 Hz, 2H), 5.93 (s, 1H), 3.85 (s, 3H), 2.22 (s, 3H), 2.11 (d, 2H), 2.10 – 1.96 (m, 2H), 1.71 – 1.38 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.3 (C), 145.5 (C), 144.1 (C), 130.9 (2xCH), 128.9 (C), 128.4 (CH), 126.6 (C), 116.8 (C), 113.8 (2xCH), 55.3 (CH_3), 27.1 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 22.0 (CH_2), 11.7 (CH_3).

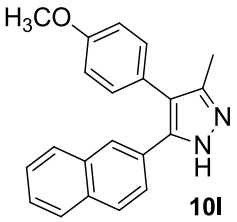
3-cyclohexyl-4-(4-methoxyphenyl)-5-methyl-1*H*-pyrazole (10k)



10k

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and ethynylcyclohexane (79 µL, 0.6 mmol) were obtained 22.7 mg of **10k** (28 % isolated yield) as a light yellow solid, m.p.= 105-110 °C. **10k** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate, 1:1) = 0.22.
HRMS (EI): calcd. for $C_{17}H_{22}N_2O$: 270,1732; found 270.1735.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.17 (d, ^3J = 8.7 Hz, 2H), 6.95 (d, ^3J = 8.7 Hz, 2H), 3.85 (s, 3H), 2.68 (tt, ^3J = 12.0, 3.3 Hz, 1H), 2.22 (s, 3H), 1.89 - 1.85 (m, 2H), 1.78 - 1.70 (m, 3H), 1.52 - 1.40 (m, 2H), 1.28 - 1.23 (m, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.2 (C), 149.8 (C), 143.1 (C), 130.8 (2xCH), 126.3 (C), 113.8 (2xCH), 55.3 (CH_3), 35.2 (CH), 33.0 (2xCH_2), 26.5 (2xCH_2), 26.0 (CH_2), 11.6 (CH_3).

4-(4-methoxyphenyl)-5-methyl-3-(naphthalen-2-yl)-1H-pyrazole(10l)



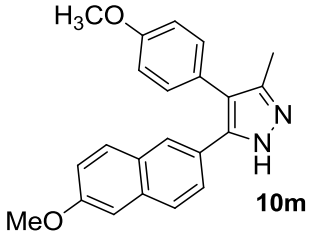
10l

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and 2-ethynyl-6-methoxynaphthalene (116.4 mg, 0.6 mmol) were obtained 72.3 mg of **10l** (70 % isolated yield) as a light brown solid, m.p.= 101-105 °C. **10l** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate, 1:1) = 0.27.

HRMS (EI): calcd. for $C_{22}H_{20}N_2O_2$: 344,1525; found 344,1522.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 7.57 (s, 1H), 7.40 (d, ^3J = 5.3 Hz, 2H), 7.34 (dd, ^3J = 5.0, 0.9 Hz, 1H), 7.19 (d, ^3J = 5.1 Hz, 2H), 7.13 (dd, ^3J = 5.2, 1.5 Hz, 1H), 7.10 (d, ^3J = 1.4 Hz, 1H), 7.03 (d, ^3J = 5.1 Hz, 2H), 5.28 (s, 3H), 5.24 (s, 3H), 4.29 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4 (C), 157.9 (C), 146.0 (C), 142.4 (C), 134.0 (C), 131.3 (2xCH), 129.8 (CH), 128.8 (C), 127.5 (C), 126.8 (CH), 126.7 (CH), 126.6 (CH), 126.0 (C), 118.9 (CH), 117.6 (C), 114.0 (2xCH), 105.6 (CH), 55.4 (CH_3), 55.3 (CH_3), 11.2 (CH_3).

3-(6-methoxynaphthalen-2-yl)-4-(4-methoxyphenyl)-5-methyl-1H-pyrazole (10m)



10m

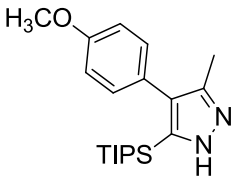
Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and 2-ethynylnaphthalene (88 µL, 0.6 mmol) were obtained 76.4 mg of **10m** (81 % isolated yield) as a brown oil. **10m** was

purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate, 2:1) = 0.17.

HRMS (EI): calcd. for $C_{21}H_{18}N_2O$: 314,1419; found 314,1422.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (bs, 1H), 7.63 (d, ^3J = 4.9 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.37 – 7.34 (m, 1H), 7.33 – 7.28 (m, 3H), 7.06 (d, *J* = 5.1 Hz, 2H), 6.90 (d, ^3J = 5.1 Hz, 2H), 5.16 (s, 3H), 4.11 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.8 (C), 145.1 (C), 141.0 (C), 133.7 (C), 132.4 (C), 130.4 (C), 130.2 (2xCH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 126.3 (2xCH) 125.9 (CH), 125.8 (C), 125.3 (CH), 119.2 (C), 113.7 (2xCH), 55.2 (CH_3), 10.8 (CH_3).

4-(4-methoxyphenyl)-5-methyl-3-(triisopropylsilyl)-1*H*-pyrazole (10n)



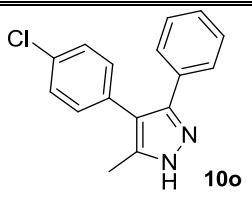
10n

Following the *general procedure,* from *N*'-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (95.5 mg, 0.3 mmol) and ethynyltriisopropylsilane (139 µL, 0.6 mmol) were obtained 79.6 mg of **10n** (76 % isolated yield, 62 % following *one pot* procedure) as a white solid, m.p.= 138-141 °C. **10n** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate, 2:1) = 0.2.

HRMS (EI): calcd. for $C_{20}H_{32}N_2OSi$: 344,2284; found 344,2282.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, ^3J = 8.6 Hz, 2H), 6.88 (d, ^3J = 8.6 Hz, 2H), 3.84 (s, 2H), 2.14 (s, 3H), 1.24 – 1.07 (m, 3H), 1.00 (d, ^3J = 7.0 Hz, 18H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.7 (C), 147.8 (C), 136.3 (C), 131.7 (2xCH), 129.1 (C), 127.7 (C), 113.3 (2xCH), 55.3 (CH_3), 18.8 (3xCH_3), 11.8 (CH_3), 11.7(CH).

4-(4-chlorophenyl)-5-methyl-3-phenyl-1*H*-pyrazole (10o)



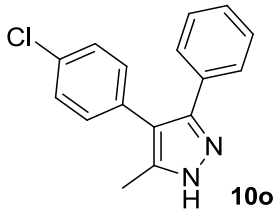
10o

Following the *general procedure,* from *N'*-(1-(4-chlorophenyl)ethylidene)-4-methylbenzenesulfonohydrazide (96.8 mg, 0.3 mmol) and phenylacetylene (67 µL, 0.6 mmol) were obtained 60.5 mg of **10o** (75 % isolated yield, 63 % following *one pot* procedure) as a white solid, m.p.= 191-195 °C. **10o** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate, 2:1) = 0.17.

HRMS (EI): calcd. for $C_{16}H_{13}ClN_2$: 268,0767; found 268,0766.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.31 – 7.23 (m, 2H), 7.23 – 7.15 (m, 5H), 7.04 (d, ^3J = 8.4 Hz, 2H), 2.10 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.4 (C), 142. (C), 132.6 (C), 132.2 (C), 131.9 (C), 131.4 (2xCH), 128.8 (2xCH), 128.6 (2xCH), 128.1 (4xCH), 116.9 (C), 11.1 (CH_3).

4-(5-methyl-3-phenyl-1*H*-pyrazol-4-yl)benzonitrile (10p)



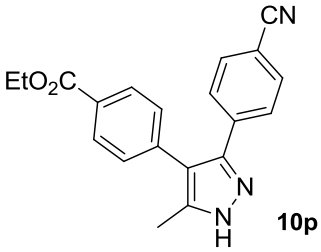
10o

Following the *general procedure,* from *N*'-(1-(4-cyanophenyl)ethylidene)-4-methylbenzenesulfonohydrazide (96.8 mg, 0.3 mmol) and phenylacetylene (, 0.6 mmol) were obtained 42.1 mg of **10p** (58 % isolated yield) as a yellow solid, m.p.= 199-201 °C. **10p** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate, 1:1) = 0.32.

HRMS (EI): calcd. for $C_{17}H_{13}N_3$: 259,1109; found 259.1110

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.62 (d, ^3J = 8.4 Hz, 2H), 7.45 – 7.17 (m, 7H), 2.19 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.9 (C), 142.4 (C), 138.8 (C), 132.4 (2xCH), 131.4 (C), 130.5 (2xCH), 128.8 (2xCH), 128.5 (CH), 128.2 (2xCH), 119.1 (C), 116.6 (C), 110.2 (C), 11.3 (CH_3).

Ethyl 4-(3-(4-cyanophenyl)-5-methyl-1*H*-pyrazol-4-yl)benzoate (10q)



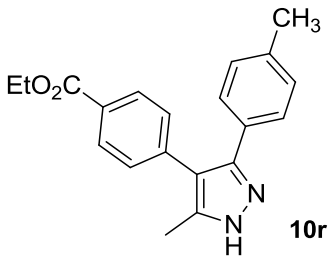
10p

Following the *general procedure,* from ethyl 4-(1-(2-tosylhydrazono)ethyl)benzoate (108.1 mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6 mg, 0.6 mmol) were obtained 71.5 mg of **10q** (72 % isolated yield, 62 % following *one pot* procedure) as a light yellow solid, m.p.= 197-200 °C. **10q** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate, 1:1) = 0.48.

HRMS (EI): calcd. for $C_{20}H_{17}N_3O_2$: 331,1321; found 311,1325.

^{1}H NMR (401 MHz, $CDCl_3$) δ 9.85 (s, 1H), 8.04 (d, ^3J = 8.3 Hz, 2H), 7.52 (d, ^3J = 8.6 Hz, 2H), 7.48 (d, ^3J = 8.6 Hz, 2H), 7.23 (d, ^3J = 8.3 Hz, 2H), 4.39 (q, ^3J = 7.1 Hz, 2H), 2.22 (s, 3H), 1.40 (t, ^3J = 7.1 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.5 (C), 146.7 (C), 140.4 (C), 137.6 (C), 137.2 (C), 132.2 (2xCH), 130.0 (2xCH), 129.8 (2xCH), 129.1 (C), 128.4 (2xCH), 118.7 (C), 117.9 (C), 111.3 (C), 61.2 (CH_2), 14.4 (CH_3), 10.4 (CH_3).

Ethyl 4-(5-methyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)benzoate (10r)

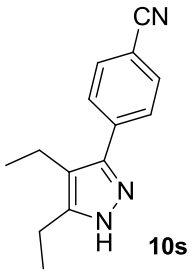


10r

Following the *general procedure,* from ethyl 4-(1-(2-tosylhydrazono)ethyl)benzoate (108.1 mg, 0.3 mmol) and *p*-tolylacetylene (78 µL, 0.6 mmol) were obtained 60.6 mg of **10r** (63 % isolated yield) as a yellow solid, m.p.= 127-

131 °C. **10r** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate, 1:1) = 0.2.
HRMS (EI): calcd. for $C_{20}H_{20}N_2O_2$: 320,1525; found 320,1516.
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.91 (d, ^3J = 8.4 Hz, 2H), 7.17 (d, ^3J = 8.5 Hz, 2H), 7.14 (d, ^3J = 8.2 Hz, 2H), 6.95 (d, ^3J = 7.9 Hz, 2H), 4.30 (q, ^3J = 7.1 Hz, 2H), 2.22 (s, 3H), 2.10 (s, 3H), 1.31 (t, ^3J = 7.1 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.7 (C), 146.3 (C), 142.5 (C), 138.8 (C), 137.8 (C), 129.8 (2xCH), 129.6 (2xCH), 129.2 (2xCH), 128.7 (C), 128.3 (C), 128.0 (2xCH), 116.8 (C), 61.0 (CH_2), 21.2 (CH_3), 14.4 (CH_3), 11.2 (CH_3).

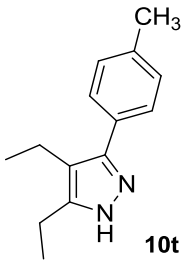
4-(4,5-diethyl-1*H*-pyrazol-3-yl)benzonitrile (10s)



10s

Following the *general procedure,* from 4-methyl-*N*'-(pentan-3-ylidene)benzenesulfonohydrazide (76.3 mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6 mg, 0.6 mmol) were obtained 35.1 mg of **10s** (52 % isolated yield, 32 % following *one pot* procedure) as a light yellow solid, m.p.= 127-130 °C. **10s** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.18.
HRMS (EI): calcd. for $C_{14}H_{15}N_3$: 225,1266; found 225,1263.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.69 (d, ^3J = 8.7 Hz, 2H), 7.65 (d, ^3J = 8.7 Hz, 2H), 2.60 (q, ^3J = 7.6 Hz, 2H), 2.57 (q, ^3J = 7.5 Hz, 2H), 1.21 (t, ^3J = 7.6 Hz, 3H), 1.11 (t, ^3J = 7.5 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.5 (C), 145.8 (C), 138.3 (C), 132.4 (2xCH), 128.1 (2xCH), 119.0 (C), 117.5 (C), 111.1 (C), 18.3 (CH_2), 16.6 (CH_2), 15.7 (CH_3), 13.7 (CH_3).

4,5-diethyl-3-(*p*-tolyl)-1*H*-pyrazole (10t)



10t

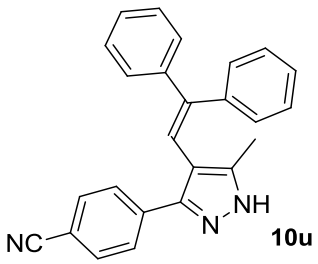
Following the *general procedure,* from 4-methyl-*N'*-(pentan-3-ylidene)benzenesulfonohydrazide (76.3 mg, 0.3 mmol) and *p*-tolylacetylene (78 µL, 0.6 mmol) were obtained 31.4 mg of **10t** (33 % isolated yield) as light yellow oil. **10t** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.17.

HRMS (EI): calcd. for $C_{14}H_{15}N_3$: 214,1470; found 214,1472.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.60 – 7.52 (m, 2H), 7.48 – 7.32 (m, 3H), 2.67 (q, ^3J = 7.6 Hz, 2H), 2.60 (q, J = 7.5 Hz, 2H), 1.29 (t, ^3J = 7.6 Hz, 3H), 1.15 (t, ^3J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ148.3 (C), 145.7 (C), 132.9 (C), 128.7 (2xCH), 127.8 (CH), 127.7 (CH), 116.8 (2xCH), 19.0 (CH_2), 16.6 (CH_2), 15.8 (CH_3), 13.7 (CH_3).

4-(4-(2,2-diphenylvinyl)-5-methyl-1*H*-pyrazol-3-yl)benzonitrile (10u)



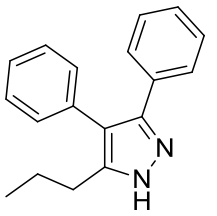
10u

Following the *one pot general procedure,* from 4,4-diphenylbut-3-en-2-one (66.7mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6 mg, 0.6 mmol) were obtained 49.9 mg of **10u** (46 % isolated yield) as a yellow solid, m.p.= 181- 182 °C. **10u** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate, 2:1) = 0.18.

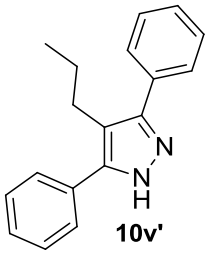
HRMS (EI): calcd. for $C_{24}H_{20}N_2$: 361,1579; found 361,1580.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (bs, 1H), 7.53 – 7.10 (m, 11H), 2.19 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.3 (C), 141.9 (C), 133.5 (C), 132.1 (C), 130.0 (2xCH), 128.4 (5xCH), 128.0 (2xCH), 127.8 (CH), 126.5 (CH), 117.9 (C), 10.9 (CH_3).

3,5-diphenyl-4-propyl-1*H*-pyrazole (10v) and **3,4-diphenyl-5-propyl-1*H*-pyrazole (10v')**



10v



10v'

Following the *general procedure,* from 4-methyl-*N*'-(1-phenylbutylidene)benzenesulfonohydrazide (94.9 mg, 0.3 mmol) and phenylacetylene (67 µL, 0.6 mmol) were obtained a 2:1 (**10v:10v'**) mixture of separable regioisomers. **10v**and **10v'** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 and 2:1 as eluent. *Rf **10v*** (hexanes/ethyl acetate; 2:1) = 0.37. *Rf **10v'*** (hexanes/ethyl acetate; 2:1) = 0.26. It was obtained 41.7 mg of **10v** (53 % isolated yield) as colourless oil (77 % Total yield, 50 % following *one pot* procedure).

- ***Regioisomer 10v:***

HRMS (EI): calcd. for $C_{18}H_{18}N_2$: 262,1470; found 262,1469.

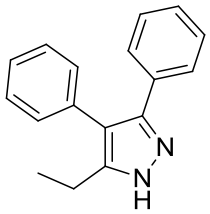
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.57 (m, 4H), 7.49 – 7.34 (m, 6H), 6.81 (bs, 1H), 2.36 – 2.25 (m, 2H), 1.11 – 0.82 (m, 2H), 0.25 (t, ^{3}J = 8.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.6 (C), 132.4 (2xC), 128.7 (4xCH), 128.4 (C), 128.0 (2xCH), 127.9 (4xCH), 116.1 (C), 25.6 (CH_2), 24.0 (CH_2), 14.1 (CH_3).

- ***Regioisomer 10v':***

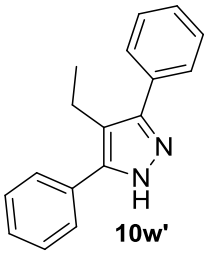
HRMS (EI): calcd. for $C_{18}H_{18}N_2$: 262,1470; found 262,1463.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.18 (m, 10H), 2.69 – 2.54 (m, 2H), 1.72 – 1.56 (m, 2H), 0.91 (t, ^{3}J = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.5 (C), 133.6 (C), 131.9 (C), 130.4 (2xCH), 129.4 (C), 128.6 (2xCH), 128.5 (2xCH), 128.0 (2xCH), 126.9 (2xCH), 118.1 (C), 27.5 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

4-ethyl-3,5-diphenyl-1*H*-pyrazole (10w) and **5-ethyl-3,4-diphenyl-1*H*-pyrazole (10w')**



10w



10w'

Following the *general procedure,* from 4-methyl-*N*'-(1-phenylpropylidene)benzenesulfonohydrazide (90.7 mg, 0.3 mmol) and phenylacetylene (67 µL, 0.6 mmol) were obtained a 1:1 (**10w:10w'**) mixture of separable regioisomers. **10w** and **10w'** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 and 2:1 as eluent. *Rf **10w*** (hexanes/ethyl acetate; 2:1) = 0.3. *Rf **10w'*** (hexanes/ethyl acetate; 2:1) = 0.22. It was obtained 20.1 mg of **10w** (28 % isolated yield) as white solid, m.p.= 165 -167 °C and 21.4 mg of 3u' (26 % isolated yield) as white solid, m.p.= 163 – 165 °C (54 % Total yield).

- ***Regioisomero 10w :***

HRMS (EI): calcd. for $C_{18}H_{18}N_2$: 262,1470; found 262,1469.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 5H), 7.47 – 7.30 (m, 6H), 2.77 (q, ^3J = 7.5 Hz, 2H), 1.09 (t, ^3J = 7.5 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.4 (C), 132.1 (2xC), 128.7 (4xCH), 128.1 (2xCH), 127.8 (4xCH), 125.0 (C), 117.6 (C), 16.8 (CH_2), 15.5 (CH_3).

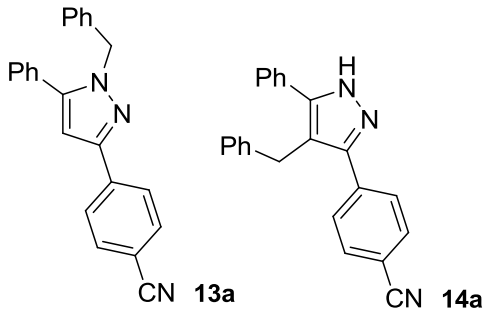
- ***Regioisomer 10w':***

HRMS (EI): calcd. for $C_{18}H_{18}N_2$: 262,1470; found 262,1463.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.35 – 7.20 (m, 4H), 7.21 – 7.02 (m, 5H), 2.59 (q, ^3J = 7.6 Hz, 2H), 1.12 (t, ^3J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.8 (C), 145.9 (C), 133.3 (C), 131.5 (C), 130.2 (2xCH), 128.5 (2xCH), 128.4 (2xCH), 127.9 (2xCH), 126.8 (2xCH), 117.5 (C), 18.8 (CH_2), 13.6 (CH_3).

