Universidad de Oviedo

Departamento de Química Orgánica e Inorgánica

Programa de Doctorado:

"Síntesis y Reactividad Química"

ORGANIC TRANSFORMATIONS EMPLOYING *N*-TOSYLHYDRAZONES AND BORONIC ACIDS: STEREOSELECTIVE REDUCTIVE COUPLINGS AND CASCADE CYCLIZATIONS

Manuel Plaza Martínez

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Manuel Plaza Martínez

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RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español/Otro Idioma: Transformaciones orgánicas empleando *N*-tosilhidrazonas y ácidos borónicos: acoplamientos estereoselectivos reductores y ciclaciones en cascada.	Inglés: Organic transformations employing *N*-tosylhydrazones and boronic acids: stereoselective reductive couplings and cascade cyclizations.

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RESUMEN (en español)

Las reacciones de acoplamiento cruzado libres de metal entre diazocompuestos o sulfonilhidrazonas y compuestos de organoboro presentan un gran potencial sintético. En la Introducción General de esta Memoria se recogen los avances pasados y recientes más significativos de la química relativa a este campo.

En el Capítulo 1, se describe una nueva reacción basada en el acoplamiento estereoselectivo reductor entre *N*-tosilhidrazonas cíclicas y ácidos alquenil borónicos. Estas reacciones representan los primeros ejemplos descritos en la literatura de transformaciones estereoselectivas empleando diazocompuestos en ausencia de catalizador metálico. Estudios computacionales realizados apoyan el raciocinio de la estereoselectividad de estas transformaciones.

En el Capítulo 2, se recogen los avances en el desarrollo de un nuevo modo de carbociclación en Química Orgánica basado en la creación de dos enlaces C-C sobre un mismo átomo de carbono. Este capítulo se ha dividido en tres partes, dependiendo de la naturaleza de los productos sintetizados a través de esta metodología: estructuras bicíclicas fusionadas (parte A), compuestos biciclicos que presentan un átomo de nitrógeno como cabeza de puente (parte B) y esqueletos espirocíclicos (parte C). De nuevo, cálculos computacionales se realizaron para apoyar la propuesta mecanística de todos estos procesos; basados en el acoplamiento diazo-borónico, reagrupamiento 1,3-borotrópico y reacción bora-aza-eno.

Finalmente, en la Parte Experimental se recogen con rigor las caracterizaciones completas de todos los compuestos sintetizados, además de análisis estereoquímicos de compuestos modelo realizados a través de técnicas de RMN.

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RESUMEN (en Inglés)

Metal-free cross-coupling reactions between diazo compounds or sulfonylhydrazones and organoboron compounds render a high synthetic potential. In the General Introduction of this Memory, the past and recent most relevant contributions to this field are covered.

In Chapter 1, a new transformation based on the stereoselective coupling between *N*-tosylhydrazones and alkenylboronic acids is described. These reactions represent the first examples described in the literature of stereoselective transformations employing diazo compounds without the need of any metal catalyst. Computational studies were carried out to support the rationale of the stereoselectivity of all these transformations.

In Chapter 2, the advances in the development of a new carbocyclization mode in Organic Chemistry based on the creation of two C-C bonds on the same carbon atom are covered. This chapter has been divided in three parts, depending on the nature of the synthesized products through this methodology: fused bicyclic structures (part A), bicyclic compounds featuring a nitrogen at a bridgehead position (part B) and spirocyclic skeletons (part C). Once again, computational studies were done to support the mechanistic proposal of all these processes; based on the diazo-boronic coupling, 1,3-borotropic rearrangement and bora-aza-ene reaction.

Finally, the Experimental Part rigorously covers the full characterization of all the products, including the stereochemical assignment of model compounds by NMR techniques.

SR. PRESIDENTE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN _____

Grow through what you go through.

Agradecimientos

Con esta tesis pongo punto final a una etapa muy importante en mi vida. Etapa de aprender, de pasar por buenos y malos momentos… Pero, sobre todo, de crecer. Como químico y como persona. A nivel personal, creo que siempre he procurado ser un buen compañero, y ésto lo he visto recompensado por la enorme cantidad de buenos amigos y amigas que he hecho durante estos años.

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tener en todos vosotros un gran amigo que quede para toda la vida, independientemente de a dónde nos lleve en el futuro a cada uno.

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Abbreviations and Acronyms

A	
Alk	alkyl
aq	aqueous
Ar	aryl
B	
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
C	
°C	Celsius degrees
cat	catalyst
COSY	Correlation Spectroscopy
Cy	cyclohexyl
D	
dba	dibenzylideneacetone
DCE	dichloroethane
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
δ	chemical shift
E	
E	electrophile
EDG	electron donating group
ee	Enantiomeric excess
EI	Electron Ionization
ESI	Electrospray Ionization
equiv	equivalent/s
Et	ethyl
EWG	Electron withdrawing group
G	
g	gram/s
GC-MS	Gas Chomatography-Mass Spectrometry
H	
h	hour/s
HMBC	Heteronuclear Multiple-Bond Correlation Spectroscopy
HMRS	High-Resolution Mass Spectroscopy
HSQC	Heteronuclear Single-Quantum Correlation Spectroscopy
Hz	Hertz/s

I	
***i*Pr**	*iso*-propyl
J	
J	coupling constant
L	
L	ligand
M	
M	metal
Me	methyl
min	minute/s
mol	mole/s
m.p.	melting point
MW	microwave
N	
N	Normality
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	nucleophile
O	
O	oxidant
P	
Pag.	page
Ph	phenyl
PMP	*p*-methoxyphenyl
ppm	parts per million
psi	psia/s
PTC	Phase Transfer Catalyst
R	
rt	room temperature
ref	reference
T	
T	temperature
t	time
TBAB	tetra-*N*-butylammonium bromide
TBAF	tetra-*N*-butylammonium fluoride
***t*-Bu**	*tert*-butyl
THF	tetrahydrofuran

TLC	Thin-Layer Cromatography
TMS	trimethylsilyl group
TOCSY	Total Correlated Spectroscopy
Tol	tolyl
Ts	tosyl
X	
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

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General introduction

Chapter 1. Metal-free stereoselective reductive couplings between *N*-tosylhydrazones and alkenylboronic acids

Chapter 2. Carbocyclization reactions employing *N*-tosyl hydrazones and boronic acids *via* allylborylation of nitriles: one-step formation of two different Csp^3-C bonds on the same carbon

General Introduction

Transition-metal-free reactions between boronic acids and *N*-tosylhydrazones or diazo compounds

The catalysis mediated by transition metals has been studied since the beginning of the last century and represents an outstanding success in the coupling reactions in organic synthesis. During the same period, the development of organometallic chemistry had also experienced a tremendous growth.[1]

Transition-metal-free reactions have been extensively explored since the early 1960s.[2] These types of reactions represent some of the most efficient, reliable and direct strategies for the C-C bond formation in chemists' repertoire. A vast number of named reactions have derived from this type of chemistry and are well-known nowadays.

One of the key features of these reactions is their ability to allow for the formation of C-C(sp^2) bonds in the lack of a metal catalyst, which use would be normally expected in this kind of processes. In this regard, the development of novel chemical reagents such as organoboron compounds has enabled the growth of this kind of transformations involving the creation of C(sp^2)-C bonds. Although one of the main applications for these reagents is the Suzuki coupling reaction (the palladium-catalyzed cross coupling between alkyl/alkenyl/aryl halides and organoboron compounds),[3] a wide range of transition-metal-free processes in which organoboron species are used are also of important relevance.

In the context of transition-metal-free transformations for the formation of carbon-carbon bonds, the reaction between diazo compounds and organoboron compounds has been deeply studied during the last decades. Diazo compounds are very reactive species, with an ample synthetic utility. However, they are generally perceived to be potentially explosive, apart from their well-known toxicity. These facts stand as an issue in their large-scale synthesis, due to their inherent

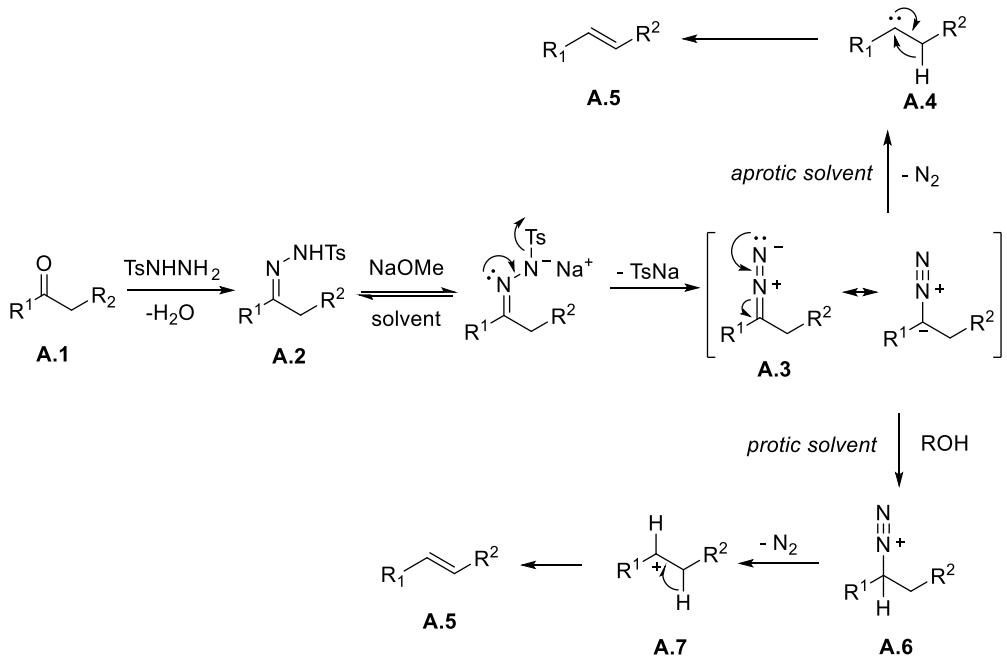
[1] For some reviews on transition-metal-catallyzed cross coupling rections, see: a) *Metal-Catallyzed Cross-Coupling reactions*; Diederich, F.; Stang, P. J. Eds.; Wiley-VCH: Weinhein, **1998**. b) Bräse, S.; de Meijere, A. *Metal-Catallyzed Cross-Coupling reactions,* 2nd ed.; de Meijere, A.; Diederich, F. Eds.; Wiley-VCH: Weinhein, **2004**.

[2] For a review, see: Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219–9280.

[3] a) Miyaura, N.; Suzuki. A. *Chem. Comm*. **1989**, *866*. b) Suzuki, A. Acc. Chem. Res. **1982**, *15*, 178.

manipulation hazards, and therefore the safest alternative is their *in situ* generation in the reaction media starting from safe precursors.

Interestingly, one of the most extended ways to *in situ* generate unstable diazo compounds lies in the employment of *N*-tosylhydrazones as safe precursors of the diazo species under mild reaction conditions (Scheme I. 1). The loss of the sulfinate group by deprotonation of the *N*-tosylhydrazones **A.2** mediated by an external base enables the formation of the deserved diazo compounds through the classical mechanism of the Bamford-Stevens reaction,[4] which was initially employed as a general way to generate olefins starting from *N*-tosylhydrazones presenting enolizable hydrogens. Depending on the nature of the solvent, the diazo compounds **A.3** can evolve through the formation of a carbocationic species **A.7** (protic solvent) or carbenic species **A.4** (protic solvent), in both cases ending up affording the same olefinic final products **A.5**. Thus, the main application of *N*-tosylhydrazones for many years was as intermediates in the deoxygenation of carbonyl compounds.



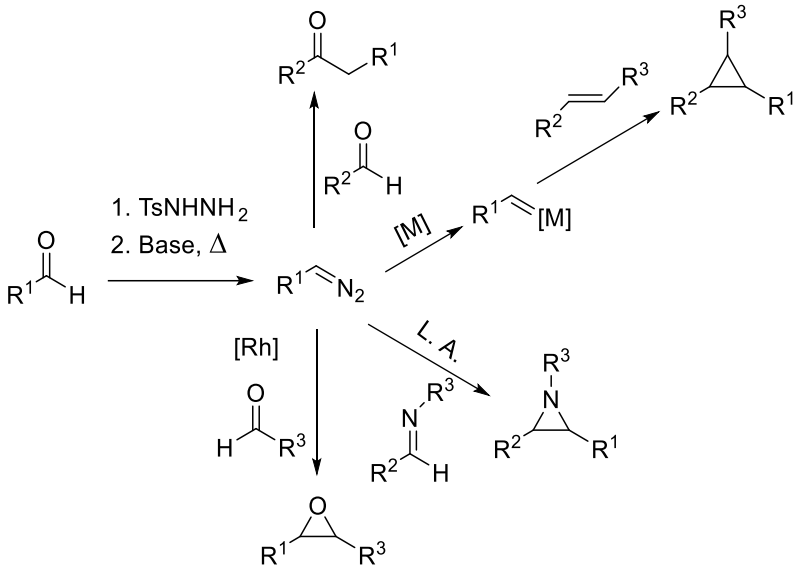
Scheme I.1. Bamford-Stevens reaction mechanism.

[4] Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735.

More recently, the *in situ* generated diazo compounds were reported to be able to participate in various transformations, such as electrocyclic reactions; 1,2-dipolar cycloadditions[5] or homologation reactions of carbonyl compounds.[6] In 2000, Aggarwal and co-workers described a general use of *N*-tosylhydrazones as safe precursors to *in situ* generate diazo compound species under relatively mild conditions. Moreover, the diazo compound could also be trapped by a transition metal species to generate a metallic carbene, which can participate in a catalytic process.[7] This strategy was employed in the development of new cyclopropanations;[8] asymmetric epoxidations;[9] asymmetric aziridations,[10] and C-H insertion reactions.[11] Some of these transformations are summarized in Scheme I.2. However, as these reactions deviate from the objective of this Introduction, they will not be considered any further.

The parallel development of synthetic strategies for the safe *in situ* generation of diazo compounds, along with the discovery of a vast array of stable organoboron compounds that can be employed in this coupling reactions, has stood as an attractive complementary combination that enabled the growth of these type of transformations.[12]

[5] Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem*. **2003**, *68*, 5381.
[6] Aggarwal, V. K.; de Vicente, J.; Pelotier, B.; Holmes, I. P.; Bonnert, R. V. *Tetrahedron Lett.* **2000**, *41*, 10327.
[7] For a review, see: Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479.
[8] Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. Org. Lett. **2001**, *3*, 2785.
[9] (a) Aggarwal, V. K. *Synlett*. **1998**, 329. (b) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Int. Chem. Ed*. **2001**, *40*, 1430.
[10] Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Int. Chem. Ed*. **2001**, *40*, 1433.
[11] For a review, see: Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev*. **2003**, *103*, 2861.
[12] For a review, see: Li, H.; Zhang, Y.; Wang, J. *Synthesis* **2013**, *45*, 3090.



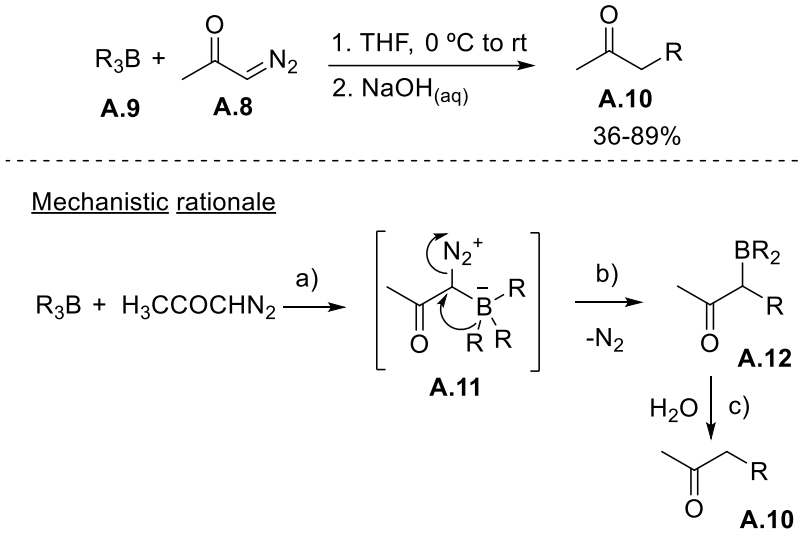
Scheme I. 2. Examples of important transformations of diazo compounds generated *in situ* from *N*-tosylhydrazones derived from aldehydes.

Considering the main topic of this thesis dissertation, in this introduction, the main goals in the metal-free coupling reactions between organoboron compounds and both diazo compound species and *N*-sulfonylhydrazones will be covered. Moreover, recently discovered sequential multicomponent coupling reactions, and cascade processes in which organoboron intermediates are trapped will also be highlighted.

I. 1. Early background: reactions with alkylboranes and either *N*-tosylhydrazones or diazocompounds

I.1.1. Reactions of diazocompounds with alkylboranes

In 1968, Hooz and coworkers reported the reaction between diazo ketones, which are stabilized diazo compounds, and alkylboranes that furnished the alkylated ketones **A.10**, with loss of a molecule of N_2 (Scheme I.3).[13] Since the alkylborane compounds **A.9** were prepared by hydroboration of the corresponding olefins, the overall transformation could be considered as a new method to homologate alkenes to ketones.



Scheme I. 3. Reactions between organoboranes and diazo ketones. Mechanistic rationale.

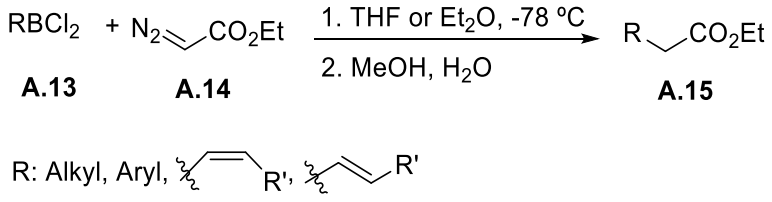
Although no mechanistic studies were undertaken when this work was published, the authors postulated the following sequence: a) Lewis acid-Lewis base interaction of the diazo ketone **A.8** with the alkylborane **A.9** to form the boronate intermediate **A.11**; b) rapid 1,2-alkyl shift with concomitant extrusion of nitrogen;

[13] Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936.

and c) boron-carbon bond fission of the α-borylketone **A.12** mediated by alkaline hydrolysis to form the final products **A.10**.

Although this reaction was initially described as a general way to homologate olefins into ketones, there were some limitations associated to this transformation. First, it must be pointed out that the employment of hindered organoboranes turned out to give poor yields in the homologation reaction. Secondly, the scant availability of the diazo species **A.8** and organoboranes **A.9** unavoidably limited the scope of the reaction. However, it must be noted that during the following years after this work was reported, the same authors continued with the development of this transformation but employing other stabilized diazo compounds; such as ethyl diazoacetate, diazoacetonitrile, bisdiazoketones and diazoacetaldehyde.[14]

The overall transformation should be considered as an original organoborane-based synthetic methodology in which a carbon-carbon bonds is formed under transition-metal-free conditions. In the next years after the publication of this work, the same kind of reactivity was employed in modified Hooz reactions of alkyldichloroboranes, aryldichloroboranes and 1-alkenyldichloroboranes **A.13** with ethyl diazoacetate **A.14** (Scheme I.4);[15] affording the corresponding alkyl, aryl or alkenylated acetates **A.15** respectively. The compounds **A.13** were synthesized through hydroboration of the corresponding olefins employing simple described methodologies.



Scheme I. 4. Reactions of dialkylchloroboranes with stabilized diazo compounds.

[14] (a) Hooz, J.; Linke, S. *J. Amer. Chem. Soc.* **1968**, *90*, 6891. (b) Hooz, J.; Gunn, D. M. *Chem. Commun.* **1969**, 139. (c) Hooz, J.; Morrison, G. F. *Can. J. Chem.* **1970**, *48*, 868.

[15] (a) Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Amer. Chem. Soc.* **1972**, *94*, 3662. (b) Hooz, J.; Bridson, J. N.; Calzada, J. G.; Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Org. Chem.* **1973**, *38*, 2574. (c) Brown, H. C.; Salunkhe, A. M. *Synlett* **1991**, 684.

The employment of the dichloroborane derivatives presented some advantages. First of all, the lower steric hindrance in comparison with the analogous trialkylboranes enabled the accommodation of bulky groups in the borane, unsatisfactory in the original Hooz reaction. Furthermore, the electron withdrawing nature of the chlorine atoms increased the electronic deficiency of the boronic center, allowing for a fast formation of the boronate intermediates. Irrespective of the mechanism involved (but proposed the same as for the Hooz reaction), these reactions took place under exceedingly mild conditions (from -65 to -78 °C).

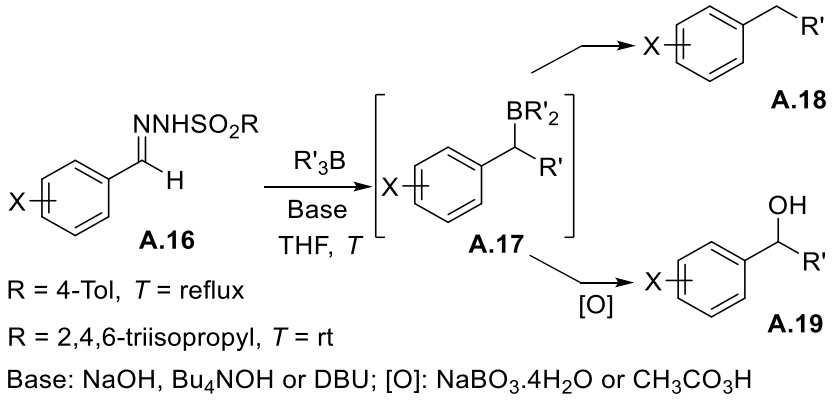
I.1.2. Reactions of alkylboranes with *N*-sulfonylhydrazones

Prof. Kabalka and coworkers described in 1994 the first reaction in which *N*-sulfonylhydrazones reacted with organoborane compounds. Their first experiments were conducted employing *N*-tosylhydrazones and trialkylboranes.[16] Later on, the work was extended to the use of trisylhydrazones[17] (much more milder reaction conditions were needed, also improving the yields of the alkylation reactions) and other sulfonylhydrazones derived from aryl or heteroaryl moieties.[18] The overall work is summarized in Scheme I. 5.

Kabalka found the distinction upon employing nucleophilic (NaOH, Bu_4NOH) or non-nucleophilic (DBU) bases in this transformation. The mechanism proposed for this reaction postulates the formation of the intermediate **A.17**. When the strongly nucleophilic bases were used, the final protonolysis products **A.18** were obtained in good yields. However, if a non-nucleophilic base as DBU was used, the deboronation of the intermediate **A.17** was prevented, and in combination with the employment of an oxidant ($NaBO_3.4H_2O$ or CH_3CO_3H, depending on the electronic properties of the arysulfonylhydrazones), the boronate **A.17** was oxidized to the alcohol derivatives **A.19**.

[16] Kabalka, G. W.; Maddox, J. T.; Bogas, E. *J. Org. Chem.* **1994**, *59*, 5530.
[17] Kabalka, G. W.; Maddox, J. T.; Bogas, E.; Tejedor, D.; Ross, E. J. *Synth. Commun.* **1996**, *26*, 999.
[18] Kabalka, G. W.; Maddox, J. T.; Bogas, E.; Kelley, S. W. *J. Org. Chem.* **1997**, *62*, 3688.

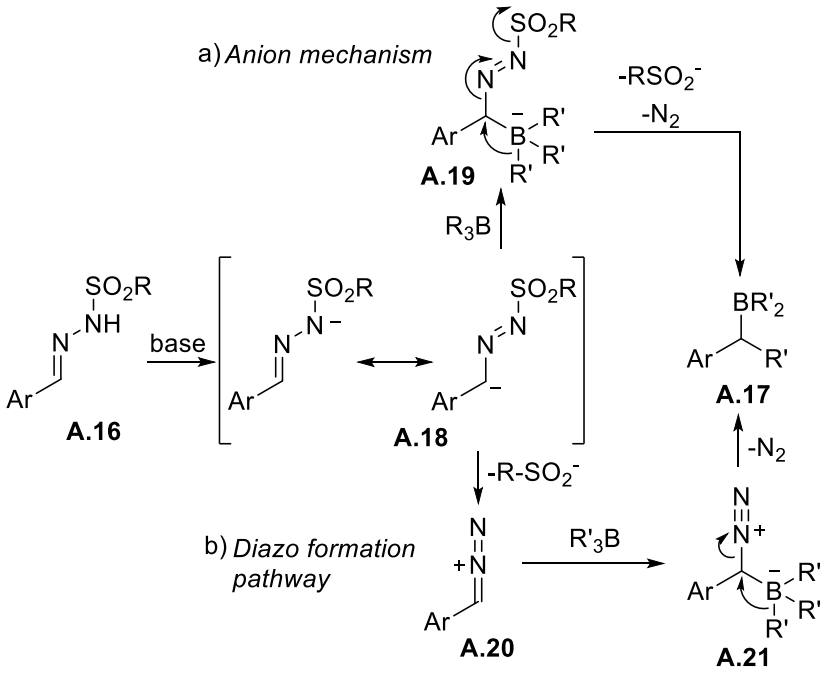
Interestingly, under these reaction conditions, the functionalization in both the sulfonylhydrazones and boranes was possible. These functionalized groups would not be compatible with the use of other more nucleophilic organometallic reagents, such as organolithium of Grignard reagents, and therefore increased the importance of Kabalka's reaction when considering other synthetic alternatives.



Scheme I. 5. First synthetic approach by Kabalka in the reaction between *N*-sulfonylhydrazones and alkylboranes.

There were two possible mechanistic courses to rationalize how the reaction took place (Scheme I.6):

a) In the first one, the anion mechanism, the deprotonation of the starting *N*-tosylhydrazone **A.16** would generate the anionic species **A.18**. The trialkylborane would then react with this anion, forming an electron-rich organoboronate **A.19** that would spontaneously undergo a 1,2-alkyl shift, expelling nitrogen and the sulfinate anion to end up forming the organoborane **A.17**. This intermediate would then be hydrolyzed to the corresponding alkylated product **A.18** or oxidized to the alcohol **A.19**.

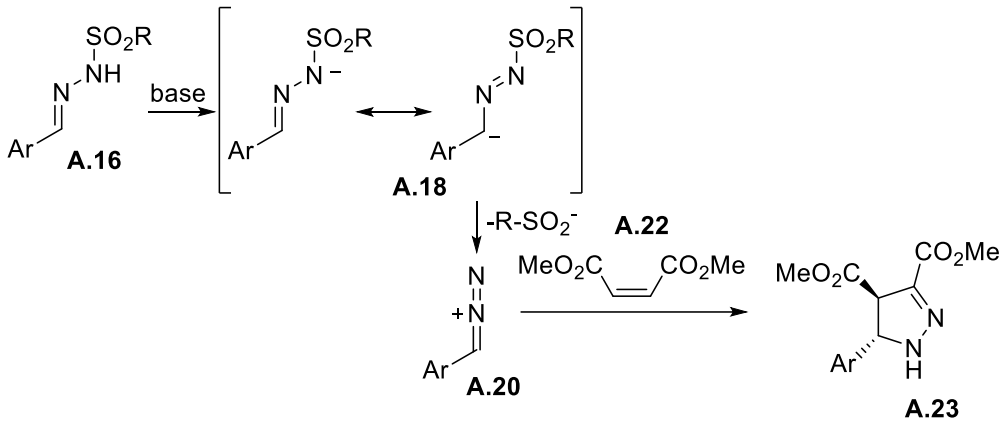


Scheme I. 6. Mechanism alternatives for the reaction between *N*-sulfonylhydrazones and alkylboranes.

b) Alternatively, the reaction could evolve through the formation of the diazo species **A.20** after deprotonation of the sulfonylhydrazone **A.16**, as previously described for the Bamford-Stevens reaction. The diazo compound would then react with the trialkylborane to form the borate complex **A.21**, in which nitrogen is released upon 1,2-alkyl shift to form the intermediate **A.17**. It must be noticed that the only difference between these two mechanistic pathways is the exact moment in which the sulfinate group is lost, and that explained the difficulty in demonstrating which course is the one that truly operated.

Some experiments were done to try to demonstrate the mechanistic pathway. It was found that the reaction of trialkylboranes with aryldiazocompounds also took place, but a large excess of the organoboron was required in comparison with the amount needed when the *in situ* generation of the diazo species took place. In parallel, in an experiment in which dimethyl maleate **A.22** was made to react with the sulfonylhydrazones under reflux in the absence of the trialkylborane, the

expected pyrazoline **A.23** derived from a 1,3-dipolar cycloaddition reaction was formed (Scheme I. 7).



Scheme I. 7. Reaction of diazo compound **A.20** with dimethyl maleate.

When the same reaction was conducted adding a tryalkylborane, the corresponding alcohol products were obtained in 80% isolated yield and none of the pyrazoline **A.23** was detected. These results pointed at the anionic pathway as the one that took place in the reaction.

However, although this methodology may seem as a potential route for the α-alkylation of carbonyl compounds, the reality was its practically inexistent impact on the synthetic methodology in the following years. This fact can be justified by the limited scope regarding the sulfonylhydrazones, restricted to those derived from aromatic aldehydes, and the previously described drawbacks of employing trialkylborane compounds.

I. 2. Reactions of *N*-sulfonylhydrazones and diazo compounds with alkyl- and arylboronic acids

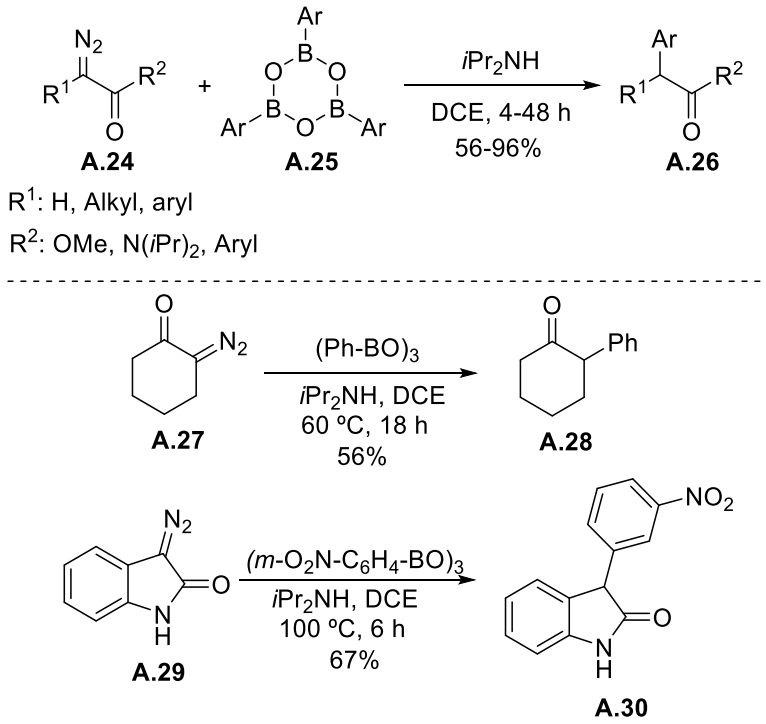
In 2009, the advances in the chemistry reported by our research group and independently, in Wang's group, marked a turning point in the future lines of work in the chemistry of *N*-sulfonylhydrazones and organoboron compounds.

I.2.1. Reactions of arylboroxines with diazo compounds

In 2009, Wang and coworkers described an alternative approach for the α-arylation of carbonyl compounds through the reaction of α-diazocarbonyl compounds and aryl boroxines under mild conditions (Scheme I.8.).[19] Both diazo compounds **A.24** and arylboroxines **A.25** are easily available, fact that increases the importance of this transformation due to the great scope that was reached through this reaction in the synthesis of α-arylated carbonyl or carboxylate compounds **A.26**. Remarkably, the reaction is compatible with the use of cyclic α-diazocarbonyl species such as compound **A.27** and the cyclic aromatic α-diazoamide **A.29** in the formation of the final α-arylated systems **A.28** and **A.30**, respectively.

Although the authors report no mechanistic evidence for these transformations, it is speculated that the mechanism is the very similar to the one described by Hooz in section I.1. The diisopropylamine is believed to neutralize acidic species that could be formed during the reaction and would decompose the diazo species, therefore improving the yield of these transformations.

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



Scheme I. 8. Reactions between arylboroxines and α-diazo carbonyl compounds.

I.2.2. Reductive couplings of *N*-sulfonylhydrazones with alkyl- and arylboronic acids

Until now in this section of the Introduction, all the reactions that were described presented two main limitations: the diazo compounds employed needed to be stabilized with an electron withdrawing group in the α position, or the use or *N*-sulfonylhydrazones was restricted to aromatic aldehydes. The main problem of *in situ* generating unstable diazo compounds is their tendency to form alkenes through the previously described Bamford-Stevens reaction.