E.7. Characterization data for compounds 13 and 14

4-(1-benzyl-5-phenyl-1*H*-pyrazol-3-yl)benzonitrile (13a) and **4-(4-benzyl-5-phenyl-1*H*-pyrazol-3-yl)benzonitrile (14a)**



Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (109.3 mg, 0.3 mmol) and 4-ethynylbenzonitrile (72.6 mg, 0.6 mmol) were obtained a 3:1 (**13a:14a**) mixture of separable regioisomers. **14a** and **13a** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* **14a** (hexanes/ethyl acetate; 5:1) = 0.05. *Rf* **13a** (hexanes/ethyl acetate; 5:1) = 0.28. It was obtained 67.4 mg of **13a** (67 % isolated yield) as a light yellow solid, m.p.= 150-153 °C and 25.2 mg of **14a** (25 % isolated yield) as a light yellow solid, m.p. = 133-139 °C. (Total yield **14a** + **13a**, 92 %)

- ***Regioisomer* 13a*:***

HRMS (EI) : calcd. for $C_{23}H_{17}N_3$: 335,1422; found 335,1420.

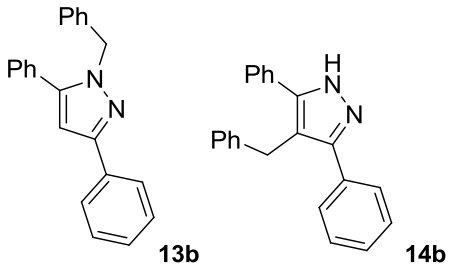
^{1}H NMR (401 MHz, $CDCl_3$) δ 7.97 (d, ^3J = 8.3 Hz, 2H), 7.69 (d, ^3J = 8.4 Hz, 2H), 7.43 – 7.42 (m, 3H), 7.38 – 7.32 (m, 2H), 7.32 – 7.24 (m, 3H), 7.10 (app. d, ^3J = 7.0 Hz, 2H), 6.71 (s, 1H), 5.40 (s, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.1 (C), 146.2 (C), 137.9 (C), 137.3 (C), 132.6 (2xCH), 130.2 (C), 129.1 (CH), 129.0 (2xCH), 128.9 (2xCH), 128.8 (2xCH), 127.8 (CH), 126.9 (2xCH), 126.1 (2xCH), 119.3 (C), 110.9 (C), 104.4 (CH), 53.6 (CH_2).

- ***Regioisomer* 14a*:***

HRMS (EI) : calcd. for $C_{23}H_{17}N_3$: 335,1422; found 335,1419.

^{1}H NMR (401 MHz,) δ 7.65 (d, ^3J = 8.4 Hz, 2H), 7.59 (d, ^3J = 8.4 Hz, 2H), 7.47 – 7.34 (m, 5H), 7.31 (app. t, ^3J = 7.3 Hz, 2H), 7.23 (app. t, ^3J = 7.3 Hz, 1H), 7.14 (d, ^3J = 7.0 Hz, 2H), 4.11 (s, 2H), 3.70 (bs, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.4 (C), 140.2 (2xC), 136.8 (C), 132.4 (2xCH), 129.5 (C), 129.1 (2xCH), 129.0 (CH), 128.8 (2xCH), 128.0 (2xCH), 127.9 (2xCH), 127.6 (2xCH), 126.4 (CH), 118.7 (C), 113.8 (C), 111.5 (C), 29.4 (CH_2).

1-benzyl-3,5-diphenyl-*1H*-pyrazole (13b) and **4-benzyl-3,5-diphenyl-*1H*-pyrazole (14b)**



13b **14b**

Following the *general procedure,* from *N*'-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (109.3 mg, 0.3 mmol) and phenylacetylene (67 µL, 0.6 mmol) were obtained a 4:1 (**13b:14b**) mixture of separable regioisomers. **13b** and **14b** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 and 2:1 as eluent. *Rf **13b*** (hexanes/ethyl acetate; 2:1) = 0.45. *Rf **14b*** (hexanes/ethyl acetate; 5:1) = 0.35. It was obtained 40.1 mg of **13b** (44 % isolated yield) as a white solid, m.p.= 119-121 °C and 17.7 mg of **14b** (19 % isolated yield) as a white solid, m.p. = 156- 158 °C. (Total yield **13b** + **14b**, 63 %)

- ***Regioisomer 13b:***

HRMS (EI) : calcd. for $C_{22}H_{18}N_2$: 310,1470; found 310,1464.

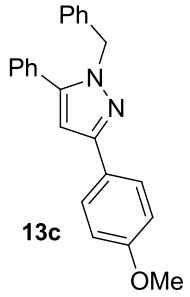
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 – 7.08 (m, 2H), 6.88 – 6.72 (m, 11H), 6.70 – 6.64 (m, 2H), 6.41 (s, 1H), 5.66 (s, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.1 (C), 145.6 (C), 137.9 (C), 133.6 (C), 130.8 (C), 129.0 (CH), 128.8 (4xCH), 128.7 (4xCH), 127.8 (CH), 127.5 (CH), 126.9 (2xCH), 125.8 (2xCH), 103.9 (CH), 53.4 (CH_2).

- ***Regioisomer 14b:***

HRMS (EI) : calcd. for $C_{22}H_{18}N_2$: 310,1470; found 310,1456.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.41 (m, 4H), 7.32 – 7.26 (m, 7H), 7.26 – 7.02 (m, 4H), 6.18 (bs, 2H), 5.41 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.6 (C), 141.1 (C), 131.5 (2xC), 130.3 (4xCH), 128.7 (2xCH), 128.6 (2xCH), 128.2 (2xCH), 128.1 (4xCH), 127.6 (CH), 126.0 (C), 125.0 (C), 29.5 (CH_2).

1-benzyl-3-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazole (13c)



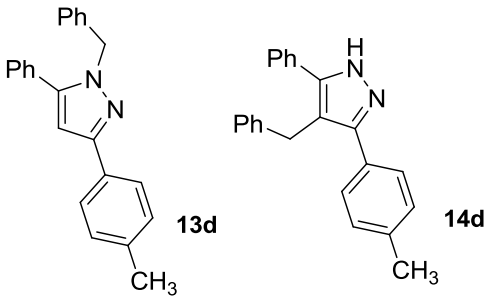
Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (109.3 mg, 0.3 mmol) and 1-ethynyl-4-methoxybenzene (79 µL, 0.6 mmol) were obtained 49.0 mg of **13c** (48 % isolated yield) as a white solid, m.p.= 102-104 °C. **13c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* (hexanes/ethyl acetate; 5:1) = 0.23.

HRMS (EI): calcd. for $C_{23}H_{20}N_2O$: 340,1576; found 340,1570.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, ^3J = 8.9 Hz, 2H), 7.49 – 7.34 (m, 5H), 7.34 – 7.24 (m, 3H), 7.17 – 7.10 (m, 2H), 6.98 (d, ^3J = 8.9 Hz, 2H), 6.63 (s, 1H), 5.42 (s, 2H), 3.87 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 150.8 (C), 145.5 (C), 137.8 (C), 130.7 (C), 128.8 (2xCH), 128.7 (2xCH), 128.6 (2xCH), 127.4 (CH), 127.0 (2xCH), 126.7 (2xCH), 126.2 (C), 114.0 (2xCH), 103.3 (CH), 55.3 (CH_3), 53.2 (CH_2).

1-benzyl-5-phenyl-3-(*p*-tolyl)-1*H*-pyrazole (13d) and **4-benzyl-5-phenyl-3-(*p*-tolyl)-1*H*-pyrazole (14d)**



Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (109.3 mg, 0.3 mmol) and *p*-tolylacetylene (78 µL, 0.6 mmol) were obtained a 6:1 (**13d:14d**) mixture of separable regioisomers. **14d** and **13d**

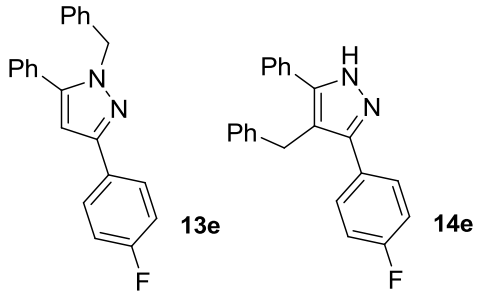
were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 and 2:1 as eluent. *Rf* **13d** (hexanes/ethyl acetate; 5:1) = 0.4. *Rf* **14d** (hexanes/ethyl acetate; 2:1) = 0.38. It was obtained 56.7 mg of **13d** (58 % isolated yield) as colourless oil and 9.6 mg of **14d** (10 % isolated yield) as colourless oil. (Total yield **14d** + **13d**: 68%)

- ***Regioisomer* 13d**

HRMS (EI) : calcd. for $C_{23}H_{20}N_2$: 324,1626; found 324,1631.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, ^3J = 8.1 Hz, 2H), 7.45 – 7.34 (m, 5H), 7.32 – 7.22 (m, 5H), 7.17 – 7.10 (m, 2H), 6.67 (s, 1H), 5.43 (s, 2H), 2.42 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.1 (C), 145.4 (C), 137.8 (C), 137.4 (C), 130.7 (C),130.7 (C), 129.3 (2xCH), 128.9 (2xCH), 128.7 (3xCH), 128.6 (2xCH), 127.4 (CH), 126.7 (2xCH), 125.6 (2xCH), 103.6 (CH), 53.3 (CH_2), 21.3 (CH_3).

1-benzyl-3-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole (13e) and **4-benzyl-3-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole (14e)**



Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (109.3 mg, 0.3 mmol) and 4-fluoro phenylacetylene (69 µL, 0.6 mmol) were obtained a 4:1 (**13e:14e**) mixture of separable regioisomers. **14e** and **13e** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 and 2:1 as eluent. *Rf* **13e** (hexanes/ethyl acetate; 5:1) = 0.42. *Rf* **14e** (hexanes/ethyl acetate; 2:1) = 0.36. It was obtained 42.8 mg of **13e** (41 % isolated yield) as white solid and 9.8 mg of **14e** (9 % isolated yield) as colourless oil. (Total yield **14e** + **13e**: 50%)

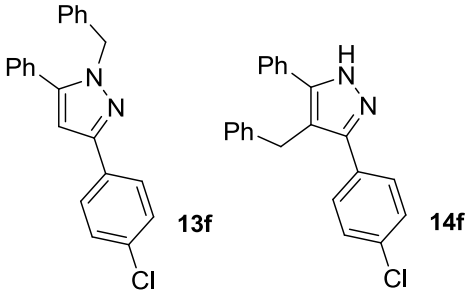
- ***Regioisómero 13e:***

HRMS (EI): calcd. for $C_{22}H_{17}FN_2$: 328,1376; found 328.1375 .

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, ^3J = 8.9, 5.4 Hz, 2H), 7.51 – 7.34 (m, 5H), 7.33 – 7.24 (m, 3H), 7.19 – 7.06 (m, 4H), 6.64 (s, 1H), 5.42 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (d, ^{1}J = 246.1 Hz, C), 150.1 (C), 145.6 (C), 137.6 (C), 130.5 (C), 129.8 (C), 129.7 (2xCH), 128.9 (CH), 128.8 (2xCH), 128.7 (2xCH), 127.5 (d, ^{2}J = 21.5 Hz, 2xCH), 127.4 (CH), 126.7 (2xCH), 115.5 (d, ^{2}J = 21.5 Hz, 2xCH), 103.5 (CH), 53.3 (CH_2).

1-benzyl-3-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole (13f) and **4-benzyl-3-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole (14f)**



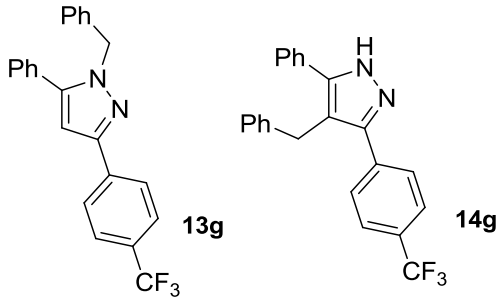
Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (109.3 mg, 0.3 mmol) and 4-chloro phenylacetylene (83.6 mg, 0.6 mmol) were obtained a 5:1 (**13f:14f**) mixture of separable regioisomers. **14f** and **13f** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 and 2:1 as eluent. *Rf* **13f** (hexanes/ethyl acetate; 5:1) = 0.41. *Rf* **14f** (hexanes/ethyl acetate; 2:1) = 0.50. It was obtained 55.7 mg of **13f** (54% isolated yield) as white solid and 10.7 mg of **14f** (10 % isolated yield) as colourless oil. (Total yield **14e** + **13e**: 64%)

- ***Regioisómero 13e:***

HRMS (EI): calcd. for $C_{22}H_{17}ClN_2$: 344,1080; found 344,1073 .

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.76 (m, 2H), 7.46 – 7.35 (m, 7H), 7.35 – 7.21 (m, 3H), 7.15 – 7.08 (m, 2H), 6.66 (s, 1H), 5.41 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.9 (C), 145.7 (C), 137.5 (C), 133.4 (C), 132.0 (C), 130.4 (C), 128.9 (2xCH), 128.8 (2xCH), 128.7 (2xCH), 128.6 (2xCH), 127.5(CH), 126.9 (2xCH), 126.8 (2xCH), 103.7 (CH), 53.3 (CH_3).

1-benzyl-5-phenyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (13g) and **4-benzyl-5-phenyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (14g)**



Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (109.3 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained a 4:1 (**13g:14g**) mixture of separable regioisomers. **14g** and **13g** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* **14g** (hexanes/ethyl acetate; 5:1) = 0.17. *Rf* **13g** (hexanes/ethyl acetate; 5:1) = 0.67. It was obtained 63.6 mg of **13g** (56 % isolated yield) as a white solid, m.p.= 127-130 °C and 21.6 mg of **14g** (19 % isolated yield) as colourless oil. (Total yield **14g** + **13g**: 75 %)

- ***Regioisomer* 13g**

HRMS (EI) : calcd. for $C_{23}H_{17}F_3N_2$: 378,1344; found 378,1342.

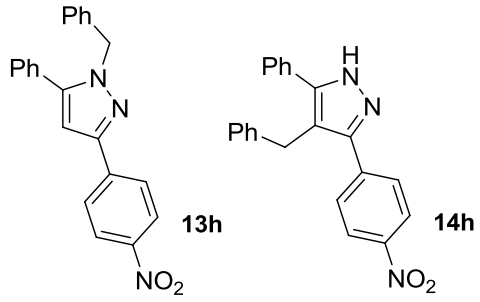
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, ^3J = 8.0 Hz, 2H), 7.68 (d, ^3J = 8.1 Hz, 2H), 7.46 – 7.41 (m, 3H), 7.41 – 7.34 (m, 2H), 7.33 – 7.25 (m, 3H), 7.13 (dd, ^3J = 7.8, 1.7 Hz, 2H), 6.73 (s, 1H), 5.43 (s, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.5 (C), 145.9 (C), 137.4 (C), 136.9 (C), 133.2 (C), 129.4 (q, ^2J = 32.2 Hz, C), 128.9 (3xCH), 128.8 (2xCH), 128.7 (2xCH), 127.6 (CH), 126.8 (2xCH), 126.1 (2xCH), 125.6 (q, ^3J = 3.6 Hz, 2xCH), 122.5 (q, ^1J = 271.8 Hz, C), 104.1 (CH), 53.4 (CH_2).

- ***Regioisomer* 14g**

HRMS (EI) : calcd. for $C_{23}H_{17}F_3N_2$: 378,1344; found 378,1332.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (bs, 1H), 7.60 (d, ^3J = 8.3 Hz, 2H), 7.54 (d, ^3J = 8.4 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.39 – 7.29 (m, 5H), 7.26 – 7.22 (m, 1H), 7.16 (app. d, ^3J = 6.9 Hz, 2H), 4.13 (s, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.4 (C), 145.9 (C), 140.7 (C), 135.9 (C), 130.4 (C), 129.9 (q, ^2J = 32.5 Hz , C), 129.1 (2xCH), 128.9 (2xCH), 128.8 (CH), 128.1 (2xCH), 127.9 (2xCH), 127.7 (2xCH), 126.5 (q, ^1J = 273.1Hz, C) 126.4 (CH), 125.6 (q, ^3J = 3.6 Hz, 2xCH), 113.6 (C), 29.6 (CH_2).

1-benzyl-3-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole (13h) and **4-benzyl-3-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole (14h)**



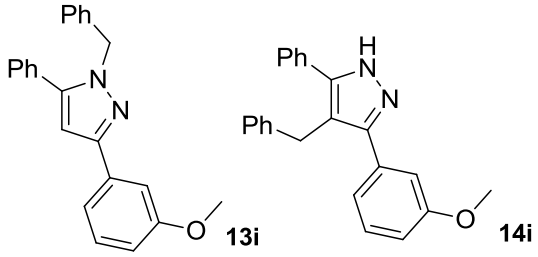
Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (6.4 mg, 0.1 mmol) and 4-nitrophenylacetylene (29.4 mg, 0.2 mmol) were obtained a 3:1 (**13h:14h**) mixture of separable regioisomers. **14h** and **13h** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 and 2:1 as eluent. *Rf* **13h** (hexanes/ethyl acetate; 10:1) = 0.18. *Rf* **14h** (hexanes/ethyl acetate; 2:1) = 0.38. It was obtained 21.2 mg of **13h** (60% isolated yield) as yellow solid and 6 mg of **14h** (17 % isolated yield) as yellow oil. (Total yield **14h** + **13h**: 77%)

- ***Regioisómero 13h:***

HRMS (EI): calcd. for $C_{22}H_{17}N_3O_2$: 355,1321; found 355,1329 .

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, ^3J = 8.9 Hz, 2H), 8.04 (d, ^3J = 9.0 Hz, 2H), 7.49 – 7.24 (m, 8H), 7.15 – 7.10 (m, 2H), 6.77 (s, 1H), 5.43 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6 (C), 147.0 (C), 146.1 (C), 139.8 (C), 137.1 (C), 130.0 (C), 129.1 (CH), 128.9 (2xCH), 128.8 (2xCH), 128.7 (2xCH), 127.7 (CH), 126.8 (2xCH), 126.0 (2xCH), 124.1 (2xCH), 104.6 (CH), 53.6 (CH_2).

1-benzyl-3-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazole and **(13i) 4-benzyl-3-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazole (14i)**



Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (109.3 mg, 0.3 mmol) and 1-ethynyl-3-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained a 5:1 (**13i:14i**) mixture of separable regioisomers. **14i** and **13i** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 and 2:1 as eluent. *Rf* **14i** (hexanes/ethyl acetate; 2:1) = 0.47. *Rf* **13i** (hexanes/ethyl acetate; 5:1) = 0.33. It was obtained 46.0 mg of **13i** (45 % isolated yield) as yellow oil and 11.2 mg of **14i** (11 % isolated yield) as light yellow oil. (Total yield **14i** + **13i**: 56 %).

- ***Regioisomer* 13i**

HRMS (EI) : calcd. for $C_{23}H_{20}N_2O$: 340,1576; found 340,1573.

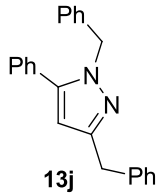
^{1}H NMR (401 MHz, $CDCl_3$) δ 7.50 – 7.46 (m, 2H), 7.43 – 7.39 (m, 3H), 7.37 (ddd, ^3J = 8.1, 4.4, 2.4 Hz, 2H), 7.33 - 7.27 (m, 4H), 7.15 – 7.10 (m, 2H), 6.90 (ddd, ^3J = 8.2, 2.5, 1.0 Hz, 1H), 6.68 (s, 1H), 5.42 (s, 2H), 3.89 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.9 (C), 150.8 (C), 145.5 (C), 137.7 (C), 134.8 (C), 130.6 (C), 129.7 (CH), 128.9 (2xCH), 128.7 (2xCH), 128.6 (2xCH), 127.4 (CH), 126.7 (2xCH), 118.3 (CH), 113.7 (CH), 110.8 (CH), 103.9 (CH), 55.4 (CH_3), 53.3 (CH_2).

- ***Regioisomer* 14i**

HRMS (EI) : calcd. for $C_{23}H_{20}N_2O$: 340,1576; found 340,1566.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 2H), 7.41 – 7.25 (m, 6H), 7.22 - 7.18 (m, 4H), 7.10 - 7.07 (m, 1H), 7.00 – 6.93 (m, 1H), 6.86 (ddd, ^3J = 8.2, 2.6, 0.8 Hz, 1H), 4.45 (bs, 1H), 4.12 (s, 2H), 3.55 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.7 (C), 147.6 (C), 141.2 (2xC), 132.8 (C), 131.4 (C), 129.8 (CH), 128.8 (2xCH), 128.6 (2xCH), 128.3 (CH), 128.1 (2xCH) , 127.5 (2xCH), 126.0 (CH), 119.8 (CH), 114.9 (CH), 112.8 (C), 112.2 (CH), 54.9 (CH_3), 29.6 (CH_2).

1,3-dibenzyl-5-phenyl-1*H*-pyrazole (13j)

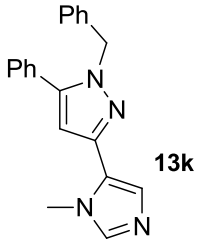


13j

Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (76.3 mg, 0.3 mmol) and prop-2-yn-1-ylbenzene (77 µL, 0.6 mmol) were obtained a 2:1 mixture of separable regioisomers, where **13j** was the major regioisomer 34.1 mg (35 % isolated yield) as a light yellow oil. **13j** was separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1. *Rf* ***13j*** (hexanes/ethyl acetate; 5:1) = 0.29.

HRMS (EI) : calcd. for $C_{23}H_{20}N_2$: 324,1626; found 324,1617.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 7H), 7.24 – 7.20 (m, 6H), 7.12 – 7.04 (m, 2H), 6.53 (s, 1H), 6.10 (s, 2H), 5.34 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.8 (C), 145.4 (C), 140.1 (C), 137.9 (C), 130.7 (C), 129.0 (2xCH), 128.9 (2xCH), 128.7 (5xCH), 128.6 (2xCH), 127.5 (CH), 126.8 (2xCH), 126.3 (CH), 105.9 (CH), 53.0 (CH_2), 34.9 (CH_2).

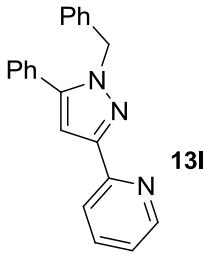
1-benzyl-3-(1-methyl-1H-imidazol-5-yl)-5-phenyl-1*H*-pyrazole (13k)



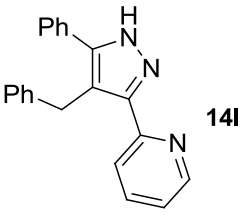
13k

Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (109.3 mg, 0.3 mmol) and 5-ethynyl-1-methyl-1H-imidazole (63 µL, 0.6 mmol) were obtained 71.7 mg of **13k** (76 % isolated yield, 63 % following *one pot* procedure) as a brown oil. **13k** was purified by flash chromatography on silica gel using a mixture of dichloromethane/methanol 10:1 as eluent. *Rf* (dichloromethane/methanol; 10:1) = 0.34.
HRMS (EI) : calcd. for $C_{20}H_{18}N_4$: 314,1531; found 314,1535.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 7.46 – 7.40 (m, 3H), 7.40 – 7.26 (m, 7H), 7.14 – 7.07 (m, 2H) , 6.53 (s, 1H), 5.37 (s, 2H), 3.95 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.0 (C), 142.1 (C), 138.9 (CH), 137.4 (2xC), 130.1 (C), 128.9 (3xCH), 128.7 (2xCH), 128.6 (2xCH), 127.8 (CH), 127.6 (CH), 126.8 (2xCH), 105.1 (CH), 53.3 (CH_3), 34.0 (CH_2).

2-(1-benzyl-5-phenyl-1H-pyrazol-3-yl)pyridine (13l) and **2-(4-benzyl-5-phenyl-1H-pyrazol-3-yl)pyridine (14l)**



13l



14l

Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (109.3 mg, 0.3 mmol) and 2-ethynylpyridine (62 µL, 0.6 mmol) were obtained a 1:1 (**13l:14l**) mixture of separable regioisomers. **14l** and **13l** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* **14l** (hexanes/ethyl acetate; 2:1) = 0.32. *Rf* **13l** (hexanes/ethyl acetate; 2:1) = 0.10. It was obtained 22.6 mg of **13l** (24 % isolated yield) as brown oil and 24.2 mg of **14l** (26 % isolated yield) as ligh brown oil. (Total yield **14l** + **13i**: 50 %).

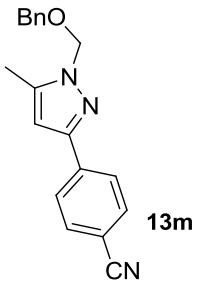
- ***Regioisomer* 13l**

HRMS (EI) : calcd. for $C_{21}H_{17}N_3$: 311,1422; found 311,1422.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 – 8.64 (m, 1H), 8.05 (d, ^3J = 8.0 Hz, 1H), 7.74 (m, 1H), 7.40 (bs, 5H), 7.33 – 7.19 (m, 5H), 7.12 (d, ^3J = 6.9 Hz, 2H), 7.05 (s, 1H), 5.45 (s, 1H).

- ***Regioisomer* 14i**

HRMS (EI) : calcd. for $C_{21}H_{17}N_3$: 311,1422; found 311,1420.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (bs, 1H), 6.96 (dd, ^3J = 6.5, 2.6 Hz, 1H), 6.93 – 6.89 (m, 2H), 6.87 – 6.67 (m, 10H), 5.03 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.7 (C), 149.4 (CH), 140.2 (2xC), 137.1 (CH), 132.6 (C), 128.7 (2xCH), 128.6 (2xCH), 128.0 (4xCH), 126.1 (2xCH), 122.6 (CH), 120.5 (CH), 113.6 (C), 29.9 (CH_2).

4-(1-((benzyloxy)methyl)-5-methyl-1*H*-pyrazol-3-yl)benzonitrile (13m)

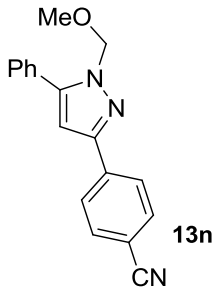


13m

Following the *general procedure,* from *N*'-(1-(benzyloxy)propan-2-ylidene)-4-methylbenzenesulfonohydrazide (99.7 mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6 mg, 0.6 mmol) were obtained 51.0 mg of **13m** (56 % isolated yield) as a yellow solid, m.p.: 112-115 °C. **13m** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* (hexanes/ethyl acetate; 5:1) = 0.15.
HRMS (EI) : calcd. for $C_{19}H_{17}N_3O$: 303,1372; found 303,1366.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, ^{3}J = 8.5 Hz, 2H), 7.68 (d, ^{3}J = 8.5 Hz, 2H), 7.42 – 7.27 (m, 5H), 6.45 (s, 1H), 5.53 (s, 2H), 4.57 (s, 2H), 2.41 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.9 (C), 141.5(C), 138.0 (C), 137.0 (C), 132.6 (2xCH), 128.6 (2xCH), 128.2 (2xCH) 126.1 (2xCH), 119.2 (C), 111.0 (C), 104.8 (CH), 77.8 (CH_2), 70.6 (CH_2), 11.0 (CH_3).

4-(1-(methoxymethyl)-5-phenyl-1*H*-pyrazol-3-yl)benzonitrile (13n)



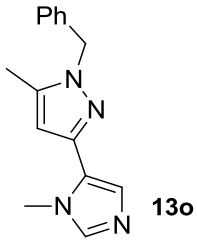
13n

Following the *general procedure,* from *N'*-(1,2-diphenylethylidene)-4-methylbenzenesulfonohydrazide (76.3 mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6 mg, 0.6 mmol) were obtained a 7:1 mixture of separable regioisomers, where **13n** was the major regioisomer 36.5 mg (42 % isolated yield) as a colourless oil. **13n** was separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1. *Rf* **13n** (hexanes/ethyl acetate; 5:1) = 0.2.

HRMS (EI) : calcd. for $C_{18}H_{15}N_3O$: 289,1215; found 289,1217.

^{1}H NMR (401 MHz, $CDCl_3$) δ 8.07 – 7.89 (m, 2H), 7.77 – 7.68 (m, 2H), 7.63 (d, ^{3}J = 7.7 Hz, 2H), 7.56 – 7.42 (m, 3H), 6.77 (s, 1H), 5.43 (s, 2H), 3.53 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.3 (C), 146.6 (C), 137.6 (C), 132.5 (2xCH), 129.6 (C), 129.1 (CH), 128.9 (2xCH), 128.9 (2xCH), 126.2 (2xCH), 119.1 (C), 111.2 (C), 104.6 (CH), 79.9 (CH_2), 57.0 (CH_3).

1-benzyl-5-methyl-3-(1-methyl-1*H*-imidazol-5-yl)-1*H*-pyrazole (13o)



13o

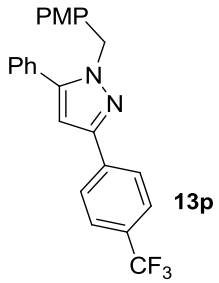
Following the *general procedure,* from 4-methyl-*N*'-(1-phenylpropan-2-ylidene)benzenesulfonohydrazide (90.7 mg, 0.3 mmol) and 5-ethynyl-1-methyl-1H-

imidazole (63 µL, 0.6 mmol) were obtained 42.4 mg of **13o** (56 % isolated yield) as a light yellow solid, m.p.: 78-80 °C. **13o** was purified by flash chromatography on silica gel using ethyl acetate as eluent. *Rf* (ethyl acetate) = 0.13.

HRMS (EI) : calcd. for $C_{15}H_{16}N_4$: 252,1375; found 252.1371.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (bs, 1H), 7.39 – 7.30 (m, 3H), 7.26 (bs, 1H), 7.17 – 7.09 (m, 2H), 6.25 (s, 1H), 5.32 (s, 2H), 3.90 (s, 3H), 2.24 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.6 (C), 139.4 (C), 138.9 (CH), 136.9 (C), 128.8 (2xCH), 127.9 (CH), 127.7 (CH), 126.7 (2xCH), 104.7 (CH), 53.1 (CH_2), 33.8 (CH_3), 11.1 (CH_3).

1-(4-methoxybenzyl)-5-phenyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (13p)



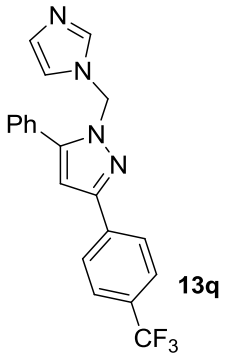
13p

Following the *one pot general procedure,* from 2-(4-methoxyphenyl)-1-phenylethanone (67.9 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 85.8 mg of **13p** (70 % isolated yield) as a white solid, m.p.: 110-111 °C. **13p** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* (hexanes/ethyl acetate; 5:1) = 0.35.

HRMS (EI) : calcd. for $C_{24}H_{19}F_3N_2O$: 408,1449; found 408,1453.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.98 (d, ^3J = 8.1 Hz, 2H), 7.66 (d, ^3J = 8.2 Hz, 2H), 7.45 – 7.38 (m, 3H), 7.38 – 7.36 (m, 2H), 7.06 (d, ^3J = 8.7 Hz, 2H), 6.82 (d, ^3J = 8.7 Hz, 1H), 6.69 (s, 1H), 5.33 (s, 2H), 3.78 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.2 (C), 149.6 (C), 145.7 (C), 137.1 (C), 130.6 (C), 129.7 (q, ^2J = 32.1 Hz, C), 129.6 (C), 129.1 (2xCH), 129.0 (CH), 128.9 (2xCH), 128.4 (2xCH), 125.9 (2xCH), 125.7 (2xCH), 125.6 (q, ^3J = 3.6 Hz, 2xCH), 124.5 (q, ^1J = 270 Hz, C) 114.1 (2xCH), 104.2 (CH), 55.4 (CH_3), 53.1 (CH_2)

1-((1*H*-imidazol-1-yl)methyl)-5-phenyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (13q)



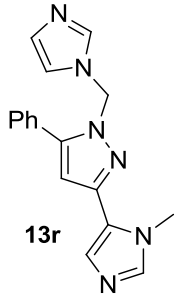
13q

Following the *general procedure,* from *N'*-(2-(1*H*-imidazol-1-yl)-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (106.3 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 81.8 mg of **13q** (74 % isolated yield) as a light brown solid, m.p.: 131-134 °C. **13q** was purified by flash chromatography on silica gel using a mixture of dichloromethane/methanol 20:1 as eluent. *Rf* (dichloromethane/methanol; 20:1) = 0.39.

HRMS (EI) : calcd. for $C_{20}H_{15}F_3N_4$: 368,1249; found 368,1256.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, ^3J = 8.3 Hz, 2H), 7.68 (d, ^3J = 8.3 Hz, 2H), 7.61 – 7.46 (m, 3H), 7.38 – 7.35 (m, 3H), 6.99 (bs, 1H), 6.90 (bs, 1H), 6.66 (s, 1H), 6.14 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.0 (C), 145.9 (C), 136.7 (C), 136.0 (C), 130.5 (q, ^2J = 28.5 Hz, C) 129.9 (CH), 129.8 (2xCH), 129.3 (C), 129.2 (2xCH), 129.1 (2xCH), 126.0 (q, ^3J = 3.6 Hz , 2xCH), 125.7 (q, ^1J = 271.9 Hz, C), 122.4 (C), 118.5 (C), 105.5 (CH), 58.7 (CH_2).

1-((1H-imidazol-1-yl)methyl)-3-(1-methyl-1H-imidazol-5-yl)-5-phenyl-1H-pyrazole (13r)



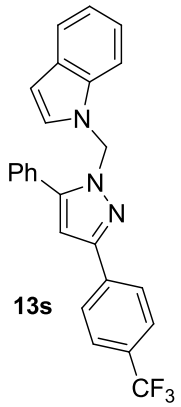
13r

Following the *general procedure,* from *N*'-(2-(1*H*-imidazol-1-yl)-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (106.3 mg, 0.3 mmol) and 5-ethynyl-1-methyl-1H-imidazole (63 µL, 0.6 mmol) were obtained 41.1 mg of **13r** (45 % isolated yield) as a colourless oil. **13r** was purified by flash chromatography on silica gel using a mixture of dichloromethane/methanol 20:1 as eluent. *Rf* (dichloromethane/methanol; 20:1) = 0.32.

HRMS (EI) : calcd. for $C_{17}H_{16}N_6$: 304,1436; found 304,1431.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.47 (m, 4H), 7.41 (bs, 1H), 7.41 - 7.34 (m, 3H), 7.00 (bs, 1H), 6.85 (bs, 1H), 6.48 (s, 1H), 6.11 (s, 2H), 3.96 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.2 (C), 143.9 (C), 136.7 (CH), 129.9 (CH), 129.8 (2xCH), 129.3 (2xCH), 129.1 (2xCH), 128.9 (C), 128.7 (C), 118.4 (CH), 106.4 (CH), 58.5 (CH_2), 29.7 (CH_3).

1-((5-phenyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-1-yl)methyl)-1*H*-indole (13s)



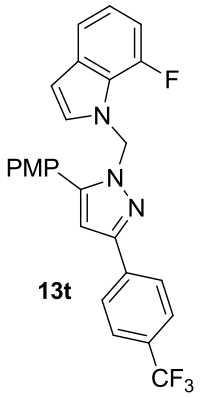
13s

Following the *general procedure,* from *N'*-(2-(1*H*-indol-1-yl)-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (121.0 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 71.4 mg of **13s** (57 % isolated yield, 23 % following *one pot* procedure) as a brown solid, m.p.: 173-177 °C. **13s** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. *Rf* (hexanes/ethyl acetate; 10:1) = 0.29.

HRMS (EI) : calcd. for $C_{25}H_{18}F_3N_3$: 417,1453; found 417,1451.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, ^3J = 8.7 Hz, 1H), 7.92 (d, ^3J = 8.8 Hz, 2H), 7.81 – 7.71 (m, 3H), 7.64 – 7.55 (m, 2H), 7.48 (s, 1H), 7.45 – 7.38 (m, 1H), 7.31 – 7.27 (m, 2H), 7.08 (d, ^3J = 3.6 Hz, 1H), 6.78 (s, 1H), 6.55 (dd, ^3J = 3.6, 0.8 Hz, 1H), 6.52 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.0 (C), 145.6 (C), 137.1 (C), 136.4 (C), 135.6 (C), 129.9 (q, ^2J = 32.7 Hz, C), 129.4 (2xCH), 129.1 (2xCH), 127.4 (CH), 125.9 (2xCH), 125.6 (q, ^3J = 3.6 Hz, 2xCH), 122.1 (CH), 120.8 (CH), 120.2(CH), 118.4 (C), 110.0 (C), 105.1 (CH), 103.1 (CH), 58.9 (CH_2).

7-fluoro-1-((5-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-1-yl)methyl)-1*H*-indole (13t)



13t

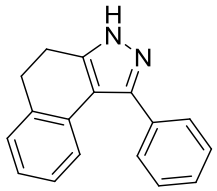
Following the *general procedure,* from *N'*-(2-(7-fluoro-1*H*-indol-1-yl)-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (126.4 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 71.2 mg of **13t** (51 % isolated yield) as a red-brown solid, m.p.: 154-158 °C. **13t** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* (hexanes/ethyl acetate; 5:1) = 0.43.

HRMS (EI) : calcd. for $C_{26}H_{19}F_4N_3O$: 465,1464; found 465,1456.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, ^3J = 8.0 Hz, 2H), 7.68 (d, ^3J = 8.2 Hz, 2H), 7.33 (d, ^3J = 7.9 Hz, 1H), 7.28 (s, 1H), 7.21 (d, ^3J = 8.8 Hz, 2H), 7.15 (d, ^3J = 3.3 Hz, 1H), 7.00 (td, ^3J = 7.9, 4.5 Hz, 1H), 6.93 (d, ^3J = 8.8 Hz, 2H), 6.84 (dd, ^3J = 13.0, 7.6 Hz, 1H), 6.63 (s, 1H), 6.56 (s, 2H), 6.52 (dd, ^3J = 3.2, 2.3 Hz, 1H), 3.87 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.3 (C), 151.6 (d, ^1J = 150 Hz, C), 150.2 (C), 145.9 (C), 136.5 (C), 132.5 (d, ^3J = 4.9 Hz, C), 130.3 (2xCH), 129.9 (q, ^2J = 32.2 Hz, C), 128.1 (CH), 125.8 (2xCH), 125.6 (q, ^3J = 3.6 Hz, 2xCH), 123.4 (d, ^2J = 9.4 Hz, C), 121.6 (C), 120.4 (d, ^4J = 7 Hz, CH), 116.7 (CH), 114.2 (2xCH), 107.8 (d, ^3J = 18.3 Hz, CH), 104.6 (d, ^2J = 30.6 Hz, C), 60.34 (d, ^4J = 7.9 Hz, CH_2), 55.4 (CH_3).

E.8. Characterization data for compounds 17.

1-phenyl-4,5-dihydro-3H-benzo[*e*]indazole (17a)



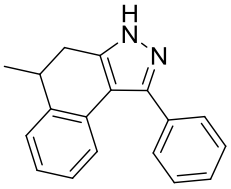
17a

Following the *general procedure,* from *N*'-(2,3-dihydro-1*H*-inden-1-ylidene)-4-methylbenzenesulfonohydrazide (90.1 mg, 0.3 mmol) and phenylacetylene (68 µL, 0.6 mmol) were obtained 31.0 mg of **17a** (42 % isolated yield) as a light brown oil. **17a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* (hexanes/ethyl acetate; 5:1) = 0.17.

HRMS (EI): calcd. for $C_{17}H_{14}N_2$: 246,1157; found 246,1161.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 2H), 7.51 – 7.39 (m, 3H), 7.30 – 7.23 (m, 2H), 7.18 – 6.94 (m, 2H), 3.02 (t, ^3J = 7.2 Hz, 1H), 2.83 (t, ^3J = 7.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.1 (C), 135.2 (C), 131.2 (C), 130.5 (C), 128.9 (2xCH), 128.9 (CH), 128.5 (CH), 128.3 (2xCH), 126.5 (CH), 125.9 (CH), 123.0 (CH), 113.8 (C), 30.1 (CH_2), 21.9 (CH_2).

5-methyl-1-phenyl-4,5-dihydro-3H-benzo[e]indazole (17b)



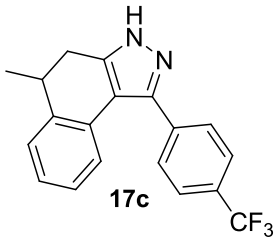
17b

Following the *general procedure,* from 4-methyl-*N*'-(3-methyl-2,3-dihydro-1*H*-inden-1-ylidene)benzenesulfonohydrazide (90.1 mg, 0.3 mmol) and phenylacetylene (68 µL, 0.6 mmol) were obtained 23.3 mg of **17b** (39 % isolated yield) as a light brown oil. **17b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.17.