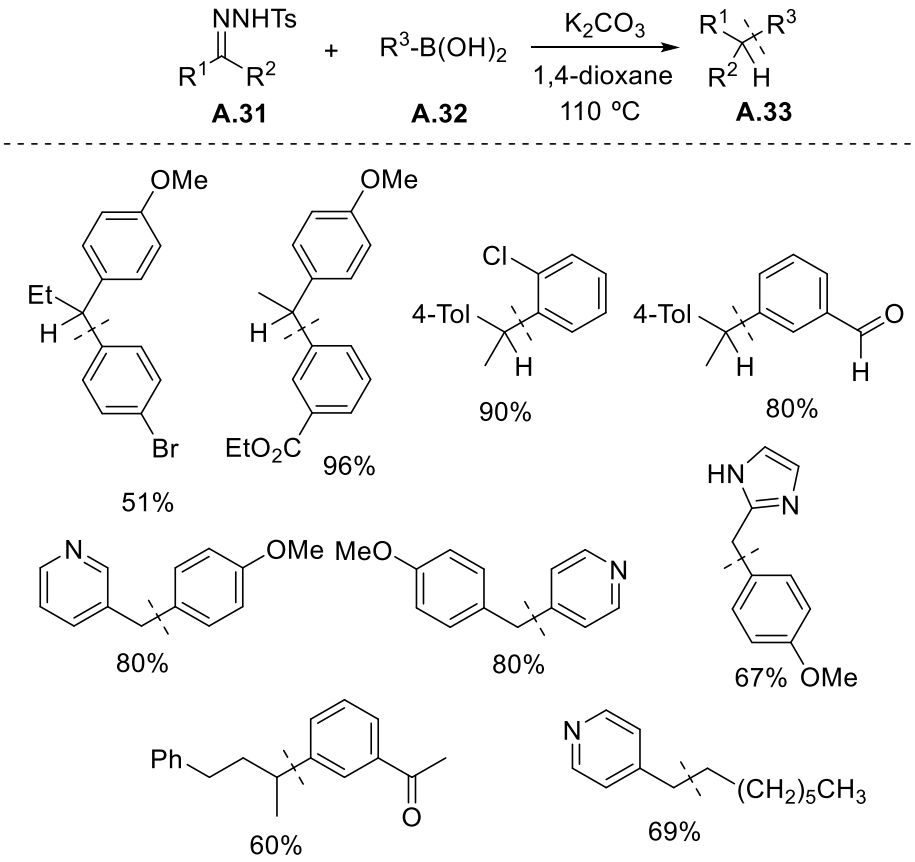
The employment of *N*-tosylhydrazones with enolizable hydrogens was popularized by our research group upon the discovery of the Pd-catalyzed cross coupling with aryl halides.[20] This transformation afforded polisubstituted alkenes with good yields in a broad scope, employing *N*-tosylhydrazones derived from both aldehydes and ketones.

In the context of the interest on the chemistry of *N*-tosylhydrazones, in 2009 our research group reported the reductive coupling of *N*-tosylhydrazones and boronic acids for the first time.[21] The use of boronic acids presents advantages in comparison with the use of other organometallic reagents,[22] such as its commercial availability, bench stability and low toxicity. Furthermore, in their manipulation under the reaction conditions of this work, no inert or dry atmosphere was needed, what increased the experimental simplicity of the reaction.

Initial experiments in which an aryltosylhydrazone was heated in the presence of an arylboronic acid and base in 1,4-dioxane as solvent led to the formation of the corresponding cross-coupling reaction in which a C-C had been formed between the hydrazonic carbon and the carbon attached to the boron center. This outstanding result encouraged the authors to try to broaden the scope of this new transformation with regard to the boronic acids and *N*-tosylhydrazones employed. Some remarkable examples of this transformation were selected and

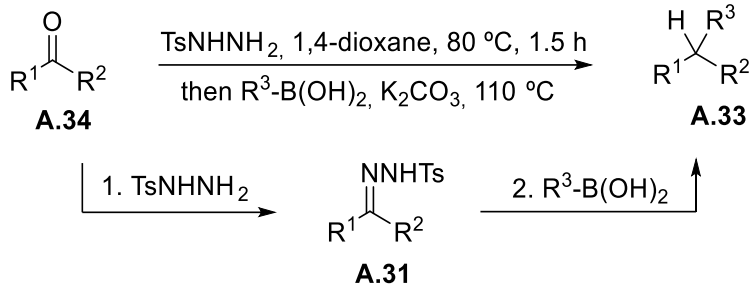
[20] (a) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 5587. (b) Barluenga, J.; Tomás-Gamasa, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem. Eur. J.* **2008**, *14*, 4792.
[21] Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494.
[22] Hall, G. D. *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*. Wiley-VCH, **2004**.

depicted in Scheme I.9. The reaction is general for *N*-tosylhydrazones derived from aryl or heteroaryl carbonyl compounds with or without enolizable hydrogens. Interestingly, *N*-tosylhydrazones derived from acyclic aliphatic aldehydes or ketones could also participate in this reaction. Moreover, the reaction is tolerant to the presence of functional groups, such as esters, nitriles, halogens or unprotected amines; fact that skips the necessity of employing protective groups prior to the transformation and enables possible further derivatization alternatives of those groups.



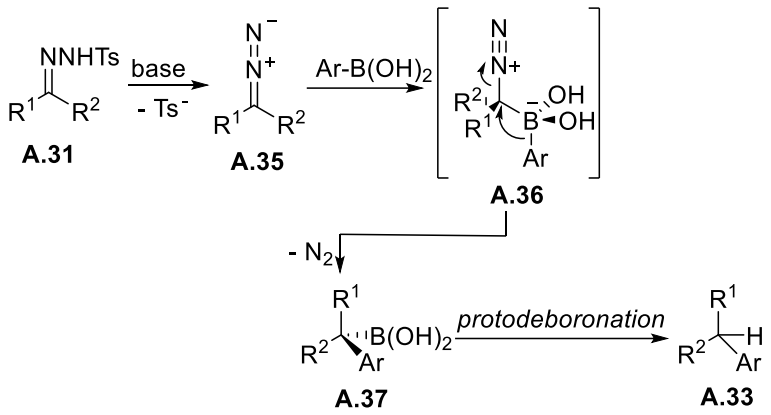
Scheme I.9. Transition-metal-free reductive coupling of *N*-tosylhydrazones with aryl and alkylboronic acids. Selected examples are shown.

Remarkably, the reaction was found to be feasible starting from the carbonyl compound in a one-pot sequence (Scheme I.10), in which the *N*-tosylhydrazones **A.31** were first of all generated in 1,4-dioxane and, after that, the boronic acids and K_2CO_3 were added. This transformation allows for the direct reductive arylation or alkylation of a carbonyl compound **A.34** in a simple way, transformation that would require several steps and/or necessity of protective groups following other different methodologies.



Scheme I.10. Reductive coupling of carbonyl compounds with boronic acids in a one-pot fashion.

The mechanism proposed for this transformation (Scheme I.11) is very similar to the one shown in section I.1.1. for the Kabalka's reaction with trialkylboranes and *N*-sulfonylhydrazones through formation of a diazo species. First, the *N*-tosylhydrazones **A.31** would decompose under thermal conditions through a Bamford-Stevens reaction to form the diazo compound **A.35**. This intermediate would react with the boronic acid in a Lewis acid-Lewis base interaction to form the zwitterionic organoborane **A.36**, in which a simultaneous 1,2-carbon boron shift and release of N_2 takes place. The mechanistic course ends up in the formation of the benzyl boronic acid **A.37**, which affords the reductive arylation products **A.33** after protodeboronation.

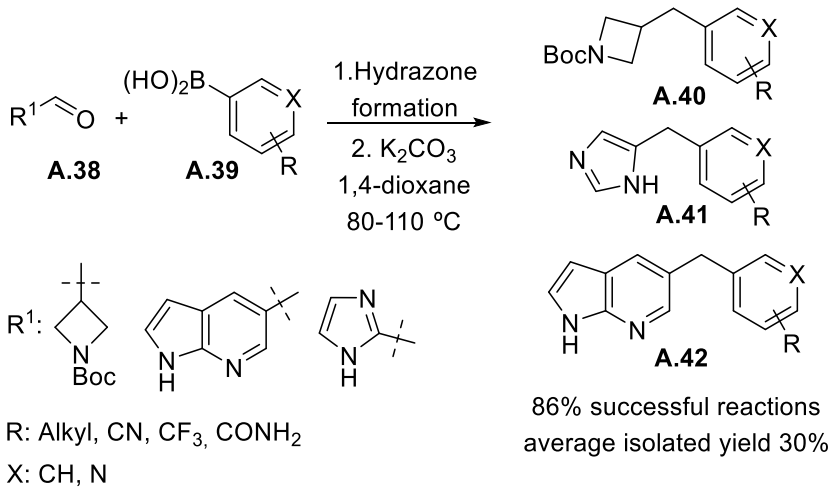


Scheme I. 11. Mechanistic rationale for the reductive coupling of *N*-tosylhydrazones and boronic acids.

All in all, this research ended up in the discovery of a novel metal-free C-C bond forming reaction. Its simplicity, generality in both coupling partners, easy availability, and functional group and solvent tolerance stand as the major highlights of this transformation.

Thanks to this outstanding achievement, some groups decided to employ this methodology for synthetic purposes in medicinal and materials chemistry. In particular, the group of Ryckmans applied the transformation to the parallel synthesis of drug-like and drug fragment-like molecules (Scheme I.12) in 2012.[23] In this context, *N*-tosylhydrazones derived from heterocyclic and heteroaryl aldehydes **A.38** were synthesized and reacted with various functionalized boronic acids **A.39**. The C-C bond forming protocol enabled the one-pot synthesis, starting from carbonyl compounds, of interesting structures for the application in drug discovery, such as the heterocyclic scaffolds **A.40**, **A.41** and **A.42**. These compounds were obtained in most of the cases (86% success index) with yields ranging from 2 to 62%.

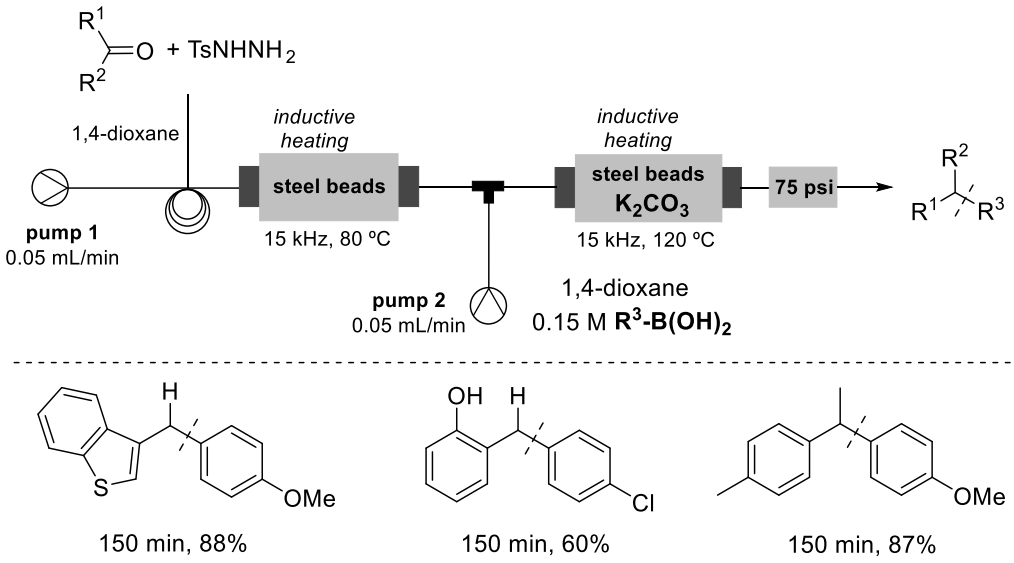
[23] Nakagawa, S.; Bainbridge, K. A.; Butcher, K.; Ellis, D.; Klute, W.; Ryckmans, T. *ChemMedChem.* **2012**, *7*, 233.



Scheme I.12. Application of the metal-free reductive coupling to the synthesis of drug-like scaffolds by Ryckmans and coworkers.

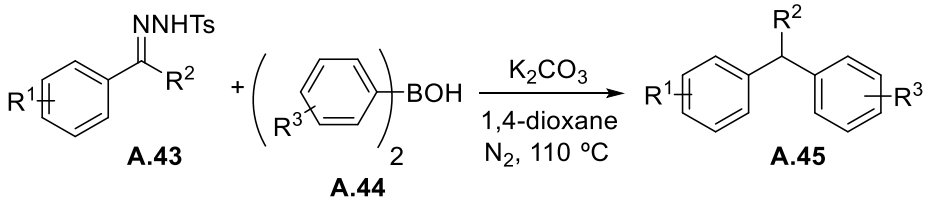
Continuing with some other applications of this reaction by other groups, in 2012 Kirschning found that the reductive coupling reaction between *N*-tosylhydrazones and arylboronic acids was doable through an optimized two-step flow protocol.[24] Starting from the respective carbonyl compounds, *N*-tosylhydrazones were formed in the first flow step. The hydrazones were directly transferred to a second flow reactor to be coupled with the boronic acids. Both steps needed heating, which was achieved thanks to electromagnetic induction being applied on a fixed bed material based on steel beads. A continuously conducted two-step flow process over a period of almost 2 days was needed to afford the corresponding coupling products. Some examples were selected, and the overall process is shown in Scheme I.13.

[24] Kupracz, L.; Kirschning, A. *J. Flow. Chem.* **2012**, *3*, 11.



Scheme I.13. Reductive coupling of carbonyl compounds and arylboronic acids following a continuous flow protocol. Selected examples are shown.

Also in 2012, Zou and coworkers reported the reductive coupling between aromatic *N*-tosylhydrazones **A.43** (derived from both aldehydes and ketones) and arylborinic acids **A.44**.[25] The procedure is compatible again with the presence of functional groups like hydroxyl, amine, halide or allyl ones. The final diarylmethanes **A.45** were synthesized with yields ranging from 14 to 93%.

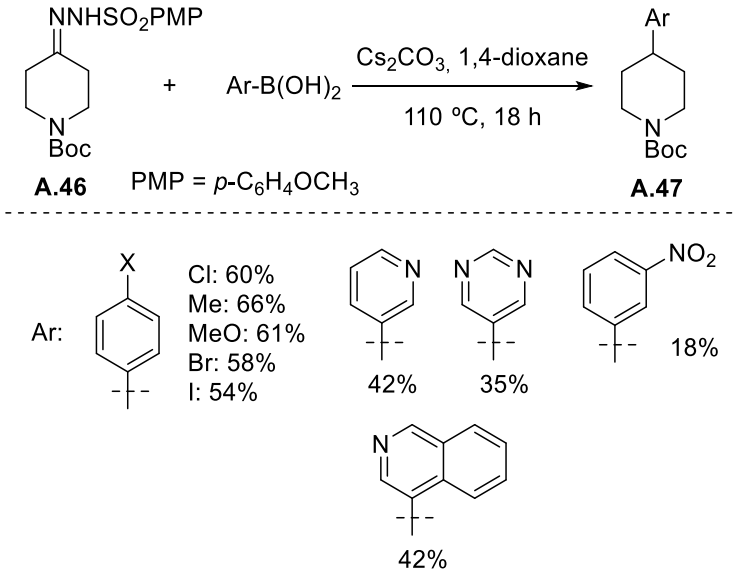


Scheme I.14. Synthesis of diarylmethanes *via* reductive coupling of *N*-tosylhydrazones and arylborinic acids.

[25] Li, X.; Feng, Y.; Lin, L.; Zou, G. *J. Org. Chem.* **2012**, *77*, 10991.

The authors highlight the higher atom economies of arylborinic acids over the employment of arylboronic acids. Nevertheless, the scarce commercial availability of borinic acids when compared with their boronic acids analogues might explain why this transformation is limited from a synthetical point of view.

In 2013, Allwood and Ley[26] extended the use of the metal-free reductive transformation to the use of cyclic *N*-tosylhydrazones (until this moment, only acyclic sulfonylhydrazones were reported to work under these conditions). More precisely, the authors reported the metal-free coupling of 4-, 5- and 6-membered saturated heterocyclic *p*-methoxyphenylsulfonylhydrazones with aryl and heteroaromatic boronic acids. The main two differences if compared to the standard reaction conditions are: a) *PMP*-sulfonylhydrazones were found give better yields in some cases and b) C_2CO_3 was found also to improve the yields when compared to the employment of the analogous carbonate K_2CO_3 as base.

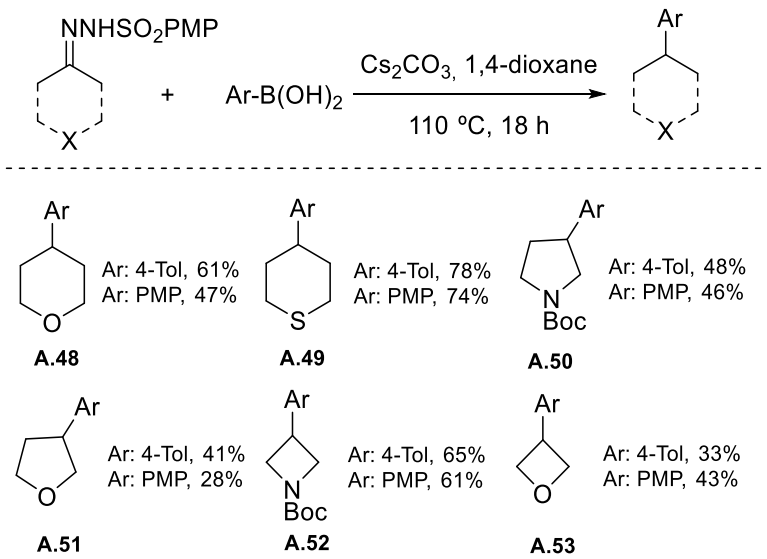


Scheme I.15. Transition-metal-free reactions of arylboronic acids with 4-piperidone *N*-sulfonylhydrazone **A.46** to form 4-aryl-*N*-Boc-piperidines **A.47**.

[26] Allwood, D. M.; Blakemore, D. C.; Brown, A. D.; Ley, S. V. *J. Org. Chem.* **2013**, *79*, 328.

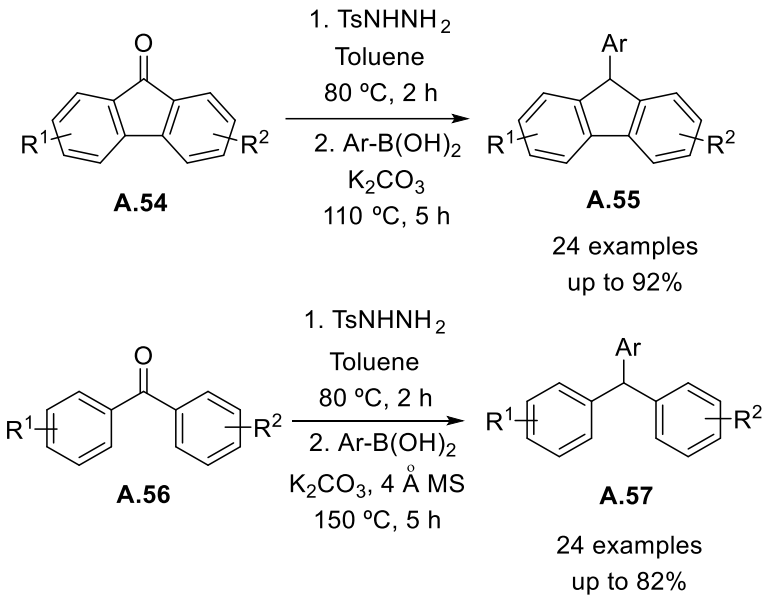
Initially, these new optimized conditions were used in the synthesis of arylated *N*-Boc-piperidines with different substitutions thanks to the versatility of the arylboronic acid employed (Scheme I.15).

The scope of this transformation was broadened thanks to the employment of other *p*-methoxyphenylsulfonylhydrazones of other cyclic carbonyl compounds, such as the 6-membered rings tetrahydro-4*H*-pyran-4-one and tetrahydro-4*H*-thiopyran-4-one; the 5-membered cyclic ketones 1-Boc-3-pyrrolidinone and dihydrofuran-3(2*H*)-one; and the 4-membered rings oxetan-3-one and 1-Boc-3-azetidinone. Respectively, the reductive coupling products 4-aryltetrahydropiranes **A.48** and 4 aryltetrahydrothiins **A.49**; 3-arylpyrrolidines **A.50** and 3-aryltetrahydrofuranes **A.51**; and 3-arylazetidines **A.52** and 3-aryloxetanes **A.53** were furnished in yields ranging from 28 to 78% (Scheme I.16).



Scheme I.16. Reaction of sulfonylhydrazones with arylboronic acids to form aryl-substituted saturated heterocycles **A.48**-**A.53**

As it was pointed out before, this reaction had also important applications in the field of materials chemistry. Concretely, the group of Liu and coworkers have applied the reductive coupling strategy between *N*-tosylhydrazones and boronic acids to the synthesis of 9-arylfluorene derivatives.[27] This methodology is carried out one-pot in two steps which involved the preparation of *N*-tosylhydrazones by reacting *p*-toluenesulfonylhydrazide with 9-fluorenone derivatives **A.54**, and subsequent reaction with a variety of arylboronic acids to afford the final 9-arylfluorene compounds **A.55** in a broad scope (Scheme I.17). The same authors also described the synthesis of triarylmethanes **A.57** following again a one-pot fashion to mix the starting diaryl ketone **A.56**, tosylhydrazide and the arylboronic acid.[28] In this case, it was needed to increase the temperature of the reaction to 150 °C to improve the yields of the transformation, explained by the lesser reactivity of the *N*-tosylhydrazones derived from **A.56** compounds.

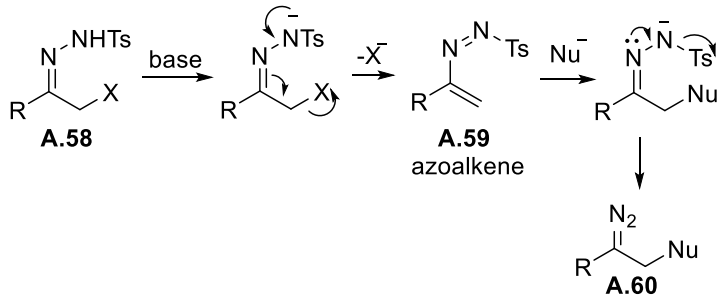


Scheme I.17 Synthesis of 9-arylfluorenes and triarylmethane derivatives by Liu and coworkers.

[27] Shen, X.; Gu, N.; Liu, P.; Ma, X.; Xie, J.; Liu, Y.; He, L.; Dai, B. *RSC Adv.* **2015**, *5*, 63726.
[28] Shen, X.; Gu, N.; Liu, P.; Ma, X.; Xie, J.; Liu, Y.; Dai, B. *Chinese J. Chem.* **2016**, *34*, 1033

I.2.3. Three-component reaction between α-halotosylhydrazones, boronic acids and indoles

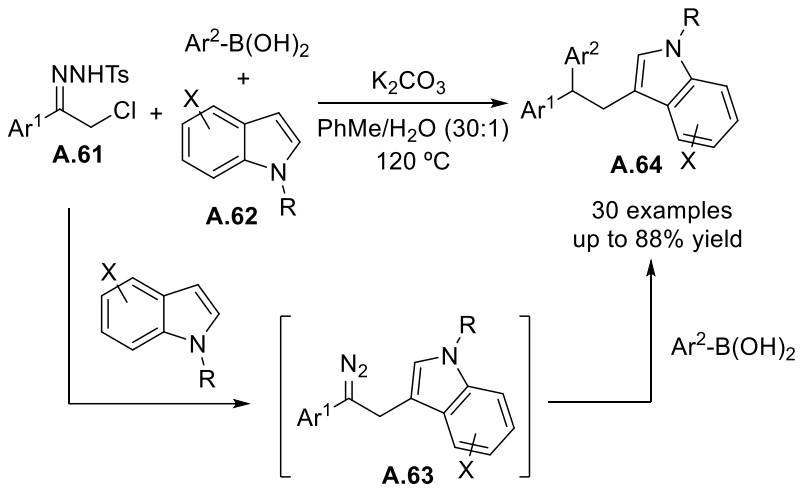
In 2016, Wang´s group reported the use of *α*-halotosylhydrazones as reagents for the formation of multiple carbon-carbon bonds in a three-component reaction.[29] While the most common reactivity of *N*-tosylhydrazones stands in their ability to *in situ* generate diazo compounds through the Bamford-Stevens reaction, α-halotosylhydrazones **A.58** do not follow this reaction pathway. In this particular case, an azoalkene **A.59** is formed. Interestingly, the azoalkenes formed *in situ* starting from α-halotosylhydrazones are highly susceptible to conjugate additions. The original idea was to generate diazo compounds **A.60** by introducing a nucleophile through the process shown in Scheme I.18.



Scheme I.18. *In situ* formation of diazo compound **A.60** from α-halotosylhydrazones in the presence of a nucleophile.

Indoles were employed as suitable nucleophiles for this transformation. The reaction was generalized for the synthesis of a variety of 3-substituted indoles **A.64**, with yields ranging from moderate to excellent. Once the intermediate **A.63** is formed after reaction of the indol **A.62** with the azoalkene derived from compounds **A.61**, a reductive arylation is achieved by the reaction of intermediate **A.63** with the arylboronic acids. It was found that a mixture 30:1 of toluene/water was optimal to reach the best reaction outcome.

[29] Wu, G.; Deng, Y.; Luo, H.; Zhou, J.; Li, T.; Zhang, Y.; Wang, J. *Chem. Commun.* **2016**, *52*, 5266.



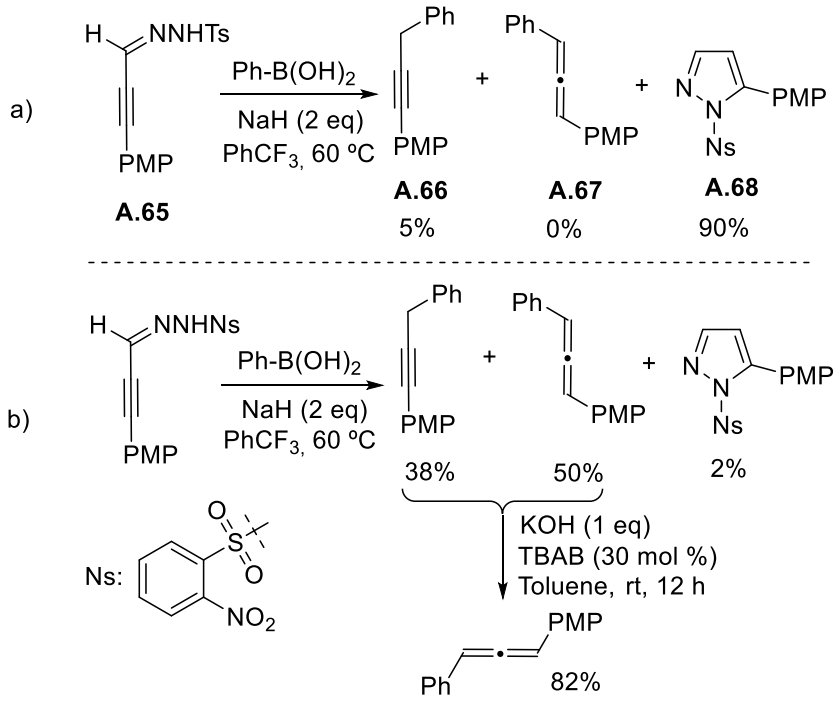
Scheme I.19. One-pot multicomponent synthesis of 3-substituted indoles **A.64**.

I. 3. Reactions between alkynyl *N*-nosylhydrazones and boronic acids: synthesis of allenes

Until this point of the Introduction, the decomposition of *N*-tosylhydrazones was described as a safe method in which donor carbenes were generated. Nevertheless, alkynyl carbenes could not be isolated employing this route to react with boronic acids, because they readily undergo intramolecular cyclization to form pyrazoles **A.68** as soon as formed from alkynyl *N*-tosylhydrazones **A.65** (Scheme I.20.a). This is the reason why the employment of this kind of hydrazones had little impact on the synthetic organic field.

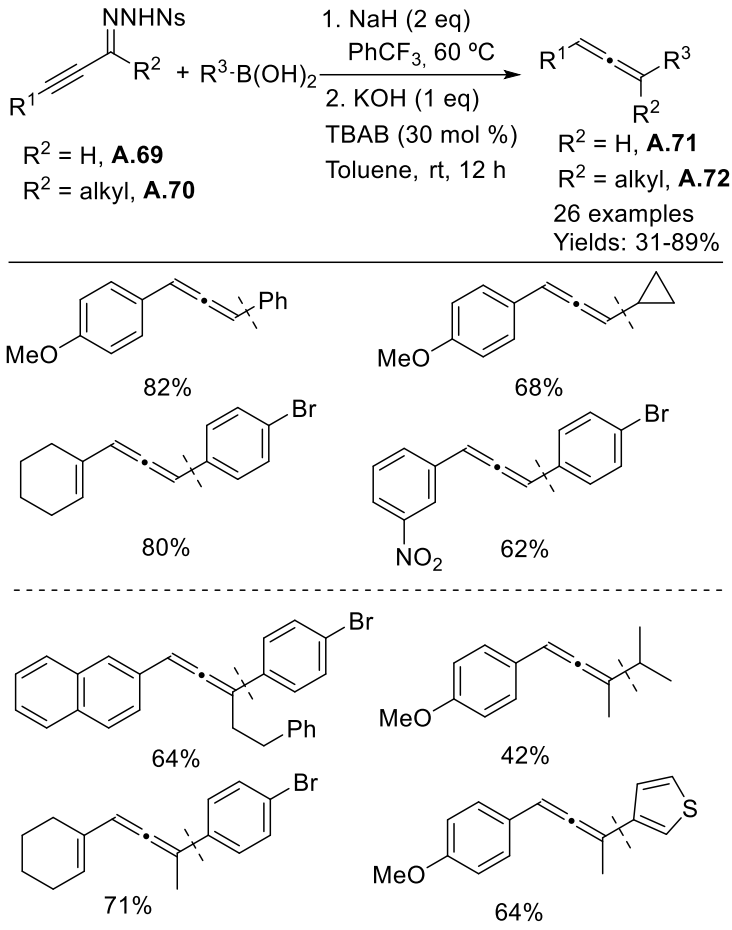
Bi's group reported in 2017 the employment of *N*-nosylhydrazones as reagents which could grant the *in situ* formation of unstable diazo compounds under much milder conditions than when employing their *N*-tosylhydrazones analogues.[30] However, in these two works the employment of silver salts as the catalysts of transformations with different purposes was found to be essential. It was not until his last seminar contribution when a transformation employing *N*-nosylhydrazones was reported in the context of transition-metal-free reactions.[31] In this work, they described the use of alkynyl *N*-nosylhydrazones as convenient sources for the *in situ* generation of alkynyl carbenes and their coupling reaction with boronic acids under metal-free conditions. In this way, the formation of the undesired pyrazole **A.68** is avoided, maximizing the yield in the formation of an allene derivative **A.67** (Scheme I.20.b).

[30] (a) Liu, Z.; Li, Q.; Yang, Y.; Bi, X. *Chem. Commun.* **2017**, *53*, 2503. (b) Liu, Z.; Li, Q.; Liao, P.; Bi, X. *Chem. Eur. J.* **2017**, *23*, 4756.
[31] Yang, Y.; Liu, Z.; Porta, A.; Zanoni, G.; Bi, X. *Chem. Eur. J.* **2017**, *23*, 9009.



Scheme I.20. Comparison of the reaction outcomes when a) *N*-tosylhydrazones or b) *N*-nosylhydrazones are employed in the reaction with arylboronic acids.

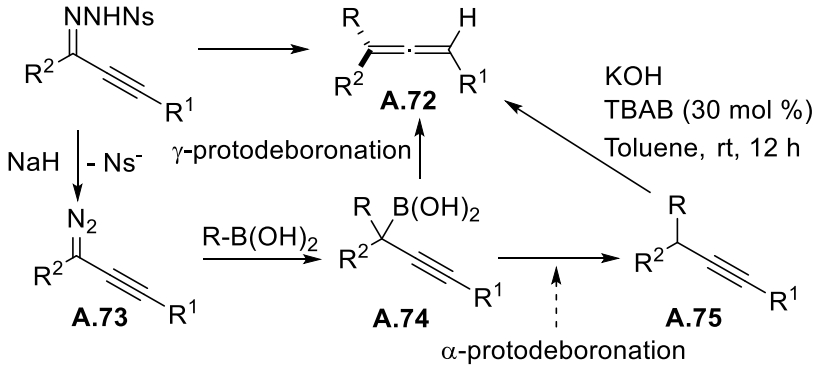
These optimized preliminary results enabled to broaden the scope for the allene synthesis. Both alkyl and arylboronic acids were found to be suitable for this transformation. Propargylic aldehydes and ketones were reported to be suitable as precursors for the *N*-nosylhydrazones **A.69** and **A.70** and their reaction with the boronic acids. In this manner, di- or trisubstituted allenes could be synthesized (compounds **A.71** and **A.72**, respectively) from moderate to good yields (selected examples are depicted in Scheme I.21).



Scheme I. 21. First metal-free reaction of alkynyl *N*-nosylhydrazones with boronic acids. Selected examples in the synthesis of di- and trisubstituted allenes are shown.

The authors propose the following mechanism for their transformation (Scheme I.22). The alkynyl *N*-nosylhydrazone would undergo a thermal decomposition mediated by base (NaH) to form the alkynyl diazomethane **A.73**. This compound would immediately react with the boronic acid to form the propargylboronic acid 75, thanks to a 1,2 migration of the group attached to the boron center. A γ-protodeboronation promoted by the given basic reaction conditions would lead to the formation of the allene **A.72**. The authors highlight this last step as the first example of a γ-protodeboronation involving a C-C triple bond. Alternatively, the intermediate **A.74** could also lead to the formation of the propargyl

derivative **A.75**, derived from a α-protodeboronation process. However, a final treatment with a mixture of potassium carbonate and TBAB would convert the compound **A.75** into the allene **A.72** in an isomerization reaction.



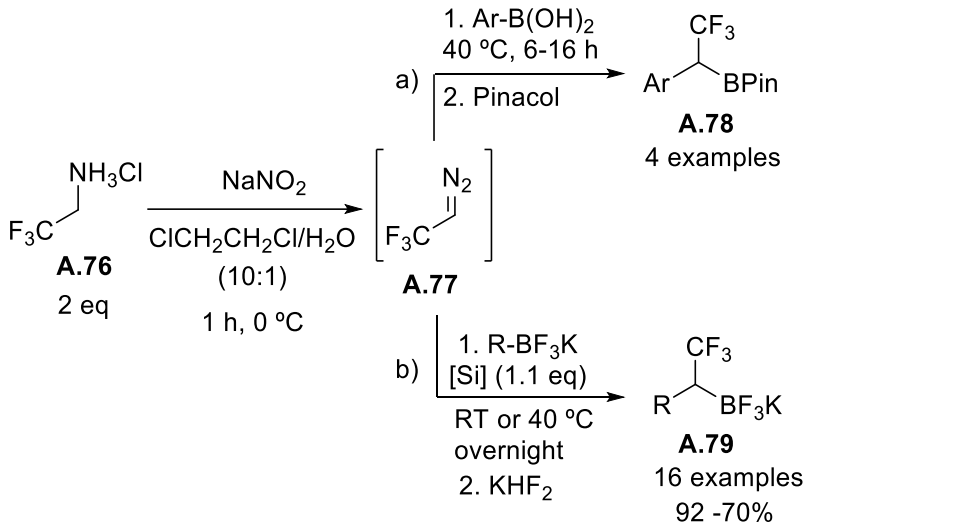
Scheme I.22. Mechanistic rationale for the formation of allenes **A.72** considering both α- and γ- protodeboronation routes of intermediate **A.74**

I. 4. Reactions with diazocompounds generated by diazotization of primary amines

The synthesis of 2,2,2-trifluorodiazoethane (CF_3CHN_2) in a large scale starting from the corresponding ammonium salt was reported in the early 1940s by Jones.[32] Nevertheless, it was not until 2010 when Carreira's group[33] started to use this reagent in synthetically relevant transformations, based on the *in situ* generation of this reagent for further reactions with other organic compounds. Carreira indicated that the reactivity of the 2,2,2-trifluorodiazoethane species was similar to the one found for ethyl diazoacetate. However, among those transformations it was not reported its reaction with organoboron compounds.

In 2013, Molander and co-workers employed Carreira's methodology to *in situ* generate CF_3CHN_2, which would then react in an unprecedented way with organoboron compounds (Scheme I.23).[34] As shown in this scheme, in the first step the 2,2,2-trifluorodiazoethane species **A.77** is generated by diazotization of the corresponding hydrochloride amine salt **A.76**. The authors reported in their publication two different reaction pathways which this intermediate could participate in. On the one hand, species **A.77** was reported to react with arylboronic acids to afford a benzylic acid that was trapped upon employment of pinacol to finally form the α-trifluoromethyl boronate derivatives **A.78** (Scheme I.23. a). It must be pointed out that, unlike when employing *N*-tosylhydrazones, the benzylic boronic acid intermediate does not undergo protodeboronation, being enough stable to be trapped with pinacol. However, the authors point some disadvantages referred to the use of boronic acids in their transformation, such as the oxidation of the α-trifluoromethylated pinacol boranes when purified by flash chromatography to the corresponding alcohols, and therefore the yield of the isolated final products significantly dropped.

[32] Gilman, H.; Jones, R. G. *J. Am. Chem. Soc*. **1943**, *65*, 1458.
[33] Morandi, B.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 938.
[34] Argintaru, O. A.; Ryu, D.; Aron, I.; Molander, G. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 13656.

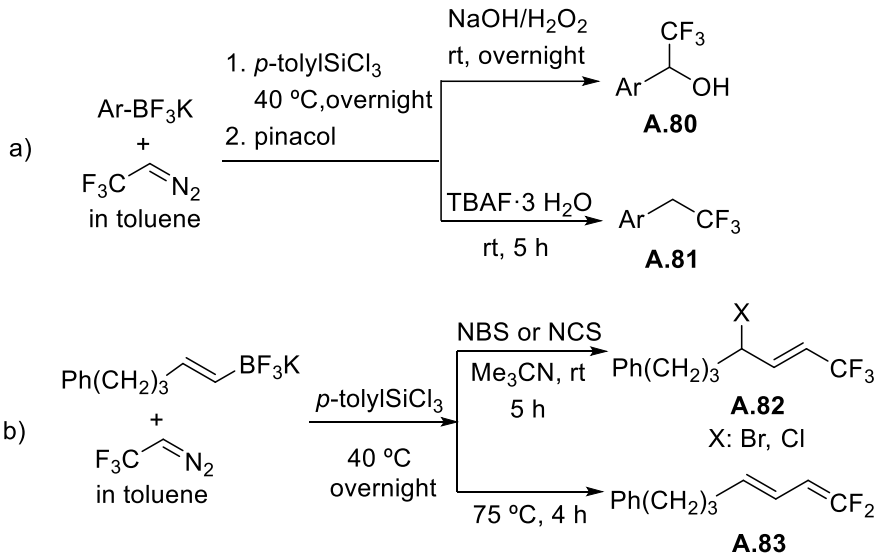


Scheme I.23. *In situ* generated 2,2,2-trifluorodiazoethane **A.77** reacts with both boronic acids (pathway a) and trifluoroborates (pathway b).

To address these issues, the authors looked for an alternative route in which other different organoboron compounds could be employed instead of boronic acids. In this regard, the analogous potassium organotrifluoroborate salts were considered. Vedejs et al. and Kim and Matteson[35] had previously described that dihaloboranes could be synthesized starting from R-BF_3K salts upon treatment with $SiCl_4$ or TMSCl. The silicon species acts as a fluorophile that exchanges the fluorine atoms in the organotrifluoroborate salts and *in situ* forms the more reactive chlorine analogues. This strategy was found to be optimal for the formation of compounds **A.79** (Scheme I.23. b), where the previously described alcohol formation was prevented by adding KHF_2 to the crude reaction mixture, and therefore the final products could be purified giving yields ranging from good to excellent ones. As pointed out in Scheme I.23, the versatility of this methodology is patented in the variety of R groups that could be present in the final compounds **A.79**, where each aryl, alkenyl, alkyl and alkynyl moieties were found to be well tolerated under these reaction conditions.

[35] (a) Vedejs, E.; Chapman, R. W.; Fields S. C.; Lin, S.; Schrimpf, M. R.; *J. Org. Chem.* **1995**, *60*, 3020. (b) Kim, B. J.; Matteson, D. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3056.

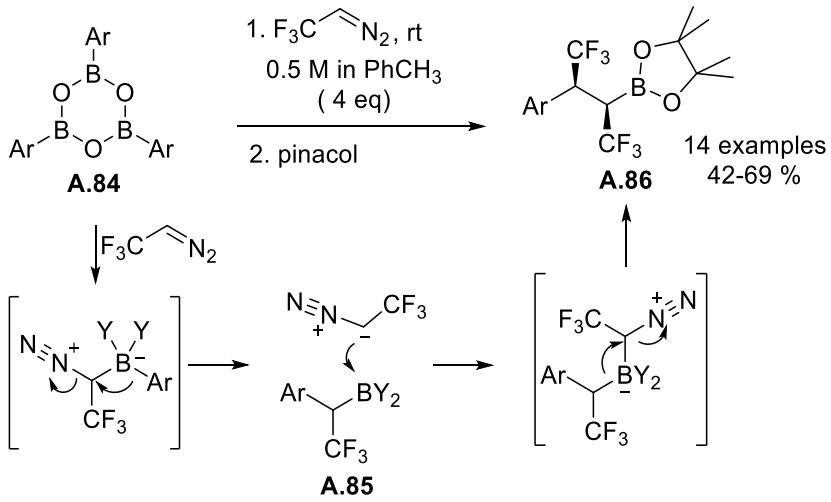
To demonstrate the potential synthetical value of α-trifuoromethylated organoboron compounds, the authors performed some experiments oriented to the functionalization of the boron-carbon bond. These reactions were carried out in situ on the α-trifuoromethylated, tricoordinate organoboron species. This strategy allowed for the synthesis of α-trifuoromethylated alcohols **A.80**, where the pinacol intermediate was oxidized employing a mixture of NaOH and H_2O_2 at r.t. Furthermore, the benzylic intermediate of the reaction could be successfully protodeboronated upon treatment with TBAF to afford the benzyl trifluoromethylated compounds **A.81** (Scheme I.24, a).



Scheme I.24. Derivatization of the reactions of 2,2,2-trifluorodiazoethane with Molander's salts.

More applications are depicted in Scheme I.24, b. For example, if the crude reaction is treated with NBS or NCl, the corresponding trifluoromethylated allyl bromides or chlorides **A.82** are formed, respectively. The authors also report a controlled β-fluoride elimination by rising the temperature of the reaction to 75°C, to form 1,1-disubstituted difluoro 1,3-butadienes **A.83**. All the results depicted in Scheme I.24 show new applicabilities of organoboron compounds beyond their common protodeboronation, and therefore standing as a turning point in the metal-free reaction arsenal between diazocompounds and organoboron compounds.

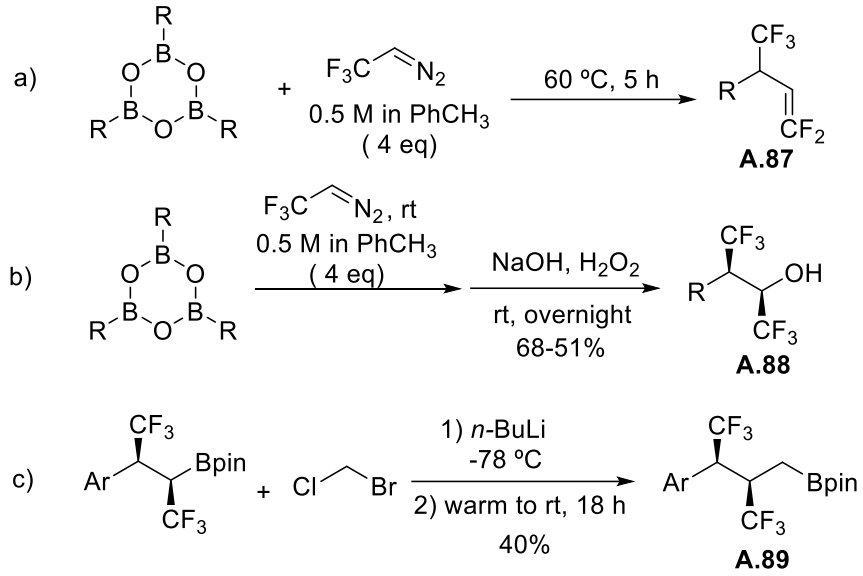
A year later, again Molander's group reported a diastereoselective synthesis of vicinal bis-trifluoromethylated alkylboron compounds based on successive insertions of 2,2,2-trifluorodiazoethane.[36] During the optimization of the previous work, the authors detected a side product which molecular size overweighed the one expected for the desired trifluoromethylated product exactly by one CF_3 group. After further experimentation, it was found that the product formed after a first diazo insertion **A.85** (1:1 adduct) was acting as a reactant for a second insertion, affording the corresponding vicinal bis-trifluoromethylated pinacol boranes **A.86** (2:1 adduct). Remarkably, the final products were obtained with high diastereoselectivity towards the *syn* isomer, and this was in accordance with some DFT calculations performed by the authors. After reoptimization of the reaction conditions (where arylboroxines were found to afford practically clean the double insertion product), the final products **A.86** were formed as the major products in the reaction, showing a moderate scope (14 examples) with good yields (Scheme I.25).



Scheme I.25. Sequential additions of two trifluorodiazoethane molecules over arylboroxines: stereoselective synthesis of bis(trifluoromethylated) alkylboronates **A.86**.

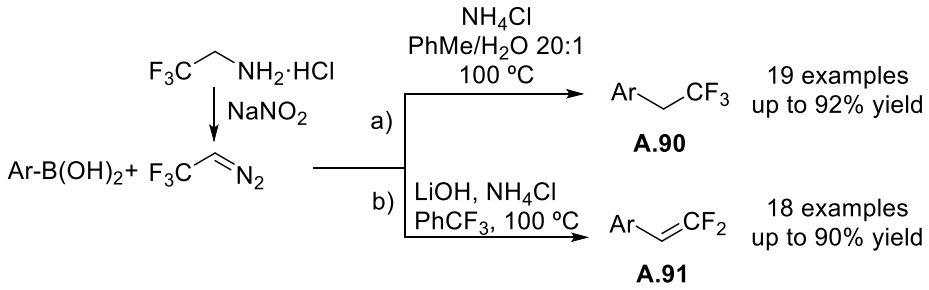
[36] Molander, G. A.; Ryu, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 14181.

The utility of these products is again highlighted by the transformation of the C-B bond into other functional groups. The final products could experiment a β-fluoride elimination selectively over the less hindered terminal CF_3 group, affording compounds **A.87** (Scheme I.26, a). Again, oxidation of the final boronate upon treatment with a $NaOH/H_2O_2$ solution gave alcohols **A.88** (Scheme I.26, b). Finally, a successful carbon-carbon bond formation was carried out by Matteson homologation formed compounds **A.89** (Scheme I.26, c).



Scheme I.26. Derivatization reactions of the 2:1 adducts obtained by reaction of CF_3CHN_2 with aryl boroxines.

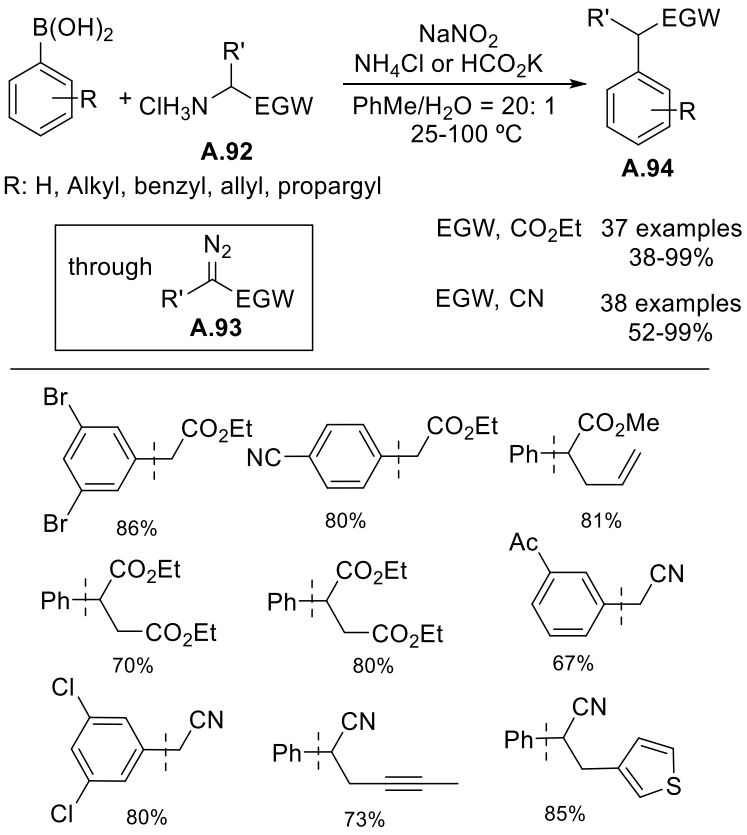
In 2014, Wang's group reported the 2,2,2-trifluoroethylation and *gem*-difluorovynilation of arylboronic acids.[37] If different reaction conditions were employed, the reaction could be selectively drove forward to either provide 2,2,2-trifluoroethylarenes **A.90** or *gem*-difluorovinylarenes **A.91** in good yields (Scheme I.27 a and b, respectively), from arylboronic acids and 2,2,2-trifluorodiazoethane as synthetic precursors.



Scheme I.27. Synthesis of 2,2,2-trifluoroethylarenes **91** and *gem*-difluorovinylarenes **92** by reaction of *in situ* generated CF_3CHN_2 with arylboronic acids.

Again in 2014, Wang and co-workers reported an unprecedented deaminative coupling of α-aminoesters and α-aminonitriles with arylboronic acids under transition-metal-free conditions. This methodology took advantage of the in situ generated stable α-diazoesters or α-diazonitriles through protonation and subsequent diazotization of the initial amine in the starting materials. Thereafter, a reductive arylation employing arylboronic acids grants the formation of compounds **A.94**. Selected examples and the overall synthetic sequence is depicted in Scheme I.28.

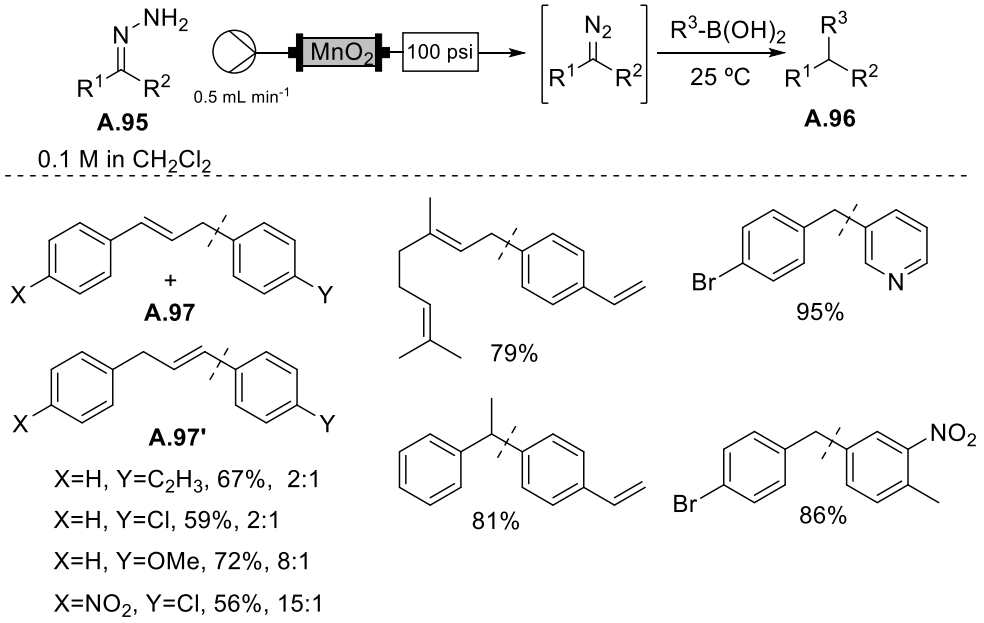
[37] Wu, G.; Deng, Y.; Wu, C.; Wang, X.; Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2014**, *2014*, 4477.



Scheme I.28. Metal-free deaminative coupling of α-aminoesters or α-aminoacetonitriles with arylboronic acids. Selected examples are shown.

I. 5. Reactions with diazo compounds generated by oxidation of hydrazones

In 2015, Ley and coworkers reported the reductive coupling between hydrazones and boronic acids under flow conditions.[38] Unstable diazocompounds were generated by *in situ* oxidation of the hydrazones **A.95** employing a column of activated MnO_2 as the oxidant (Scheme I.29). The arylated products **A.96** were obtained under mild conditions with yields ranging from good to excellent ones (48%-95%). The reaction time depended on the electronic nature of the arylboronic acid (faster for electron rich or neutral ones, slower or harsher conditions required for electron poor ones). The reaction tolerates different functionalities, such as ethers, halogens, nitro groups, and even heterocycles as pyridine.

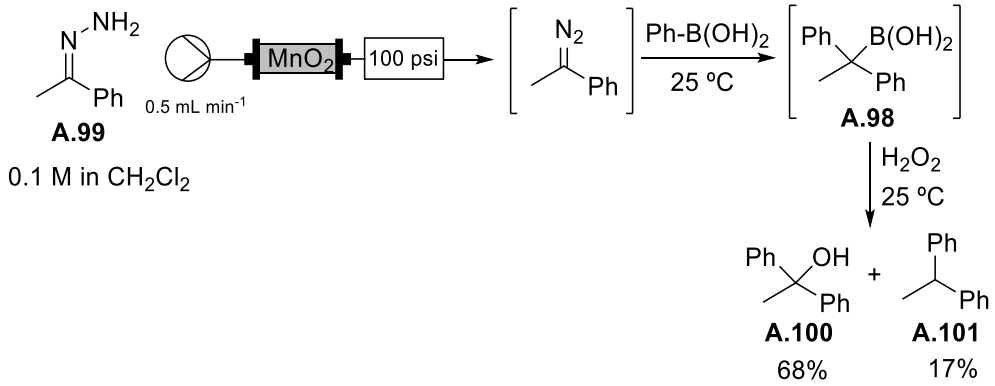


Scheme I.29. Flow protocol for the *in situ* oxidation of hydrazones to form diazocompounds and subsequent reaction with boronic acids.

[38] Tran, D. N.; Battilocchio, C.; Lou, S.-B.; Hawkins, J. M.; Ley S. V. *Chem. Sci.*, **2015**, *6*, 1120.

The employment of vinyl diazo compounds was found to be compatible with this methodology, although a mixture of regioisomers **A.97** and **A.97'** (ranging from 2:1 to 15:1) was usually obtained depending on the electronic properties of the aryl ring in the boronic acid. A 1,3-borotropic rearrangement is proposed to justify the regioselectivity of this transformation prior to the protodeboronation step.

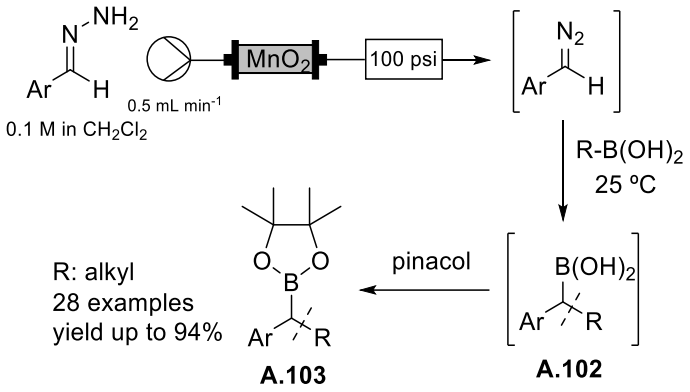
Interestingly, during some experimentation oriented to elucidate mechanistic proofs about this flow transformation, the authors could trap the boronic acid intermediate **A.98** prior to protodeboronation by oxidation upon treatment with H_2O_2, giving a mixture of the corresponding alcohol species **A.100** and the protodeboronation product **A.101** (Scheme I.30), in which the alcohol was mainly obtained.



Scheme I.30. Interception of the boronic intermediate **A.98** by treatment with hydrogen peroxide as oxidant.

Ley´s most relevant work using flow conditions is based on the development of iterative C-C bond forming sequences using transiently generated boronic acids.[39] These intermediates derive again from the reaction of diazocompounds generated under flow conditions and boronic acids at room temperature. First of all, Ley developed a methodology to trap the transient boronic acids with pinacol at room temperature (Scheme I.31) prior to the protodeboronation step.

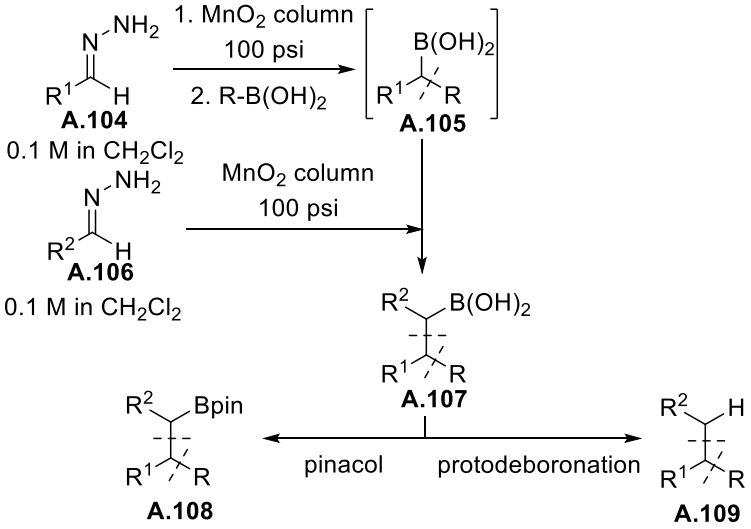
[39] Battilocchio, C.; Fleist, F.; Hafner, A.; Simon, M.; Tran, D. N.; Allwood, D. M.; Blakemore, D. C.; Ley. S. V. *Nat. Chem*. **2016**, *8*, 360.



Scheme I.31. Transiently generated boronic acids **A.102** were trapped with pinacol to form boronates **A.103**.

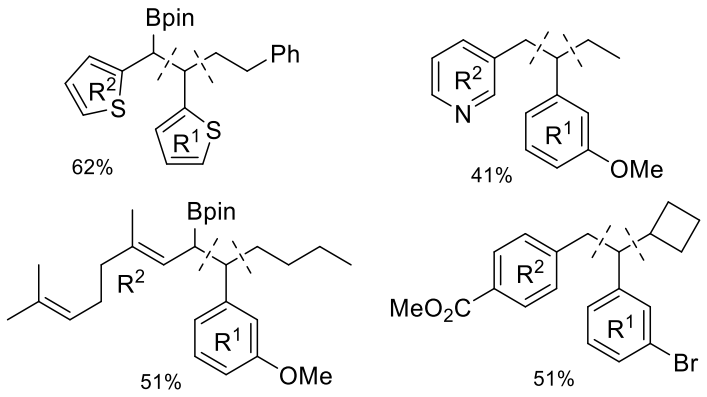
During the experimentation of this part, the authors noticed that an unexpected product had been minoritarily formed in all of the reactions: a second equivalent of diazocompound had reacted with the transient boronic acid **A.102** to end up forming a double-addition of the diazocompound to the initial boronic acid. Inspired with this result, Ley and coworkers decided to develop an iterative sequence in which the double-addition product was the major product of the reaction.

The experimental procedure of this iterative transformation is represented in Scheme I.32. In a first reactor, the diazocompound derived from hydrazine **A.104** is formed by oxidation mediated by the MnO_2 column, and reacted with the boronic acid R-$B(OH)_2$ ending up forming the transient boronic acid **A.105**. From a different reactor, a solution of a second diazocompound derived from the oxidation of hydrazine **A.106** was mixed with the initial solution where the secondary boronic acid **A.105** was. Reaction between both species would generate a new boronic acid **A.107**, which incorporates both hydrazonic fragments in an elegant way. The final products were finally trapped upon esterification with pinacol to form alcohols **A.108**, or protodeboronation to afford compounds **A.109**. This iterative process was found to effectively operate for the sequential addition of up to three different units of the diazocompounds.



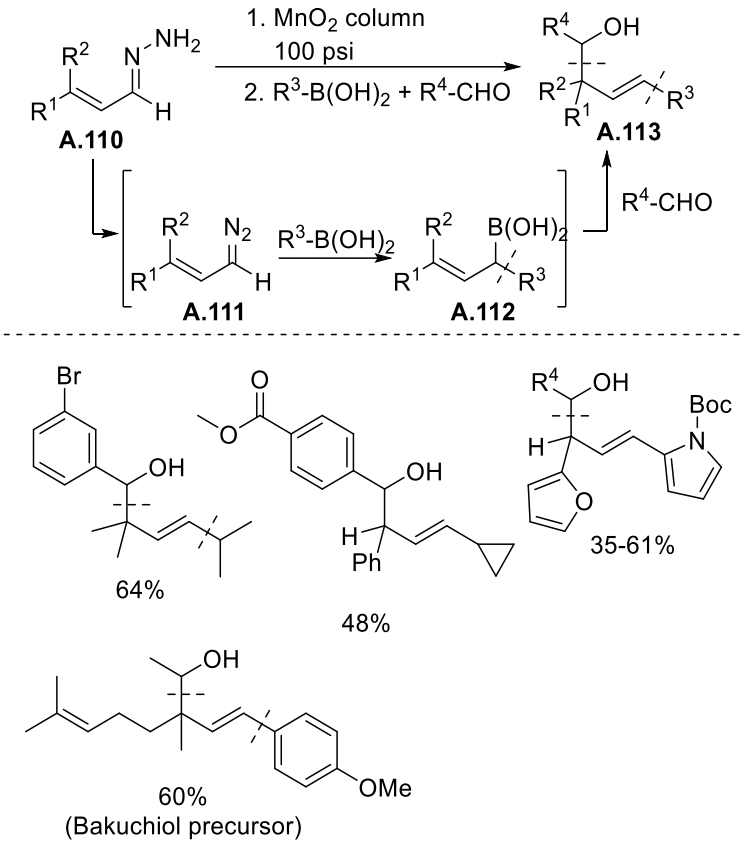
Scheme I.32. Ley's iterative process for the sequential addition of diazo compounds to the initial boronic acid.

Although some of the intermediates were observed to be unstable, and therefore prone to protodeboronation, in most of the cases was it possible to isolate them and then further react with a subsequent diazo compound species. This fact encouraged the authors to examine the scope of the diazo species. Diazo compounds bearing both electron donating and electron withdrawing groups in the aryl fragment were proven to give excellent yields in the formation of the final pinacol boronates. This observation confirms that the transient boronic acids had been formed in high yields prior to the esterification step. This transformation enabled to rapidly increase molecular complexity in a sequential manner starting from very simple starting materials in an unprecedented way. An ample scope of products could be easily synthesized through this approach. Some selected examples are shown in Scheme I.33.



Scheme I.33. Highlighted examples of the iterative flow coupling process in which multiple C-C bonds are formed.

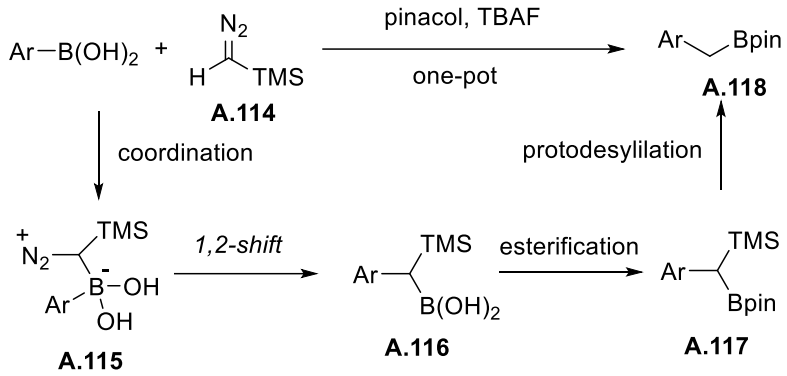
This sequential interception was extended to a cascade reaction in which transiently generated allylboronic acids reacted with aldehydes (Scheme I.34). Starting with the α,β-unsaturated hydrazones **A.110**, decomposition by the oxidant MnO_2 would form intermediate **A.111**, which immediately reacted with the boronic acid to form the allylboronic acid **A.112**. Taking advantage of the well-known reactivity of allylborons with aldehydes, the latter intermediate was finally trapped with an aldehyde (R^4-CHO). A variety of homoallylic alcohols **A.113** could be obtained following this procedure with excellent yields. As a proof of concept of this last part, the authors extended their work to the synthesis of a Bakuchiol precursor using this iterative coupling method.



Scheme I.34. Allylboronic intermediates are trapped with aldehydes to form homoallylic alcohols **A.113**.

I. 6. Reactions between boronic acids and trimethylsilyl diazomethane

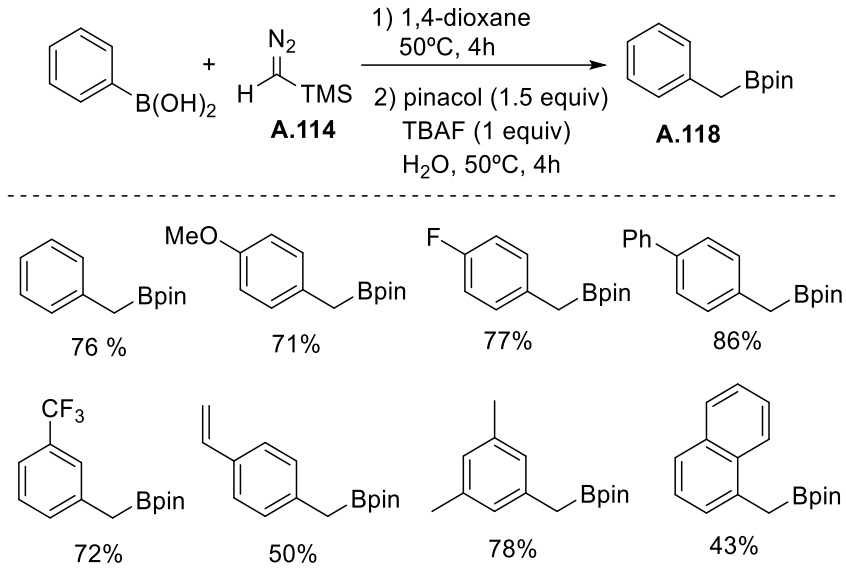
In 2016, Wang´s group developed a transition metal-free reaction to build up benzyl boronates starting from arylboronic acids and $TMSCHN_2$ in one pot, with a final trapping with pinacol.[40] The mechanism of this transformation is represented in Scheme I.35. After coordination of the electron-rich diazo atom to the electron deficient boron center, a 1,2-shift of the aryl group takes place to form a new C-C bond and form the intermediate **A.116**. Posterior esterification to form boronate **A.117** and protodesylilation would afford the final benzyl boronates **A.118**.



Scheme I.35. Mechanistic sequence for the coupling between $TMSCHN_2$ and arylboronic acids.

The reaction worked well with a variety of boronic acids, and also with a good tolerance to group functionalities. The corresponding benzyl pinacol boronates are formed with yields varying from moderate to good ones (41-81%). Selected examples and the reaction conditions are represented in Scheme I.36.

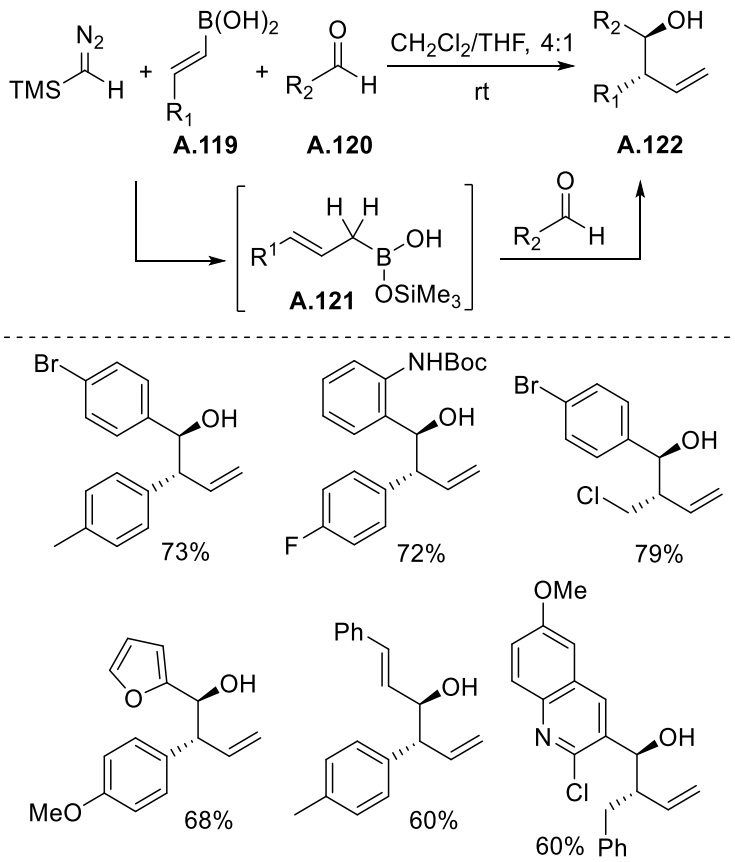
[40] Wu, C.; Wu, G.; Zhang, Y.; Wang. J. *Org. Chem. Front.* **2016**, *3*, 817.