HRMS (EI): calcd. for $C_{18}H_{16}N_2$: 260,1313; found 260,1310.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 2H), 7.51 – 7.43 (m, 3H), 7.34 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.28 (dd, ^{3}J = 4.0, 2.9 Hz, 1H), 7.14 (td, ^{3}J = 7.4, 1.5 Hz, 1H), 7.06 (td, ^{3}J = 7.5, 1.5 Hz, 1H), 3.24 – 3.10 (m, 1H), 2.89 (dd, ^{3}J = 15.5, 5.8 Hz, 1H), 2.58 (dd, ^{3}J = 15.5, 6.2 Hz, 1H), 1.32 (d, ^{3}J = 7.0 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.6 (C), 141.0 (C), 140.1 (C), 131.5 (C), 129.8 (C), 128.9 (2xCH), 128.7 (CH), 128.5 (2xCH), 127.1 (CH), 126.4 (CH), 126.0 (CH), 123.2 (CH), 113.1 (C), 34.5(CH), 29.2(CH_2), 20.7(CH_3).

5-methyl-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3*H*-benzo[*e*]indazole (17c)



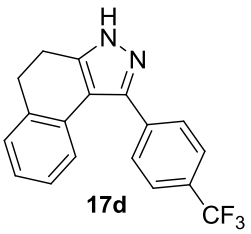
17c

Following the *general procedure,* from 4-methyl-*N*'-(3-methyl-2,3-dihydro-1*H*-inden-1-ylidene)benzenesulfonohydrazide (90.1 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (, 0.6 mmol) were obtained 43.3 mg of **17c** (45 % isolated yield) as a light yellow solid, m.p.= 103-108 °C. **17c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.26.

HRMS (EI): calcd. for $C_{19}H_{15}F_3N_2$: 328,1187; found 328.1190.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.79 (d, ^{3}J = 8.1 Hz, 2H), 7.70 (d, ^{3}J = 8.2 Hz, 2H), 7.38 – 7.22 (m, 2H), 7.13 (m, 2H) , 3.27 – 3.05 (m, 1H), 2.82 (dd, ^{3}J = 15.6, 5.9 Hz, 1H), 2.49 (dd, ^{3}J = 15.6, 6.4 Hz, 1H), 1.31 (d, ^{3}J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.6 (C), 141.9 (C), 139.9 (C), 136.1 (C), 130.7 (q, ^{2}J = 32.6 Hz, C), 129.4 (C), 129.0 (2xCH), 127.4 (CH), 126.7 (CH), 126.6 (CH), 125.9 (q, ^{3}J = 3.4 Hz, CH), 124.3 (q, ^{1}J = 272.3 Hz, C), 123.2 (CH), 113.9 (C), 34.4 (CH), 28.8 (CH_2), 20.6 (CH_3).

1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3H-benzo[*e*]indazole (17d)



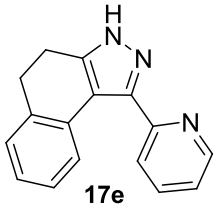
17d

Following the *general procedure,* from *N*'-(2,3-dihydro-1*H*-inden-1-ylidene)-4-methylbenzenesulfonohydrazide (90.1 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 53.7 mg of **17d** (57 % isolated yield) as a light brown solid, m.p.= 191-194 °C. **17d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.31.

HRMS (EI): calcd. for $C_{18}H_{13}F_3N_2$: 314,1031; found 314.1034.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.74 (d, ^3J = 8.1 Hz, 2H), 7.65 (d, ^3J = 8.2 Hz, 2H), 7.27 - 7.20 (m, 2H), 7.09 (app. pd, ^3J = 7.4, 1.6 Hz, 2H), 2.97 (t, ^3J = 7.3 Hz, 2H), 2.65 (t, ^3J = 7.3 Hz, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.5 (C), 142.0 (C), 136.0 (C), 134.9 (C), 130.5 (q, ^2J = 32.6 Hz, C), 130.2 (C), 128.8 (2xCH), 128.6 (CH), 126.7 (CH), 125.7 (q, ^3J = 3.7 Hz, 2xCH), 124.0 (q, ^1J = 272.1 Hz, C), 122.9 (CH), 114.4 (C), 29.9 (CH_2), 21.2 (CH_2).

1-(pyridin-2-yl)-4,5-dihydro-3*H*-benzo[*e*]indazole (17e)



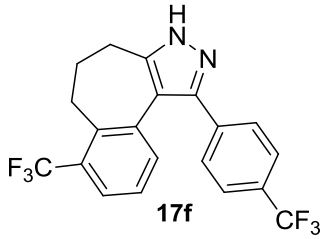
17e

Following the *general procedure,* from 4-methyl-*N*'-(3-methyl-2,3-dihydro-1*H*-inden-1-ylidene)benzenesulfonohydrazide (90.1 mg, 0.3 mmol) and 2-ethynylpyridine (62 µL, 0.6 mmol) were obtained 37.8 mg of **17e** (51 % isolated yield, 43 % following *one pot* procedure) as a light brown oil. **17e** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:1 as eluent. *Rf* (hexanes/ethyl acetate; 1:1) = 0.08.

HRMS (EI): calcd. for $C_{16}H_{13}N_3$: 247,1109; found 247,1102.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (bs, 1H), 8.74 (bs, 1H), 7.95 (bs, 1H), 7.78 (t, ^{3}J = 7.7 Hz, 1H), 7.68 – 7.59 (m, 1H), 7.37 – 7.24 (m, 2H), 7.22 – 7.11 (m, 2H), 3.08 – 2.99 (m, 2H), 2.98 – 2.81 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.5 (C), 149.6 (CH), 138.2 (C), 137.0 (CH), 136.2 (2xC), 130.6 (C), 128.6 (CH), 126.6 (CH), 126.3 (CH), 123.9 (CH), 123.1 (CH), 122.3 (CH), 114.6 (C), 30.4 (CH_2), 22.2 (CH_2).

7-(trifluoromethyl)-1-(4-(trifluoromethyl)phenyl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]pyrazole (17f)



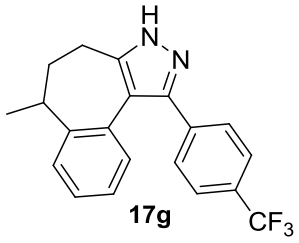
17f

Following the *general procedure,* from 4-methyl-*N*'-(5-(trifluoromethyl)-3,4-dihydronaphthalen-1(2*H*)-ylidene)benzenesulfonohydrazide (110.5 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 35.2 mg of **17f** (34 % isolated yield) as a colourless oil. **17f** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.45.

HRMS (EI): calcd. for $C_{20}H_{14}F_6N_2$: 396,0905; found 396,0905.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (bs, 1H), 7.94 (s, 4H), 7.69 (d, ^{3}J = 8.4 Hz, 1H), 7.58 (d, ^{3}J = 8.2 Hz, 1H), 7.35 (t, ^{3}J = 8.5 Hz, 1H), 3.01 (t, ^{3}J = 7.6 Hz, 2H), 2.55 (t, ^{3}J = 7.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.5 (C), 142.4 (C), 135.4 (C), 133.3 (C), 132.1 (C), 130.9 (q, ^{2}J = 32.8 Hz, C), 128.9 (q, ^{2}J = 32.6 Hz, C), 128.7 (2xCH), 127.9 (q, ^{1}J = 272.1 Hz, C),126.4 (2xCH), 125.9 (q, ^{3}J = 3.6 Hz, 2xCH), 123.4 (q, ^{3}J = 5.7 Hz, 2xCH), 120.3 (q, ^{1}J = 272.4 Hz, C), 113.7 (C), 25.64 (CH_2), 19.2 (CH_3).

6-methyl-1-(4-(trifluoromethyl)phenyl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]pyrazole (17g)



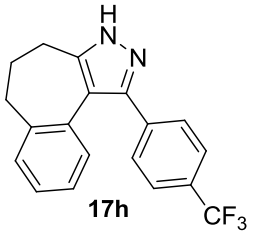
17g

Following the *general procedure,* from 4-methyl-*N*′-(4-methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)benzenesulfonohydrazide (98.5 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 66.8 mg of **17g** (65 % isolated yield) as a light yellow solid, m.p.= 103-108 °C. **17g** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.31.

HRMS (EI): calcd. for $C_{20}H_{17}F_3N_2$: 342,1344; found 342,1337.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (bs, 1H), 7.68 (d, ^3J = 8.1 Hz, 2H), 7.54 (d, ^3J = 8.2 Hz, 2H), 7.43 (d, ^3J = 7.7 Hz, 1H), 7.33 – 7.22 (m, 1H), 7.13 (td, ^3J = 7.5, 1.1 Hz, 1H), 7.01 (dd, ^3J = 7.6, 1.3 Hz, 1H), 3.16 – 2.93 (m, 1H), 2.75 – 2.56 (m, 1H), 2.51 – 2.37 (m, 1H), 2.27-2.24 (m, 2H), 1.93-1.82 (m, 2H), 1.40 (d, ^3J = 6.9 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.5 (C), 143.5 (C), 135.5 (C), 132.7 (C), 129.9 (q, ^2J = 32.6 Hz, C), 128.6 (C), 128.1 (2xCH), 126.7 (CH), 126.0 (CH), 125.8 (CH), 125.5 (q, ^3J = 3.4 Hz, 2xCH), 122.0 (q, ^1J = 272.1 Hz, C), 117.0 (C), 39.6 (CH_2), 34.6 (CH), 22.6 (CH_2), 19.2 (CH_3).

1-(4-(trifluoromethyl)phenyl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]pyrazole (17h)



17h

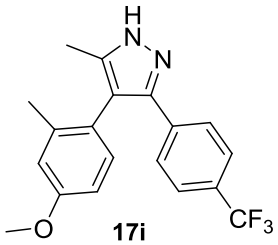
Following the *general procedure,* from *N*′-(3,4-dihydronaphthalen-1(*2H*)-ylidene)-4-methylbenzenesulfonohydrazide (94.3 mg, 0.3 mmol) and 1-ethynyl-4-

(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 78.8 mg of **17h** (80 % isolated yield) as a white solid, m.p.= 191-195 °C. **17h** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.22.

HRMS (EI): calcd. for $C_{19}H_{15}F_3N_2$: 328,1187; found 328,1186.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (bs, 1H), 7.64 (d, ^3J = 8.1 Hz, 2H), 7.53 (d, ^3J = 8.2 Hz, 2H), 7.30 (dd, ^3J = 7.5, 1.1 Hz, 1H), 7.18 (td, ^3J = 7.4, 1.5 Hz, 1H), 7.09 (td, ^3J = 7.5, 1.4 Hz, 1H), 6.99 (dd, ^3J = 7.6, 1.3 Hz, 1H), 2.74 (app. t, ^3J = 6.6 Hz, 2H), 2.57 (app. t, ^3J = 7.4 Hz, 2H), 2.27 – 2.03 (m, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.6 (C), 144.5 (C), 140.6 (C), 136.1 (C), 132.8 (C), 130.0 (q, ^2J = 32.7 Hz , C) 129.8 (CH), 128.8 (CH), 128.4 (2xCH), 126.8 (CH), 126.4 (CH), 125.6 (q, ^3J = 3.3 Hz, CH), 124.2 (q, ^1J = 271.8 Hz, C), 117.1 (C), 32.7 (CH_2), 30.4 (CH_2), 22.9 (CH_2).

8-methoxy-1-phenyl-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]pyrazole (17i)



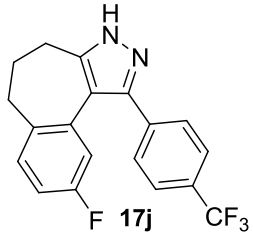
17i

Following the *one pot general procedure,* from 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (52.9 mg, 0.3 mmol) and phenylacetylene (, 0.6 mmol) were obtained 67.9 mg of **17i** (78 % isolated yield) as a light brown solid, m.p.= 142-144 °C. **17i** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.17.

HRMS (EI): calcd. for $C_{19}H_{18}N_2O$: 290,1419; found 290.1411.

^{1}H NMR (401 MHz, $CDCl_3$) δ 9.31 (bs, 1H), 7.52 - 7.50 (m, 2H), 7.32 - 7.31 (m, 3H), 6.97 (d, ^3J = 8.5 Hz, 1H), 6.85 (d, ^3J = 2.6 Hz, 1H), 6.64 (dd, ^3J = 8.5, 2.7 Hz, 1H), 3.81 (s, 3H), 2.72 - 2.69 (m, 2H), 2.63 – 2.59 (m, 2H), 2.24 – 2.03 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.1 (C), 148.2 (C), 143.2 (C), 142.1 (C), 131.5 (C), 129.8 (CH), 128.7 (2xCH), 128.2 (CH), 128.1 (2xCH), 125.7 (C), 116.3 (CH), 115.1 (CH), 111.5 (C), 55.3 (CH_3), 33.0 (CH_2), 30.3 (CH_2), 23.2 (CH_2).

9-fluoro-1-(4-(trifluoromethyl)phenyl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]pyrazole (17j)



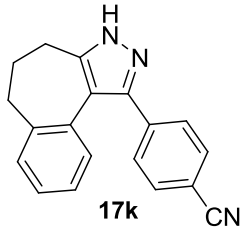
17j

Following the *general procedure,* from *N'*-(7-fluoro-3,4-dihydronaphthalen-1(*2H*)-ylidene)-4-methylbenzenesulfonohydrazide (99.7 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 66.5 mg of **17j** (64 % isolated yield) as a light yellow solid, m.p.= 190-194 °C. **17j** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.23.

HRMS (EI): calcd. for $C_{19}H_{14}F_4N_2$: 346,1093; found 346,1089.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (bs, 1H), 7.64 (d, ^3J = 8.3 Hz, 2H), 7.58 (d, ^3J = 8.4 Hz, 2H), 7.26 (dd, ^3J = 8.0, 5.5 Hz, 1H), 6.89 (td, ^3J = 8.5, 2.7 Hz, 1H), 6.69 (dd, ^3J = 9.8, 2.7 Hz, 1H), 2.72 (app. t, ^3J = 6.6 Hz, 2H), 2.55 (app. t, ^3J = 7.4 Hz, 2H), 2.29 – 2.01 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.3 (d, ^1J = 243.6 Hz, C), 146.5 (C), 144.6 (C), 136.1 (C), 135.3 (C), 134.3 (d, ^3J = 8.3 Hz, C), 130.9 (d, ^3J = 8.3 Hz, CH), 130.3 (q, ^2J = 32.6 Hz, C), 128.3 (2xCH), 125.6 (q, ^3J = 3.4 Hz, CH), 124.0 (q, ^1J = 277.4 Hz, C), 116.2 (C), 115.2 (d, ^2J = 22.0 Hz, CH), 113.4 (d, ^3J = 8.3 Hz, CH), 31.8 (CH_2), 30.2 (CH_2), 22.6 (CH_2).

4-(3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]pyrazol-1-yl)benzonitrile (17k)



17k

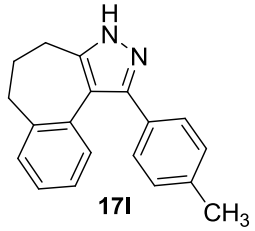
Following the *general procedure,* from *N'*-(3,4-dihydronaphthalen-1(*2H*)-ylidene)-4-methylbenzenesulfonohydrazide (94.3 mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6 mg, 0.6 mmol) were obtained 70.2 mg of **17k** (82 % isolated yield) as a yellow solid, m.p.= 154-158 °C. **17k** was purified by flash chromatography on

silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.11.

HRMS (EI): calcd. for $C_{19}H_{15}N_3$: 285,1266; found 285,1272.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (bs, 1H), 7.68 (d, ^3J = 8.5 Hz, 2H), 7.59 (d, ^3J = 8.4 Hz, 2H), 7.33 (dd, ^3J = 7.4, 0.9 Hz, 1H), 7.21 (td, ^3J = 7.4, 1.4 Hz, 2H), 7.12 (td, ^3J = 7.5, 1.3 Hz, 1H), 6.99 (dd, ^3J = 7.6, 1.1 Hz, 1H), 2.76 (t, ^3J = 6.6 Hz, 2H), 2.62 (t, ^3J = 7.4 Hz, 2H), 2.28 – 2.11 (m, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.1 (C), 144.3 (C), 140.4 (C), 137.2 (C), 132.3 (2xCH), 129.8 (CH), 128.7 (CH), 128.5 (2xCH), 126.9 (CH), 126.4 (CH), 118.7 (C), 117.2 (C), 111.4 (C), 32.5 (CH_2), 30.3 (CH_2), 22.6 (CH_2).

1-(*p*-tolyl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]pyrazole (17l)



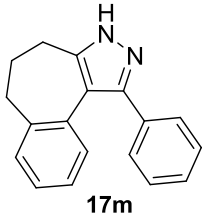
17l

Following the *general procedure,* from *N'*-(3,4-dihydronaphthalen-1(*2H*)-ylidene)-4-methylbenzenesulfonohydrazide (94.3 mg, 0.3 mmol) and *p*-tolylacetylene (67 µg, 0.6 mmol) were obtained 33.7 mg of **17k** (82 % isolated yield) as a colourless oil,. **17l** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.22.

HRMS (EI): calcd. for $C_{19}H_{18}N_2$: 274,1470; found 274,1477.

^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 2H), 7.39 – 7.31 (m, 3H), 7.21 – 7.12 (m, 2H), 7.11 – 7.06 (m, 2H), 6.72 (s, 1H), 2.76 (t, ^3J = 6.7 Hz, 1H), 2.66 (t, ^3J = 7.4 Hz, 1H), 2.23 (dd, ^3J = 13.9, 6.8 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.5, 133.3, 131.4, 129.4, 128.7, 128.2, 127.9, 126.3, 126.1, 32.6, 30.4, 23.2.

1-phenyl-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]pyrazole (17m)



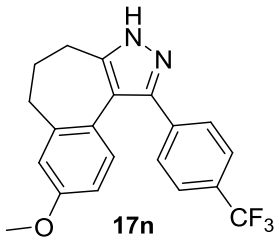
17m

Following the *general procedure,* from *N'*-(3,4-dihydronaphthalen-1(*2H*)-ylidene)-4-methylbenzenesulfonohydrazide (94.3 mg, 0.3 mmol) and phenylacetylene (67 µL, 0.6 mmol) were obtained 35.2 mg of **17m** (45 % isolated yield) as a light yellow oil. **17m** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.25.

HRMS (EI): calcd. for $C_{18}H_{16}N_2$: 260,1313; found 260,1303.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 2H), 7.35 – 7.27 (m, 4H), 7.20 – 7.10 (m, 1H), 7.10 – 6.99 (m, 2H), 2.74 (t, ^3J = 6.7 Hz, 2H), 2.64 (t, ^3J = 7.4 Hz, 2H), 2.26 – 2.07 (m, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.6 (C), 143.5 (C), 140.5 (2xC), 133.3 (C), 131.4 (C), 129.4 (CH), 128.7 (CH), 128.6 (2xCH), 128.2 (CH), 128.0 (2xCH), 126.3 (CH), 126.1 (CH), 32.6 (CH_2), 30.4 (CH_2), 23.1 (CH_2).

8-methoxy-1-(4-(trifluoromethyl)phenyl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]pyrazole (17n)



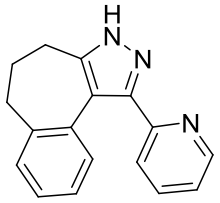
17n

Following the *general procedure,* from *N'*-(6-methoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)-4-methylbenzenesulfonohydrazide (103.3 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 64.5 mg of **17n** (60 % isolated yield) as a brown solid, m.p.= 89-93 °C. **17n** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.12.

HRMS (EI): calcd. for $C_{20}H_{17}F_3N_2O$: 358,1293; found 358,1291.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (bs, 1H), 7.55 (d, ^3J = 8.1 Hz, 2H), 7.43 (d, ^3J = 8.3 Hz, 2H), 6.82 (d, ^3J = 8.5 Hz, 1H), 6.77 (d, ^3J = 2.7 Hz, 1H), 6.56 (dd, ^3J = 8.5, 2.7 Hz, 1H), 3.73 (s, 3H), 2.61 (t, ^3J = 6.5 Hz, 2H), 2.47 (t, ^3J = 7.4 Hz, 2H), 2.16 – 1.98 (m, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.2 (C), 146.2 (C), 143.8 (C), 142.0 (C), 136.0 (C), 129.8 (q, C), 129.7 (CH), 128.2 (2xCH), 125.4 (q, CH), 124.8 (C), 124.1 (q, C), 116.7 (C), 115.2 (CH), 111.5 (CH), 55.2 (CH_3), 32.8 (CH_2), 30.0 (CH_2), 22.7 (CH_2).

1-(pyridin-2-yl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]pyrazole (17o)



17o

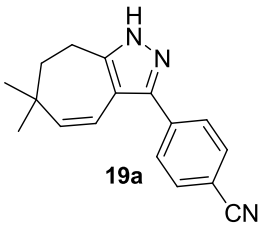
Following the *general procedure,* from 4-methyl-*N'*-(4-methyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)benzenesulfonohydrazide (98.5 mg, 0.3 mmol) and 2-ethynylpyridine (62 µL, 0.6 mmol) were obtained 52.5 mg of **17o** (67 % isolated yield) as a colourless oil. **17o** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 1:2 as eluent. *Rf* (hexanes/ethyl acetate; 1:2) = 0.17.