Scheme I.36. General procedure and selected examples for the reaction between arylboronic acids and trimethylsilyldiazomethane

In parallel to Wang's work, Ley´s group extended their work based on flow chemistry to a multicomponent metal-free approach to build up homoallylic alcohols (Scheme I.37).[41] This transformation consists in the reaction of *E*-alkenylboronic acids **A.119** with $TMSCHN_2$, forming *in situ* the homologated allylboronic acid intermediates **A.121**. These species are eventually intercepted with aldehydes **A.120** to furnish the corresponding homoallyl alcohols **A.122**. The procedure was extended to batch conditions to broaden the scope and generality of this multicomponent transformation. Selected examples of the scope are shown in Scheme I.37.

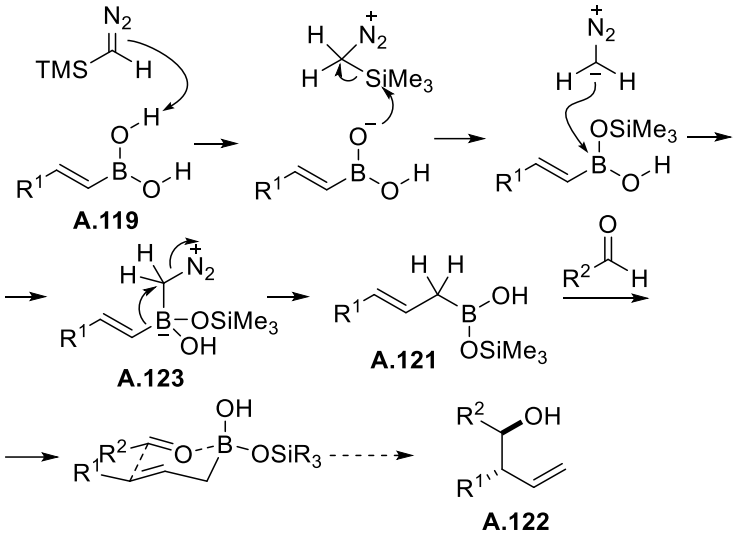
[41] Poh, J.-S.; Lau, S.-H.; Dykes, I. G. ; Tran, D. N.; Battilocchio C.; Ley, S. V. *Chem. Sci.* **2016**, *7*, 6803.



Scheme I.37. Sequential C-C bond forming reactions enabled the synthesis of homoallylic alcohols starting from $TMSCHN_2$, alkenylboronic acids and aldehydes. Selected examples are shown.

Based on previous mechanistic studies, the authors put forward the following mechanistic proposal for this reaction (Scheme I.38). In the first step, $TMSCHN_2$ is protonated by the vinylboronic acid **A.119**. A highly reactive diazomethane species is formed, which interacts in a Lewis base- Lewis acid with the alkenylboronic acid to form the zwitterionic species **A.123**. Now, a classical 1,2-carbon boron shift takes place to form the corresponding allylboronic acid **A.121**. The aldehyde then reacts with this intermediate to furnish the final product **A.122** after deborylation.

The authors indicated that current efforts were being paid to develop an enantiomeric version of this process.



Scheme I.38. Synthesis of homoallylic alcohols starting from $TMSCHN_2$, alkenylboronic acids and aldehydes: mechanistic rationale.

I. 7. Conclusions of the introduction

In this Introduction, an overview on the most important reactions between diazo compounds and organoboron compounds has been covered.

The employment of *N*-sulfonylhydrazones as safe precursors to *in situ* generate the diazo species; along with the usage of boronic acids as the organoboron source has enabled a tremendous growth in this field based on the synthetic advantages inherent to both coupling partners.

Furthermore, the implementation of different mild methodologies for the generation of diazo compounds (diazotization and oxidation of hydrazones under flow conditions) has allowed the development of sequential reactions to trap boronic intermediates in an intermolecular fashion.

The recent advances in this class of transformations have risen these reactions as very powerful and reliable methodologies for carbon-carbon bond forming methodologies nowadays. Moreover, this field is still believed to present potential for the discovery of new reactions between diazo compounds and organoboron compounds.

Chapter 1

Metal-free stereoselective reductive couplings between *N*-tosylhydrazones and alkenylboronic acids

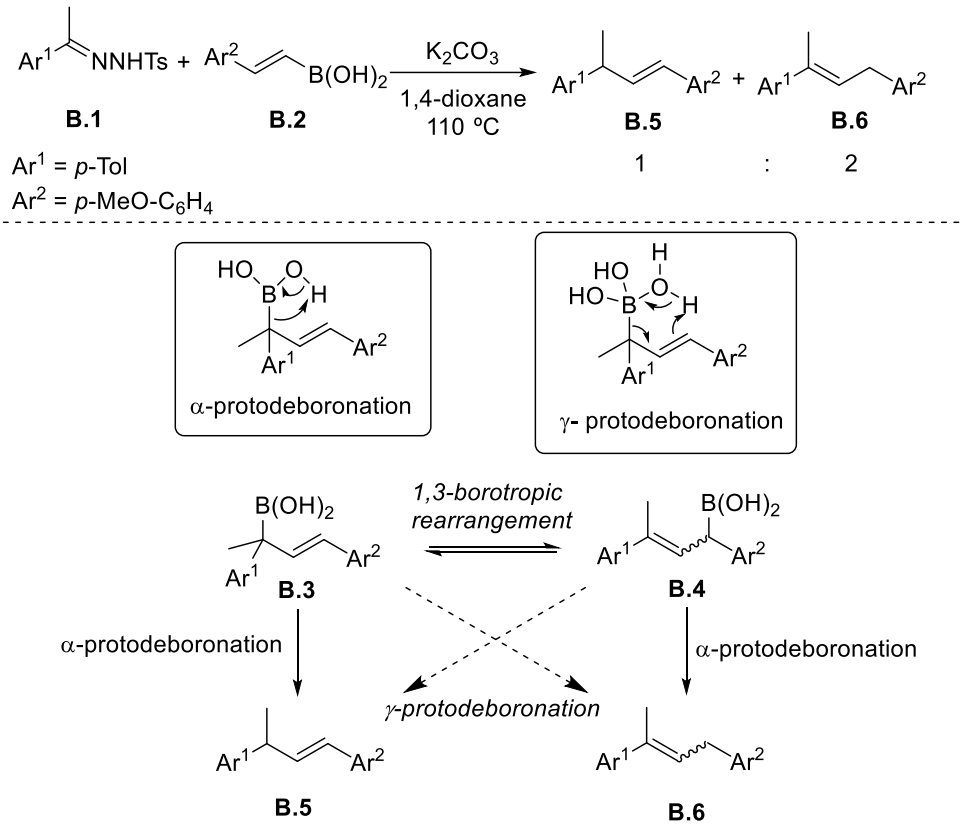
1.1 Introduction. Early work in the reactions between *N*-tosylhydrazones and alkenylboronic acids.

All the transformations described in the General Introduction were mainly focused on the reaction between aryl or alkyl substituted organoboron compounds with either diazocompounds or *N*-sulfonylhydrazones.

Our research group also reported in 2009 the first transformation involving alkenylboronic acids and *N*-tosylhydrazones.[42] This reaction was not as effective from a synthetical point of view as its analogous reductive coupling with aryl or alkylboronic acids, given that two regioisomers of the double bond were formed as the the final products.

In particular, when *N*-tosylhydrazones derived from acetophenones **B.1** reacted with alkenylboronic acids **B.2** in the presence of base and heating, a 1:2 mixture of regioisomers **B.5** and **B.6** was obtained (Scheme 1.1). Two possible mechanistic pathways could explain this regioselectivity.

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

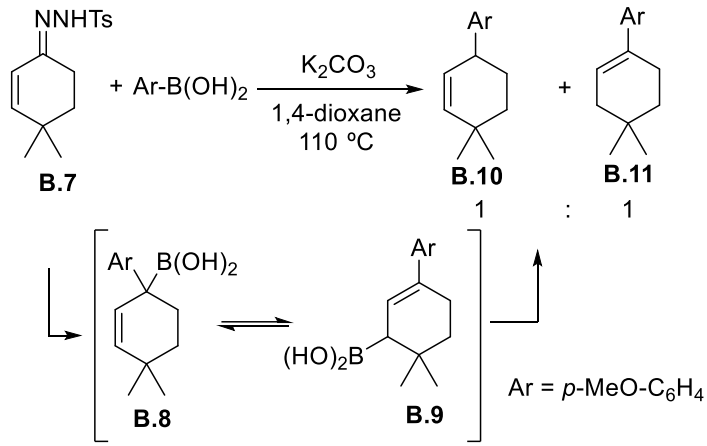


Scheme 1.1. Regioselectivity in the first reactions between alkenylboronic acids and *N*-tosylhydrazones **B.1**.

The first rationale is based on a 1,3-borotropic rearrangement in the allylboronic acid intermediate proposed for these transformations. In this regard, two possible intermediates (**B.3** and **B.4**) could be formed in the reaction, and the α-protodeboronation of each of them would lead to the corresponding final product: **B.5** (preserving the initial position of the double bond when compared to the alkenylboronic acid **B.2**) or **B.6** (where the double bond had shifted) respectively.

Alternatively, we could consider that a γ-protodeboronation reaction could take place in the allylboronic acids **B.3** and **B.4**, and therefore again both possible regioisomers **B.6** and **B.5** would be respectively formed.

The same results were obtained when an α,β-unsaturated *N*-tosylhydrazone **B.7** was explored in the reaction with arylboronic acids, rendering this time a 1:1 mixture of the corresponding regioisomers **B.10** and **B.11**. The formation of the intermediate **B.8** and **B.9** (due to the 1,3-B shift) and their subsequent protodeboronation could explain again the lack of regioselectivity observed in this transformation.



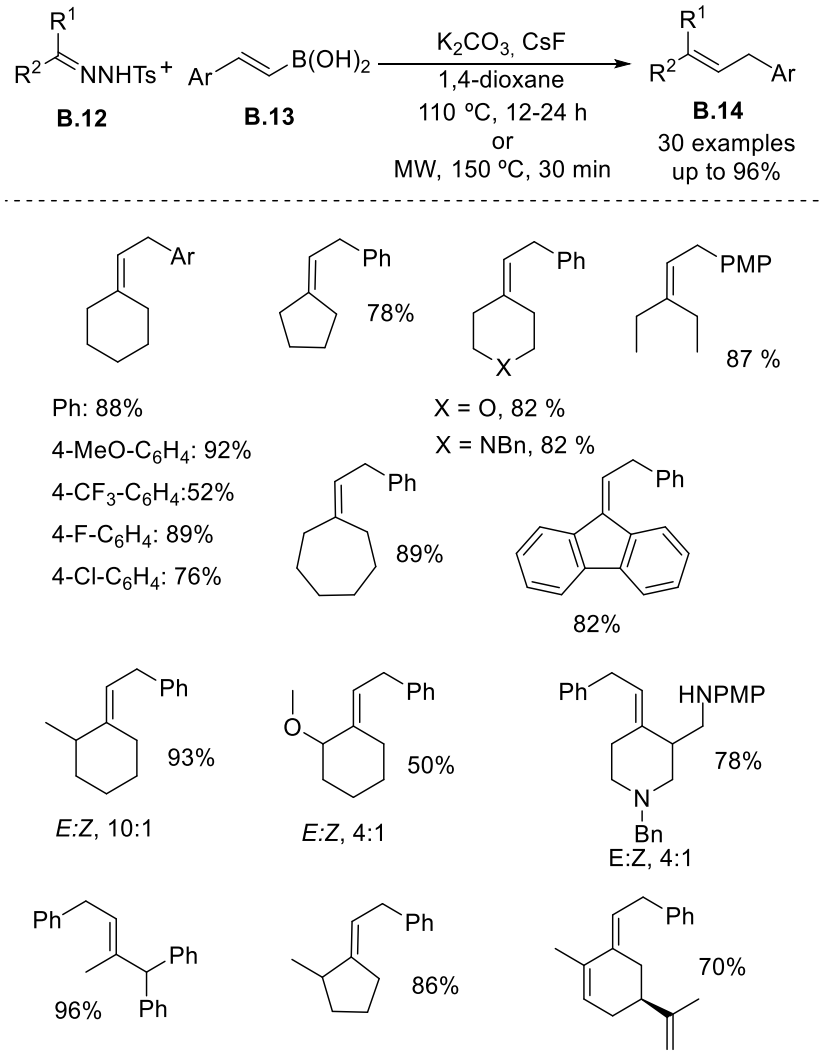
Scheme 1.2. Employment of the α,β-unsaturated *N*-tosylhydrazone **B.7** in the reaction with arylboronic acids.

With the aim of improving the regioselectivity of these transformations, an intense study of the reaction conditions and substrates was made oriented to drive the reaction to the formation of only one regioisomer of the double bond.[43] It was observed that structure of the *N*-tosylhydrazones and the alkenylboronic acids, as well as the base employed in the transformation, had a direct impact on the reaction outcome.

In this regard, the reaction between *N*-tosylhydrazones **B.12** with 2-aryl substituted alkenylboronic acids **B.13** led to the formation of only one regioisomer in the final products **B.14**. Noticiable, the double bond had shifted in all of the final compounds depicted in Scheme 1.3, and thus this reaction conditions were found to be general as a way to olefinate *N*-tosylhydrazones when employing this kind of boronic acids. An ample array of trisubstituted olefins **B.14** were synthesized through

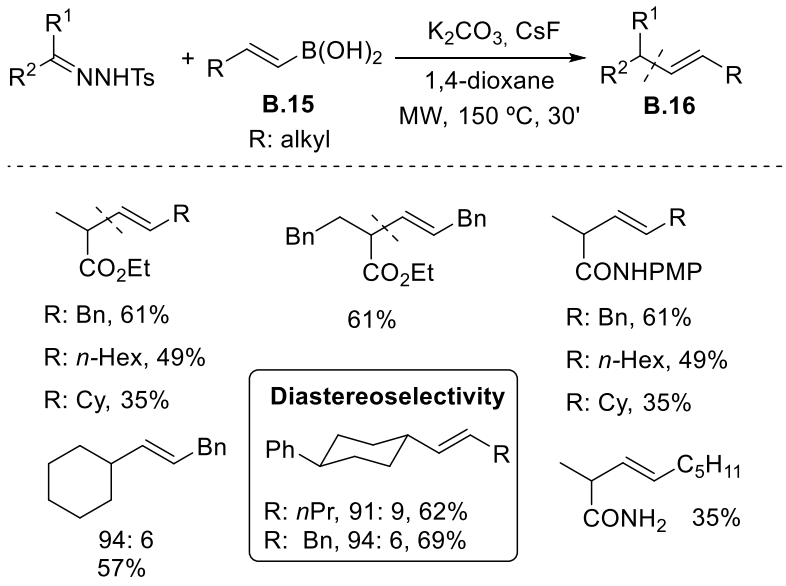
[43] Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 5953.

this transformation, where the reaction was general for each acyclic, cyclic and heterocyclic *N*-tosylhydrazones. When non-symmetrical *N*-tosylhydrazones were employed, the final olefinic products were furnished as a mixture of *E*/*Z* diastereoisomers, with moderate to very good diastereoselectivity towards the *E* isomer.



Scheme 1.3. Olefination reactions of *N*-tosylhydrazones **B.12** when 2-aryl substituted alkenylboronic acids **B.13** were employed. Selected examples are shown.

On the other hand, when employing alkyl substituted alkenylboronic acids **B.15**, the regioselectivity of the transformation was found to be exactly the opposite as the one obtained in the previous case. This time, the position of the double bond in comparison with the starting boronic acids had not shifted in any of the cases explored, affording the final products **B.16** as unique regioisomers (Scheme 1.4). Importantly, this reaction should be considered as a reductive alkenylation of the starting *N*-tosylhydrazones. This transformation enabled the formation of both a Csp^3-H and Csp^3-Csp^2 on the hydrazonic carbon, so therefore the diastereoselectivity of the transformation could be explored. Delightfully, when the *N*-tosylhydrazone derived of the 4-phenylcyclohexanone was employed, the final reductive alkenylation products were obtained with total regioselectivity and high diastereoselectivity towards the isomer that held both the phenyl and alkenyl moieties in an equatorial arrangement (Scheme 1.4).



Scheme 1.4. Reductive alkenylation reactions between *N*-tosylhydrazones and 2-alkyl substituted alkenylboronic acids **B.15**.

To sum everything up, it must be pointed out that the regioselectivity of the transformation was found to be predictable depending on the substitution of both the *N*-tosylhydrazones and alkenylboronic acids, which is essential from a synthetical point of view in terms of utility of the reaction. The expected regioselectivity is represented in the Table 1.1.

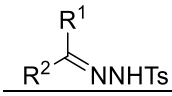
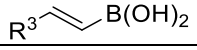
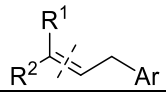
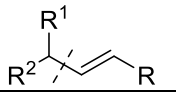
				
alkyl	**aryl**	**aryl**	**95-90**	**5-10**
alkyl	**alkyl**	**aryl**	**100**	**0**
aryl	**aryl**	**aryl**	**100**	**0**
alkyl	COX	aryl	50	50
alkyl	aryl	alkyl	50	50
alkyl	**alkyl**	**alkyl**	**5-10**	**95-90**
alkyl	**COX**	**alkyl**	**0**	**100**

Table 1.1. Prediction of the reaction outcome depending on the substitution of the *N*-tosylhydrazones and alkenylboronic acids.

1.2 Results and discussion

1.2.1 Objective and general considerations

As depicted in the previous section, in the context of the reductive alkenylation reactions between *N*-tosylhydrazones derived from 4-substituted cyclohexanones and 2-alkyl substituted alkenylboronic acids; the reaction showed facial diastereoselectivity towards the formation of only one stereoisomer in the final products derived from the reductive alkenylation (Scheme 1.4).

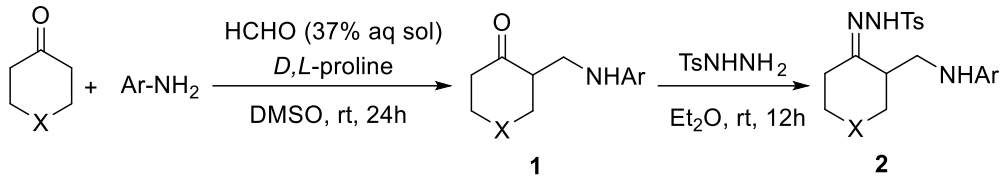
To the best of our knowledge, this is the first example described in the literature of a stereoselective reaction employing diazo compounds without the need of any catalyst, although there are numerous examples for metal-catalyzed transformations.[44] This is due to the lack of stereoselectivity inherent to these transformations, fact that limits their synthetic applicability.[45] The facial diastereoselectivity observed in these prelimiray results encouraged us to examine other substitutions in different cyclic *N*-tosylhydrazones to explore the stereoselectivity of the transformation.

This synthetic approach would stand as an attractive way to diastereoselectively alkenylate carbonyl compounds by means of an unprecedented transformation that would require several steps and/or necessity of protective groups through other alternative methodologies.

[44] Cuenca, A. B.; Cid, J.; Garcia-Lopez, D.; Carbo, J. J.; Fernandez, E. *Org. Biomol. Chem.* **2015**, *13*, 9659.
[45] (a) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 2434. (b) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 6614-6617.

1.2.2. Optimization

The first attempt to develop the previously described stereoselective reductive alkenylation of substituted cyclic *N*-tosylhydrazones was performed with cyclohexanones substituted in the α position. Concretely, an array of cyclohexanone Mannich adducts **1** was synthesized through the synthetic sequence described in Scheme 1.5 employing previously described methodologies; [46] as the precursors for the subsequent reaction with alkenylboronic acids.

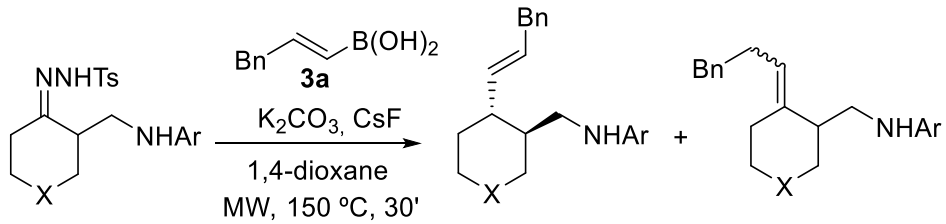


Scheme 1.5. Procedure for the synthesis of *N*-tosylhydrazone Mannich adducts **2**.

Once the *N*-tosylhydrazones **2(a-d)** were synthesized, the reductive alkenylation was conducted employing *trans*-3-phenyl-1-propen-1-ylboronic acid **3**, potassium carbonate as base, cesium fluoride as additive and 1,4-dioxane as solvent. The reactions were initially heated under microwave irradiation for 30 minutes (Scheme 1.6).

The employment of the *N*-tosylhydrazone **2a** gave promising results, considering the very good yield in the formation of the alkenylated product **4a**; and importantly, where only one diastereisomer of the reductive alkenylation product was formed. However, a minor amount (mixture 10:1) of both diastereoisomers *E*/*Z* of the olefination product **5a** had also been formed during this transformation. When the *N*-tosylhydrazones **2b-d** were employed, a considerable formation of the undesired olefination products **5b-d** was observed. At this point, it was clear that the reaction conditions needed optimization to drive the reaction to the exclusive formation of regioisomers **4**.

[46] Barluenga, J.; Quiñones, N.; Cabal, M.-P.; Aznar, F; Valdés, C. *Angew. Chem. Int. Ed*. **2011**, *50*, 2350.



Ar: *p*-MeO-C_6H_4

a, X = CH_2	10	1	75%
b, X = N-Bn	6	1	66%
c, X = N-Boc	3	1	45%
d, X = O	5	1	66%

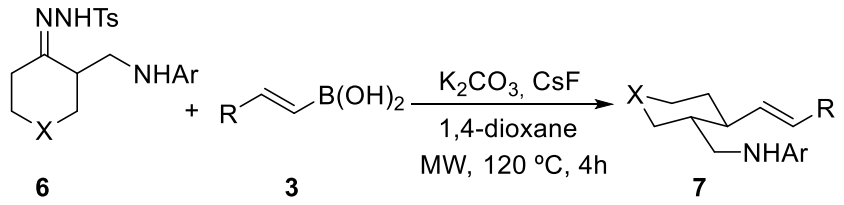
Scheme 1.6. First reactions between alkenylboronic acids and *N*-tosylhydrazones derived of Mannich adducts.

With this purpose, various new conditions were tested employing different combinations of bases (Na_2CO_3, K_2CO_3, Cs_2CO_3, CsF and Li*O*t*Bu*); solvents (THF, 1,4-dioxane, MeOH and CH_3CN), temperatures (ranging from 90 to 150 °C), and heating source (classical heating or microwave irradiation). The best results were obtained when the reaction was run at 120 °C under microwave irradiation (4h), employing two equivalents of each base K_2CO_3 and CsF, and 1,4-dioxane as the solvent of the reaction. Much to our pleasure, under these conditions the reaction afforded the compounds **4** as the unique products (with less than 5% of products **5** detected in the crude of the reaction), and most importantly, as single diastereoisomers.

Once the reaction conditions were optimized, it was decided to explore other different substitutions in the *N*-tosylhydrazones to generalize our reaction. Hopefully, the presence of other substitutions would also lead to the formation of the corresponding reductive alkenylation regioisomer, and again as one diastereoisomer.

1.2.3 Generalization of the reaction for the stereoselective synthesis of 1,2-disubstituted cyclic systems

The new optimized conditions were applied to the reaction of different *N*-tosylhydrazones derived from the previously described Mannich adducts. Importantly, the transformation was compatible with different substitutions in the alkenylboronic acid, as well as other functionalities in both the cyclohexanone and aromatic rings (Table 1.2). The final products derived from the reductive alkenylation reaction were remarkably obtained as single isomers. These promising results encouraged us to examine other substitutions in the starting cyclohexanones to check if the reaction was again regio- and diastereoselective.



6 **3** **7**

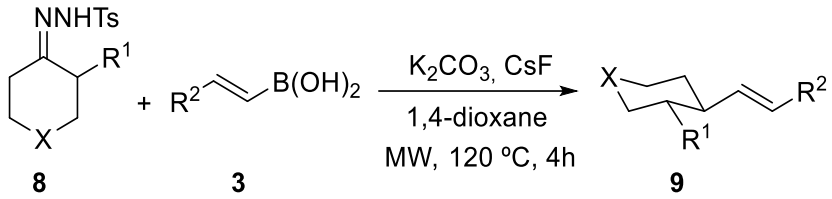
Compound	R	X	Ar	Yield (%)[a]
7a	Bn	CH_2	PMP	62
7b	Bn	NBn	PMP	68
7c	Bn	N-Boc	PMP	56
7d	Bn	O	PMP	60
7e	Bn	CH_2	4-Tol	65
7f	*n*-C_6H_{13}	CH_2	4-Tol	66
7g	*n*-C_4H_9	CH_2	4-Tol	52

[a] Isolated yield after column chromatography.

Table 1.2. General scope for the stereoselective synthesis of alkenylated Mannich adducts **7**.

A combination of bidimensional NMR experiments with homonuclear decoupling enabled the stereochemical assignment of compounds **7**, indicating that both substituents in the cyclohexanone ring were in the corresponding equatorial position, in a *trans* arrangement (see section E.2.5 of the Experimental Part for detailed discussion). Noticiable, the same stereochemistry was observed when the *N*-tosylhydrazones derived from *N*-protected systems and pyranone were employed.

Thereafter, we continued our work testing different *N*-tosylhydrazones derived from other 2-substituted cyclohexanones and *N*-Boc-piperidones **8**. Delightfully, when various alkenylboronic acids were tested in the reaction, the formation of the final products was achieved with total regio- and diastereoselectivity. Once again, the substitution in the cyclohexanone ring induced total diastereoselection towards the formation of the isomer **9**, which presented both substituents (the side chain and the alkenyl group) in equatorial position. The scope of the reaction is shown in the Table 1.3.



8 **3** **9**

Compound	R^1	R^2	X	Yield (%)[a]
9a	CH_3	Bn	-CH_2-	52
9b	CH_3	*n*-Hexyl	-CH_2-	56
9c	CH_3	-$(CH_2)_2$OTBDMS	-CH_2-	60
9d	Bn	Bn	-CH_2-	56
9e	Allyl	Bn	NBoc	58
9f	Allyl	*n*-Propyl	NBoc	50
9g	Allyl	*n*-Hexyl	NBoc	50
9h	Allyl	-$(CH_2)_2$OTBDMS	NBoc	65
9i	Ph	Bn	-CH_2-	55
9j	Ph	*n*-Propyl	-CH_2-	51
9k	CF_3	Bn	-CH_2-	63

[a] Isolated yield after column chromatography.

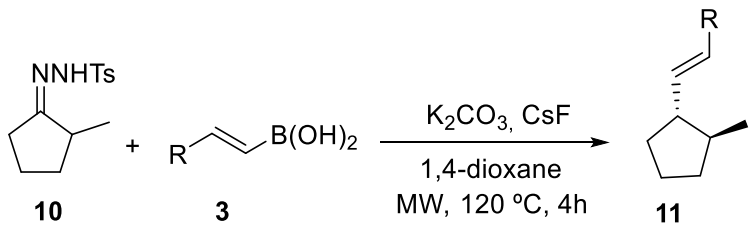
Table 1.3. Diastereoselective synthesis of 1,2-disubstituted cyclohexanes and *N*-Boc-piperidines **9**.

The reaction was compatible with the presence of various substitutions in the side chain of the cyclohexanone ring of compounds **8** (methyl, benzyl, allyl, phenyl and trifluoromethyl groups). Remarkably, the presence of bulky groups like phenyl or CF_3 also led to the formation of a single diastereoisomer after the reaction with the alkenylboronic acids. Again, various substitutions were explored in the alkenylboronic acids, unaffecting the reaction outcome. Particularly interesting was the example **9h**, where the final product presented an allyl and OTBS moieties, enabling further derivatization of the final stereoisomers.

Finally, it was decided to explore the stereoselectivity of our transformation with 2-substituted cyclopentanones. It must be indicated that, unlike the

cyclohexanone rings, where the stereoselectivity could be induced by its chair conformation, in this case the preferred envelope conformation in the cyclopentanones could promote different stereoselection outcomes in the transformation.

Nevertheless, then the *N*-tosylhydrazone derived from the 2-methylcyclopentanone **10** reacted with the alkenylboronic acids, again unique regio- and diastereoisomers **11** were obtained (Scheme 1.7). This diastereoisomer presented a *trans* disposition of both substituents in the ring, analogously to the results observed when the substituted cyclohexanes **9** were synthesized (see section E.3.5 of the Experimental Part for a detailed discussion. Therefore, the stereoselection when employing 2-substituted cyclopentanones was identical to the previous cases.



11a, R^1 = Me, R^2 = *Bn*, 73 %
11b, R^1 = Me, R^2 = *n*-C_4H_9, 62 %
11c, R^1 = Me, R^2 = *n*-C_6H_{13}, 48 %

Scheme 1.7. Stereoselective synthesis of 1,2-disubstituted cyclopentanes **11**.

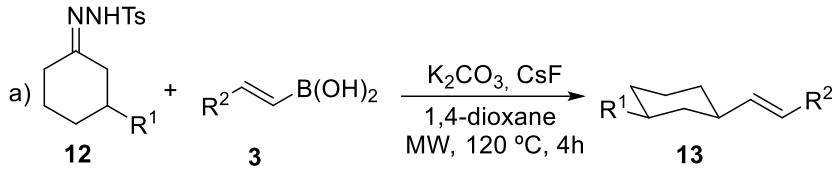
1.2.4. Generalization of the reaction for the stereoselective synthesis of 1,3- and 1,4-disubstituted cyclic systems

The next part of the work was devoted to the exploration of 1,3- and 1,4-disubstituted cyclohexanones. The substitution is again expected to create facial diastereoselectivity in the addition of the alkenylboronic acids. With this purpose, the *N*-tosylhydrazones derived from different 3-substituted cyclohexanones were employed; as well as the previously described *N*-tosylhydrazone derived from the 4-phenylcyclohexanone, where the first preliminary results of diastereoselection had been observed.

The general scope for both transformations is depicted in Scheme 1.8. On the one hand, when employing *N*-tosylhydrazones **12**, the final 1,3-disubstituted cyclohexanes **13** were found to present both substitutions in a *cis* arrangement, and both in equatorial position (see section E.2.4 of the Experimental Part for a detailed discussion).

On the other hand, when the reaction of the *N*-tosylhydrazone derived from the 4-phenylcyclohexanone **14** was tested this time under the optimized conditions, the final 1,4 disubstituted cyclohexanes **15** were obtained with total regio- and diastereoselectivity (Scheme 1.8b), holding both substituents in equatorial position and in a *trans* arrangement (see section E.2.3 of the Experimental Part for a detailed discussion).

Remarkably, the stereochemistry observed in these examples was the one expected due to our previous experience. Therefore, this fact rises the importance of the transformation, given that the stereoselectivity in the alkenylation reaction can be predicted prior to the reaction, increasing its synthetical value.

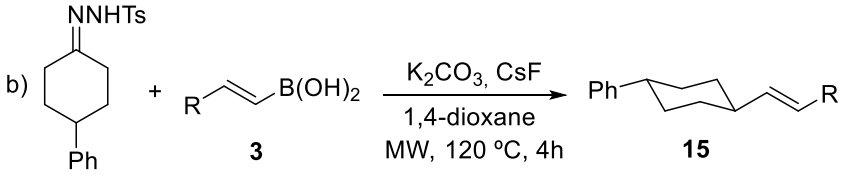


13a, R^1 = Me, R^2 = Bn, 57 %

13b, R^1 = 2-Br-C_6H_4, R^2 = Bn, 58 %

13c, R^1 = 2-Br-C_6H_4, R^2 = *n*-C_3H_7, 50 %

13d, R^1 = 2-Br-C_6H_4, R^2 = *n*-C_4H_9, 52 %



15a, R = *Bn*, 60 %

15b, R = *n*-C_3H_7, 75 %

15c, R = $(CH_2)_2$OTBDMS, 51 %

Scheme 1.8. Stereoselective synthesis of 1,3- and 1,4-disubstituted cyclohexanes **13** and **15**.

1.2.5. Synthesis of enantiomerically pure alkenes from (-)-menthol

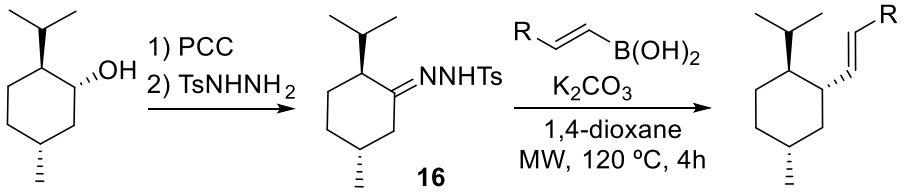
Encouraged by our previous results, we decided to carry out an enantiomeric version of these transformations. It must be first of all pointed out the challenge this reaction represents. 2-Substituted cyclohexanones are well-known epimerizable compounds under basic conditions. This fact can be rationalized by the favoured formation of the enol tautomer under basic conditions, which after reprotonation would racemize the initial chiral 2-substituted cyclohexanone. Therefore, the retention of the configuration in the potentially epimerizable α-center would be in risk in the reaction with the corresponding alkenylboronic acid under basic conditions.