HRMS (EI): calcd. for $C_{17}H_{15}N_3$: 261,1266; found 261,1261.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (bs, 1H), 8.68 (bs, 1H), 7.70 (app. d, ^3J = 8.0 Hz, 1H), 7.60 (t, ^3J = 7.7 Hz, 1H), 7.42 – 7.32 (m, 2H), 7.31 – 7.17 (m, 3H), 2.75 – 2.69 (m, 4H), 2.25 (p, ^3J = 7.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.1 (C), 149.9 (CH), 149.1 (C), 141.3 (C), 137.7 (C), 137.1 (CH), 133. (C), 130.0 (CH), 129.1 (CH), 127.4 (CH), 126.6 (CH), 123.3 (CH), 121.4 (CH), 117.9 (C), 32.7 (CH_2), 31.3 (CH_2), 23.9 (CH_2).

E.9. Characterization data for compounds 19 and 20

4-(6,6-dimethyl-1,6,7,8-tetrahydrocyclohepta[c]pyrazol-3-yl)benzonitrile (19a)



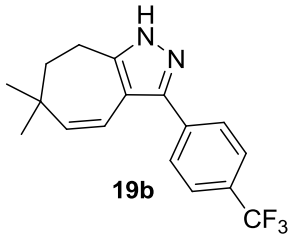
19a

Following the *general procedure,* from *N*'-(4,4-dimethylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfonohydrazide (79.0 mg, 0.3 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (101 µL, 0.6 mmol) were obtained 56.1 mg of **19a** (61 % isolated yield) as a light yellow solid, m.p.= 137-140 °C. **19a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.42.

HRMS (EI): calcd. for $C_{17}H_{17}F_3N_2$: 306,1344; found 306,1340.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (bs, 1H), 7.61 (s, 4H), 6.12 (d, ^3J = 11.9 Hz, 2H), 5.43 (d, ^3J = 11.9 Hz, 2H), 2.65 – 2.61 (m, 2H), 1.74 – 1.51 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.7 (C), 146.1 (C), 138.4 (CH), 136.0 (C), 129.8 (q, ^2J = 32.4 Hz, C), 128.9 (2xCH), 125.4 (q, ^3J = 3.7 Hz, 2xCH), 124.1 (q, ^1J = 272.2 Hz, C), 114.8 (CH), 114.3 (C), 37.4 (C), 35.8 (CH_2), 30.2 (2xCH_3), 22.3 (CH_2)

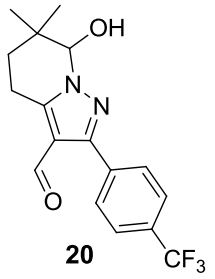
6,6-dimethyl-3-(4-(trifluoromethyl)phenyl)-1,6,7,8-tetrahydrocyclohepta[*c*]pyrazole (19b)



19b

Following the *general procedure,* from *N*'-(4,4-dimethylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfonohydrazide (79.0 mg, 0.3 mmol) and 4-ethynylbenzonitrile (72.6 mg, 0.6 mmol) were obtained 66.4 mg of **19b** (84 % isolated yield) as a yellow solid, m.p.= 137-140 °C. **19b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. *Rf* (hexanes/ethyl acetate; 2:1) = 0.17.
HRMS (EI): calcd. for $C_{17}H_{17}N_3$: 263,1422; found 263,1415.
^{1}H NMR (401 MHz, $CDCl_3$) δ 7.71 (d, ^3J = 8.4 Hz, 2H), 7.67 (d, ^3J = 8.4 Hz, 2H), 7.28 (bs, 1H), 6.12 (d, ^3J = 12.0 Hz, 1H), 5.53 (d, ^3J = 12.0 Hz, 1H), 2.95 – 2.87 (m, 2H), 1.84 – 1.71 (m, 2H), 1.13 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.7 (C), 145.8 (C), 139.0 (CH), 137.2 (C), 132.3 (2xCH), 129.0 (CH), 118.7 (C), 114.5 (CH), 111.4 (C), 37.4 (C), 35.8 (CH_2), 30.2 (2xCH_3), 22.4 (CH_2).

4-(4-formyl-7-hydroxy-6,6-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridin-2-yl)benzonitrile (20)



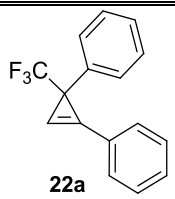
20

A 250 ml schlenk under inert atmosphere was charged with 4-(6,6-dimethyl-1,6,7,8-tetrahydrocyclohepta[c]pyrazol-3-yl)benzonitrile (**19b**) and 40 ml dichloromethane. The system was cooled at -78 °C and ozone is bubbled through the solution. The reaction was monitored by TLC. After 20 min, 2 ml of SMe_2 was added and was cooled down to room temperature. The reaction was extracted with (3x30 ml) of water and the organic phase was washed with brine, dried over $MgSO_4$ and filtered. Solvent was removed under reduced pressure. Purifiation of the residue by flash chromatography on silica gel (hexanes/ethyl acetate = 2:1, *Rf* = 0.29) afforded **20** as a white solid, (m.p.= 183-187 °C, 139.6 mg, 65 %).

HRMS (EI): calcd. for $C_{17}H_{17}N_3O_2$: 295,1321; found 295,1327.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.80 (d, ^3J = 8.4 Hz, 2H), 7.75 (d, ^3J = 8.4 Hz, 2H), 5.26 (s, 1H), 3.26 (ddd, ^3J = 19.0, 6.3, 3.8 Hz, 1H), 3.03 (ddd, ^3J = 19.0, 9.8, 6.7 Hz, 1H), 2.03 (ddd, ^3J = 13.9, 9.8, 6.4 Hz, 1H), 1.60 (ddd, ^3J = 13.8, 6.6, 3.8 Hz, 1H), 1.02 (s, 3H), 0.99 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.9 (CHO), 152.8 (C), 145.7 (C), 136.1 (C), 132.5 (2xCH), 129.8(2xCH), 118.6 (C), 116.8 (C), 113.0 (C), 85.9 (CH), 34.9 (C), 27.8 (CH_2), 24.0 (CH_3), 23.6 (CH_3), 20.5 (CH_2).

E.10. Characterization data for compounds 22

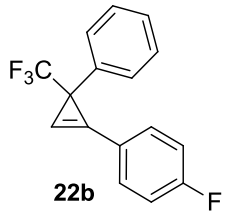
(1-(trifluoromethyl)cycloprop-2-ene-1,2-diyl)dibenzene (22a)



22a

Following the *general procedure* but employing C_6F_6 as solvent*,* from 4-methyl-*N*'-(2,2,2-trifluoro-1-phenylethylidene)benzenesulfonohydrazide (120.7 mg, 0.3 mmol) and phenylacetylene (68µ mg, 0.6 mmol) were obtained 31.2 mg of **22a** (40 % isolated yield) as a red oil. **22a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. *Rf* (hexanes/ethyl acetate; 10:1) = 0.34.
^{1}H NMR (401 MHz, $CDCl_3$) δ 8.14 (dd, ^{3}J = 7.8, 1.7 Hz, 2H), 7.79 – 7.77 (m, 2H), 7.56 – 7.50 (m, 3H), 7.47 – 7.44 (m, 3H), 7.39 (bs, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.4, 159.6, 151.5, 133.4, 132.7, 131.6, 130.4, 129.8, 129.6, 129.3, 129.2, 129.1, 128.8, 128.3, 128.3, 127.7, 125.2, 124.1, 122.4. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -69.8

1-fluoro-4-(3-phenyl-3-(trifluoromethyl)cycloprop-1-en-1-yl)benzene (22b)



22b

Following the *general procedure* but employing C_6F_6 as solvent*,* from 4-methyl-*N*'-(2,2,2-trifluoro-1-phenylethylidene)benzenesulfonohydrazide (120.7 mg, 0.3 mmol) and 4-fluorophenylacetylene (68µ mg, 0.6 mmol) were obtained 41.8 mg of **22b** (75 % isolated yield) as a red oil. **22b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 20:1 as eluent. *Rf* (hexanes/ethyl acetate; 20:1) = 0.36.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 2H), 7.51 – 7.46 (m, 3H), 7.42 (dd, ^{3}J = 8.4, 5.4 Hz, 2H), 7.19 – 7.16 (m, 1H), 7.05 – 6.96 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.4, 159.6, 151.5, 133.4, 132.7, 131.6, 130.4, 129.8, 129.6, 129.3, 129.2, 129.1, 128.8, 128.3, 128.3, 127.7, 125.2, 124.1, 122.4.

PARTE B: SÍNTESIS DE PIRAZOLES QUIRALES A TRAVÉS DE UNA SECUENCIA DE CICLOADICIÓN 1,3-DIPOLAR Y UN REAGRUPAMIENTO [1,5]-SIGMATRÓPICO CON MIGRACIÓN DE UN GRUPO ESTEREOGÉNICO CON RETENCIÓN DE LA CONFIGURACIÓN.

E.11. Characterization dat Synthesis and characterization data for ketones 25 and *N*-tosylhydrazones 26, 30, 8, 10 and 36.

E.11.1. Ketones 25:

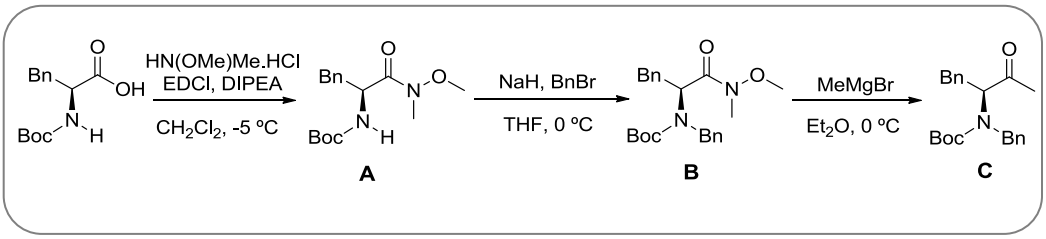
All of the chiral ketones were synthesized from the corresponding carboxylic acid. Therefore, the Weinreb amide was firstly prepared from the carboxylic acid followed by an alkylation of this amide employing different Grignard reagents. The general procedure was described in literature.[4]

Compounds **25a**[250] (R^1 = Me), **25b**[251] (R^1 = Et) and **25c**[252] (R^1 = Ph) exhibit physical and spectroscopic data in agreement with those reported. However, the chromatographic data of HPLC to confirm the enantiomeric excess and the employed conditions are indicated in Section 9.

E.11.2. Tosylhydrazones 26, 30 and 36:

These compounds were prepared following the procedure described in literature.[253,254] The HPLC chromatographic data to confirm the enantiomeric purity of carbonyl compound 6 is indicated in Section 9.

E.11.3. Synthesis and characterization data for ketone and N-tosylhydrazone 32:



[250] C. Rodríguez, G. de Gonzalo, M. W. Fraaije, V. Gotor, *Tetrahedron Asym.* **2007**, *18*, 1338.
[251] A. H. Cherney, N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 7442.
[252] P. M. Lundin, J. Esquivias, G. C. Fu, *Angew. Chem. Int. Ed.* **2008**, *48*, 154.
[253] J. Barluenga, M. Escribano, F. Aznar, C. Valdés, *Angew. Chem. Int. Ed*. **2010**, *49*, 6856 – 6859.
[254] D.P. Ojha, K. R. Prabhu, *J. Org. Chem.* **2013**, *78*, 12136.

- ***Procedure for the synthesis of the Weinreb amide (B):***

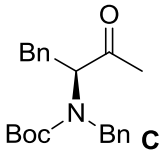
To a solution of *L*-Boc-phenylalanine (2.65 g, 10 mmol) in 70 mL of CH_2Cl_2 at -5 °C, HCl-HN(OMe)Me (0.99 g, 10 mmol) and ethyldiisopylamine (1.8 mL, 10 mmol) are added. Then, a solution of EDCl (1.96 g, 10 mmol) in 20mL CH_2Cl_2 is added dropwise. After 1 h at -5 °C, the mixture is washed with 1M HCl (2x30 mL). The organic layers are collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the Weinreb amide **A** (2.93 g, 95%). The crude residue is the essentially pure Weinreb amide , which is not purified and can be used for the next step.

For the corresponding benzylation of the Weinreb amide, to a suspension of NaH (0.45g, 18.8 mmol) in dry THF (75 mL), a solution of **A** in dry THF was added dropwise with stirring. The suspension was stirred at r.t. for 1h. Benzyl bromide (1.4 mL, 1.17 mmol) was added dropwise at 25 °C and stirring continued for 24 h. After addition of H_2O (dropwise), the mixture was acidified with HCl until pH = 2 in the aqueous layer and extracted with CH_2Cl_2 (3 x 100mL). The combined organic layers were washed with 1M HCl, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (Hexanes/ethyl acetate: 2:1, *Rf* = 0.19). It was obtained 1.59 g of **B** (43% of isolated yield).[255]

- ***Procedure for the synthesis of the methyl ketone (C):***

To a solution of **B** (0.74 g, 1.9 mmol) in 20 mL of Et_2O at 0 °C, is added dropwise, methylmagnesium bromide (1.9 mL of a 3 M solution in Et_2O, 5.7 mmol). A white precipitate quickly appears. The mixture is stirred at 0 °C for 1 h and then quenched with a NH_4Cl aqueous saturated solution (2x100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. It was obtained 0.6 g of **C** (91 % of isolated yield).

(*S*)-*tert*-butyl benzyl(3-oxo-1-phenylbutan-2-yl)carbamate (C)



C

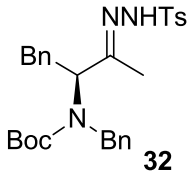
Yield: 91 %, Colourless oil.

[255] The spectroscopic data in agreement with those reported. T. L. Harris, R. J. Worthington, C. Melander, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4516.

HRMS (EI): calcd. for $C_{22}H_{27}NO_3$: 353,1991; found 353,1996.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H), 7.23 – 7.10 (m, 5H), {4.82 (d, ^3J = 14.6 Hz, 0.6H) + 4.54 (d, ^3J = 15.1 Hz, 0.4H)}, {3.98 (dd, ^3J = 9.3, 5.4 Hz, 0.4H) + 3.65 (dd, ^3J = 9.4, 4.7 Hz, 0.6H)}, 3.37 (dd, ^3J = 14.2, 4.6 Hz, 1H), 3.10 (d, ^3J = 14.6 Hz, 1H), 2.94 (dd, ^3J = 13.9, 9.4 Hz, 1H), {1.84 (s, 1H) + 1.75 (s, 2H)}, 1.52 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.2 (C), 154.8 (C), 138.8 (C), {137.5 (C) + 137.1 (C)}, {129.6 (2xCH) + 129.5 (2xCH)}, 129.4 (2xCH), 128.7 (2xCH), {128.6 (2xCH) + 128.5 (2xCH)}, {127.9 (CH) + 127.6 (CH)}, 126.6 (CH), {81.7 (C) + 80.1 (C)}, {67.7 (CH) + 67.3 (CH)}, 52.0 (CH_2), {35.0 (CH_2) + 34.1 (CH_2)}, {28.4 (3xCH_3) + 28.1 (3xCH_3)}, {26.9 (CH_3) + 26.41(CH_3)}.
$[\alpha]_D^{15}$ = -103.9 (c = 0.13 in CH_2Cl_2).

(*S*)-*tert*-butyl benzyl(1-phenyl-3-(2-tosylhydrazono)butan-2-yl)carbamate (32)



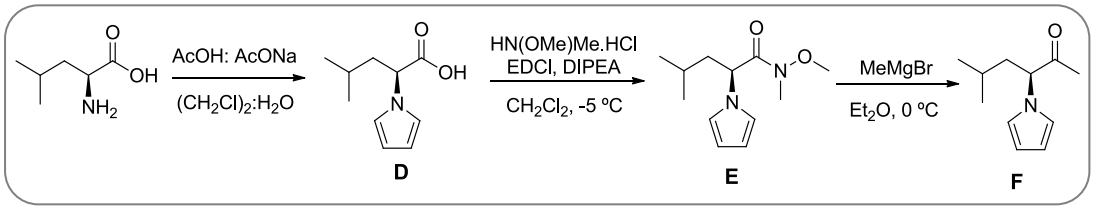
32

Yield: 34 %, Colourless oil. R_f 0.35 (Hexanes/Ethyl acetate, 2:1).

HRMS (EI): calcd. for $C_{29}H_{35}N_3O_4$: 521,2348; found 521,2341.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, ^3J = 7.3 Hz, 2H), 7.45 – 7.35 (m, 2H), 7.26 – 7.02 (m, 8H) 6.90 – 6.81 (m, 2H), {5.13 (bs, 0.5H) + 4.67 (bs, 0.5H)}, {4.39 (s, 0.5H) + 4.36 (s, 0.5H)}, 3.99 – 3.78 (m, 1H), 3.21 (bs, 1H), 2.95 (dd, ^3J = 14.0, 8.9 Hz, 1H), 2.48 (s, 3H), {1.34 (s, 4.5H) + 1.28 (s, 4.5H)}, {1.24 (s, 1.5H) + 1.10 (s, 1.5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.8 (C), 155.1 (C), 144.4 (C), 138.9 (C), 138.6 (C), 135.4 (C), 129.6 (2xCH), 129.5 (2xCH), 129.4 (CH), 129.0 (CH), 128.3 (3xCH), 128.1 (3xCH), 127.1 (CH), 126.1 (CH), 80.4 (C), {62.8 (CH) + 61.0 (CH)}, {46.6 (CH_2) + 46.5 (CH_2)}, 34.7 (CH_2), 28.1 (CH_3), 21.7 (CH_3), {15.1 (CH_3) + 14.6 (CH_3)}.
$[\alpha]_D^{15}$ = -11.0 (c = 0.13 in CH_2Cl_2)

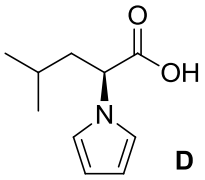
E.11.4. Synthesis and characterization data for ketone and N-tosylhydrazone 34:



- Procedure for the synthesis of pyrrol derivative D:

L-Leucine (2.6 g, 20 mmol) and NaOAc (1.7 g, 20.5 mmol) were taken in H_2O (9.3 mL), AcOH (3.1 mL) and 1,2-dichloromethane (12.4 mL) and heated at 90 °C for 5 min. To this solution 2,5-dimethoxytetrahydrofuran (2.7 mL, 20.2 mmol) was added and heated at 90 °C for 18 hours. The reaction was allowed to cool to room temperature and diluted with ethyl acetate (50 mL). The organic layer was washed with 15 mL of satured aq. NaCl and 40 mL of H_2O and dried over anhydrous Na_2SO_4. The reaction mixture was gel-filtered through a plug of silica gel with hexanes/ethyl acetate (4:1) and the solution was concentrated to give the pirrol derivative.

(*S*)-4-methyl-2-(1*H*-pyrrol-1-yl)pentanoic acid (D)



D

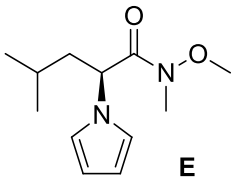
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (app. t, ^3J = 2.1 Hz, 2H), 6.22 (app. t, ^3J = 2.1 Hz, 2H), 4.71 (dd, ^3J = 10.1, 5.7 Hz, 1H), 2.16 – 1.86 (m, 2H), 1.58 – 1.37 (m, 1H), 1.00 – 0.85 (m, 6H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.6 (C), 120.1 (2xCH), 108.7 (2xCH), 59.87 (CH), 41.1 (CH_2), 24.6 (CH), 22.7 (CH_3), 21.5 (CH_3).
$[\alpha]_D^{15}$ = -37.0 (c = 0.32 in CH_2Cl_2)

The spectroscopy data are in agreement with those reported in *J. Am. Chem. Soc.* **2013**, *135*, 9608.

- Procedure for the synthesis of the methyl ketone F:

The corresponding methyl ketone was prepared following the previously explained procedure. To a solution of (*S*)-4-methyl-2-(1*H*-pyrrol-1-yl)pentanoic acid (3.39 g, 12.78 mmol) in 90 mL of CH_2Cl_2 at -5 °C, HCl-HN(OMe)Me (1.27 g, 12.78 mmol) and ethyldiisopylamine (2.3 mL, 10 mmol) are added. Then, a solution of EDCl (2.50 g, 12.78 mmol) in 20mL CH_2Cl_2 is added dropwise. After 1 h at -5 °C, the mixture is washed with 1M HCl (2x60 mL). The organic layers are collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the Weinreb amide **E** (3.44 g, 97%). The crude residue is the essentially pure Weinreb amide, which is not purified and can be used for the next step. To a solution of **E** (3.44 g, 15.3 mmol) in 200 mL of Et_2O at 0 °C, methylmagnesium bromide (15.3 mL of a 3 M solution in Et_2O, 45.9 mmol) is added dropwise. A white precipitate quickly appears. The mixture is stirred at 0 °C for 1 h and then quenched with a NH_4Cl aqueous saturated solution (2x200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. It was obtained 2.18 g of **F** as a yellow oil (80 % of isolated yield).