However, our research group reported various works in which the formation of the *N*-tosylhydrazones prevented the epimerization in the α-center of these class of compounds, given that the formation of the corresponding enol tautomer is minimized once the hydrazone is formed.[47]

We decided to focus our efforts in the synthesis of the enantiomerically pure *N*-tosylhydrazone **16**, which is derived from the natural product (-)-menthol. This compound was prepared in two steps (Scheme 1.9). All this synthetic sequence had been previously described by Prince and co-workers.[48] First, a classical oxidation of the secondary alcohol mediated by PCC afforded the corresponding menthone derivative. Next, formation of the *N*-tosylhydrazone **16** was achieved by a careful control of the temperature and reaction conditions. Finally, the reaction of **16** was carried out under our standard conditions for the reductive alkenylation reactions.

[47](a) Barluenga, J.; Escribano, M.; Aznar, F.; Valdes, C. *Angew. Chem.* **2010**, *122*, 7008.; *Angew. Chem. Int. Ed.* **2010**, *49*, 6856. (b) Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem.* **2015**, *127*, 13933.; *Angew. Chem. Int. Ed.* **2015**, *54*, 13729.

It must be noticed that both menthone and *N*-tosylhydrazone **16** had been previously reported to suffer partial epimerization in some reactions.[48] However, an enantiomeric version of other Shapiro reactions with menthol derivatives was reported *via* its *N*-tosylhydrazone.[49]



Scheme 1.9. Overall synthetic sequence for the enantioselective formation of 1,2,5-trisubstituted cyclohexanes starting from (-)-menthol.

Much to our pleasure, the final 1,2,5-trisubstituted cyclohexanes **17** were synthesized as unique enantiomers. Importantly, this fact shows that the overall process starting from (-)-menthol had taken place without epimerization of the α-center.

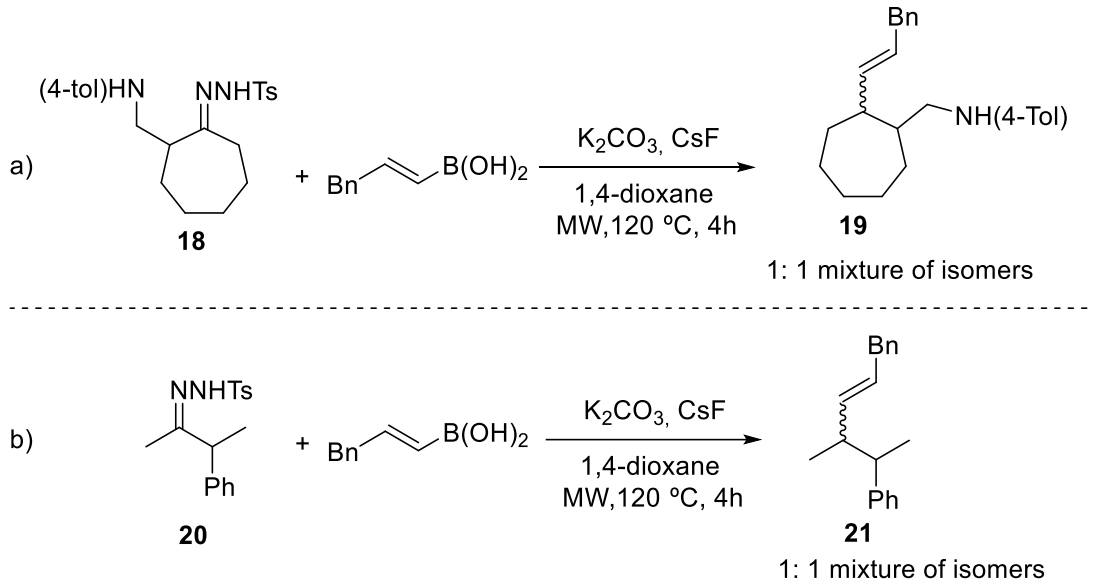
Analysis of bidimensional NMR experiments (see section E.2.6 of the Experimental Part for a detailed discussion) revealed that once again, each substituent was in equatorial position in the cyclohexane ring.

[48] Garner, M. C.; Mossman, B. C.; Prince, M. E. *Tetrahedron Lett.* **1993**, *34*, 4273.
[49] Álvarez, S.; Pazos-Randulfe, Y.; Khanwalkar, H.; Germain, P.; Álvarez, R.; Gronemeyer, H.; de Lera, A. R. *Bioor. Med. Chem.* **2008**, *16*, 9719.

1.2.6. Limitations of the stereoselectivity in the reductive alkenylation reactions

Until this moment, all the substrates explored afforded the final reductive alkenylation products as single regio- and diastereoisomers. However, it must be also indicated the cases where this stereoselectivity could not be achieved (Scheme 1.10). When the reaction between a 2-substituted *N*-tosylhydrazone derived from a cycloheptanone **18** reacted under the standard conditions with the corresponding alkenylboronic acid, an analysis of the crude reaction by NMR and GC/MS revealed that a mixture 1:1 of both diastereoisomers **19** had been formed (Scheme 1.10, a).

On the other hand, when an acyclic precursor **20** was employed in the reaction (Scheme 1.10, b), again a mixture 1:1 of both diastereoisomers **21** was detected in the crude of the reaction.

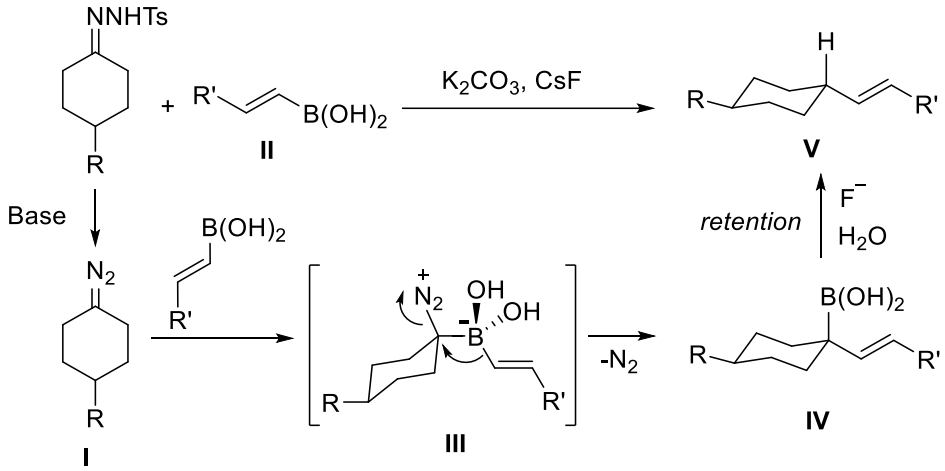


Scheme 1.10. Limitations of the stereoselective reaction between substituted N-tosylhydrazones and alkenylboronic acids.

Some conclusions can be put forward according to our experimental evidences. First of all, a rigid cyclic system in the *N*-tosylhydrazones precursors is required to provide stereoselectivity in the transformation. Moreover, only the corresponding 5- or 6-membered rings drove to reductive alkenylated products with total stereoselection.

1.2.7. Mechanistic proposal for the stereoselective reductive alkenylations: DFT calculations.

Due to our previous experience in the reaction with *N*-tosylhydrazones and boronic acids, we proposed the next mechanistic rationale for the stereoselective reaction between substituted *N*-tosylhydrazones and 2-alkyl substituted alkenylboronic acids (Scheme 1.11).



Scheme 1.11. Mechanistic rationale for the reaction between 2-substituted alkenylboronic acids and cyclic *N*-tosylhydrazones.

The mechanistic pathway proposed would involve the following steps: 1) decomposition of the *N*-tosylhydrazone mediated by base through the classical Bamford-Stevens reaction to form the diazocompound species **I**; 2) reaction with the alkenylboronic acid **II** to form the zwitterionic species **III**, in which a concomitant release of nitrogen and 1,2-carbon boron migration took place to form the allylboronic acid **IV**; and 3) protodeboronation of intermediate **IV** to form the final reductive alkenylation products **V**.

It must be pointed out that it has been previously described that the protodeboronation of tertiary organoboron compounds takes place with retention of configuration: the hydrogen atom is introduced in the position previously

occupied by the boron atom.[50] Therefore, if we assume that this fact also applies for our transformation, then the step in which the stereoselectivity is created must be the addition of the alkenylboronic acid to the diazocompound species.

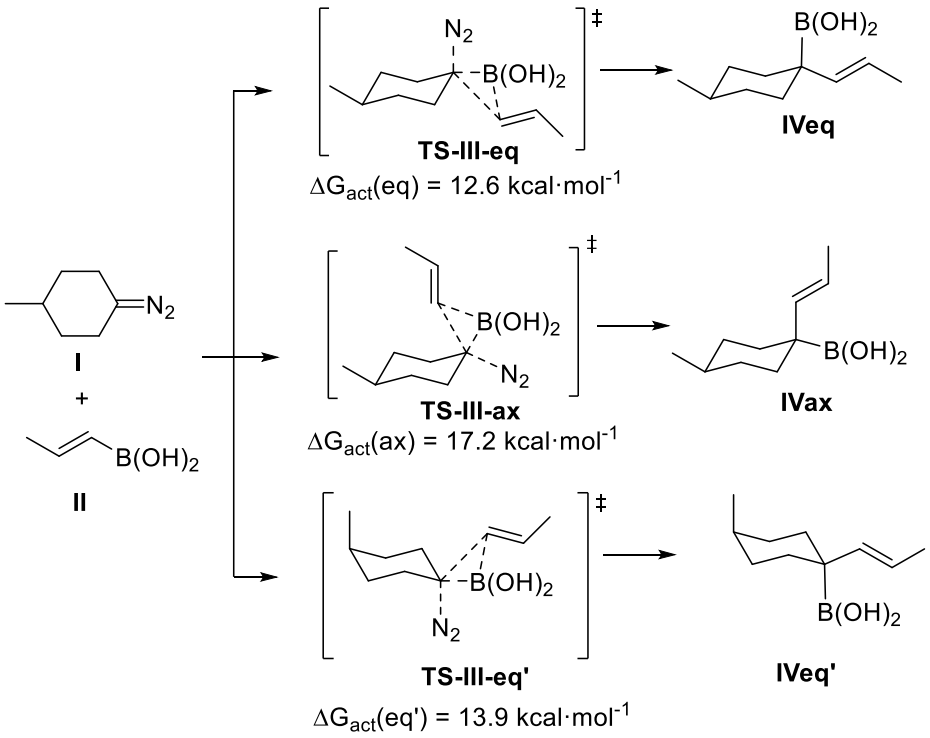
To rationalize the stereoselectivity in this step, we decided to carry out DFT-based computational calculations to elucidate the energy differences in the possible approximations of the boronic acid to the diazocompound species.

As a model reaction, we considered the addition of (*E*)-propenylboronic acid **II** to 1-diazo-4-methylcyclohexane **I**, to simplify the following calculations (Scheme 1.12).[51] As a initial geometry, we considered the conformation that featured the methyl group in an equatorial position (predicted as the most stable geometry).

Much to our surprise, our first calculations pointed at the boronate species being not an intermediate, but a transition state in the potential energy surface. In accordance with this observation, the addition of the alkenylboronic acid to the diazocompound took place through a concerted but very asynchronic process, where the release of N_2, the formation of the Csp^3-B bond, the cleavage of the B- Csp^2 bond and the formation Csp^3-Csp^2 bond should occur in one single step.

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

[51] The calculations were carried out with the Gaussian09 package of programs (see Experimental Part for complete reference) employing the M06-2X hybrid functional and the 6-311++G** basis set. Solvation energies were calculated through the PCM approximation from the optimized structures at the same level of theory. See the Experimental Part for detailed discussion.



Scheme 1.12. DFT study in the addition of the boronic acid **II** to the diazocompound **I**. Calculations were carried out at the M06-2X/6-311++G**/PCM(1,4-dioxane) level.

Given that an axial or equatorial approaches from the boronic acid to the diazo compound could take place, two different transition states should be considered (**TS-III-ax** and **TS-III-eq**). The Figures 1.1-1.3 represent each possible transition states **TS-III-eq**, **TS-III-ax** and **TS-III-eq'** (where the methyl group is set in an axial disposition in the cyclohexane ring) respectively.[52]

[52] All the three-dimensional modelled structures have been rendered with CylView

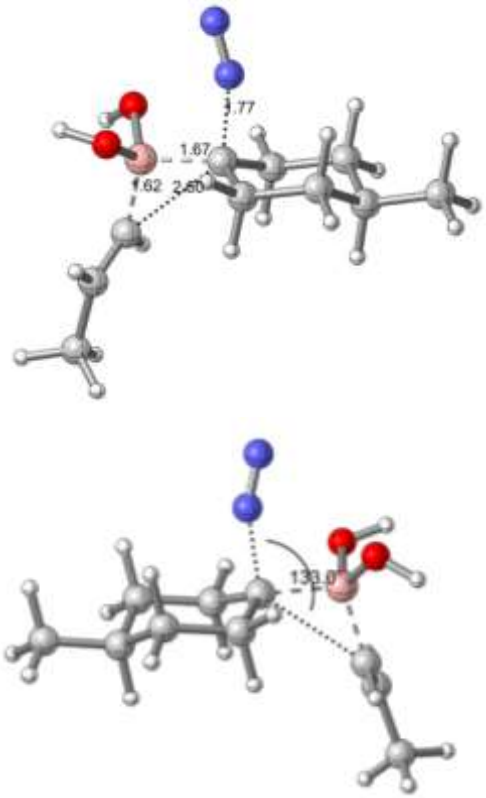


Figure 1.1. Optimized geometry for **TS-III-eq**. Critical bond distances are shown (in Å).

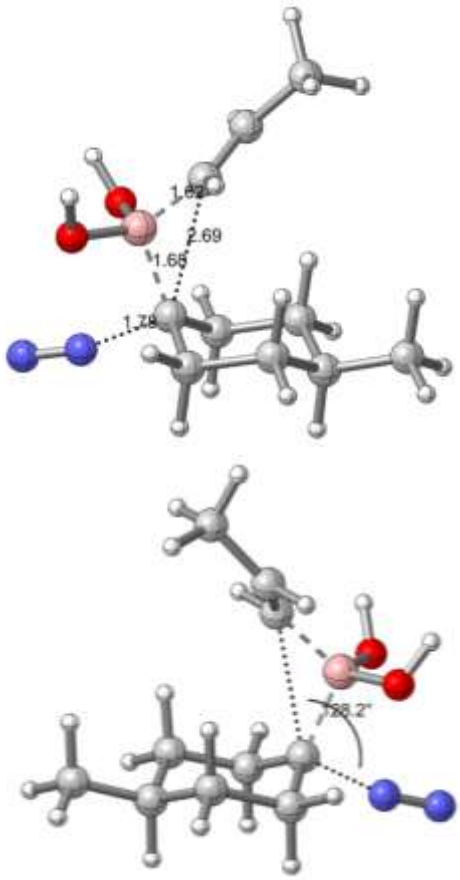


Figure 1.2. Optimized geometry for **TS-III-ax**. Critical bond distances are shown (in Å).

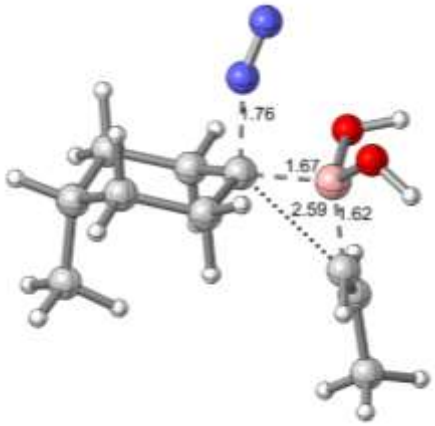


Figure 1.2. Optimized geometry for **TS-III-eq'**. Critical bond distances are shown (in Å).

Both transition states **TS-III-ax** and **TS-III-eq** presented common features. As explained before, they both share the common structure of a concerted but very asynchronous transition state: the Csp^3-B bond is almost formed (1.67 Å), but a very long distance (2.60-2.70 Å) is observed for the incipient formation of the Csp^3-Csp^2 bond.

The equatorial approximation was also modelled considering a diazocompound that presented the methyl group in an axial disposition, which would lead to the formation of **IVeq'** after addition of the alkenylboronic acid. In this regard, a new transition state **TS-III-eq'** was located with an activation free energy of 13.9 kcal·mol^{-1}. Considering the low difference in energy in comparison with the analogous equatorial trajectory where the methyl group was in equatorial position ($\Delta\Delta G$(eq-eq') = 1.3 kcal·mol^{-1}), this approximation may seem to be considered. However, given that we experimentally employed bulkier groups in that position, a higher value of free activation is expected for those cases in the corresponding addition of the alkenylboronic acid to the diazo compound because of the steric hindrance, so this **TS-III-eq'** will not be considered any further.

The relative energies for all the calculated structures are summarized in the Table 1.4. For a better accuracy of the energy values, we considered the solvent effect (1,4-dioxane) in our calculations. Paying attention to this table, we can

conclude that the equatorial approximation (which would lead to the formation of **TS-III-eq**; ΔG_{act}(equatorial) = 12.6 kcal·mol^{-1}) is clearly favoured over the axial one (ΔG_{act}(axial) = 17.2 kcal·mol^{-1}). Therefore, a noticiable difference in energy ($\Delta\Delta G_{act}$(axial-eq) = 4.6 kcal·mol^{-1}) was found in the formation of both transition states. This observation can be rationalized through the higher steric hindrance caused by the axial hydrogens in the cyclohexane ring in the axial approach of the bulky alkenylboronic acid.

	I+II	**TS-III-eq**	**TS-III-ax**	**TS-III-eq'**	**IVeq+N_2**	**IVax+N_2**
Eel rel	0	7.0	10.3	8.0	-62.5	-61.1
ΔG(gas) **rel**	0	18.3	22.5	19.6	-59.2	-57.9
$\Delta\Delta G_{act}$(gas)			4.2	1.3		
ΔG(1,4-dioxane) **rel**	0	**12.6**	**17.2**	13.9	-64.8	-63.5
$\Delta\Delta G_{act}$(1,4-dioxane)			**4.6**	1.3		

Table 1.4. Relative energies in kcal·mol^{-1} obtained at the M06-2X/6-311++G** level.

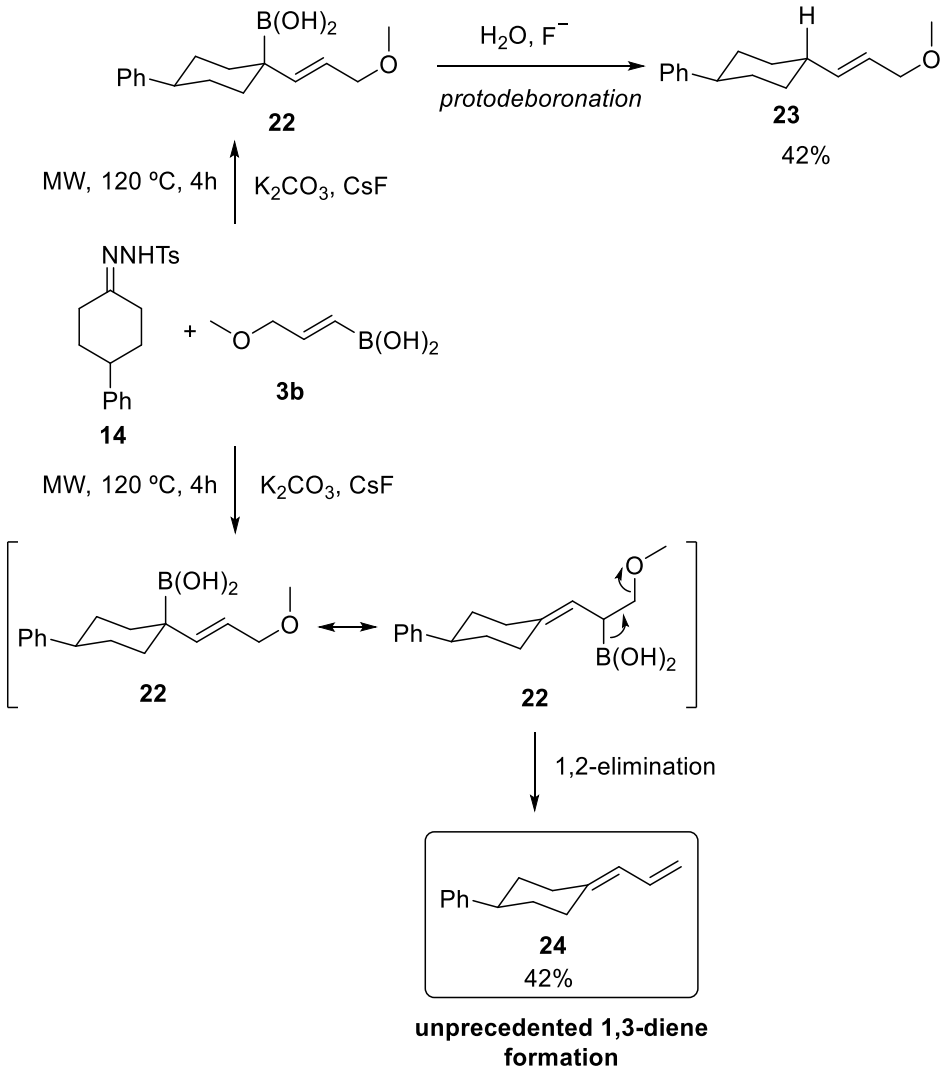
Considering these results, the formation of **IVeq** would therefore outcompete the one of **IVax**. As we pointed out before, assuming that the protodeboronation step goes on with retention of the initial configuration, the alkenylated products **V** that presented both substituents in equatorial position should be formed according to our calculations. This is in total agreement with our experimental observations.

In summary, our calculations indicate that the stereochemical control in the reaction is due to the favoured approximation of the boronic acid to the diazo compound through an equatorial trajectory. This fact explains appropriately why the reactions with cyclohexane *N*-tosylhydrazones substituted at positions 2 or 4 give *trans* isomers, while those substituted at position 3 provide *cis* isomers.

1.2.8. Deviations of the reaction: new transition-metal-free synthesis of dienes through the reaction of *N*-tosylhydrazones and alkenylboronic acids.

During the generalization of the reaction, we employed the *N*-tosylhydrazone derived from the 4-phenylcyclohexanone in combination with (*E*)-3-methoxyprop-1-en-1-ylboronic acid under the standard conditions. Surprisingly, an unexpected reaction outcome was observed in this transformation (Scheme 1.13): apart from the expected protodeboronation product derived of the classical reductive alkenylation **23**; a 1,3-diene **24** which incorporated the organic part of the alkenylboronic acid had been formed. This compound could have been formed because of a 1,3 borotropic rearrangement/1,2 elimination sequence that competed with the common protodeboronation pathway. Unfortunately, both products were obtained in a mixture 1:1 determined by analysis of the crude of the reaction by NMR and GC/MS.

The synthetic value of these preliminary results must be remarked. This transformation could represent an unprecedented transition metal-free reaction for the synthesis of 1,3-dienes, which are high-value compounds as synthetic intermediates in many reactions. The simplicity and generality of the reaction could stand as the major highlights of this transformation, given that this reaction could be extended to the use of presumably any available *N*-tosylhydrazone with (*E*)-3-methoxyprop-1-en-1-ylboronic acid.

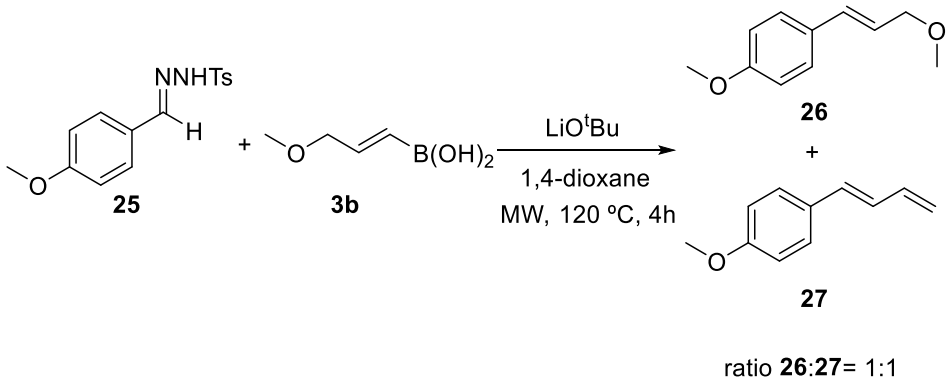


Scheme 1.13. Unexpected 1,3-diene formation through the reaction of alkenylboronic acids and *N*-tosylhydrazones.

In order to drive the reaction to the exclusive formation of the 1,3-dienes **24**, intending to exclude the protodeboronation reaction, an intense optimization was carried out trying different reaction conditions. Combination of several bases (K_2CO_3, CsF, LiO^tBu, KF, Li_2CO_3, K_3PO_4, Cs_2CO_3, LiOH, $KHCO_3$, Na_2CO_3), solvents (1,4-dioxane, pentane, toluene, THF, CH_3CN), temperatures (from 90 to 150 °C), ratio **14**/**3b** (from 1:1 to 1:4) and heating source (classical heating and MW) was tested. Much to our

dismay, the analysis of the crude of the reactions by NMR and GC/MS did not reveal any improvement in all of the new conditions tested. It must be pointed out that only the use of LiO^tBu gave the same results as the ones obtained with the mixture K_2CO_3/CsF.

Next, we decided to examine the reaction of other substrates that potentially could react through this alcoxide elimination pathway, like the *N*-tosylhydrazone **25**. Again, in this cases a 1:1 mixture of the 1,3-diene **27** and protodeboronation product **26** was detected in the crude of the reaction.



Scheme 1.14. Reaction with *N*-tosylhydrazones derived or aromatic aldehydes and (*E*)-3-methoxyprop-1-en-1-ylboronic acid.

It must be pointed out that still some optimization of the reaction conditions and exploration of other substrates is doable. The potential synthetic applications of this reaction are evident; if it is finally possible to outcompete the protodeboronation route in favour of the formation of the 1,3-dienes. Current efforts are being paid in our research group to address these issues and continue with this work.

1.3. Conclusions

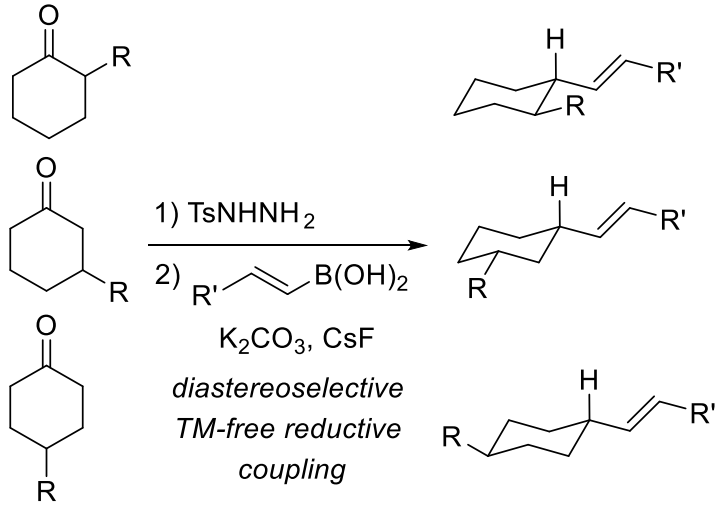
We have developed a novel synthetic methodology for a stereoselective reductive alkenylation of cyclic carbonylyc compounds *via N*-tosylhydrazones and alkenylboronic acids. Noteworthy, apart from the coupling partners, only K_2CO_3/CsF as bases and 1,4-dioxane as solvent are needed. This transformation does not need the presence of any catalyst, what increases its simplicity and greenness.

In this reaction, a Csp^3-Csp^2 and Csp^3-H bonds are created stereoselectively in the same carbon atom, where the alkenyl group is incorporated in the ecuatorial position on the final cyclic compounds. This observation was in accordance with some DFT-based studies we carried out, where we found that the ecuatorial approach of the boronic acid to the diazocompound was clearly favoured over the axial one; and therefore a stereoretentive protodeboronation would lead to the final products as single isomers.

As far as we know, this reaction might represent the first example described in the literature of a stereoselective transition-metal-free reaction employing diazo compounds. The potential applications of our reaction are evident given the vast variety of enantiomerically pure substituted cyclohexanones and cyclopentanones available, both synthetically and commercially.

As a deviation of the reaction, an unexpected synthetic pathway for the formation of 1,3-dienes employing *N*-tosylhydrazones and alkenylboronic acids was found. However, until this moment it was not possible to optimize the reaction conditions to the exclusive chemoselective formation of the 1,3-dienes, which are always formed together with a same proportion of the corresponding reductive alkenylated products.

1.4. Graphical summary



Chapter 2

Carbocyclization reactions employing *N*-tosyl hydrazones and boronic acids *via* allylborylation of nitriles: one-step formation of two different Csp^3-C bonds on the same carbon atom

2.1 Introduction

The synthesis of polycyclic molecules with novel tridimensional scaffolds is a subject of great interest in organic synthesis, given that they enable the exploration of unknown areas of the chemical space in the search of new biologically active molecular structures.[53]

When looking for potential drug candidates, apart from the well-known Lipinsky rules (Rule of Five); two features that have gained considerable attention during the last years are the total Csp^3 fraction of the molecule and the presence of chiral carbon atoms. These properties provide the molecular structures with a three-dimensional character that increase the molecular complexity and make the final compounds more natural product-like. A correlation between success in drug discovery and molecular complexity has been found by many research groups.[54]

In this context, polycyclic molecules featuring quaternary carbon centers at bridgehead positions are particularly attractive, because the rigidity imposed by the quaternary center enforces specific three-dimensional structures. The formation of these centers orientates the functional groups present in the molecules and reduces the number of rotable bonds. This fact may display a key role in the potential interactions of this kind of molecules with the targeted biological receptors.

Examples of these classes of structures are the fused bicyclic scaffolds **C.I**, bicyclic structures **C.II** and spirocyclic skeletons **C.III** (Figure 2.1). Therefore, preparation of such architecturally complex molecules employing simple and flexible methodologies currently stands as a challenging goal in diversity oriented synthesis.

[53] (a) Marson, C. M. *Chem. Soc. Rev.* **2011**, *40*, 5514. (b) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun.* **2010**, *1*, 80. (c) Garcia-Castro, M.; Kremer, L.; Reinkemeier, C. D.; Unkelbach, C.; Strohmann, C.; Ziegler, S.; Ostermann, C.; Kumar, K. *Nat. Commun.* **2015**, *6*, 6516.

[54] Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.

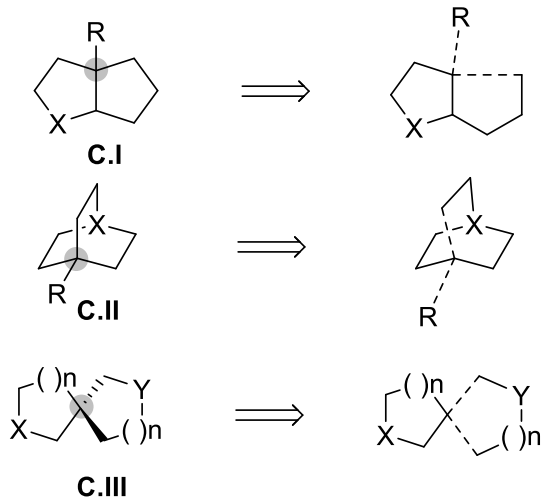


Figure 2.1. Molecular structures which present a quaternary all-carbon center at bridgehead positions formed by the creation of two new C-C bonds on the same carbon atom.

The formation of multiple C-C bonds in a single step on the same carbon atom is one of the most challenging transformations in organic synthesis. Noticiable, this class of transformations would be crucial in the construction of all the structures depicted in Figure 2.1, which would implicate the formation of an all-carbon quaternary center. Importantly, these transformations normally involve a catalyst that acts as a molecular assembler of the starting materials. There is a wide variety of transition-metal catalyzed reactions oriented to the formation of spiro and non-spiro all-carbon quaternary stereocenters, based on the employment of titanium, copper, gold, palladium and other transition metals. Some recent reviews centered in synthetic pathways to build all-carbon quaternary stereocenters are suggested to the interested reader.[55]

New strategies to produce higher degrees of molecular complexity based on operationally simple, metal-free and stoichiometrical transformations remain a worthwhile pursuit in preparative organic chemistry for the synthesis of cyclic molecules bearing all-carbon quaternary centers; because of their previously

[55] For some recent reviews on all-carbon quaternary stereocenters: (a) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181. (b) Ling, T.; Rivas, F. *Tetrahedron* **2016**, *72*, 6729.

described vital importance in the synthesis and design of drug-like compounds and natural products.

In the following parts of this Chapter (A, B, C), new synthetic methodologies for the formation of each compounds featuring the general scaffolds **C.I**, **C.II** and **C.III** will be covered.

Importantly, all the procedures describe will involve the creation of all-carbon quaternary centers through the formation of two new C-C bonds on the same carbon atom with incorporation of a side chain. The reactivity is in all of the cases based on the employment of *N*-tosylhydrazones and boronic acids, where the formation of complex three-dimensional structures is achieved starting from simple precursors through unprecedented domino carbocyclization reactions.