(*S*)-*N*-methoxy-*N*,4-dimethyl-2-(1*H*-pyrrol-1-yl)pentanamide (E)

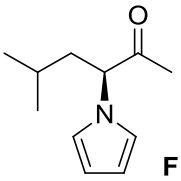


E

HRMS (EI): calcd. for $C_{12}H_{20}N_2O_2$: 224.1525; found 224.1499.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (app. t, ^3J = 2.1 Hz, 1H), 6.16 (app. t, ^3J = 2.1 Hz, 2H), 5.15 (dd, ^3J = 9.2, 5.9 Hz, 1H), 3.53 (s, 3H), 3.21 (s, 3H), 2.04 – 1.74 (m, 2H), 1.46 – 1.28(m, 1H), 0.96 (d, ^3J = 6.6 Hz, 3H), 0.91 (d, ^3J = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8 (C), 120.0 (2xCH), 108.2 (2xCH), 61.3 (CH), 55.9 (CH_3), 41.8 (CH_2), 32.2 (CH_3) 24.4 (CH), 22.9 (CH_3), 21.9 (CH_3).
$[\alpha]_D^{15}$ = -29.0 (c = 0.21 in CH_2Cl_2).

(*S*)-5-methyl-3-(1*H*-pyrrol-1-yl)hexan-2-one (F)

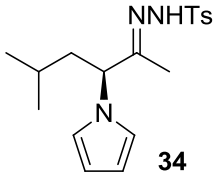


F

HRMS (EI): calcd. for $C_{11}H_{17}N_2$: 224.1525; found 224.1499.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (t, ^3J = 2.1 Hz, 2H), 6.24 (t, ^3J = 2.1 Hz, 2H), 4.53 (dd, ^3J = 9.5, 6.1 Hz, 1H), 1.99 (s, 3H), 1.94 – 1.83 (m, 2H), 1.56 – 1.34 (m, 1H), 0.94 (d, ^3J = 6.4 Hz, 3H), 0.92 (d, ^3J = 6.6 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 206.5 (C), 120.0 (2xCH), 109.2 (2xCH), 66.6 (CH), 39.1 (CH_2), 26.1 (CH), 24.5 (CH_3), 23.1 (CH_3), 21.5 (CH_3).
$[\alpha]_D^{15}$ = -36.0 (c = 0.18 in CH_2Cl_2)

(*S*)-4-methyl-*N*'-(5-methyl-3-(1*H*-pyrrol-1-yl)hexan-2-ylidene)benzenesulfonohydrazide (34)



34

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, ^3J = 8.3 Hz, 2H), 7.48 (s, 1H), 7.35 (d, ^3J = 8.1 Hz, 2H), 6.50 (app. t, ^3J = 2.1 Hz, 2H), 6.11 (app. t, ^3J = 2.1 Hz, 2H), 4.56 (app. t, ^3J = 7.7 Hz, 1H), 2.48 (s, 3H), 1.87 – 1.71 (m, 2H), 1.57 (s, 3H), 1.35 – 1.16 (m, 1H), 0.88 (d, ^3J = 6.6 Hz, 3H), 0.84 (d, ^3J = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.0 (C), 144.3 (C), 135.1 (C), 129.6 (2xCH), 128.1 (2xCH), 119.4 (2xCH), 108.5 (2xCH), 62.8 (CH), 40.1 (CH_2), 24.4 (CH_3), 22.6 (CH), 22.3 (CH_3), 21.6 (CH_3), 12.1 (CH_3).
$[\alpha]_D^{15}$ = -5.0 (c = 0.11 in CH_2Cl_2)

E.12. Experimental procedures

E.12.1 General procedure *A* for the synthesis of chiral pirazoles from tosylhydrazones 25 and terminal alkynes 11 using conventional heating.

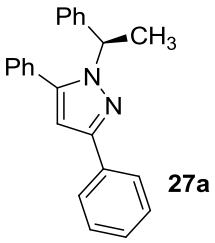
A reaction tube was charged with the tosylhydrazone **3** (0.3 mmol), the terminal alkyne (0.6 mmol), potassium carbonate (83 mg, 0.6 mmol) and dioxane (2.4 ml). The system was heated at 110 °C with stirring and reflux for 24 hours. The reaction was monitored by GCMS. When the reaction was completed, the reaction crude was cooled down to room temperature, the solvent was eliminated, and a saturated solution of $NaHCO_3$ and dichloromethane were added and the layers were separated. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with $NaHCO_3$, brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Finally, products were purified by flash chromatography on silica gel.

E.12.2. General procedure *B* for the synthesis of chiral pirazoles from tosylhydrazones 30, 32, 34, 26 and terminal alkynes 11 using conventional heating.

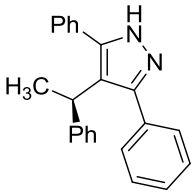
A reaction tube was charged with the tosylhydrazone **3** (0.3 mmol), the terminal alkynes (0.6 mmol), potassium carbonate (83 mg, 0.6 mmol) or cesium carbonate (196 mg, 0.6 mmol), dioxane or acetonitrile (2.4 ml). The system was heated at 110 °C with stirring and reflux for 24 hours. The reaction was monitored by GCMS. When the reaction was completed, the crude reaction was cooled down to room temperature. Then, a saturated solution of NH_4Cl and dichloromethane were added and the layers were separated. The aqueous phase was extracted two times with dichloromethane. The combined organic layers were washed with water, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. Finally, the products were purified by flash chromatography on silica gel.

E.13. Characterization data for compounds 27, 28

(*R*)-3,5-diphenyl-1-(1-phenylethyl)-1*H*-pyrazole (27a) and **(*R*)-3,5-diphenyl-4-(1-phenylethyl)-1*H*-pyrazole (28a)**



27a



28a

Following the *general procedure A,* from (*R*)-*N'*-(1,2-diphenylpropylidene)-4-methylbenzenesulfonohydrazide (113.5 mg, 0.3 mmol) and phenylacetylene (67 µL, 0.6 mmol) were obtained a 6:1 (**27a:28a**) mixture of separable regioisomers. **27a** and **28a** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 and 2:1 as eluent. *Rf* ***27a*** (hexanes/ethyl acetate; 10:1) = 0.44. *Rf* ***28a*** (hexanes/ethyl acetate; 2:1) = 0.49. It was obtained 49 mg of **27a** (51 % isolated yield) as a white solid, m.p.= 78 - 79 °C and 10 mg of **28a** (9% of isolated yield) as a light yellow oil. (Total yield **27a** + **28a**: 60%)

- ***Regioisomer 27a:***

HRMS (EI): calcd. for $C_{23}H_{20}N_2$: 324,1626; found 324,1624.

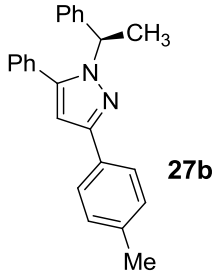
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.82 (m, 2H), 7.36 – 7.31 (m, 5H), 7.25 – 7.14 (m, 8H), 6.53 (s, 1H), 5.43 (q, ^3J = 7.0 Hz, 1H), 1.86 (d, ^3J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) 150.5 (C), 145.2 (C), 143.3 (C), 134.0 (C), 131.1 (C), 129.4 (2xCH), 128.7 (4xCH), 128.6 (3xCH), 127.6 (CH), 127.4 (CH), 126.4 (2xCH), 125.8 (2xCH), 103.6 (CH), 58.0 (CH), 22.8 (CH_3).
ee > 99% [Chiralcel IC column, *n*-hexane/ethanol = 99/1, 0.1 mL/min, λ_{max} 252.0 nm; t_R = 58.4 min (<0.5%) and 61.0 min (>99%).
$[\alpha]_D^{24}$ = -149.3 (c = 0.13 in CH_2Cl_2)

- ***Regioisomer 28a:***

HRMS (EI): calcd. for $C_{23}H_{20}N_2$: 324,1626; found 324,1631.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.08 (m, 15H), 4.40 (q, ^3J = 7.3 Hz, 1H), 3.97 (bs, 1H), 1.42 (d, ^3J = 7.4 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$)

(*R*)-5-phenyl-1-(1-phenylethyl)-3-(*p*-tolyl)-1*H*-pyrazole (27b)



27b

Following the *general procedure A*, from (*R*)-*N'*-(1,2-diphenylpropylidene)-4-methylbenzenesulfonohydrazide (113.5 mg, 0.3 mmol) and *p*-tolylacetylene (68 µL, 0.6 mmol) were obtained a 7:1 (**27b:28b**) mixture of separable regioisomers. **27b** and **28b** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 and 2:1 as eluent. *Rf **27b*** (hexanes/ethyl acetate; 5:1) = 0.36. *Rf **28b*** (hexanes/ethyl acetate; 2:1) = 0.36. It was obtained 57 mg of **27b** (54 % isolated yield) as a light yellow solid, m.p.= 81 - 83 °C and 9 mg of **28b** (10% of isolated yield) as a colouless oil. (Total yield **27b** + **28b**: 64%)

- ***Regioisomer 27b:***

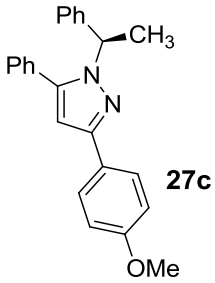
HRMS (EI): calcd. for $C_{24}H_{22}N_2$: 338,1783; found 338,1786.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, ^3J = 8.1 Hz, 1H), 7.43 (m, 1H), 7.37 – 7.19 (m, 3H), 6.61 (s, 1H), 5.54 (q, *J* = 7.0 Hz, 1H), 2.42 (s, 1H), 1.97 (d, *J* = 7.0 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.4 (C), 145.0 (C), 143.2 (C), 137.2 (C), 131.1 (C), 131.0 (C), 129.3 (2xCH), 129.2 (2xCH), 128.5 (3xCH), 128.5 (2xCH), 127.2 (CH), 126.3 (2xCH), 125.6 (2xCH), 103.3 (CH), 57.9 (CH), 22.6 (CH_3), 21.3 (CH_3).

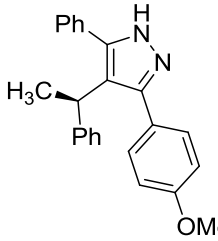
ee > 99% [Chiralcel IC column, *n*-hexane/ethanol = 99.7/0.3, 0.1 mL/min, λ_{max} 257.8 nm; t_R = 66.4 min (<0.5 %) and 75.5 min (>99%).

$[\alpha]_D^{15}$ = -146.67 (c = 0.11 in CH_2Cl_2)

(*R*)-3-(4-methoxyphenyl)-5-phenyl-1-(1-phenylethyl)-1*H*-pyrazole (27c) and **(*R*)-3-(4-methoxyphenyl)-5-phenyl-4-(1-phenylethyl)-1*H*-pyrazole (28c)**



27c



28c

Following the *general procedure A*, from (*R*)-*N'*-(1,2-diphenylpropylidene)-4-methylbenzenesulfonohydrazide (113.5 mg, 0.3 mmol) and 4-methoxyphenylacetylene (79 µL, 0.6 mmol) were obtained a 15:1 (**27c: 28c**) mixture of separable regioisomers. **27c** and **28c** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 and 2:1 as eluent. *Rf* **27c** (hexanes/ethyl acetate; 5:1) = 0.36. *Rf* **28c** (hexanes/ethyl acetate; 2:1) = 0.24. It was obtained 69 mg of **27c** (65 % isolated yield) as a white solid, m.p.= 94 - 98 °C and 3 mg of **28c** (3% of isolated yield) as a colorless oil. (Total yield **27c** + **28c**: 68%)

- ***Regioisomer 4c:***

HRMS (EI): calcd. for $C_{24}H_{22}N_2O$: 354,1732; found 354,1734.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, ^3J = 8.8 Hz, 1H), 7.33 – 7.31 (m, 3H), 7.27 – 7.06 (m, 7H), 6.88 (d, ^3J = 8.8 Hz, 2H), 6.45 (s, 1H), 5.42 (q, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 1.86 (d, ^3J = 7.0 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.4 (C), 150.3 (C), 145.1 (C), 143.3 (C), 131.2 (2xC), 129.3 (2xCH), 128.7 (2xCH), 128.6 (2xCH), 127.3 (CH), 127.1 (2xCH) , 126.9 (2xCH) , 126.4 (2xCH), 114.1 (CH), 103.1 (CH), 57.9 (CH), 55.5 (CH_3), 22.7 (CH_3).
ee = 93% [Chiralcel IC column, *n*-hexane/ethanol = 97/3, 0.3 mL/min, λ_{max} 259.9 nm; t_R = 22.0 min (96%) and 24.4 min (3%).
$[\alpha]_D^{15}$ = -121.5 (c = 0.07 in CH_2Cl_2)

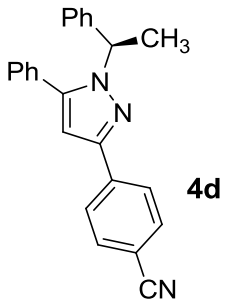
- ***Regioisomer 5c:***

HRMS (EI): calcd. for $C_{24}H_{22}N_2O$: 354,1732; found 354,1736.

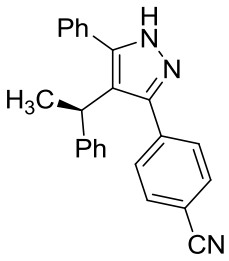
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 9H), 7.24 – 7.21 (m, 3H), 6.85 (d, ^3J = 8.7 Hz, 2H), 4.40 (q, ^3J = 7.0 Hz, 1H), 3.83 (s, 3H), 1.44 (d, ^3J = 7.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.7 (C), 146.1 (C), 132.2 (C), 130.0 (2xC), 128.9 (C), 128.8 (2xCH), 128.4

(2xCH), 128.2 (2xCH), 127.4 (2xCH), 127.0 (CH) , 125.8 (CH) , 125.6 (CH), 124.4 (C), 124.2 (C), 114.3 (C), 113.8 (CH), 55.3 (CH_3), 33.6 (CH), 22.7 (CH_3).

(*R*)-4-(5-phenyl-1-(1-phenylethyl)-1*H*-pyrazol-3-yl)benzonitrile (4d) and **(*R*)-4-(5-phenyl-4-(1-phenylethyl)-1*H*-pyrazol-3-yl)benzonitrile (5d)**



4d



5d

Following the *general procedure A*, from (*R*)-*N'*-(1,2-diphenylpropylidene)-4-methylbenzenesulfonohydrazide (113.5 mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6 mg, 0.6 mmol) were obtained a 5:1 (**4d:5d**) mixture of separable regioisomers. **4d** and **5d** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 and 2:1 as eluent. *Rf* **4d** (hexanes/ethyl acetate; 5:1) = 0.32. *Rf* **5d** (hexanes/ethyl acetate; 2:1) = 0.25. It was obtained 74 mg of **4d** (71 % isolated yield) as a white solid, m.p.= 116 - 118 °C and 14 mg of **5d** (13% of isolated yield) as a light brown solid, m.p. = 164 - 116 °C. (Total yield **4d** + **5d**: 84%)

- ***Regioisomer 4d:***

HRMS (EI): calcd. for $C_{24}H_{19}N_3$: 349,1579; found 349,1570.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, ^3J = 8.6 Hz, 2H), 7.69 (d, ^3J = 8.6 Hz, 2H), 7.46 – 7.38 (m, 3H), 7.34 – 7.26 (m, 4H), 7.23 – 7.20 (m, 3H), 6.65 (s, 1H), 5.52 (q, ^3J = 7.0 Hz, 1H), 1.93 (d, ^3J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.5 (C), 145.7 (C), 142.7 (C), 138.4 (C), 132.6 (2xCH), 130.5 (C), 129.4 (2xCH), 129.0 (CH), 128.8 (2xCH), 128.7 (2xCH), 127.6 (CH), 126.4 (2xCH), 126.1 (2xCH), 119.4 (C), 110.7 (C), 104.2 (CH), 58.3 (CH), 22.7 (CH_3).
ee = 98% [Chiralcel IA column, *n*-hexane/isopropanol = 95/5, 0.5 mL/min, λ_{max} 282.9 nm; t_R = 42.7 min (1%) and 61.9 min (99%).
$[\alpha]_D^{15}$ = -53.7 (c = 0.08 in CH_2Cl_2)

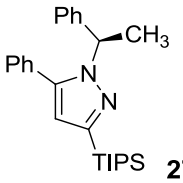
- ***Regioisomer 5d:***

HRMS (EI): calcd. for $C_{24}H_{19}N_3$: 349,1579; found 349,1575.

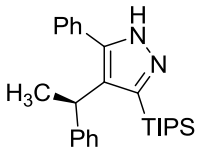
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, ^3J = 8.4 Hz, 2H), 7.43 (d, ^3J = 8.4 Hz, 2H), 7.42 – 7.20 (m, 10H), 4.56 (bs, 1H), 4.40 (q, ^3J = 7.3 Hz, 1H), 1.45 (d, ^3J = 7.4 Hz, 3H). **^{13}C NMR** (75

MHz, $CDCl_3$) δ 145.2 (C), 144.6 (C), 137.3 (C), 132.0 (2xCH), 130.0 (C), 129.3 (2xCH), 129.1 (CH), 128.7 (2xCH), 128.7 (2xCH), 128.5 (2xCH), 127.2 (2xCH), 126.2 (CH), 125.7 (C), 120.9 (C), 118.7 (C), 111.7 (C), 33.4 (CH), 19.9 (CH_3).

(*R*)-5-phenyl-1-(1-phenylethyl)-3-(triisopropylsilyl)-1*H*-pyrazole (27e) and **(*R*)-5-phenyl-4-(1-phenylethyl)-3-(triisopropylsilyl)-1*H*-pyrazole (28e)**



27e



28e

Following the *general procedure A*, from (*R*)-*N'*-(1,2-diphenylpropylidene)-4-methylbenzenesulfonohydrazide (113.5 mg, 0.3 mmol) and (triisopropylsilyl)acetylene (129 µL, 0.6 mmol) were obtained a 3:1 (**27e: 28e**) mixture of separable regioisomers. **27e** and **28e** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 30:1 and 5:1 as eluent. *Rf* **27e** (hexanes/ethyl acetate; 30:1) = 0.46. *Rf* **28e** (hexanes/ethyl acetate; 5:1) = 0.29. It was obtained 69 mg of **27e** (57 % isolated yield) as a white solid, m.p.= 136 - 138 °C and 32 mg of **28e** (25% of isolated yield) as a colourless oil. (Total yield **27e** + **28e**: 82%)

- ***Regioisomer* 27e*:***

HRMS (EI): calcd. for $C_{26}H_{36}N_2Si$: 404,2648; found 404,2652.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 3H), 7.32 – 7.19 (m, 7H), 6.43 (s, 1H), 5.51 (q, *J* = 7.0 Hz, 1H), 1.91 (d, *J* = 7.0 Hz, 3H), 1.46 – 1.32 (m, 3H), 1.18 (d, *J* = 7.2 Hz, 18H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.2 (C), 144.0 (C), 143.0 (C), 131.7 (C), 129.3 (2xCH), 128.5 (2xCH), 128.4 (CH), 128.1 (CH), 127.1 (2xCH), 126.5 (CH), 114.2 (CH), 57.9 (CH), 23.2 (3xCH), 18.9 (6xCH_3), 11.5 (CH_3).
>99% *ee* [Chiralcel ODH column, *n*-hexane =100, 0.1 mL/min, λ_{max} 201.3 nm; t_R = 43.0 min (<0.5 %) and 48.3 min (>99%).
$[\alpha]_D^{15}$ = -140.6 (c = 0.16 in CH_2Cl_2)

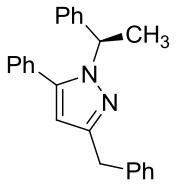
- ***Regioisomer* 28e*:***

HRMS (EI): calcd. for $C_{26}H_{36}N_2Si$: 404,2648; found 404,2653.

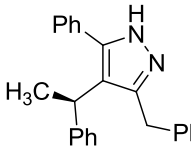
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.08 (m, 10H), 6.15 (bs, 1H), 4.39 (q, ^3J = 7.2 Hz, 1H), 1.48 (d, ^3J = 7.3 Hz, 3H), 1.45 – 1.41 (m, 3H), 1.15 (d, *J* = 7.4 Hz, 9H), 1.10 (d, ^3J = 7.4 Hz, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.9 (C), 146.0 (C), 137.9 (C), 134.7 (C), 130.4 (C), 129.6

(2xCH), 128.0 (2xCH), 127.7 (2xCH), 127.7 (2xCH), 127.4 (CH), 125.7 (CH), 34.9 (CH), 20.5(3xCH), 19.0 (3xCH_3), 18.9 (3xCH_3) , 12.1 (CH_3).