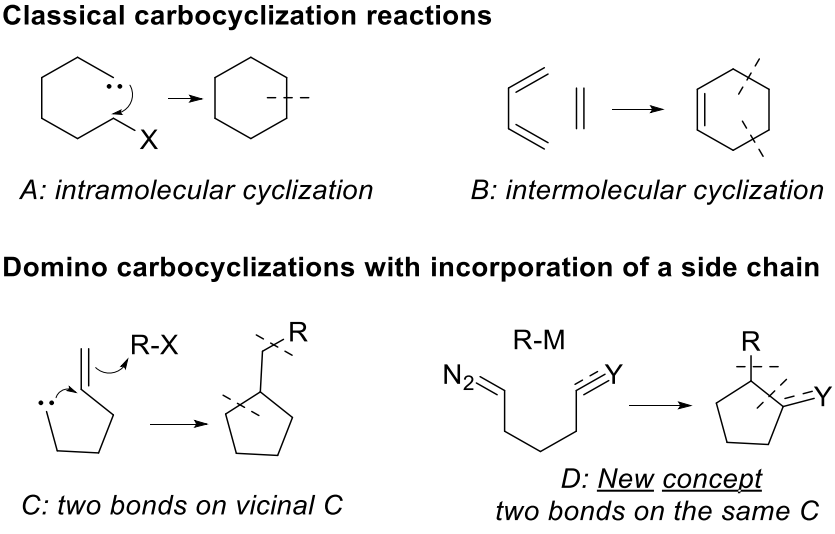
Chapter 2. Part A

Stereoselective Domino Carbocyclizations of γ- and δ-Cyano-*N*-Tosylhydrazones with Alkenylboronic acids with Formation of Two Different Carbon-Carbon Bonds On a Quaternary Stereocenter

2.A.1 Introduction

Carbocyclization reactions have attracted relentless attention over the last decades, due to their immense synthetic versatility in the formation of different C-C bonds to build up the desired carbocycles. The transformation of simple acyclic starting materials into monocyclic, bicylic and polycyclic scaffolds featuring controlled levels of regio-, diastereo- and/or enantioselectivity make of these transformations an unequalled and powerful tool in organic synthesis.

All efforts have been made to be fully comprehensive with regards to selection in referencing and coverage throughout this brief introduction. It is impossible to cover all the developments in so vast an area in this section; where any omission would be unintentional. Therefore, some books which cover carbocyclization reactions in an extensive manner are suggested.[56]



Scheme 2.A.1. Different modes of carbocyclization reactions involving a) intra- and intermolecular classical cyclizations and b) domino reactions with incorporation of a side chain.

[56] (a) Ma, S. *Handbook of Cyclization Reactions*; Wiley-VCH: Weinheim Germany, 2009. (b) Li, J. J. *Name Reactions for Carbocyclic Ring Formations*; John Wiley & Sons: Hoboken NJ, 2010.

In a carbocyclization transformation, at least one new carbon-carbon bond must be formed during the reaction to produce the final cyclic compound. A general classification for this type of reactions can be made attending to the cyclization mode (Scheme 2.A.1; A and B): *intramolecular cyclizations*, in which a connection of two different atoms in a single acyclic precursor is achieved forming one new C-C bond; and *intermolecular cyclizations*, where the formation of two different new C-C bonds allows for joining together two different molecules.

Straightforward methods to construct cyclic carbon frameworks with higher degrees of molecular complexity in few steps are increasingly important. In this context, domino reactions attract significant attention due to their inherent ability to allow for multi-step processes in a single synthetic operation.[57]

When unsaturated reactants hold internal substituents that can behave as potential nucleophiles, electrophilic reagents often bring about cyclizations (Scheme 2.A.1, C). In this regard, domino cyclization reactions that take place with simultaneous incorporation of a side chain are very relevant. The final products would present two new C-C bonds created at each carbon of the unsaturation. There are numerous examples of these type of carbocyclization reactions reported in the literature through electrophilic, transition-metal catalyzed or radical mechanisms.[58]

[57] Tietze, L. F. *Domino Reactions: Concepts for Efficient Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2014.

[58] (a) Cong, H.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 3788. (b) Vlaar, T.; Ruijter, E.; Orru, R. V. A. *Adv. Synth. Catal.* **2011**, *353*, 809. (c) Loertscher, B. M.; Castle, S. L. *Comprehensive Organic Synthesis 2 Ed*; P. Knochel, G. A. M., Ed.; Elsevier: Amsterdam, Netherlands, 2014; Vol. 4, p 742. (d) Geoghegan, K.; Evans, P. *Science of Synthesis, Cross Coupling and Heck-Type Reactions*; Thieme: Stuttgart, Germany, 2013; Vol. 3, p 391. (e) Machotta, A. B.; Oestreich, M. *The Mizoroki–Heck Reaction*; John Wiley & Sons, Ltd: Chichester, UK, 2009, p 179.

Even more challenging are the carbocyclization reactions that take place with formation of two new C-C bonds on the same carbon atom in one-pot. The simplest type of these transformations are the classical three-membered ring formation reactions, which normally involve the employment of a metal carbene and a multiple-bond functionality, where two C-C bonds would connect the carbene atom with both vicinal atoms of the unsaturation.

However, during the last years many research groups have made great contributions in the context of complex reactions involving the creation of two new C-C bonds on the same carbon atom. [59] It is important to notice that all these transformations always require the use of a transition metal as the catalyst of the reaction.

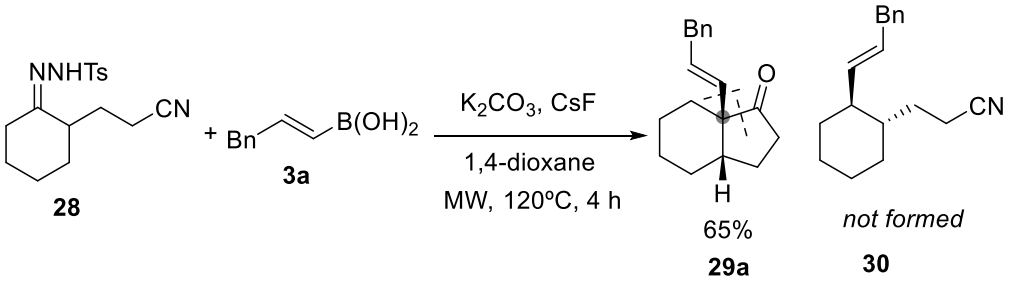
Still considering carbocyclization modes in organic synthesis, cascade reactions that would involve the formation of two different C-C bonds on the same carbon atom, one to form the cycle, and the other one to incorporate a side chain; have no precedents in organic synthesis (Scheme 2.A.1, D). These novel domino carbocyclization reactions would enable previously unthinkable retrosynthetic disconnections for the synthesis of complex molecules and the exploration of new areas of the chemical space.

[59] (a) Yada, A.; Fujita, S.; Murakami, M. *J. Am. Chem. Soc.* **2014**, *136*, 7217. (b) Paraja, M.; Pérez-Aguilar, M. C.; Valdés, C. *Chem. Commun.* **2015**, *51*, 16241. (c) Paraja, M.; Valdés, C. *Chem. Commun.* **2016**, *52*, 6312. (d) Xu, S.; Chen, R.; Fu, Z.; Zhou, Q.; Zhang, Y.; Wang, J. *ACS Catalysis* **2017**, *7*, 1993. (e) Xia, Y.; Liu, Z.; Liu, Z.; Ge, R.; Ye, F.; Hossain, M.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2014**, *136*, 3013. (f) Gutiérrez-Bonet, Á.; Juliá-Hernández, F.; de Luis, B.; Martin, R. *J. Am. Chem. Soc.* **2016**, 138, 6384. (g) Li, S.-S.; Lin, H.; Liu, C.- F.; Xia, Y.-Q.; Zhang, X.-M.; Dong, L. *Adv. Synth. Catal.* **2016**, 358, 1595.

2.A.2 Results and discussion

2.A.2.1 Objective and general considerations

During the generalization of the reductive alkenylation reaction employing *N*-tosylhydrazones and alkenylboronic acids we found a particular example in which the expected alkenylation product had not been formed (Scheme 2.A.2). Concretely, when employing the *N*-tosylhydrazone derived from the 2-(2-cyanoethyl)cyclohexanone **28** in the reaction with *trans*-3-phenyl-1-propen-1-ylboronic acid **3a** under the standard conditions (2 eq. of K_2CO_3, 2 eq. of CsF, 1,4-dioxane as solvent, 4h under MW heating), none of the reductive alkenylation product **30** had been formed. Careful analysis by NMR and GC/MS enabled the identification of the carbocycle **29a** as the unique product of the reaction. Much to our pleasure, the final bicyclic ketone was formed as a single isomer under our transition-metal-free conditions.



Scheme 2.A.2. Unexpected formation of the carbocycle **29** in the reaction between 1 and *trans*-3-phenyl-1-propen-1-ylboronic acid

Importantly, the formation of the product **29a** would involve the carbocyclization mode described in Scheme 2.1, D. The ultimate result was the creation of two new Csp^3-Csp^2 bonds on the hydrazonic carbon atom: one to form the new fused 5-membered cycle, and the other one to incorporate the alkenyl chain. Very importantly, the new carbocycle had been formed as a single isomer with total diastereoselectivity, corresponding to a *cis* fusion of both cycles.

Thus, the overall reaction outcome stood in a stereoselective creation of an all-carbon quaternary center with formation of two new C-C bonds on the same carbon atom, under simple transition-metal-free conditions. It should be noticed the

rapid increase in molecular complexity in one step starting from very simple precursors.

This impressive achievement took us by surprise at the beginning, but we rapidly envisaged that a generalization of the reaction could be possible for the construction of other different carbocycles with different substitutions. In the next part, a detailed discussion of the optimization, generalization and applicability of this novel transformation will be described.

2.A.2.1 Optimization

Setting the reaction conditions described in Scheme 2.A.2. as our starting point, we decided to try new combinations of solvents, bases and temperatures to improve the yield in the formation of the carbocycle **29a**.

First of all, it was found that the presence of CsF was not needed in this transformation. This fact left potassium carbonate as the only base needed in the reaction, in which two equivalents were also proven to be optimal. Several different bases were tried, (LiO^tBu, KF, Li_2CO_3, K_3PO_4, Cs_2CO_3, LiOH, $KHCO_3$, Na_2CO_3), but in all of that cases the cyclization product **29a** was not formed.

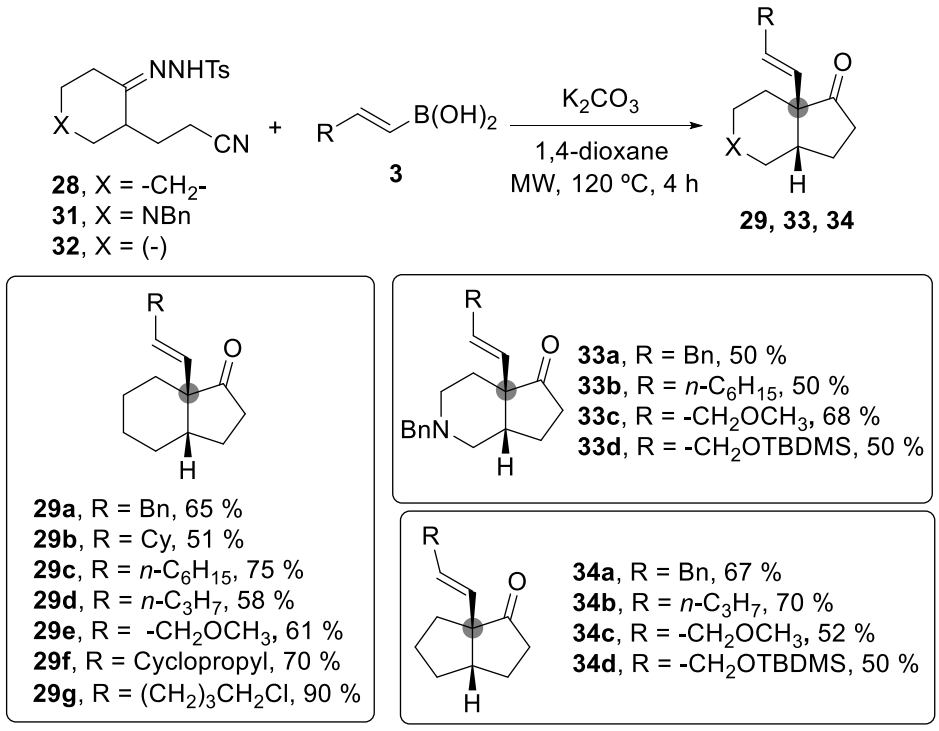
Among all the different solvents tested (1,4-dioxane, pentane, toluene, THF and CH_3CN), 1,4-dioxane was found to be the only one in which the carbocyclization product **29a** was furnished. Moreover, it was also found that a 1:2 ratio of **28** and **3a** gave the best yield in the formation of compound **29a**.

Next, once K_2CO_3 was found as the unique optimal base and 1,4-dioxane as the solvent, different temperatures were set (from 90 to 150 °C). In this range, the best reaction outcome was found at 120 °C. Any temperature below 120 °C led to a substantial drop in the yield; whereas if the temperature was risen over that temperature, the reductive alkenylation reaction to form product **30** became a competing process with the cyclization pathway. It must also be pointed out that microwave irradiation turned out to be essential, given that the yield significantly dropped when trying classical heating in an oil bath at 120 °C for 16h. The best reaction outcome was reached with MW heating for 4 hours.

This optimization in the reaction conditions led to an extremely simple protocol where only the base (K_2CO_3), solvent (1,4-dioxane) and both coupling partners (the *N*-tosylhydrazone and the alkenylboronic acid) were needed for the transformation.

2.A.2.2 Generalization of the reaction for the stereoselective synthesis of bicyclic pentanones

Taking into consideration the potential that this unprecedented reaction offered, we firstly wanted to examine its scope with regard to different *N*-tosylhydrazones. An ample variety of alkenylboronic acids turned out to be suitable for the reaction with γ-cyano α-substituted *N*-tosylhydrazones derived from cyclohexanones (**28**) or cyclopentanones (**32**); and *N*-protected piperidones (**31**) as described in Table 1. The reaction proceeded gratifyingly even with functionalized alkenylboronic acids, leaving the functionalization untouched after the reaction took place (compounds **29e**, **29g**, **33c**, **33d**, **34c** and **34d**). These compounds would therefore be useful for further derivatization. Reaction yields normally range from moderate to excellent ones, as seen in Scheme 2.A.3.



Scheme 2.A.3. Stereoselective synthesis of bicyclic cyclopentanones **29**, **33** and **34**.

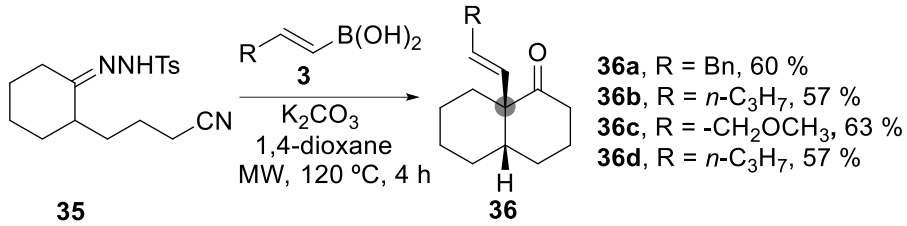
It must be pointed out that, under these reaction conditions, in all of the cases the bicyclic cyclopentanones **3**, **5** and **7** were afforded as the unique reaction products, with none of the possible products derived of the reductive alkenylation being formed in any of these transformations.

Moreover, bidimensional experiments and selective nOes over the olefinic hydrogens enabled in all of the cases the assignment of the stereochemistry in the final fused bicycles (see sections E.3.4 and E.3.5 of the Experimental Part for a detailed discussion). Noticiable, the isomer derived of a *cis* fusion was obtained in all of the cases, independently of the size of the starting *N*-tosylhydrazone ring **28** or **32** (6 or 5-membered cyclic ketone, respectively); or the use of heterocyclic ketones **31**.

Encouraged by the results in the generalization of the stereoselective synthesis of bicyclic cyclopentanones **29**, **33** and **34**; we decided to examine the scope of the reaction to other different *N*-tosylhydrazones substituted with cyano groups.

2.A.2.3 Generalization of the reaction for the stereoselective synthesis of *cis*-decalinones and 2,2-disubstituted cyclopentanones

Once the scope was established for the formation of octahydroindanones, we wondered if the reaction would be compatible with the construction of a six-membered ring. If this reaction were successful, a general method for the stereoselective synthesis of decalinones with substitution in one of the bridgehead atoms would be possible. Much to our pleasure, when the *N*-tosylhydrazone **35** reacted with the alkenylboronic acids **3** under our standard metal-free conditions, the final products derived of the carbocyclization reaction **36** were furnished as the unique products of the reaction and, importantly, as pure diastereoisomers (Scheme 2.A.4). As the previous cases, the stereochemical assignment by 2D-NMR pointed at the *cis*-fusion isomer as the one being formed in our transformation (see section E.3.3 of the Experimental Part for a detailed discussion).

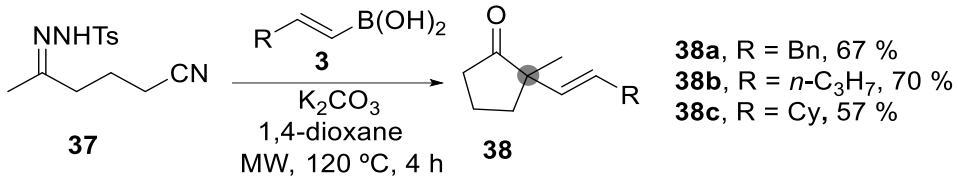


Scheme 2.A.4. Stereoselective synthesis of *cis*-decalinones **36**.

The importance of the *cis*-fusion must be highlighted. While there are more available general methodologies for the synthesis of hydrindanones and decalinones (given their importance as structural motifs in natural products, like steroids), there is a dearth of efficient ways to assemble these systems with an acyclic vinyl group at the analogous bridgehead atom. In fact, to the best of our knowledge, there are no previously described methodologies for the synthesis of this type of systems with *cis* substitution at the bridgehead atoms. This fact rises the importance of our transformation because of the access to the novel chemical space this chemistry opens up.

At this point, the reaction conditions seem to be very practical and robust, and this provided a unique and powerful access to fused [6,6], [5,6] and [5,5] rings with vinyl substitution at a bridgehead atom with total stereocontrol. However, we also wanted to examine the reaction outcome if an acyclic precursor was employed in the transformation.

Delightfully, when the acyclic *N*-tosylhydrazone **37** reacted with alkenylboronic acids **3** under the standard conditions, the final 2,2-disubstituted cyclopentanones **38** were formed as the unique products of the reaction (Scheme 2.A.5). Noticiable, the cyclopentanones present an all-carbon quaternary stereocenter in the α position.



Scheme 2.A.5. Synthesis of 2,2-disubstituted cyclopentanones **38**.

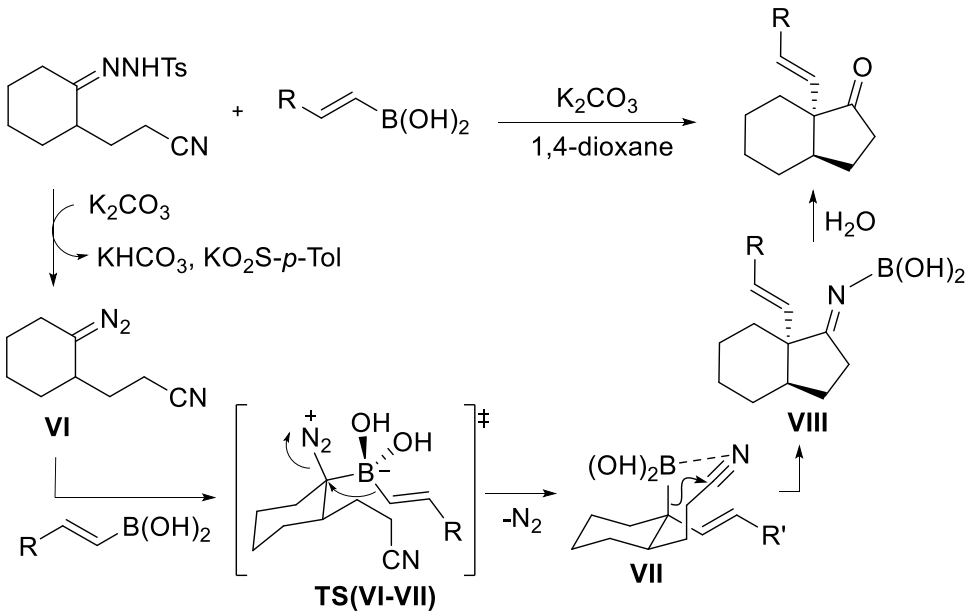
In these particular cases, it must be noticed the molecular complexity this methodology enables starting from extremely simple acyclic precursors in one step. Furthermore, the construction of 2,2-disubstituted cyclopentanones is of vital importance in natural product synthesis.[60] Therefore, this methodology opens the access to the formation of cyclic ketones bearing different substitutions and functionalizations.[61]

[60] Streuff, J.; Feurer, M.; Bichovski, P.; Frey, G.; Gellrich, U. *Angew. Chem., Int. Ed.* **2012**, *51*, 8661.
[61] (a) Shu, X.-z.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5844. (b) Okamoto, R.; Tanaka, K. *Org. Lett.* **2013**, *15*, 2112. (c) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725.

2.A.2.4 Mechanistic rationale and additional experiments

Given our previous experience in the reactions between *N*-tosylhydrazones and alkenylboronic acids,[62] we initially proposed the following mechanistic rationale for the cyclization reaction (Scheme 2.A.6). First of all, decomposition of the *N*-tosylhydrazone mediated by base would lead to the formation of the diazocompound **VI**. Next, a stereoselective addition of the alkenylboronic acid through an equatorial trajectory to the diazocompound would form the allylboronic intermediate **VII**. At this point, where the protodeboronation reaction was prone to occur; a stereoretentive nucleophilic attack over the nitrile group took place, furnishing the imine **VIII**. Finally, an *in situ* hydrolisis of the imine afforded the final bicyclic ketones as the sole products of the reaction.

In the part B of this chapter, a more detailed mechanistic proposal based on DFT computational studies will be discussed (Section 2.B.2.7.2).



Scheme 2.A.6. Mechanistic proposal for the addition-cyclization sequence in the formation of carbocyclization products.

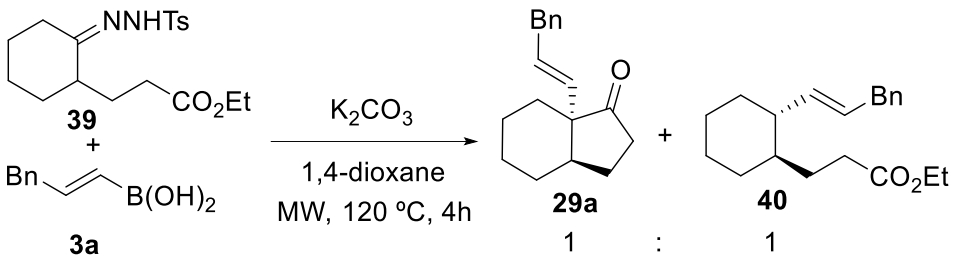
[62] Plaza, M.; Pérez-Aguilar, M. C.; Valdés, C. *Chem. Eur. J.* **2016**, *22*, 6253.

The intramolecular allylborylation of carbonyl compounds and aldehydes is well-known,[63] and it is a common stablished methodology for the formation of cyclic homoallylic alcohols, which are intermediates of high synthetic value. However, to the best of our knowledge, this would be the first example of an intramolecular transition-metal-free allylborylation reaction employing nitriles reported in the literature. There is only one previously reported example of intramolecular addition of boronates to nitriles, but it is restricted to the use of aromatic ones; and required the employment of a silver catalyst.[64]

The attack of the allylboronic acid to the nitrile group would implicate that either a polar or a radical mechanism was involved during this transformation. To exclude the possibility of the radical pathway, a reaction was carried out with TEMPO as a radical scavenger; but no drop in the yield was detected in the formation of the final cyclization products, nor TEMPO adducts in the crude of the reaction by NMR and GC/MS.

To provide additional evidence for the polar mechanism, we decided so synthesize a *N*-tosylhydrazone bearing a different electrophile instead of a nitrile: an ester functionality. When *N*-tosylhydrazone **39** reacted with *trans*-3-phenyl-1-propen-1-ylboronic acid under the standard conditions, a mixture 1:1 of the bicyclic cyclopentanone **29a** and protodeboronation product **40** was obtained in the reaction. This fact demonstrated that the ester functionality is a proper electrophile for the cyclization, although not as suitable as the cyano group, which exclusively promoted the cyclization pathway.

[63] Kramer, G.W.; Brown, H.C. *J. Org. Chem*. **1977**, *42*, 2292.
[64] Zhao, W.; Montgomery, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 12683.



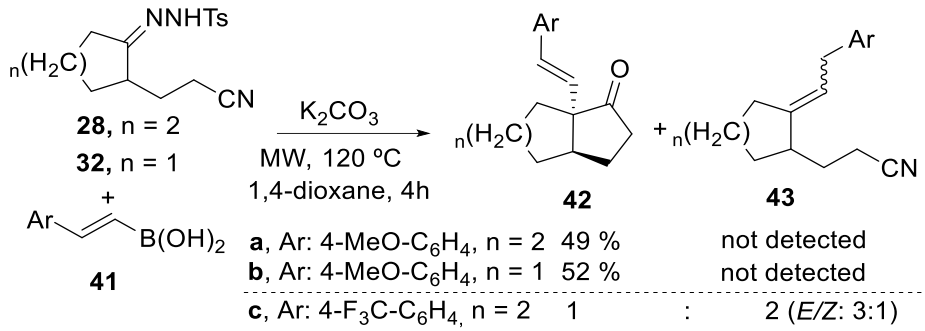
Scheme 2.A.7. Reaction of a *N*-tosylhydrazone with a tethered ester functionality **39** and alkenylboronic acid **3a**

As it can be seen in the previous case, a determining aspect in this transformation is that the cyclization pathway must outcompete the spontaneous protodeboronation of the allylboronic acid intermediate **VII**. As it was described until this point, when 2-alkyl substituted alkenylboronic acids are employed, the carbocyclization products are solely obtained. However, in a previous communication in our research group, we reported the different behaviour of the alkenylboronic acids depending on the substitution attached to the vinyl group in their reaction with *N*-tosylhydrazones.[65] Therefore, different reaction outcomes could be expected in this reaction when employing 2-aryl substituted alkenylboronic acids.

In this context, when *N*-tosylhydrazones **28** and **32** were made to react with *trans*-2-(4-methoxyphenyl)vinylboronic acid, the alkenylboronic acid presented the same behaviour as its analogues **3**, and only the carbocyclization products **42** were formed in the reaction.

However, if *trans*-2-(4-trifluoromethylphenyl)vinylboronic acid was employed in the transformation, a mixture 1:2 of the corresponding bicycle **42** and protodeboronation product **43** was detected by analysis of the crude by NMR and GC/MS. This fact stood as an evidence that the electronic effects in the aryl ring played a decisive role in the pathway the allylboronic acid intermediate could follow.

[65] Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem. Int. Ed.* **2012**, *51*, 5953.

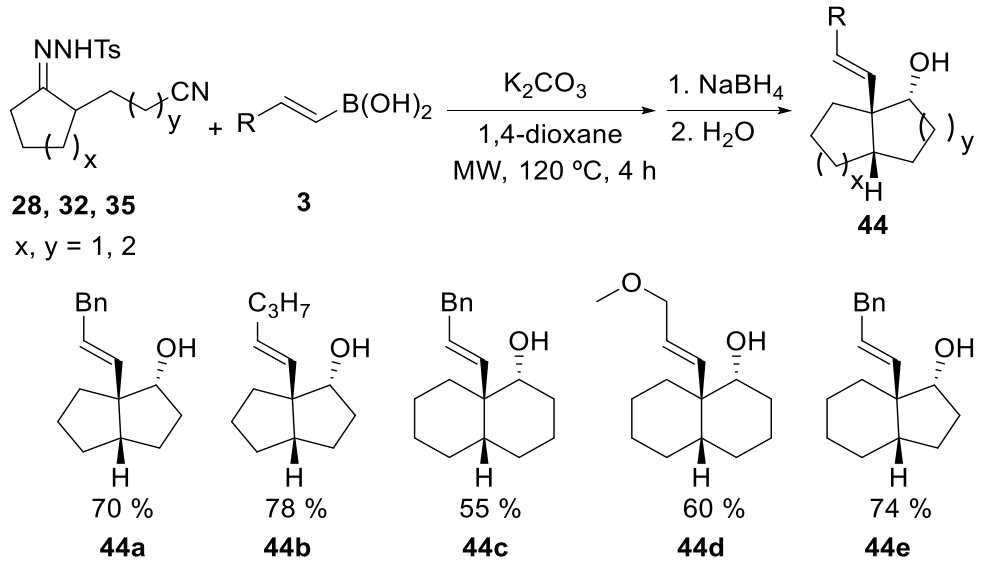


Scheme 2.A.8. Reactions with *N*-tosylhydrazones **28** and **32** with 2-aryl substituted alkenylboronic acids **41**.

2.A.2.5. One-pot cyclization/reduction: synthesis of homoallylic alcohols

As rationalized in section 2.A.2.4, the reactions should proceed through the formation of a transient imine **VIII** (Scheme 2.A.6). Trying to increase the synthetical value of our transformation, we intended to trap that imine upon *in situ* reduction with $NaBH_4$ to form the corresponding primary amine derivative. Therefore, to eliminate the water that was formed in the reaction in the decomposition of the *N*-tosylhydrazones mediated by K_2CO_3, a small amount of Na_2SO_4 was added. Once the vial was put out of the microwave apparatus, it was uncapped, and the sodium borohydride was added in a one-pot fashion. Subsequent quenching with water was expected to afford the corresponding amines.

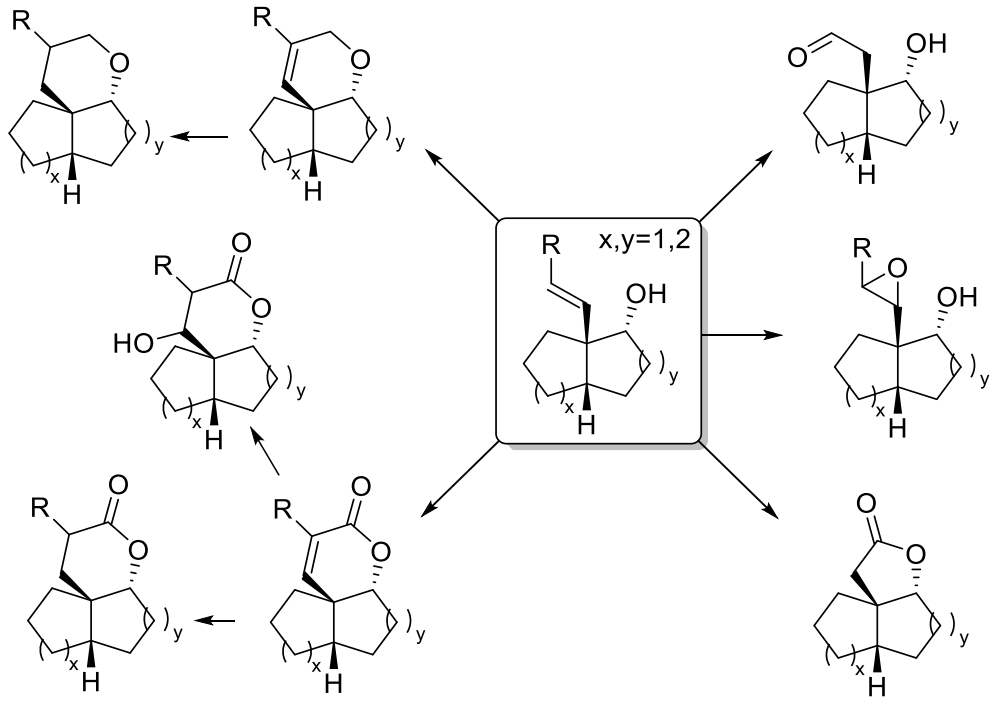
However, a careful analysis of the products by IR, NMR and GC/MS revealed that the alcohol derivatives **44** were formed instead of the expected amines. Clearly, the highly unstable imine, at 120 °C in a basic media, was hydrolyzed to the corresponding ketone. Therefore, treatment with $NaBH_4$ gave the homoallylic alcohols **44** (Scheme 2.A.9).



Scheme 2.A.9. Synthesis of homoallylic alcohols **17** through a one-pot cyclization/reduction sequence

Obviously, the presence of $NaSO_4$ was not needed any longer in this one-pot fashion. Gratifyingly, the homoallylic alcohols **44** were furnished as single diastereoisomers. Although this was not our desired synthetic intention, the grade of molecular complexity that is actually achieved should not be understated, given that these compounds present three different contiguous stereocenters created with total stereocontrol in one-pot. This stereoselectivity was the same in all of the products **44** independently of the size of the starting *N*-tosylhydrazone employed (**28**, **32**, **35**). The stereochemical assignment of these compounds is discussed in detail in section E.3.5 of the Experimental Part.

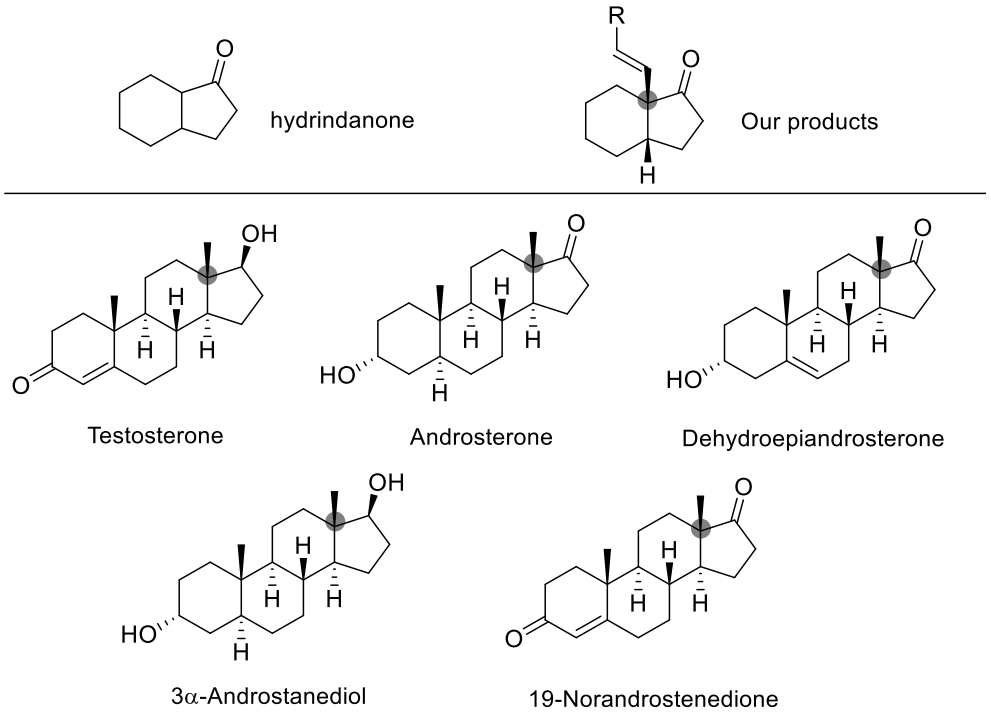
Moreover, it must be pointed out that homoallylic alcohols are intermediates of high synthetical value in organic synthesis. These compounds can be potentially functionalized at either or both the formed alcohol and alkene through transformations such as oxidation, cyclization or ozonolysis. The incorporation of certain functionalities along the allylic backbone thanks to the employment of different alkenylboronic acids could therefore give rise to products with expanded functionality. These routes would provide access to important synthons such as β-hydroxy carbonyls, cyclic ethers and both saturated and unsaturated lactones. A graphical summary of some of these potential processes is depicted in Scheme 2.A.10.