(*R*)-3-benzyl-5-phenyl-1-(1-phenylethyl)-1*H*-pyrazole (27f) and **(*R*)-3-benzyl-5-phenyl-4-(1-phenylethyl)-1*H*-pyrazole (28f)**



27f



28f

Following the *general procedure A*, from (*R*)-*N'*-(1,2-diphenylpropylidene)-4-methylbenzenesulfonohydrazide (113.5 mg, 0.3 mmol) and 3-phenyl-1-propyne (77 µL, 0.6 mmol) were obtained a 5:1 (**27f: 28f**) mixture of separable regioisomers. **27f** and **28f** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 and 2:1 as eluent. *Rf* **27f** (hexanes/ethyl acetate; 10:1) = 0.21. *Rf* **28f** (hexanes/ethyl acetate; 2:1) = 0.33. It was obtained 33 mg of **27f** (33 % isolated yield) as a light yellow solid, m.p.= 66 - 67 °C and 7 mg of **28f** (7% of isolated yield) as a light yellow oil.(Total yield **27f** + **28f**: 40%)

- ***Regioisomer 27f:***

HRMS (EI): calcd. for $C_{24}H_{22}N_2$: 338,1783; found 338,1776.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.01 (m, 15H), 6.04 (s, 1H), 5.50 (q, ^3J = 7.0 Hz, 1H), 4.11 (s, 2H), 1.94 (d, ^3J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.3 (C), 144.8 (C), 143.3 (C), 140.4 (C), 131.2 (C), 129.2 (2xCH), 129.0 (2xCH), 128.6 (2xCH), 128.6 (2xCH), 128.4 (3xCH), 127.2 (CH), 126.3 (2xCH), 126.2 (CH), 105.6 (CH), 57.4 (CH), 35.1 (CH_2), 22.4 (CH_3).
97% *ee* [Chiralcel ODH column, *n*-hexane/isopropanol = 98/2, 0.2 mL/min, λ_{max} 208.0 nm; t_R = 29.9 min (2 %) and 34.2 min (99%).
$[\alpha]_D^{15}$ = 18.9 (c = 0.27 in CH_2Cl_2)

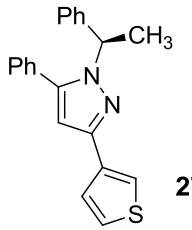
- ***Regioisomer 28f:***

HRMS (EI): calcd. for $C_{24}H_{22}N_2$: 338,1783; found 338,1771.

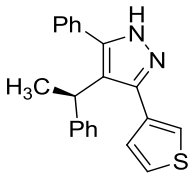
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.35 (m, 5H), 7.35 – 7.16 (m, 8H), 7.14 – 7.03 (m, 2H), 4.35 (q, ^3J = 7.2 Hz, 1H), 3.75 (s, 2H), 1.54 (d, ^3J = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.1 (C), 138.3 (C), 132.3 (C), 128.8 (2xCH), 128.7 (C), 128.6 (2xCH), 128.5 (2xCH), 128.5

(2xCH), 128.2 (2xCH), 128.1 (CH), 127.3 (2xCH), 126.5 (CH), 125.8 (CH), 125.5 (C), 120.2 (C), 33.3 (CH), 32.6 (CH_2), 20.3 (CH_3).

(*R*)-5-phenyl-1-(1-phenylethyl)-3-(thiophen-3-yl)-1*H*-pyrazole (27g) and **(*R*)-5-phenyl-4-(1-phenylethyl)-3-(thiophen-3-yl)-1*H*-pyrazole (28g)**



27g



28g

Following the *general procedure A*, from (*R*)-*N'*-(1,2-diphenylpropylidene)-4-methylbenzenesulfonohydrazide (113.5 mg, 0.3 mmol) and 3-ethynylthiophene (62 μL, 0.6 mmol) were obtained a 8:1 (**27g: 28g**) mixture of separable regioisomers. **27g** and **28g** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 and 2:1 as eluent. *Rf* **27g** (hexanes/ethyl acetate; 10:1) = 0.37. *Rf* **28g** (hexanes/ethyl acetate; 2:1) = 0.33. It was obtained 56 mg of **27g** (57 % isolated yield) as a yellow solid, m.p. = 102 - 104 °C and 9 mg of **28g** (9% of isolated yield) as a colourless oil. (Total yield **27g** + **28g**: 66%)

- ***Regioisomer* 27*g*:**

HRMS (EI): calcd. for $C_{21}H_{18}N_2S$: 330,1191; found 330,1181.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, ^3J = 3.0, 1.2 Hz, 1H), 7.63 (dd, ^3J = 5.0, 1.2 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.40 (dd, ^3J = 5.0, 3.0 Hz, 1H), 7.37 – 7.22 (m, 8H), 6.55 (s, 1H), 5.55 (q, ^3J = 7.0 Hz, 1H), 1.98 (d, ^3J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.9 (C), 144.9 (C), 143.2 (C), 135.9 (C), 131.0 (C), 129.3 (2xCH), 128.7 (4xCH), 128.6 (2xCH), 127.3 (CH), 126.4 (2xCH), 125.8 (CH), 120.3 (CH), 103.9 (CH), 57.9 (CH), 22.6 (CH_3).
ee = 98% [Chiralcel IC column, *n*-hexane/isopropanol = 99/1, 0.5 mL/min, λ_{max} 250.8 nm; t_R = 9.6 min (99 %) and 10.9 min (1%).
$[\alpha]_D^{15}$ = -19.5 (c = 0.09 in CH_2Cl_2)

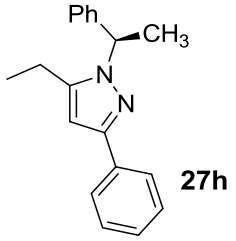
- ***Regioisomer* 28*g*:**

HRMS (EI): calcd. for $C_{21}H_{18}N_2S$: 330,1191; found 330,1205.

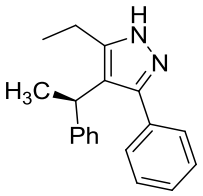
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.32 (m, 9H), 7.27 – 7.21 (m, 3H), 7.17 – 7.09 (m, 2H), 4.54 (bs, 1H), 4.46 (q, ^3J = 7.3 Hz, 1H), 1.48 (d, ^3J = 7.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.7 (C), 132.5 (C), 132.4 (C), 131.6 (C), 128.9 (C), 128.7 (2xCH), 128.5(2xCH), 128.4

(2xCH), 127.8 (CH), 127.3 (2xCH), 125.9 (CH), 125.7 (CH), 125.6 (CH), 123.9 (CH), 121.4 (C), 33.6 (CH), 19.8 (CH_3).

(*R*)-5-ethyl-3-phenyl-1-(1-phenylethyl)-1*H*-pyrazole (27h) and **(*R*)-5-ethyl-3-phenyl-4-(1-phenylethyl)-1*H*-pyrazole (28h)**



27h



28h

Following the *general procedure A*, from (*R*)-4-methyl-*N*'-(2-phenylpentan-3-ylidene)benzenesulfonohydrazide (99.1 mg, 0.3 mmol) and phenylacetylene (67 µL, 0.6 mmol) were obtained a 8:1 (**27h: 28h**) mixture of separable regioisomers. **27h** and **28h** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 and 2:1 as eluent. *Rf* **27h** (hexanes/ethyl acetate; 10:1) = 0.36. *Rf* **28h** (hexanes/ethyl acetate; 2:1) = 0.22. It was obtained 35 mg of **27h** (45 % isolated yield) as a light yellow solid, m.p.= 55 - 57 °C and 15 mg of **28h** (19% of isolated yield) as a colourless oil. (Total yield **27h** + **28h**: 64%)

- ***Regioisomer* 27*h:***

HRMS (EI): calcd. for $C_{19}H_{20}N_2$: 276,1626; found 276,1633.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.89 (m, 2H), 7.45 (app. t, ^3J = 7.5 Hz, 2H), 7.39 – 7.26 (m, 4H), 7.26 – 7.20 (m, 2H), 6.45 (s, 1H), 5.47 (q, ^3J = 7.0 Hz, 1H), 2.77 – 2.40 (m, 2H), 2.04 (d, ^3J = 7.0 Hz, 3H), 1.26 (t, ^3J = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.7 (C), 145.9 (C), 143.1 (C), 134.4 (C), 128.7 (2xCH), 128.6 (2xCH), 127.4 (CH), 127.3 (CH), 126.1 (2xCH), 125.6 (2xCH), 101.2 (CH), 58.0 (CH), 22.3 (CH_3), 19.0 (CH_2), 12.7 (CH_3).
92% *ee* [Chiralcel ADH column, *n*-hexane/isopropanol = 98/2, 0.2 mL/min, λ_{max} 254.4 nm; t_R = 24.8 min (4%) and 27.1 min (96%).
$[\alpha]_D^{15}$ = -256.9 (c = 0.19 in CH_2Cl_2)

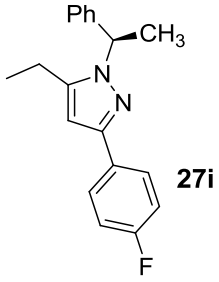
- ***Regioisomer* 28*h:***

HRMS (EI): calcd. for $C_{19}H_{20}N_2$: 276,1626; found 276,1628.

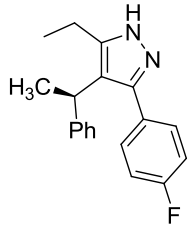
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.31 (m, 5H), 7.31 – 7.15 (m, 5H), 4.33 (q, ^3J = 7.4 Hz, 1H), 2.53 – 2.26 (m, 2H), 1.62 (d, ^3J = 7.4 Hz, 3H), 1.07 (t, ^3J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.4 (2xC), 132.4 (C), 128.6 (2xCH), 128.5 (2xCH), 128.1 (2xCH), 128.0

(2xCH), 127.2 (CH), 125.7 (2xCH), 125.6 (C), 119.3 (C), 33.3 (CH), 20.4 (CH_3), 19.3 (CH_2), 12.9 (CH_3).

(*R*)-5-ethyl-3-(4-fluorophenyl)-1-(1-phenylethyl)-1*H*-pyrazole (27i) and **(*R*)-5-ethyl-3-(4-fluorophenyl)-4-(1-phenylethyl)-1*H*-pyrazole (28i)**



27i



28i

Following the *general procedure A*, from (*R*)-4-methyl-*N*'-(2-phenylpentan-3-ylidene)benzenesulfonohydrazide (99.1 mg, 0.3 mmol) and 1-ethynyl-4-fluorobenzene (69 µL, 0.6 mmol) were obtained a 2:1 (**27i: 28i**) mixture of separable regioisomers. **27i** and **28i** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 and 2:1 as eluent. *Rf* **27i** (hexanes/ethyl acetate; 10:1) = 0.31. *Rf* **28i** (hexanes/ethyl acetate; 2:1) = 0.13. It was obtained 43 mg of **27i** (58 % isolated yield) as a white solid, m.p.= 95 - 97 °C and 9 mg of **28i** (12% of isolated yield) as a light yellow oil. (Total yield **27i** + **28i**: 70%)

- ***Regioisomer* 27*i*:**

HRMS (EI): calcd. for $C_{19}H_{19}FN_2$: 294,1532; found 294,1530.

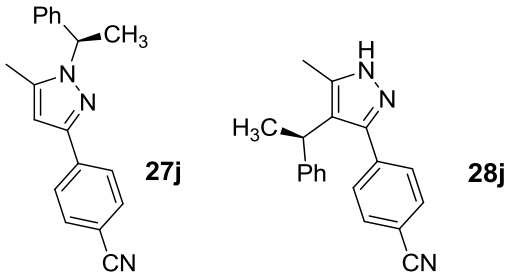
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.75 (m, 2H), 7.36 – 7.24 (m, 3H), 7.23 – 7.16 (m, 2H), 7.16 – 7.04 (m, 2H), 6.36 (s, 1H), 5.44 (q, ^3J = 7.0 Hz, 1H), 2.70 – 2.36 (m, 2H), 2.00 (d, ^3J = 7.0 Hz, 3H), 1.23 (t, ^3J = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.3 (d, ^1J = 245.4 Hz, C), 148.7 (C), 146.0 (C), 142.9 (C), 130.4 (C), 128.6 (2xCH), 127.3 (d, ^3J = 8Hz, 2xCH),127.1 (CH), 126.0 (2xCH), 115.3 (d, ^2J = 21.5 Hz, 2xCH), 101.0 (CH), 57.8 (CH), 22.1 (CH_3), 18.9(CH_2), 12.6 (CH_3).
99% *ee* [Chiralcel ADH column, *n*-hexane/isopropanol = 99/1, 0.3 mL/min, λ_{max} 250.6 nm; t_R = 18.1 min (0.7%) and 21.6 min (99.3%).
$[\alpha]_D^{15}$ = -11.4 (c = 0.07 in CH_2Cl_2)

- ***Regioisomer* 28*i*:**

HRMS (EI): calcd. for $C_{19}H_{19}FN_2$: 294,1532; found 294,1526.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.17 (m, 4H), 7.14 – 7.08 (m, 1H), 6.94 (app. t, ^3J = 8.6 Hz, 1H), 6.48 (bs, 1H), 4.16 (q, ^3J = 7.3 Hz, 1H), 2.50 – 2.28 (m, 2H), 1.50 (d, ^3J = 7.4 Hz, 1H), 1.02 (t, ^3J = 7.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.6 (d, ^1J = 247.2 Hz, C), 147.0 (C), 145.2 (C), 130.4 (d, ^3J = 8.1 Hz, 2xCH), 128.7 (C), 128.5 (C), 128.2 (2xCH), 127.2 (2xCH), 125.83 (CH), 115.4 (d, ^2J = 21.5 Hz, 2xCH), 33.4 (CH), 20.4 (CH_3), 19.4 (CH_2), 13.1 (CH_3).

(*R*)-4-(5-methyl-1-(1-phenylethyl)-1*H*-pyrazol-3-yl)benzonitrile (27j) and **(*R*)-4-(5-methyl-4-(1-phenylethyl)-1*H*-pyrazol-3-yl)benzonitrile (28j)**



Following the *general procedure A*, from (*R*)-4-methyl-*N*'-(3-phenylbutan-2-ylidene)benzenesulfonohydrazide (94.9 mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6 mg, 0.6 mmol) were obtained a 1:1 (**27j: 28j**) mixture of separable regioisomers. **27j** and **28j** were separated and purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 and 2:1 as eluent. *Rf* **27j** (hexanes/ethyl acetate; 10:1) = 0.31. *Rf* **28j** (hexanes/ethyl acetate; 2:1) = 0.13. It was obtained 37 mg of **27j** (43 % isolated yield) as a light yellow solid, m.p.= 119 - 121 °C and 31 mg of **5j** (36% of isolated yield) as a yellow solid, m. p. = 98 – 101 °C .(Total yield **27j** + **28j**: 79%)

- ***Regioisomer 27j:***

HRMS (EI): calcd. for $C_{19}H_{17}N_3$: 287,1422; found 287,1422.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (app. d, ^3J = 8.6 Hz, 2H), 7.68 (app. d, ^3J = 8.6 Hz, 2H), 7.39 – 7.22 (m, 3H), 7.21 – 7.18 (m, 2H), 6.43 (s, 1H), 5.46 (q, ^3J = 7.0 Hz, 1H), 2.22 (s, 3H), 2.00 (d, ^3J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.7 (C), 142.4 (C), 140.3 (C), 138.6 (C), 132.5 (2xCH), 128.8 (2xCH), 127.6 (CH), 126.1 (2xCH), 125.9 (2xCH), 119.5 (C), 110.4 (C), 103.9 (CH), 58.4 (CH), 22.1 (CH_3), 11.4 (CH_3).

97% *ee* [Chiralcel ADH column, *n*-hexane/isopropanol = 98/2, 0.2 mL/min, λ_{max} 283.5 nm; t_R = 58.8 min (1.5%) and 66.7 min (98.5%).

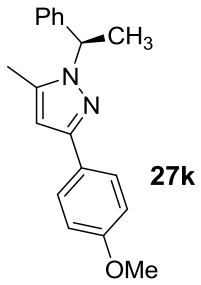
$[\alpha]_D^{15}$ = -239.7 (c = 0.12 in CH_2Cl_2)

- ***Regioisomer 28j:***

HRMS (EI): calcd. for $C_{19}H_{17}N_3$: 287,1422; found 287,1423.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (bs, 1H), 7.61 (d, ^3J = 8.4 Hz, 2H), 7.51 (d, ^3J = 8.4 Hz, 2H), 7.35 – 7.26 (m, 2H), 7.26 – 7.15 (m, 3H), 4.27 (q, ^3J = 7.3 Hz, 1H), 2.01 (s, 3H), 1.61 (d, ^3J = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.4 (C), 144.7 (C), 140.4 (C), 138.1 (C), 132.3 (2xCH), 129.2 (2xCH), 128.4 (2xCH), 127.2 (2xCH), 126.2 (CH), 120.3 (C), 118.8 (C), 111.5 (C), 33.7 (CH), 20.5 (CH_3), 11.5 (CH_3).

(*R*)-3-(4-methoxyphenyl)-5-methyl-1-(1-phenylethyl)-1*H*-pyrazole (27k)



27k

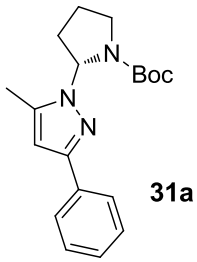
Following the *general procedure A,* from (*R*)-4-methyl-*N*'-(3-phenylbutan-2-ylidene)benzenesulfonohydrazide (94.9 mg, 0.3 mmol) and 1-ethynyl-4-methoxybenzene (79 µL, 0.6 mmol) were obtained 35.0 mg of **27k** (40 % isolated yield) as a light yellow solid, m.p.= 127 - 130 °C. **27k** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 20:1 as eluent. *Rf* (hexanes/ethyl acetate, 20:1) = 0.2.

HRMS (EI): calcd. for $C_{19}H_{20}N_2O$: 292,1576; found 292,1578.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (app. d, ^3J = 8.9 Hz, 2H), 7.41 – 7.24 (m, 3H), 7.21 – 7.18 (m, 2H), 6.95 (app. d, ^3J = 8.9 Hz, 2H), 6.30 (d, ^3J = 0.6 Hz, 1H), 5.44 (q, ^3J = 7.0 Hz, 1H), 3.86 (s, 3H), 2.18 (d, ^3J = 0.6 Hz, 3H), 1.99 (d, ^3J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.0 (C), 149.4 (C), 142.9 (C), 139.4 (C), 128.6 (2xCH), 127.2 (CH), 127.1 (C), 126.8 (2xCH), 126.0 (2xCH), 113.9 (2xCH), 102.6 (CH), 57.9 (CH), 55.3 (CH_3), 21.9 (CH_3), 11.3 (CH_3).

E. 14. Characterization data for compounds 31, 33 and 34.

(*R*)-*tert*-butyl 2-(5-methyl-3-phenyl-1*H*-pyrazol-1-yl)pyrrolidine-1-carboxylate (31a)[256]



31a

Following the *general procedure A,* from (*S*)-*tert*-butyl 2-acetylpyrrolidine-1-carboxylate (114.4 mg, 0.3 mmol) and phenylacetylene (68 µL, 0.6 mmol) were obtained 69.6 mg of **7a** (71 % isolated yield) as a light yellow oil. **7a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* (hexanes/ethyl acetate, 5:1) = 0.18.

HRMS (EI): calcd. for $C_{19}H_{25}N_3O_2$: 327,1947; found 327,1943.

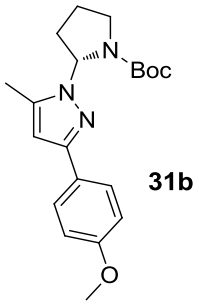
^{1}H NMR (300 MHz, C_6D_6) δ 7.99 – 7.95 (m, 2H), 7.23 (t, ^3J = 7.5 Hz, 2H), 7.10 (t, ^3J = 7.3 Hz, 1H), {6.15 (s, 0.3H) + 6.12 (s, 0.7H)}, {5.83 (d, ^3J = 6.9 Hz, 0.7H) + 5.49 (dd, ^3J = 5.5, 2.3 Hz, 0.3H)}, {4.09 – 3.95 (m, 0.3H) + 3.82 – 3.65 (m, 0.7H)}, {3.50 (dd, ^3J = 17.6, 7.7 Hz, 0.3H) + 3.28 (dd, ^3J = 17.7, 8.1 Hz, 0.7H)}, {2.74 (dd, ^3J = 18.1, 9.4 Hz, 0.6H) + 2.27 – 2.25 (m, 0.4H)}, {2.40 (s, 2H) + 1.97 (s, 1H)}, 1.71 – 1.43 (m, 3H), {1.33 (s, 6H), 1.26 (s, 3H)}. **^{13}C NMR** (75 MHz, $CDCl_3$) δ {154.4 (C) + 153.8 (C)}, {150.4 (C) + 150.2 (C)}, {140.4 (C) + 138.8 (C)}, {134.2 (C) + 134.1 (C)}, 128.5 (2xCH), 127.4 (CH), 125.6 (2xCH), 102.0 (CH), {80.4 (C) + 79.9 (C)}, {69.5 (CH) + 69.0 (CH)}, 46.9 (CH_2), {34.3 (CH_2), 33.0 (CH_2)}, {28.5 (3xCH_3), 28.4 (3xCH_3)}, {23.9 (CH_2) + 22.5 (CH_2)}, 11.4 (CH_3).