Scheme 2.A.10. Possible derivatization alternatives of our homoallylic alcohols **44**.

2.A.2.6. Application of the domino reaction to the structural modification of androsterone

Given the *cis*-hydrindanone nature of our final products, we realized that a structural modification of one of the androsteroid derivatives depicted in Scheme 2.A.11 could be possible. Noticiable, all of these compounds present an angular methyl in the all-carbon quaternary stereocenter next to the carbonyl (or hydroxyl) functionality. Among all the structures shown, the one we considered optimal for our proposed transformation was the enantiomerically pure androsterone.

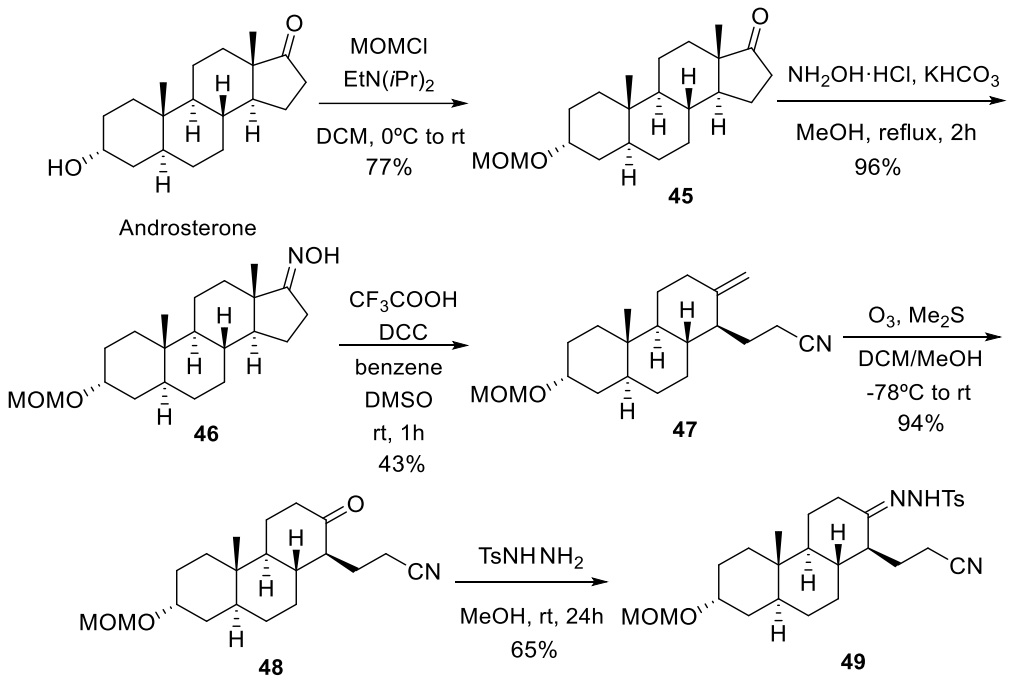


Scheme 2.A.11. Selection of important steroids bearing the hydrindanone core

We realized that the group of Hu[66] and Covey[67] reported different publications in which androsteroid derivatives bearing a carbonyl functionality tethered with a side chain containing a cyano group were prepared. This kind of

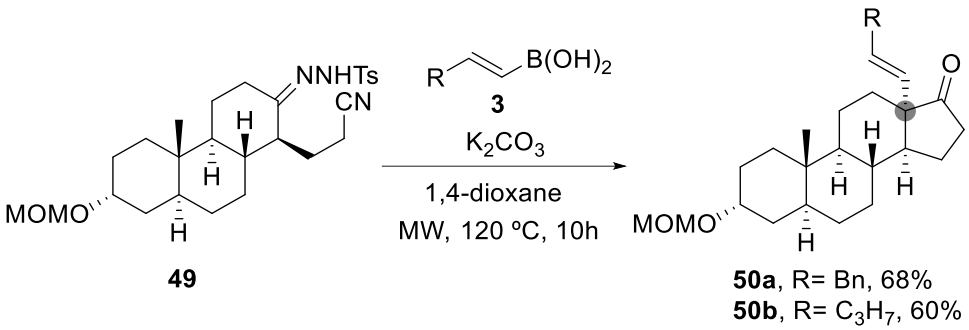
[66] Jiang, X.; Wang, C.; Hu, Y.; Hu, H.; Covey, D. F. *J. Org. Chem.* **2000**, *65*, 3555.
[67] Han, M.; Covey, D. F. *J. Org. Chem.* **1996**, *61*, 7614.

compounds would actually be ideal substrates for our reaction with the alkenylboronic acids to promote the domino cyclization. A depiction of our application of the previously described similar synthetic route but starting from androsterone to form our compound of interest **49** is presented in the Scheme 2.A.12.



Scheme 2.A.12. Depiction of synthetic sequence from androsterone to *N*-tosylhydrazone **49**.

Starting from commercially available androsterone, a first step consisted in the protection of the hydroxyl group with cloromethyl methyl ether to form compound **45**. Next, the formation of the corresponding oxime derivative **46** was achieved under classical conditions for this type of transformations. Subsequent abnormal Beckmann rearrangement mediated by DCC and CF_3COOH afforded compound **47**, which after ozonolysis gave the ketonitrile **48**. Delightfully, reaction of this compound with tosylhydrazide afforded the corresponding *N*-tosylhydrazone **49** in good yield.



Scheme 2.A.13. Application of the domino cyclization to the stereoselective synthesis of androsterone derivatives **50**.

At that point, our reaction was put to the test when *N*-tosylhydrazone **49** and the alkenylboronic acids were mixed in 1,4-dioxane in the presence of K_2CO_3, although in this case a longer reaction time (10h) was needed to ensure total consumption of **49** (Scheme 2.A.13).

Much to our pleasure, under these slightly modified reaction conditions, the carbocyclization products **50** were obtained as unique stereoisomers (see section E.3.6 of the Experimental Part for a detailed discussion).

All in all, this novel reaction represents an unprecedented way to reconstruct the five membered ring of the androsterone through our domino reaction, in which the angular methyl was replaced with an alkenyl chain; and the configuration of that quaternary center was inverted.

By this way, we have demonstrated that our reaction could also be employed when more complex and sterically demanding *N*-tosylhydrazones were utilized; and importantly preserving once again the total stereocontrol in the formation of the new all-carbon quaternary stereocenter. Specifically, this transformation gave access to a new family of androsteroid compounds, which therefore would present unknown biological properties.

2.A.2.7. Derivatization of the bicyclic products through a vinylation/oxy-Cope/Alder-ene synthetic sequence

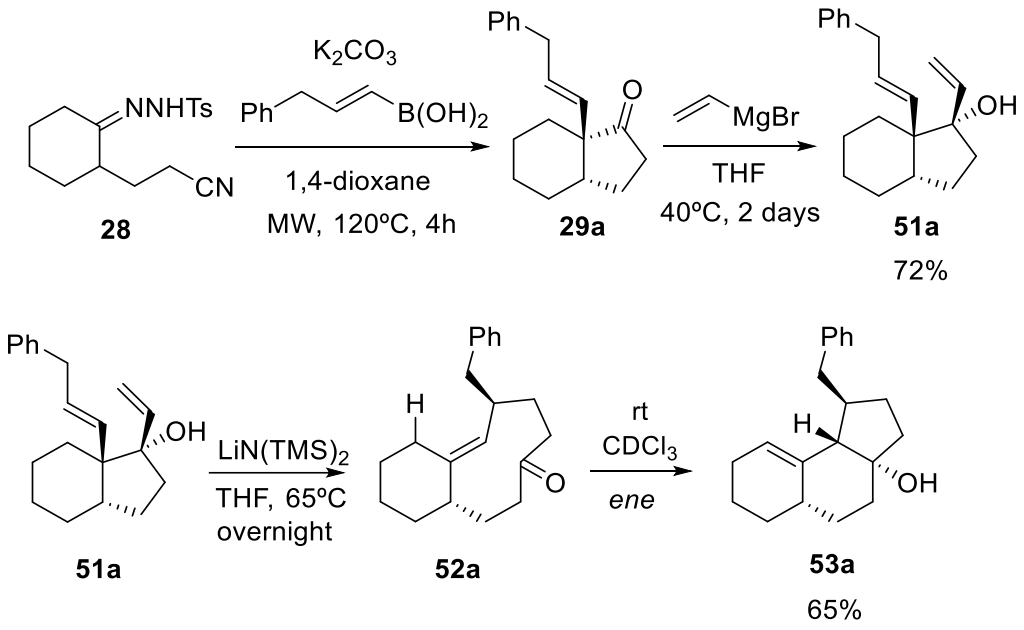
As it was described in section 2.A.2.5, the addition of $NaBH_4$ to our bicyclic compounds **29** was a stereoselective transformation in which only one isomer of the corresponding homoallylic alcohols **44** was obtained. Encouraged by these results, we envisioned that the analogous addition of a Grignard reagent to our bicyclic ketones **29** could therefore provide access to a unique isomer in the corresponding products. Moreover, the addition of vinyl magnesium bromide would construct systems in which an oxy-Cope rearrangement could certainly take place at high temperatures. This overall transformation would represent an interesting methodology for the synthesis of complex polisubstituted 9-membered rings, which are common scaffolds in a variety of natural products with diverse biological activities.[68]

Therefore, we started the synthetic sequence by chosing compound **29a** as our starting material for the vinylation reaction (Scheme 2.A.14). Reaction of **29a** with vinylmagnesium bromide in THF at 40 °C for 48 hours afforded the formation of compound **51a** as the expected single isomer. As it can be seen in the scheme, this compound presents an optimal geometry for an oxy-Cope rearrangement to take place. Therefore, treatment of **51a** with the strong base $LiN(TMS)_2$ in anhydrous THF at 65 °C for 16 hours furnished compound **52a**, as a single isomer due to the concerted nature of the anionic oxy-Cope rearrangement. Much to our surprise, after the purification of compound **52a** by flash chromatography, we observed that a new compound had been formed in $CDCl_3$ at room temperature in less than 15 minutes. After careful analysis by NMR, we concluded that a spontaneous transannular ene reaction had taken place in compound **52a** to form **53a**, which was also obtained as a unique diastereoisomer.

It must be pointed out that Barriault and co-workers had previously reported a synthetic procedure based on a tandem oxy-Cope/Claisen/ene sequence for the

[68] Huber, T.; Wildermuth, R.E.; Magauer, T. *Chem. Eur. J.* **2018**, doi.org/10.1002/chem.201705919

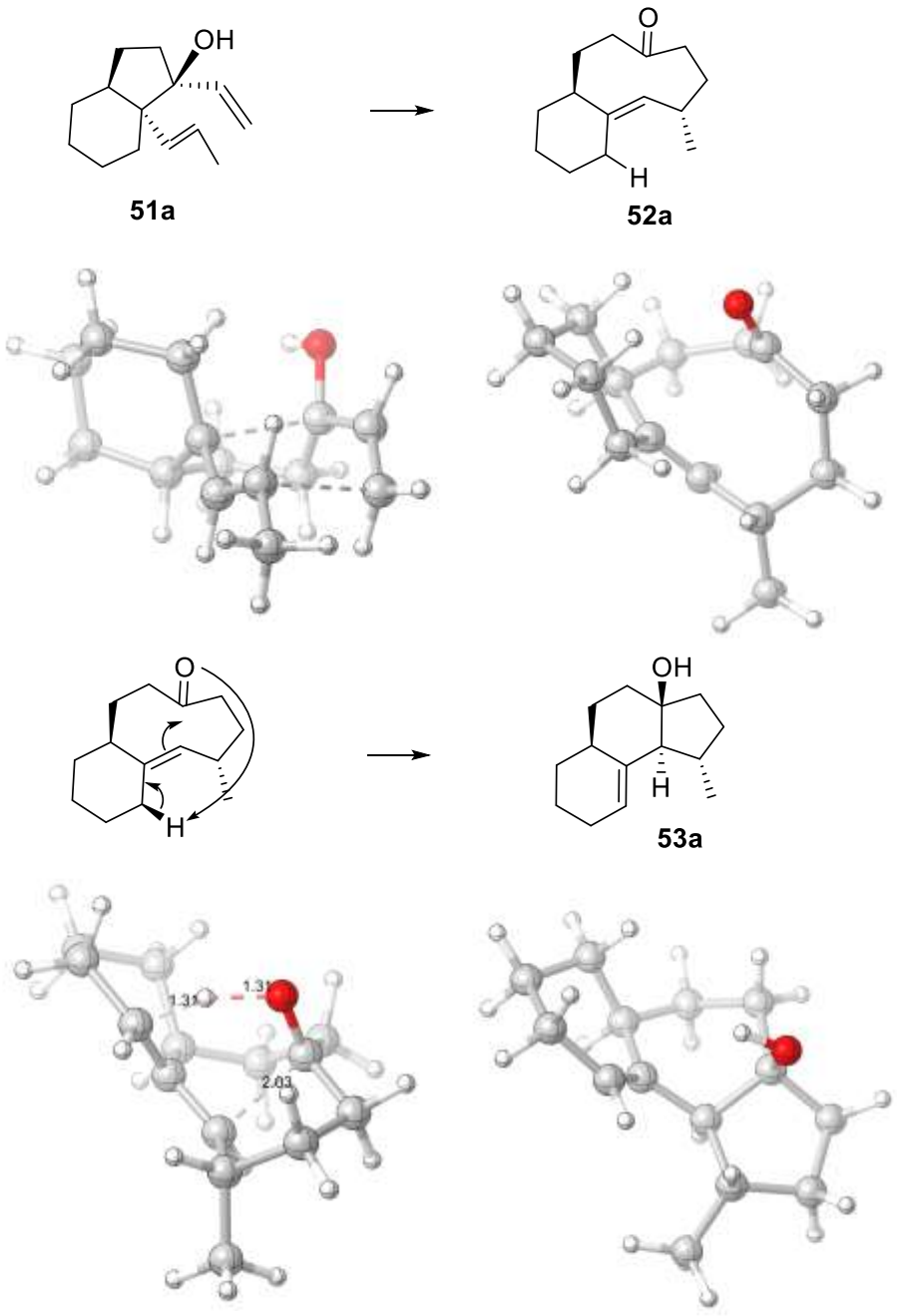
formation of large rings,[69] where the spontaneous final ene reaction at room temperature is very similar to our case.



Scheme 2.A.14. Synthesis of polycyclic alcohol **53a** through the vinylation/anionic oxy-Cope/transannular ene sequence

To provide a more intuitive view of how these processes took place, we ran some calculations to illustrate the molecular geometries of the different products in this overall sequence (Scheme 2.A.15).[70]

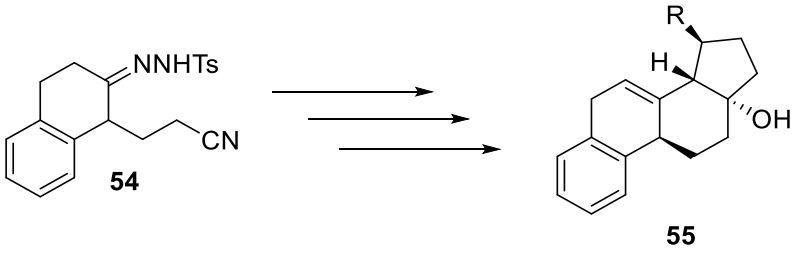
[69] Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc*. **2004**, *126*, 8569.
[70] All the structures have been rendered with Cylview. The benzyl group has been replaced with a methyl group for simplicity in the modelling.



Scheme 2.A.15. Structural modelling of the oxy-Cope and transannular ene reactions. Critical distances are shown in Å.

While it is true that the synthetic value of this methodology may seem limited to some extent; we intend to expand this route for the synthesis of much more complex systems, which would remind of the cyclopentaneperhydrophenantrene core of steroids (Scheme 2.A.16).

Thus, if we started this sequence from *N*-tosylhydrazone **54**, which carbonyl precursor could be prepared by cyanoethylation of the commercially available β-tetralone, the synthesis of the steroid-like compounds **55** could be doable through our proposed methodology. Forthcoming efforts will be paid to continue with this work in our research group.

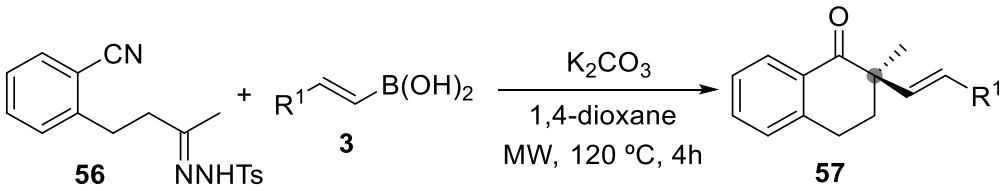


Scheme 2.A.16. Synthetic proposal for the domino carbocyclization/vinylation/anionic oxy-Cope/ene sequence for the construction of steroid-like compounds **55**.

2.A.2.8. Application of the domino carbocyclization reaction for the synthesis of 2,2-disubstituted α-tetralones

All the previous cyclization reactions employing alkenylboronic acids took place when the nucleophilic attack of the allylboronic intermediate took place over a nitrile attached to a C-sp^3 system. Thus, we wanted in investigate whether the reaction could also be compatible with aromatic nitriles, as this reaction would also provide cyclic structures with great synthetical value.

With this purpose, we synthesized the *N*-tosylhydrazone **56** bearing an aromatic (Scheme 2.A.17). Gratifyingly, the expected 2,2-disubstituted tetralones **57** were obtained as the unique products in very good yields, independently of the alkenylboronic acid employed. The way in which molecular complexity is achieved in the final products starting from simple acyclic precursors in one synthetic step is once again noteworthy.



Compound	R^1	Yield (%)
57a	Bn	78
57b	$-CH_2OCH_3$	86
57c	$-(CH_2)_2CH_3$	70
57d	$-(CH_2)_3CH_3$	50
57e	$-(CH_2)_2CH_2Cl$	60

Scheme 2.A.17. Synthesis of 2,2-disubstituted α-tetralones **57** in the reaction of *N*-tosylhydrazone **56** with alkenylboronic acids **3**.

It must be noticed the synthetic importance of these type of transformations. Although there are several methodologies described in the literature for the synthesis of 2,2-disubstituted tetralones; in all of the cases the double substitution

is achieved by either alkylating a previously monoalkylated tetralone or following a double alkylation pathway starting from commercially available unsubstituted tetralones.[71] To the best of our knowledge, there is not a single synthetic approach in with an acyclic precursor gave rise to this kind of compounds in a transition-metal-free and unique step. Moreover, the biological and clinical importance of α-tetralone containing scaffolds is shown in the vast number of publications in which these class of compounds are involved in the last decades.[72]

At this point, we are currently expanding the reaction scope for the employment of other systems in our research group.

[71] For some recent works on the synthesis of 2,2-disubstituted α-tetralones, see: (a) Grigalunas, M.; Ankner, T.; Norrby, P.-O.; Wiest, O.; Helquist, P. *J. Am. Chem. Soc.* **2015**, *137*, 7019. (b) Kang, J. Y.; Johnston, R. C.; Snyder, K. M.; Cheong, P. H.-Y.; Carter, R. G. *J. Org. Chem.* **2016**, *81*, 3629. (c) Beltran, F.; Fabre, I.; Ciofini, I.; Miesch, L. *Org. Lett.* **2017**, *19*, 5042.

[72] For the importance of α-tetralone scaffolds in natural products and drug discovery, see: (a) Dwivedi, G. R.; Upadhyay, H. C.; Yadav, D. K.; Singh, V.; Srivastava, S. K.; Khan, F.; Darmwal, N. S.; Darokar, M. P. *Chem. Biol. Drug. Des*. **2014**, *83*, 482. (b) Charest, M. G.; Siegel, D. R.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 8292. (c) Miron-Lopez, G.; Bazzocchi, I. L.; Jimenez-Diaz, I. A.; Moujir, L. M.; Quijano-Quiñones, R.; Quijano, L.; Mena-Rejon, G. J. *Bioorganic Med. Chem. Lett.* **2014**, *24*, 2105. (d) Taber, G. P.; Pfisterer, D. M.; Colberg, J. C. *Org. Process Res. Dev.* **2004**, *8*, 385. (e) Hussein, A. a; Bozzi, B.; Correa, M.; Capson, T. L.; Kursar, T. a; Coley, P. D.; Solis, P. N.; Gupta, M. P. *J. Nat. Prod.* **2003**, *66*, 858.

2.A.2.9. Limitations of the stereoselective domino carbocyclization reaction

Until this moment in Chapter 2.A, we have shown the advances in this new carbocyclization mode based on the reaction between alkenylboronic acids and *N*-tosylhydrazones.

However, there were some cases in which the cascade carbocyclization did not take place. For a better understanding, the limitations regarding the boronic acids and *N*-tosylhydrazones will be discussed independently.

2.A.2.9.1. Limitations of the domino carbocyclization with respect to the boronic acids employed

The carbocyclization reaction proceeds with optimal results when 2-alkyl substituted alkenylboronic acids were employed.

In the section 2.A.2.4, it has already been shown that depending on the electronic properties of the aryl ring when employing 2-arylethenylboronic acids, the protodeboronation pathway could become a competing process with the desired carbocyclization reaction.

We also tried to expand the reaction to the use of aryl- and alkylboronic acids. Much to our dismay, when the reactions of these boronic acids were run with the corresponding *N*-tosylhydrazone **28** under the standard conditions, the formation of the Bamford-Stevens olefin was detected in the crude of the reactions as the main product; without any of the reductive coupling or cyclization products being formed.

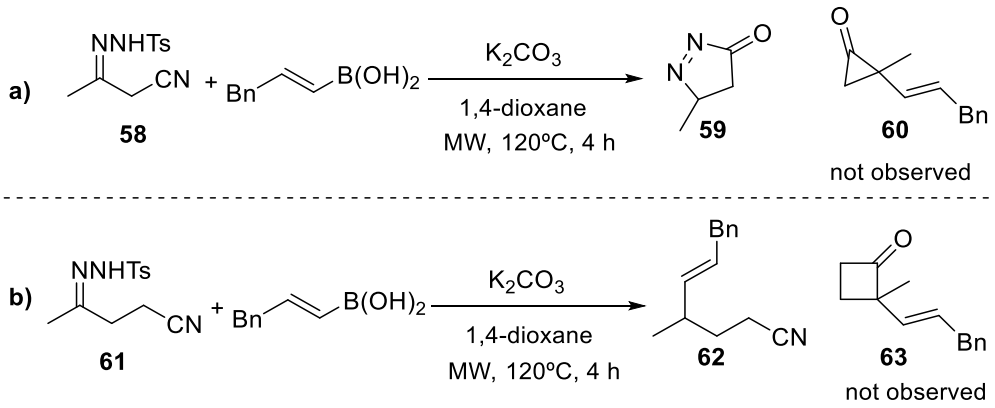
These results indicate that the formation of the allylboronic intermediate is essential for the cyclization to take place. A justification for this fact will be provided in section 2.B.2.6 based on DFT computational studies.

2.A.2.9.2. Limitations of the domino carbocyclization with respect to the size of the *N*-tosylhydrazones employed

As it was previously presented, the cyclization pathway worked well for the formation of [6,6] [6,5] and [5,5] fused systems; as well as the formation of the 2,2-disubstituted cyclopentanones. Thus, it is appropriate for the assembly of five and six-membered rings. Taking this into consideration, we wanted to examine if the same methodology could be applied to build larger and smaller ring systems.

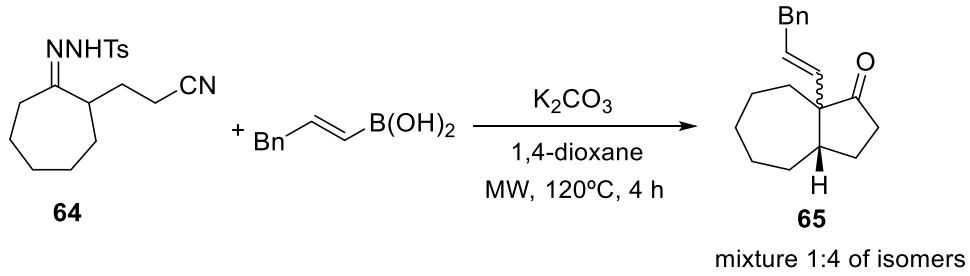
In an attempt to obtain the cyclopropanone derivative **60** (Scheme 2.A.17), it was observed the formation of the pyrazoline **59** without further incorporation of the alkenylboronic acid (Scheme 2.A.17, a). Clearly, after deprotonation of the *N*-tosylhydrazone **58**, an intramolecular nucleophilic attack took place over the nitrile group for form the compound **59**; preventing the formation of the corresponding diazocompound and therefore killing the expected reactivity of the starting *N*-tosylhydrazone.

When the 2,2-disubstituted cyclobutanone **63** was pursued in the reaction between *N*-tosylhydrazone **61** and alkenylboronic acids, the product corresponding of the reductive alkenylation **62** was the only one detected in the reaction crude (Scheme 2.A.17, b). The formation of the 4-membered ring was not as favoured as it was the case for the 5 or 6-membered analogues, which is reasonable from a thermodinamical point of view.



Scheme 2.A.17. Attempt to build the three and four-membered rings through the domino cyclization reaction.

Regarding the stereoselectiviy of the reaction, when we employed an *N*-tosylhydrazone derived of a 7-membered ring **64**, we obtained a 1:4 mixture of diastereoisomers in the formation of the carbocyclization product **65** (Scheme 2.A.18). These results did not take us by surprise, given that we have previously described in this memory that the reactions between *N*-tosylhydrazones derived from 7-membered cyclic ketones with alkenylboronic acids led to the formation of mixtures of diastereoisomers. We think that this lack of stereoselectivity is due to the non-stereoselective nature of the addition of the alkenylboronic acids to the diazocompound derived of the thermal decomposition of **64**.



Scheme 2.A.18. Limitations in the stereoselectivity of the domino reaction.

2.A.3. Conclusions

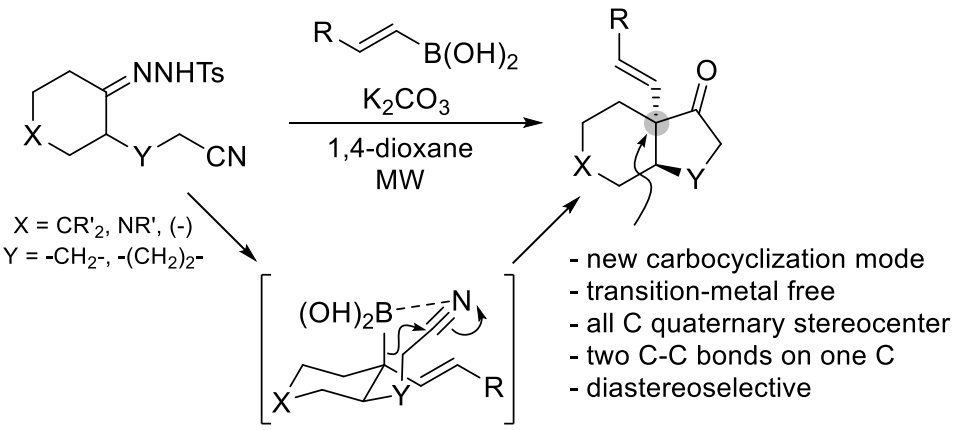
In part A of Chapter 2, it was described a novel carbocyclization reaction employing *N*-tosylhydrazones with a cyano group attached to the side chain and alkenylboronic acids.

Our methodology enabled an unprecedented, simple, transition-metal-free construction of a variety of fused cyclohexanones and cyclopentanones with total stereoselectivity in the formation of a new all-carbon quaternary stereocenter. Moreover, this transformation also allowed for the synthesis of a variety of 2,2-disubstituted cyclopentanones if an acyclic *N*-tosylhydrazone was employed. Finally, our methodology was applied in a stereoselective structural modification of androsterone, giving rise to a new family of previously undescribed steroid derivatives.

We found applications of our carbocyclization reactions for the synthesis of policyclic compounds and disubstituted α-tetralones; respectively described in parts 2.7 and 2.8 of this chapter. We are currently working in these methodologies in our research group, already with satisfactory advances that we plan to publish in the near future.

The carbocyclization reaction worked perfectly when *N*-tosylhydrazones with tethered cyanide groups at an optimal position reacted with alkenylboronic acids. The limitations with respect of the boronic acids and *N*-tosylhydrazones employed have been fairly stated in part 2.9 of this chapter.

2.A.4. Graphical summary



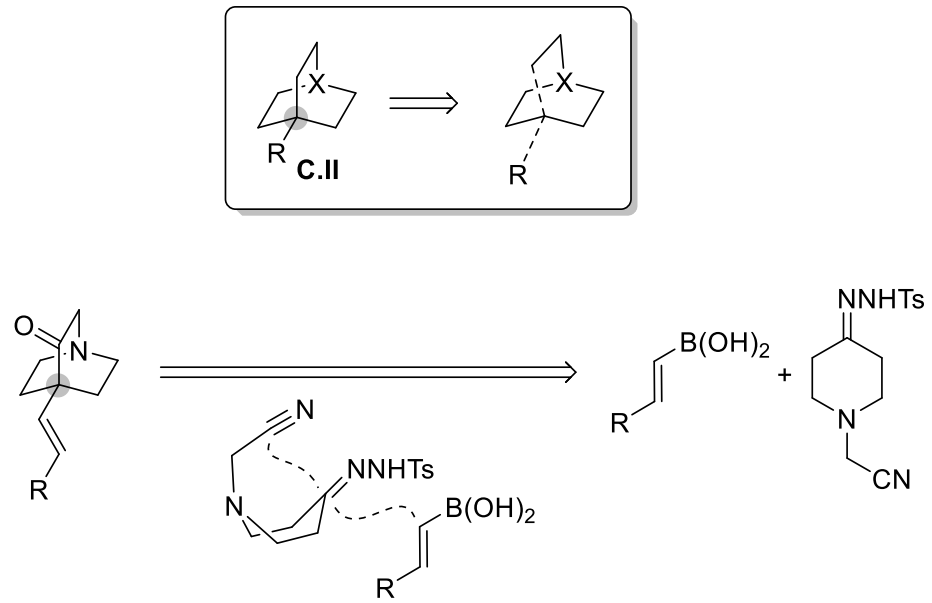
Chapter 2. Part B

Transannular heterocyclization reactions based on domino reactions of *N*-tosylhydrazones and alkenylboronic acids through allylborylation of nitriles: DFT-based mechanistic insight

2.B.1 Introduction

As pointed in the introduction of chapter 2, new synthetic methodologies for the construction of the bicyclic molecules **C.II** described in figure 2.1 would be of great interest in organic synthesis. Particularly, these structures feature a quaternary stereocenter at one of the bridgehead atoms, which is not easy to form in a single step starting from acyclic precursors.

We envisioned that taking advantage of the novel carbocyclization mode described in part A of chapter 2, a transannular cyclization would represent an original way that could give access to the previously described scaffolds **C.II** (Scheme 2.B.1). Concretely, if it was possible to synthesize an *N*-tosylhydrazone derived from a 4-piperidone with a cyanomethyl group attached to the nitrogen; this compound would actually be a suitable starting material in which a transannular heterocyclization could take place in its reaction with alkenylboronic acids.



Scheme 2.B.1. Initial rationale for the synthesis of bicyclic structures **C.II** through a transannular cyclization between *N*-tosylhydrazones and alkenylboronic acids.

Furthermore, these reactions would provide access to compounds featuring a 3-quinuclidinone core. This kind of scaffolds have been revealed as important building blocks in a wide range of pharmacologically active compounds having anticancer activity,[73] anti-Alzheimer's effect,[74] nicotinic receptors inhibitory activity,[75] and antihistamine bronchodilating effect.[76] Therefore, new methodologies for the synthesis oh this class of compounds are in a relentless pursuit in diverse oriented synthesis to drug discovery.[77]

[73] Soni, J. Y.; Sanghvi, S.; Devkarb, R. V.; Thakore, S. *RSC Adv*. **2015**, *5*, 82112.

[74] Rodríguez-Franco, M. I.; Dorronsoro, I.; Castro, A.; Martínez, A.; Badía, A.; Baños, J. E. *Bioorg. Med. Chem*. **2003**, *11*, 2263.

[75] Arias, H. R.; López, J. J.; Feuerbach, D.; Fierro, A.; Ortells, M. O.; Pérez, E. G. *Int. J. Biochem. Cell Biol*. **2013**, *45*, 2420.

[76] Villani, F. J.; Mann, T. A.; Wefer, E. A. *J. Med. Chem*. **1975**, *18*, 666.