97% *ee* [Chiralcel ADH column, *n*-hexane/isopropanol = 99/1, 0.1 mL/min, λ_{max} 254.4 nm; t_R = 65.5 min (1.5%) and 78.5 min (98.5%).

$[\alpha]_D^{15}$ = -6.0 (c = 0.23 in CH_2Cl_2)

[256] The signals splitting from rotamers are indicated between brackets. Experiments at different temperatures were carried out to prove the presence of these rotamers.

(*R*)-*tert*-butyl 2-(3-(4-methoxyphenyl)-5-methyl-1*H*-pyrazol-1-yl)pyrrolidine-1-carboxylate (31b)



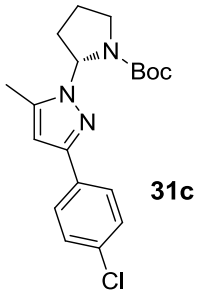
31b

Following the *general procedure A,* from (*S*)-*tert*-butyl 2-acetylpyrrolidine-1-carboxylate (114.4 mg, 0.3 mmol) and 4-methoxyphenylacetylene (79 µL, 0.6 mmol) were obtained 51.5 mg of **31b** (41 % isolated yield) as a colourless oil. **31b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* (hexanes/ethyl acetate, 5:1) = 0.20.

HRMS (EI): calcd. for $C_{20}H_{27}N_3O_3$: 357,2052; found 357,2050.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, ^3J = 8.6 Hz, 2H), 7.33 (d, ^3J = 8.6 Hz, 2H), 6.24 (s, 1H), {6.01 (bs, 0.5H) + 5.89 (bs, 1H)}, 3.79 – 3.72 (m, 1H), 3.66 – 3.37 (m, 1H), 2.81 (dd, ^3J = 18.4, 8.2 Hz, 0.5 H), {2.51 (s, 1.5H) + 2.37 (s, 1.5H)}, 2.29 – 2.17 (m, 2H), 2.15 – 1.98 (m, 1.5H), {1.44 (s, 4.5H) + 1.31 (s, 4.5H)}. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.0 (C), {154.3 (C) + 153.7 (C)}, 149.9 (C), {140.2 (C) + 138.6 (C)}, 126.9 (C), 126.7 (2xCH), 113.8 (2xCH), 101.4 (CH), {80.2 (C) + 79.8 (C)}, {69.3 (CH) + 68.8 (CH)}, 55.3 (CH_3), 46.8 (CH_2), {34.2 (CH_2), 33.0 (CH_2)}, {28.4 (3xCH_3), 28.3 (3xCH_3)}, {23.7 (CH_2) + 22.4 (CH_2)}, 11.3 (CH_3).
80% *ee* [Chiralcel ADH column, *n*-hexane/isopropanol = 98/2, 0.5 mL/min, λ_{max} 260.3 nm; t_R = 19.5 min (90%) and 23.0 min (10%).
$[\alpha]_D^{15}$ = -30.9 (c = 0.05 in CH_2Cl_2)

(*R*)-*tert*-butyl 2-(3-(4-chlorophenyl)-5-methyl-1*H*-pyrazol-1-yl)pyrrolidine-1-carboxylate (31c)



31c

Following the *general procedure A,* from (*S*)-*tert*-butyl 2-acetylpyrrolidine-1-carboxylate (114.4 mg, 0.3 mmol) and 4-chlorophenylacetylene (83.6 mg, 0.6 mmol) were obtained 57.1 mg of **31c** (45 % isolated yield) as a colourless oil. **31c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* (hexanes/ethyl acetate, 5:1) = 0.31.

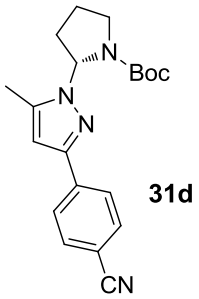
HRMS (EI): calcd. for $C_{19}H_{24}ClN_3O_2$: 361,1557; found 361,1555.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, ^3J = 8.6 Hz, 2H), 6.92 (d, ^3J = 8.8 Hz, 2H), 6.19 (s, 1H), {6.00 (bs, 0.5H) + 5.87 (bs, 1H)}, {3.91 – 3.81 (m, 0.5H) + 3.80 – 3.72 (m, 0.5H)}, 3.60 – 3.48 (m, 1H), 2.79 (dd, ^3J = 18.4, 8.2 Hz, 0.5 H), {2.51 (s, 1.5H) + 2.38 (s, 1.5H)}, 2.29 – 2.06 (m, 2H), 2.00 – 1.91 (m, 1.5H), {1.44 (s, 4.5H) + 1.31 (s, 4.5H)}. **^{13}C NMR** (75 MHz, $CDCl_3$) δ {154.3 (C) + 153.6 (C)}, 149.0 (C), {140.5 (C) + 138.9 (C)}, {132.6 (C) + 132.5 (C)}, 128.5 (2xCH), 126.7 (2xCH), 101.9 (CH), {80.2 (C) + 79.9 (C)}, {69.4 (CH) + 69.0 (CH)}, 46.8 (CH_2), {34.1 (CH_2), 32.9 (CH_2)}, {28.4 (3xCH_3), 28.3 (3xCH_3)}, {23.7 (CH_2) + 22.3 (CH_2)}, 11.3 (CH_3).

>99% *ee* [Chiralcel ADH column, *n*-hexane/isopropanol =99/1, 0.2 mL/min, λ_{max} 260.3 nm; t_R = 42.8 min (>99%) and 45.6 min (<0.5 %)

$[\alpha]_D^{15}$ = -4.1 (c = 0.17 in CH_2Cl_2.

(*R*)-*tert*-butyl 2-(3-(4-cyanophenyl)-5-methyl-1*H*-pyrazol-1-yl)pyrrolidine-1-carboxylate (7d)



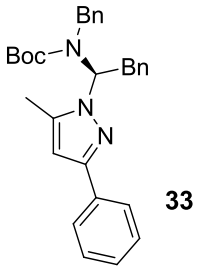
31d

Following the *general procedure A,* from (*S*)-*tert*-butyl 2-acetylpyrrolidine-1-carboxylate (114.4 mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6 mg, 0.6 mmol) were obtained 74.9 mg of **31d** (61 % isolated yield) as a light yellow oil. **31d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* (hexanes/ethyl acetate, 5:1) = 0.19.

HRMS (EI): calcd. for $C_{20}H_{24}N_4O_2$: 352,1899; found 352,1903.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, ^3J = 8.4 Hz, 2H), 7.65 (d, ^3J = 8.4 Hz, 2H), 6.32 (bs, 1H), {6.05 (bs, 0.5H) + 5.91 (bs, 1H)}, {3.94 – 3.92 (m, 0.5H) + 3.61 – 3.49 (m, 0.5H)}, 3.58 – 3.50 (m, 1H), 2.77 – 2.73 (m, 1H), {2.53 (s, 1.5H) + 2.40 (s, 1.5H)}, 2.35 – 2.06 (m, 3H), {1.44 (s, 4.5H) + 1.31 (s, 4.5H)}. **^{13}C NMR** (75 MHz, $CDCl_3$) δ {154.2(C) + 153.5 (C)}, {148.3 (C) + 148.2 (C)}, {140.9 (C) + 139.3 (C)}, {138.5 (C) + 138.3 (C)}, 132.3 (2xCH), 125.7 (2xCH), 119.3 (C), 110.2 (C), 102.6 (CH), {80.4 (C) + 80.0 (C)}, {69.6 (CH) + 69.2 (CH)}, 46.9 (CH_2), {34.2 (CH_2), 32.9 (CH_2)}, {28.4 (3xCH_3), 28.2 (3xCH_3)}, {23.7 (CH_2) + 22.2 (CH_2)}, 11.3 (CH_3).

(*R*)-*tert*-butyl benzyl(1-(5-methyl-3-phenyl-1*H*-pyrazol-1-yl)-2-phenylethyl)carbamate (33)



33

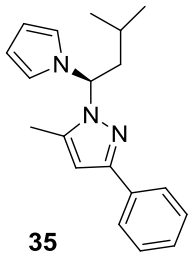
Following the *general procedure B,* from (*S*)-*tert*-butyl benzyl(1-phenyl-3-(2-tosylhydrazono)butan-2-yl)carbamate (156.5 mg, 0.3 mmol) and phenylacetylene (68 μL,

0.6 mmol) were obtained 63.1 mg of **33** (45 % isolated yield) as a light yellow oil. **33** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. *Rf* (hexanes/ethyl acetate, 5:1) = 0.43.

HRMS (EI): calcd. for $C_{30}H_{33}N_3O_2$: 467,2573; found 467,2577.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, ^3J = 7.1 Hz, 2H), 7.43 (t, ^3J = 7.4 Hz, 2H), 7.34 (d, ^3J = 7.2 Hz, 1H), 7.22 – 7.05 (m, 10H), {6.75 – 6.70 (m, 0.7 H) + 6.52 – 6.46 (m, 0.3H)}, 6.25 – 6.11 (m, 1H), 4.81 – 4.73 (m, 2H), 3.84 – 3.69 (m, 1H), 3.51 – 3.30 (m, 1H), 2.16 (bs, 3H), 1.41 – 1.31 (m, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.3 (C), 150.2 (C), 140.9 (C), 139.9 (C), 136.7 (C), 134.0 (C), 129.4 (2xCH), 128.5 (3xCH), 128.3 (CH), 127.9 (2xCH), 127.4 (CH), 126.7 (CH), 126.6 (CH), 126.4 (CH), 125.6 (3xCH), 102.5 (CH), 80.7 (C), {69.4 (CH) + 68.0 (CH)},{46.3 (CH_2) + 45.2 (CH_2)}, 39.0 (CH_2), 28.1 (3xCH_3), 10.7 (CH_3).
>99% *ee* [Chiralcel ADH column, *n*-hexane/isopropanol =95/5, 0.1 mL/min, λ_{max} 253.2 nm; t_R = 44.6 min (<0.5 %) and 49.4 min (>99%).
$[\alpha]_D^{15}$ = -80.7 (c = 0.14 in CH_2Cl_2).

(*R*)-5-methyl-1-(3-methyl-1-(1*H*-pyrrol-1-yl)butyl)-3-phenyl-1*H*-pyrazole (35)



35

Following the *general procedure B,* from (*S*)-4-methyl-*N*′-(5-methyl-3-(1*H*-pyrrol-1-yl)hexan-2-ylidene)benzenesulfonohydrazide (104.2 mg, 0.3 mmol) and phenylacetylene (68 µL, 0.6 mmol) were obtained 69.8 mg of **35** (72 % isolated yield) as a white solid, m.p.= 69 - 70 °C. **35** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 20:1 as eluent. *Rf* (hexanes/ethyl acetate, 20:1) = 0.24.

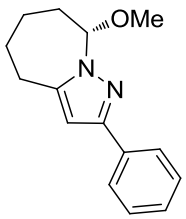
HRMS (EI): calcd. for $C_{19}H_{23}N_3$: 293,1892; found 293,1883.

^{1}H NMR (300 MHz, $CDCl_3$) (major rotamer) δ 7.85 (d, ^3J = 8.1 Hz, 2H), 7.43 (t, ^3J = 7.4 Hz, 2H), 7.38 – 7.29 (m, 1H), 6.96 (t, ^3J = 2.2 Hz, 2H), 6.34 (s, 1H), 6.18 (t, ^3J = 2.2 Hz, 2H), 6.10 (t, ^3J = 7.5 Hz, 1H), 2.67 – 2.39 (m, 2H), 2.36 (s, 3H), 1.57 – 1.43 (s, 1H), 1.01 (t, ^3J = 7.4 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) (major rotamer) δ 150.6 (C), 139.5 (C), 133.8 (C), 128.5 (2xCH), 127.6 (CH), 125.7 (2xCH), 119.0 (2xCH),108.7 (2xCH), 103.6 (CH), 69.0 (CH), 43.6 (CH_2), 24.5 (CH), 22.5 (CH_3), 22.3 (CH_3), 11.1 (CH_3).

98% *ee* [Chiralcel ADH column, *n*-hexane/isopropanol =98/2, 0.3 mL/min, λ_{max} 252.0 nm; t_R = 14.1 min (1 %) and 15.2 min (99%).
$[\alpha]_D^{15}$ = -239.4 (c = 0.15 in CH_2Cl_2).

E.15. Characterization data for compounds 37 and 38

(*S*)-8-methoxy-2-phenyl-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine (37a)



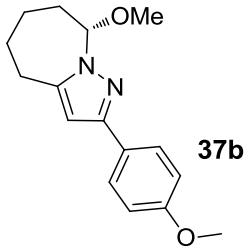
37a

Following the *general procedure B,* from (*S*)-*N*'-(2-methoxycyclohexylidene)-4-methylbenzenesulfonohydrazide (88.9 mg, 0.3 mmol) and phenylacetylene (68 µL, 0.6 mmol) were obtained 46.5 mg of **37a** (64 % isolated yield) as a colourless oil. **37a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. *Rf* (hexanes/ethyl acetate, 10:1) = 0.18.

HRMS (EI): calcd. for $C_{15}H_{18}N_2O$: 242,1419; found 242,1418.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.73 (m, 2H), 7.46 – 7.35 (m, 2H), 7.35 – 7.18 (m, 1H), 6.36 (s, 1H), 5.57 (dd, ^3J = 4.7, 1.4 Hz, 1H), 3.25 (s, 3H), 3.00 – 2.86 (m, 1H), 2.86 – 2.69 (m, 1H), 2.39 – 2.24 (m, 1H), 2.22 – 1.96 (m, 2H), 1.90 – 1.77 (m, 1H), 1.72 (bs, 1H), 1.54 – 1.33 (m, 1H).. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.4 (C), 145.4 (C), 133.6 (C), 128.5 (2xCH), 127.5 (CH), 125.6 (2xCH), 103.8 (CH), 91.7 (CH), 55.7 (CH_3) , 32.6 (CH_2), 27.4 (CH_2), 25.9 (CH_2), 23.2 (CH_2).
>99% *ee* [Chiralcel ADH column, *n*-hexane/ethanol =99/1, 0.2 mL/min, λ_{max} 252.0 nm; t_R = 29.5 min (<0.5 %) and 36.5 min (>99%).
$[\alpha]_D^{15}$ = -12.9 (c = 0.08 in CH_2Cl_2).

(*S*)-8-methoxy-2-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine (37b)



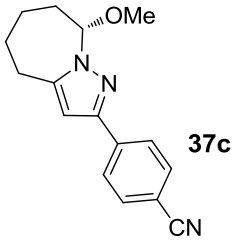
37b

Following the *general procedure B,* from (*S*)-*N*'-(2-methoxycyclohexylidene)-4-methylbenzenesulfonohydrazide (88.9 mg, 0.3 mmol) and 4-methoxyphenylacetylene (79 µL, 0.6 mmol) were obtained 41.6 mg of **37b** (51 % isolated yield) as a white solid, m.p.= 92 – 93 °C. **37b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. *Rf* (hexanes/ethyl acetate, 10:1) = 0.14.

HRMS (EI): calcd. for $C_{16}H_{20}N_2O_2$: 272,1525; found 272,1528.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, ^3J = 8.8 Hz, 2H), 6.94 (d, ^3J = 8.8 Hz, 2H), 6.28 (s, 1H), 5.56 (d, ^3J = 3.6 Hz, 1H), 3.85 (s, 3H), 3.24 (s, 3H), 2.93 (dd, ^3J = 14.8, 5.6 Hz, 1H), 2.76 (app. t, ^3J = 13.9 Hz, 1H), 2.37 – 2.24 (m, 1H), 2.22 – 1.95 (m, 2H), 1.90 – 1.70 (m, 2H), 1.55 – 1.35 (m, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.2 (C), 149.2 (C), 145.3 (C), 126.8 (2xCH), 126.4 (C), 114.0 (2xCH), 103.4 (CH), 91.6 (CH), 55.6 (CH_3), 55.3 (CH_3), 32.6 (CH_2), 27.4 (CH_2), 25.9 (CH_2), 23.2 (CH_2).
>99% *ee* [Chiralcel ADH column, *n*-hexane/isopropanol =95/5, 032 mL/min, λ_{max} 257.9 nm; t_R = 25.8 min (>99%) and 27.6 min (<0.5 %).
$[\alpha]_D^{15}$ = -11.3 (c = 0.12 in CH_2Cl_2).

(*S*)-4-(8-methoxy-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepin-2yl)benzonitrile (37c)



37c

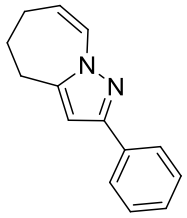
Following the *general procedure B,* from (*S*)-*N*'-(2-methoxycyclohexylidene)-4-methylbenzenesulfonohydrazide (88.9 mg, 0.3 mmol) and 4-ethynylbenzonitrile (78.6

mg, 0.6 mmol) were obtained 56.9 mg of **37c** (71 % isolated yield) as a light yellow solid, m.p.= 78 – 79 °C. **37c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. *Rf* (hexanes/ethyl acetate, 10:1) = 0.11.

HRMS (EI): calcd. for $C_{16}H_{17}N_3O$: 267,1372; found 267,1383.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, ^3J = 8.5 Hz, 2H), 7.67 (d, ^3J = 8.5 Hz, 2H), 6.40 (s, 1H), 5.55 (d, ^3J = 3.4 Hz, 1H), 3.24 (s, 3H), 2.95 (dd, ^3J = 14.9, 5.7 Hz, 1H), 2.83 – 2.73 (m, 1H), 2.41 – 2.23 (m, 1H), 2.23 – 1.97 (m, 2H), 1.93 – 1.71 (m, 2H), 1.54 – 1.34 (m, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.4 (C), 146.0 (C), 138.1 (C), 132.4 (2xCH), 125.8 (2xCH), 119.2 (C), 110.6 (C), 104.3 (CH), 92.1 (CH), 55.8 (CH_3) , 32.5 (CH_2), 27.3 (CH_2), 25.8 (CH_2), 23.0 (CH_2).
>99% *ee* [Chiralcel ADH column, *n*-hexane/isopropanol =95/5, 0.3 mL/min, λ_{max} 279.3nm; t_R = 23.0 min (<0.5 %) and 28.7 min (>99%).
$[\alpha]_D^{15}$ = -21.8 (c = 0.06 in CH_2Cl_2).

2-phenyl-5,6-dihydro-4*H*-pyrazolo[1,5-*a*]azepine (38)



38

A reaction tube was charged with N'-(2-methoxycyclohexylidene)-4-methylbenzenesulfonohydrazide **37a** (89 mg, 0.3 mmol), phenylacetylene (52 µL, 0.45 mmol), cesium carbonate (147 mg, 0.45 mmol) and dioxane (2.4 ml). The system was heated at 110 °C with stirring and reflux for 12 hours. Once the established time has expired, boron trifluoride tetrahydrofuran complex was added (52 µL, 0.45 mmol). When the reaction was completed, the crude reaction was again cooled down to room temperature. Then, a saturated solution of NH_4Cl and dichloromethane were added and the layers were separated (20 mL). The aqueous phase was extracted two times with dichloromethane (2x10 mL). The combined organic layers were washed with water (10 mL), dried over $MgSO_4$ and filtered. Solvent was removed under reduced pressure. Finally, the crude of the reaction was purified by chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. *Rf* (hexanes/ethyl acetate, 10:1) = 0.24.

HRMS (EI): calcd. for $C_{14}H_{14}N_2$: 210,1157; found 210,1161.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.46 – 7.37 (m, 2H), 7.33 (dt, ^{3}J = 4.8, 2.0 Hz, 1H), 7.04 (dt, ^{3}J = 10.3, 2.0 Hz, 1H), 6.37 (s, 1H), 5.34 – 5.12 (m, 1H), 3.04 – 2.81 (m, 2H), 2.60 – 2.40 (m, 2H), 2.11 – 1.89 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.2 (C), 145.0 (C), 133.1 (C), 128.6 (2xCH), 128.1 (CH), 127.8 (CH), 125.6 (2xCH), 113.4 (CH), 103.4 (CH), 30.0 (CH_2), 26.6 (CH_2), 23.7 (CH_2).