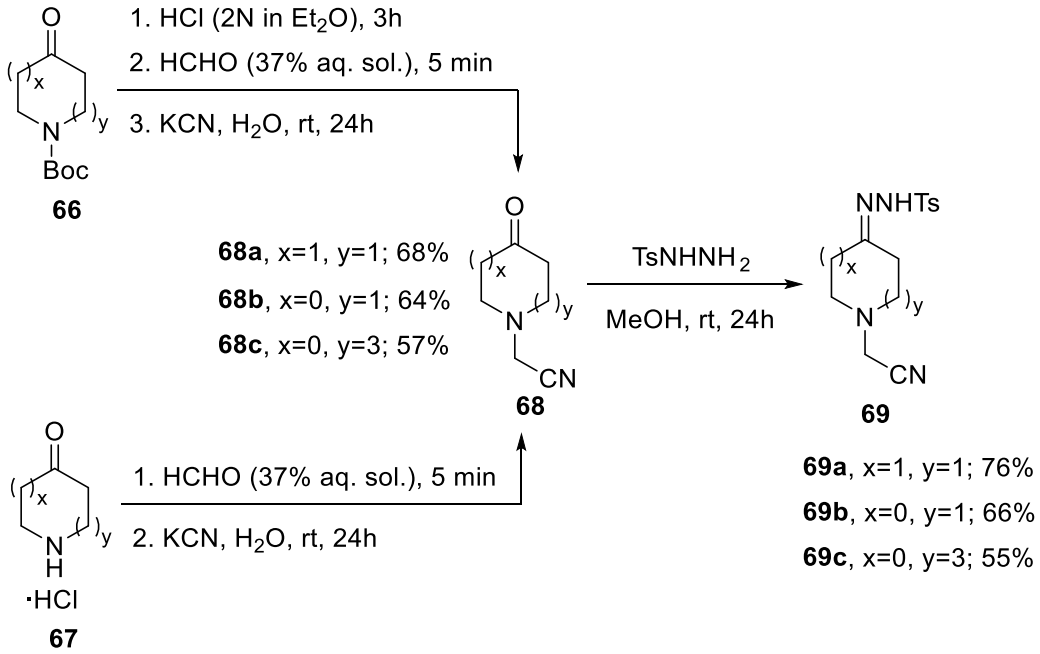
[77] For some recent examples of the employment of 3-quinuclidinones in the synthesis of biologically active compounds see: (a) Quadri, M.; Matera, C.; Silnović, A.; Pismataro, M. C.; Horenstein, N. A.; Stokes, C.; Papke, R. L.; Dallanoce, C. *ChemMedChem* **2017**, *12*, 1335. (b) Del Bello, F.; Bonifazi, A.; Giorgioni, G.; Petrelli, R.; Quaglia, W.; Altomare, A.; Falcicchio, A.; Matucci, R.; Vistoli, G.; Piergentili, A. *Eur. J. Med. Chem.* **2017**, *137*, 327. (c) Hill, M. D.; Fang, H.; Digavalli, S. V.; Healy, F. L.; Gallagher, L.; Post-Munson, D.; Chen, P.; Natale, J.; Benitex, Y.; Morgan, D.; Lodge, N.; Bristow, L.; Macor, J. E.; Olson, R. E. *Bioor. Med. Chem. Lett.* **2017**, *27*, 578. (d) Cook, J.; Zusi, F. C.; McDonald, I. M.; King, D.; Hill, M. D.; Iwuagwu, C.; Mate, R. A.; Fang, H.; Zhao, R.; Wang, B.; Cutrone, J.; Ma, B.; Gao, Q.; Knox, R. J.; Matchett, M.; Gallagher, L.; Ferrante, M.; Post-Munson, D.; Molski, T.; Easton, A.; Miller, R.; Jones, K.; Digavalli, S.; Healy, F.; Lentz, K.; Benitex, Y.; Clarke, W.; Natale, J.; Siuciak, J. A.; Lodge, N.; Zaczek, R.; Denton, R.; Morgan, D.; Bristow, L. J.; Macor, J. E.; Olson, R. E. *J. Med. Chem.* **2016**, *59*, 11171.

2.B.2. Results and discussion

2.B.2.1. Objective and general considerations

As we stated in the introduction of this chapter, we envisaged that the reaction between *N*-tosylhydrazones bearing a cyanomethyl moiety attached to the piperidonic nitrogen and alkenylboronic acids could stand as an unprecedented simple way of constructing the 3-quinuclidinone core, which features the bicyclic scaffold **C.II**.

With this purpose, the first of all a general method for the synthesis of the *N*-tosylhydrazones needed for this kind of transformations had to be devised. Gratifyingly, after some experimentation, an appropriate methodology for this synthesis was achieved (Scheme 2.B.2).

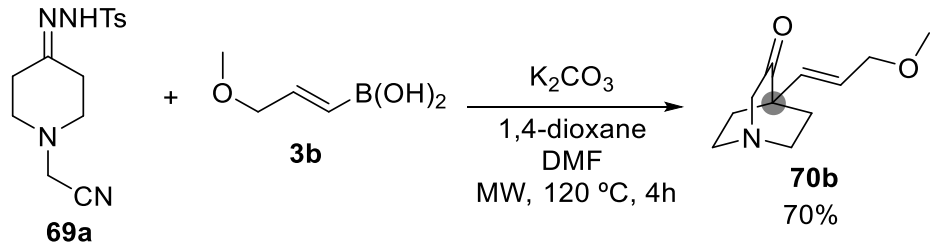


Scheme 2.B.2. Synthetic route for the formation of *N*-tosylhydrazones **69**.

The synthesis was conducted from *N*-Boc derivatives **66** or directly the hydrochloride salts **67** depending on their commercial availability. Once the hydrochloride salts were formed, treatment with KCN and a 37% aqueous solution of formaldehyde assembled the *N*-cyanomethylated piperidone or pyrrolidinone derivatives **68**. Finally, reaction with tosylhydrazide under classical conditions led to the formation of our desired *N*-tosylhydrazones **69**.

2.B.2.2. Optimization

The first attempt in the reaction of this systems with alkenylboronic acids was conducted under our standard conditions (2 eq. of K_2CO_3; 1,4-dioxane as solvent; 4 hours under microwave irradiation) employing the *N*-tosylhydrazone **69a**. However, after the reaction time was completed, the starting material **69a** was recovered. After some experimentation, we realized that the highly polar *N*-tosylhydrazone salt *in situ* formed was not soluble in 1,4-dioxane. To address this issue, we tried the addition of a small amount of DMF to solubilize this salt; although the 1,4-dioxane still was still employed as the solvent of the reaction. Delightfully, under these new conditions, the bicyclic quinuclidinone **70b** was obtained in a good yield after flash chromatography. It needs to be pointed out the high polarity of this compound, which needed a 95:5 mixture of dichloromethane and methanol for the purification in classical silica chromatography. We believe this fact had to do with the highly piramidalized nature of the bridgehead nitrogen, which enhanced the retention of this compound in the polar SiO_2 pad.

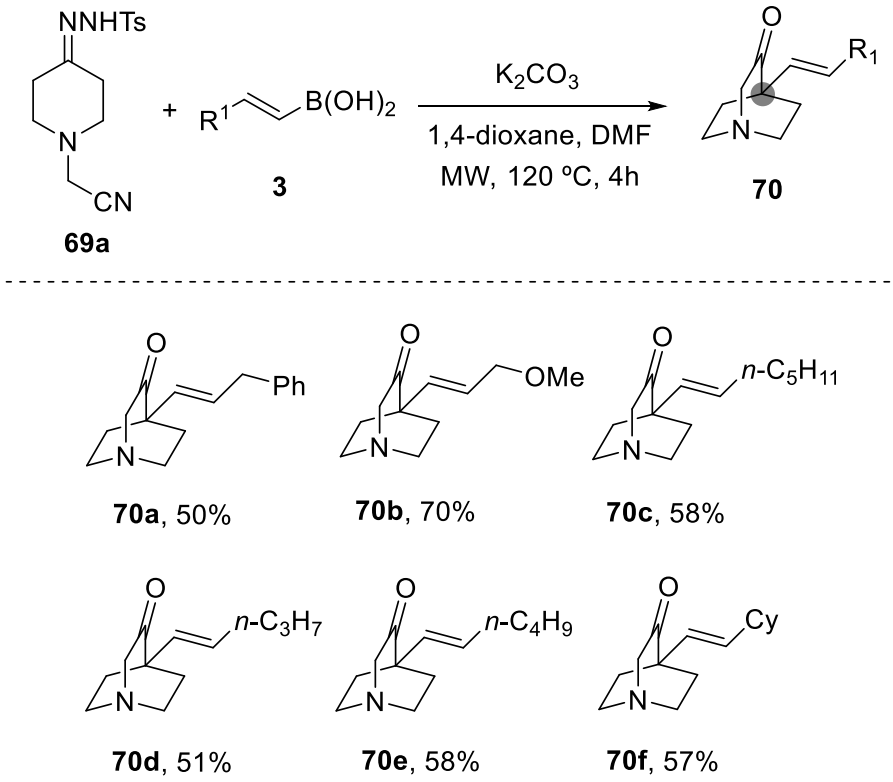


Scheme 2.B.3. First successful results for the heterocyclization reaction between *N*-tosylhydrazone **69a** and alkenylboronic acid **3b**

In this way, we apparently found proper reaction conditions for the synthesis of 3-quinuclidinones through a transannular cyclization reaction between alkenylboronic acids and *N*-tosylhydrazones. In the next part, the generalization of this reaction will be shown.

2.B.2.3. Generalization of the transannular cyclization reaction between *N*-tosylhydrazones and alkenylboronic acids

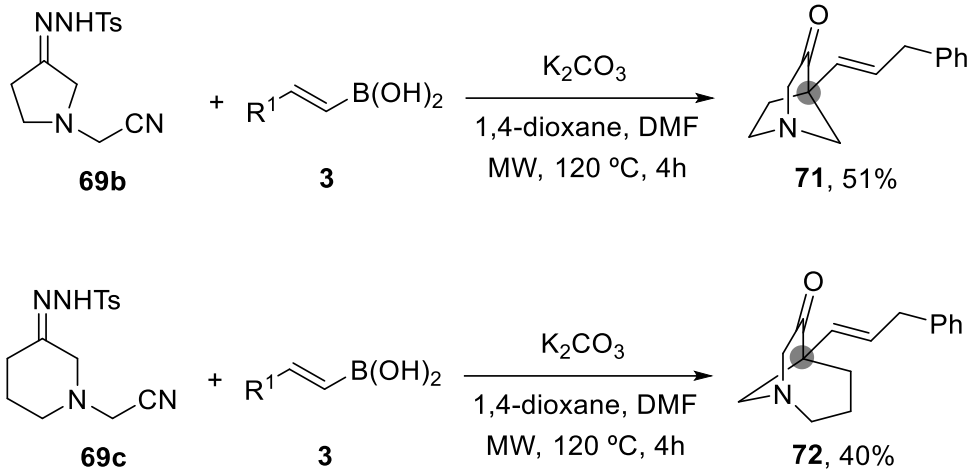
Next, different alkenylboronic acids **2** and *N*-tosylhydrazones with different length of chains (**69a**, **69b** and **69c**) were employed for the transannular cyclization under the optimized conditions.



Scheme 2.B.4. Scope of the transannular cyclization between *N*-tosylhydrazone **69a** and alkenylboronic acids **3**.

The scope of the reaction is depicted in scheme 2.B.4. Much to our pleasure, the final 3-quinuclidinones were obtained in all of the cases with yields ranging from moderate to good ones. The reaction was found to be general when different alkenylboronic acids **3** were employed. Particularly attractive is the compound **70b**, which presents a methoxy moiety in the side chain that allows for further derivatization.

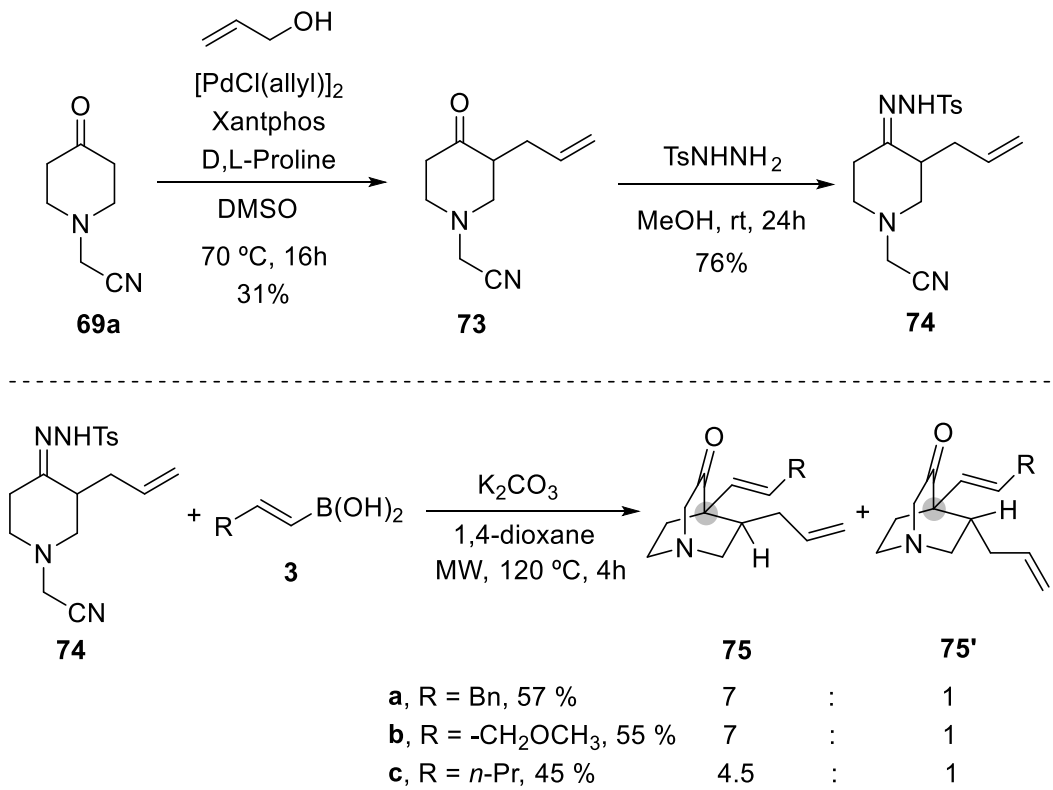
Moreover, when the *N*-tosylhydrazones of the cyanomethylated 3-pyrrolidinone (**69b**) and 3-piperidinone (**69c**) were employed, the final bicyclic compounds were also obtained (**71** and **72**, respectively). Noteworthy, different lengths in the chains of the *N*-tosylhydrazones did not affect the reaction outcome, in which an alkenyl moiety is attached in the newly formed quaternary center of the bicyclic structures **70**, **71** and **72**.



Scheme 2.B.5. Scope of the transannular cyclization between *N*-tosylhydrazones **69b** and **69c** with alkenylboronic acids **3**.

2.B.2.4. Stereoselectivity in the synthesis of the 3-quinuclidinone structures

To examine the stereoselectivity of the transannular cyclization reaction, we employed a suitable *N*-tosylhydrazone derived of an α-substituted cyanomethylated *N*-piperidone. Concretely, the α-allyl-*N*-tosylhydrazone **74** was employed in the reaction with alkenylboronic acids. In this case, the addition of DMF could be skipped thanks to the higher solubility of the *N*-tosylhydrazone salt derived of **74** in 1,4-dioxane.



Scheme 2.B.6. Stereoselectivity in the reaction of the α-allyl-*N*-tosylhydrazone **74** with alkenylboronic acids.

The reaction was compatible with the substitution in the α position of the tosylhydrazone, given that the 3-quinuclidinones were furnished in good yields. However, it must be pointed out that the reaction took place with partial

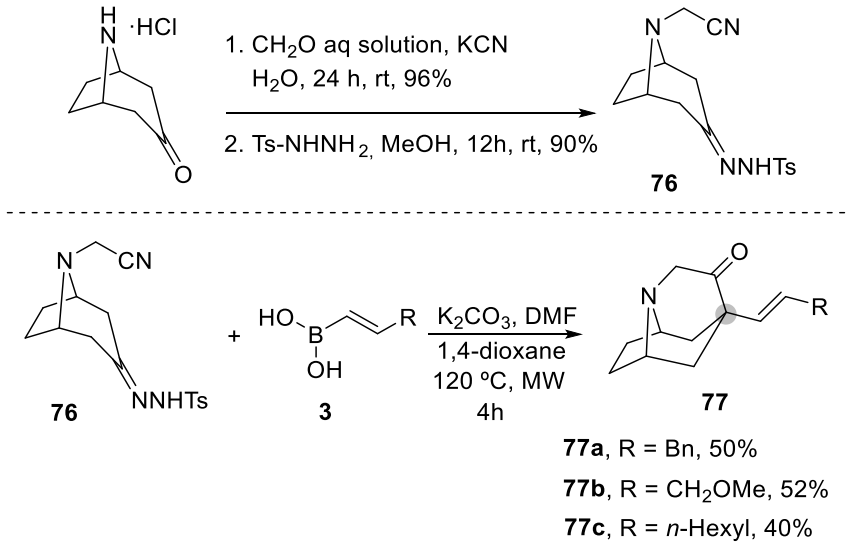
stereoselectivity (mixtures ranging from 7:1 to 4.5:1 of diastereoisomers **75** and **75'** were obtained).

The stereochemical assignment of these compounds was carefully determined by NMR tecniques (see section E.4.3 of the Experimental Part for a detailed discussion). Much to our pleasure, the major isomer presented the alkenyl chain in a *trans* arrangement with respect to the allyl moiety. This observation is in accordance with our previous experience for the synthesis of 1,2-disubstituted cyclohexanes derived of reductive alkenylation, as described in chapter 1 of this memory.

2.B.2.5. Synthesis of tropinone derivatives through the transannular heterocyclization of the *N*-tosylhydrazone 76 with alkenylboronic acids

The development of new methodologies for the synthesis of complex polycyclic molecules containing a nitrogen as a bridgehead atom has always been a challenging pursuit.[78] Most of the alkaloids are built on those motifs, and we can find uncountable examples of this type of structures in natural products. In fact, there is an important family of alkaloids that present the tropane structure, like the stimulant cocaine or the anticholinergics atropine and ecgonine.

Therefore, we noticed that the *N*-cyanomethylated tosylhydrazone **76** derived of the commercially available nortropinone hydrochloride would be an ideal substrate for our reaction with alkenylboronic acids. Indeed, the transannular heterocyclization proceeded smoothly to furnish the final products **77**, which feature an unprecedented tricyclic core in the tropinone structure.



Scheme 2.B.7. Synthesis of tropinone derivatives **77**.

[78] a) Manna, S. K.; Mandal, A.; Mondal, S. K.; Adak, A. K.; Jana, A.; Das, S.; Chattopadhyay, S.; Roy, S.; Ghorai, S. K.; Samanta, S.; Hossain, M.; Baidya, M. *Org. Biomol. Chem*. **2015**, *13*, 8037. b) Della, E. W.; Knill, A. M. *J. Org. Chem*. **1996**, *61*, 7529.

2.B.2.6. Mechanistic considerations of the transannular heterocyclization: DFT-based calculations

At this point, the carbocyclization reactions only seemed to work properly if alkenylboronic acids were employed in the reaction with the *N*-tosylhydrazones. One possible explanation for that is the formation of the highly reactive allylboronic intermediate. In order to provide some mechanisitic insight for these transformations, a DFT-based computational study was carried out. In particular, the transannular heterocyclization to form the final 3-quinuclidinone compounds was selected for this study.

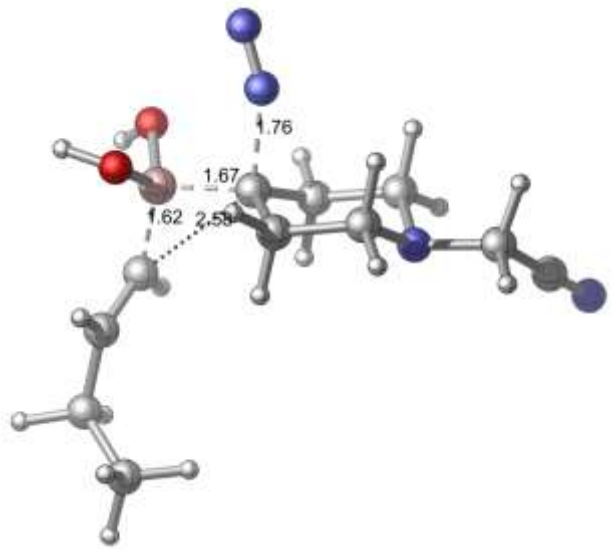
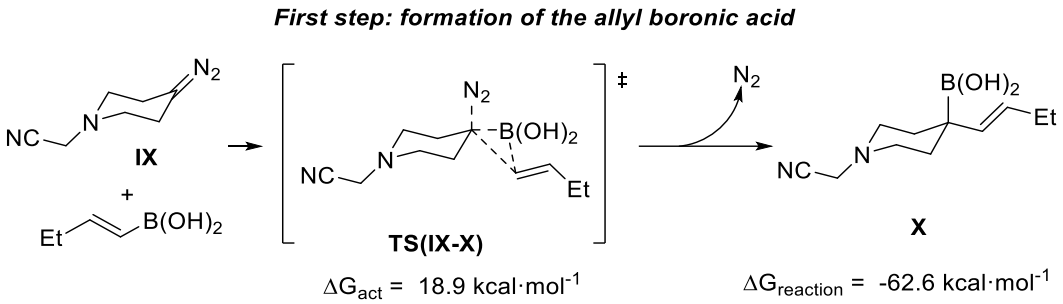


Figure 2.B.1. Depiction of the calculated transition state **TS (IX-X)**.

Analogously to the mechanism proposed for the reductive alkenylation in chapter 1; the first step involved the reaction of the diazo compound **IX** derived from the decomposition of the *N*-tosylhydrazone with the alkenylboronic acid. The more favoured equatorial trajectory in the approximation of the boronic acid to compound **IX** through the transition state **(IX-X)** would afford the formation of the allylboronic intermediate **X** as a single isomer (Scheme 2.B.8).[79] This initial step featured an

[79] [a] The calculations were carried out at the M06-2X/6-311++G**(PCM, 1,4-dioxane) level. [b] The relative Gibbs free energies are given in kcal·mol^{-1}.

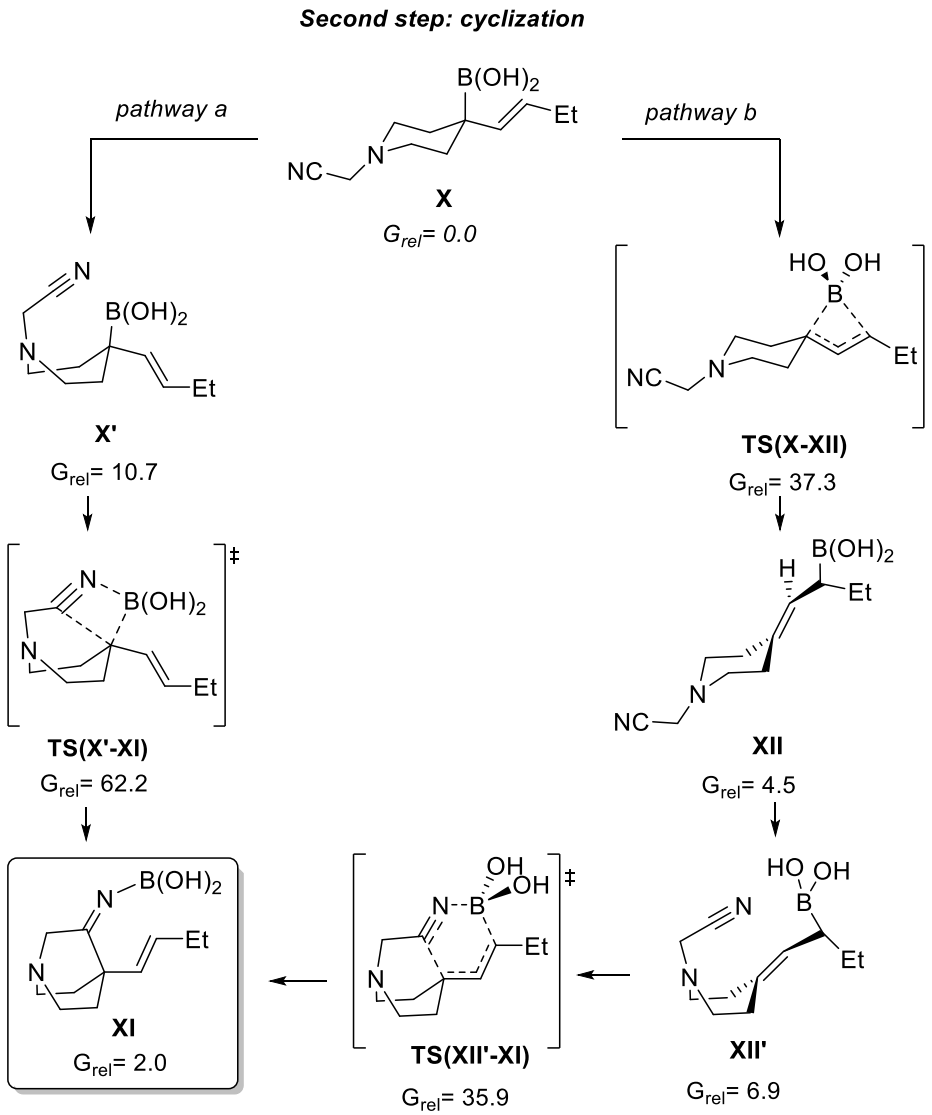
energetic barrier of 18.9 kcal·mol^{-1} and is highly exergonic ($\Delta G_{reaction}$ = -62.6 kcal·mol^{-1}).



Scheme 2.B.8. Formation of the allylboronic intermediate **X**.

Regarding now the cyclization process, the allylboronic acid **X** could follow two different pathways to form the carbocyclization products **XI** (Scheme 2.B.9). *Pathway a* involved a chair/boat twist isomerization from **X** to **X'**; followed by an alpha attack of the allylboronic acid to the nitrile carbon through the transition state **X'-XI**. However, this step featured an unreachable energetic barrier of 62 kcal·mol^{-1}, and therefore this pathway was discarded.

Alternatively, we considered the step-wise *pathway b* involving a 1,3-borotropic rearrangement to form a new allylboronic acid **XII**. Now, a chair/boat twist isomerization would form intermediate **XII'**. Finally, a bora-aza-ene reaction though a six-centered cyclic transition state **XII'-XI** would afford the carbocyclization product **XI**. The 1,3-borotropic rearrangement was found to be the rate determining step of the carbocyclization process, with an energetic barrier of 37 kcal·mol^{-1}. Therefore, this route is the one we propose for the cyclization process.



Scheme 2.B.9. Cyclization process: possible reaction pathways *a* and *b*.

An important conclusion that must be indicated is that the formation of the allylboronic intermediate **XII** is key for the carboborylation reaction of the nitrile through the six-centered transition state **(XII'-XI)** to take place. This observation could explain why the cyclization process when employing aryl and alkylboronic acids does not take place, given that in those cases the formation of an allylboronic intermediate is not involved in the transformation.

A better illustration of the transition states for the cyclization processes is provided in Figures 2.B.2, 2.B.3 and 2.B.4.[80]

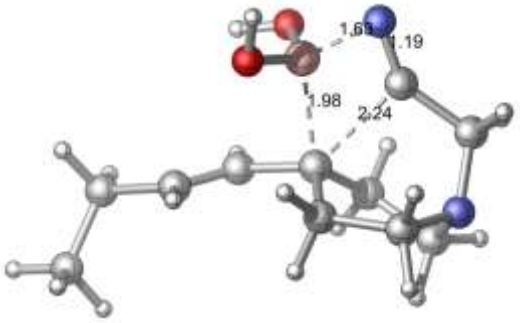


Figure 2.B.2. Depiction of the calculated transition state **TS (X'-XI**) involving the alpha attack of the allylboronic acid to the nitrile group.

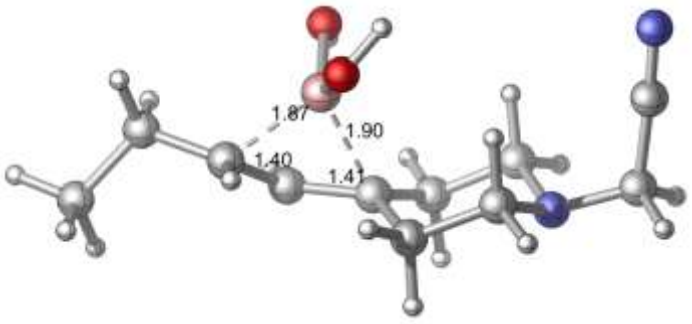


Figure 2.B.3. Representation of the calculated transition state **TS (X-XII)** in the 1,3-borotropic rearrangement.

[80] The three-dimensional structures of the transition states have been rendered with Cylview.

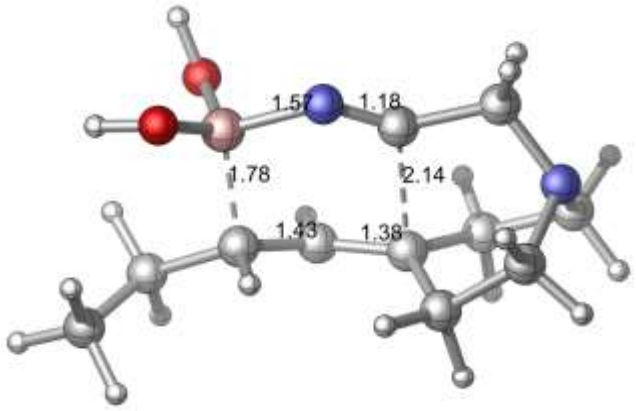


Figure 2.B.4. Illustration of the calculated transition state **TS (XII-XI)** for the carboborylation of the nitrile group.

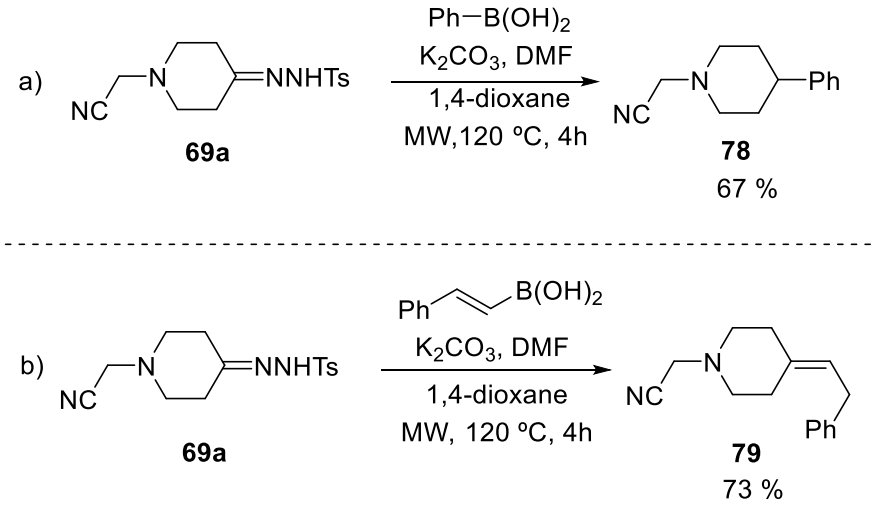
2.B.2.7. Limitations of the transannular heterocyclization reaction

2.B.2.7.1. Reaction with other boronic acids

As it was the case for the domino carbocyclization reaction described in part A of this chapter, some cases were found in which the corresponding cyclization did not take place.

When trying arylboronic acids, like phenylboronic acid, the transannular heterocyclization did not occur, and the corresponding product derived from the protodeboronation reaction **78** was exclusively obtained. This result was not surprising given the reasons indicated in the previous section.

Next, when we tried a styrylboronic acid, the olefination product **79** was furnished and again no cyclization product was formed. As it was pointed in the introduction of this chapter, the substitution in the alkenylboronic acid is critical in the reaction with *N*-tosylhydrazones, and therefore this result was not stunning.

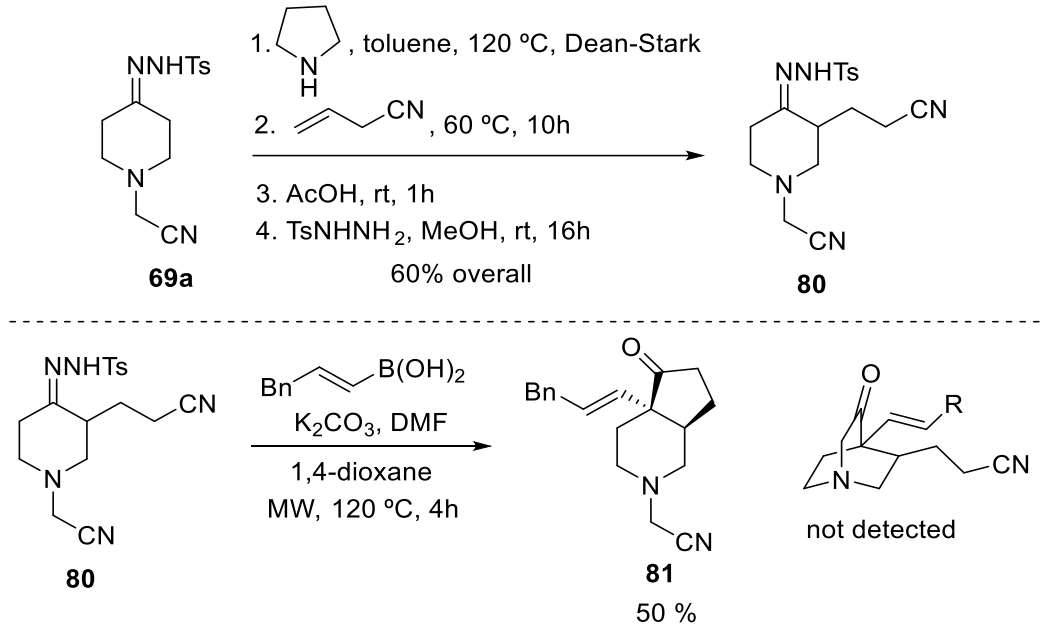


Scheme 2.B.10. Reaction of other boronic acids with the *N*-tosylhydrazone **69a**.

Finally, when the reaction was tested employing *N*-tosylhydrazone **69a** and *iso*-butylboronic acid as an example of an alkylboronic acid, a complex mixture was obtained with no cyclization product observed.

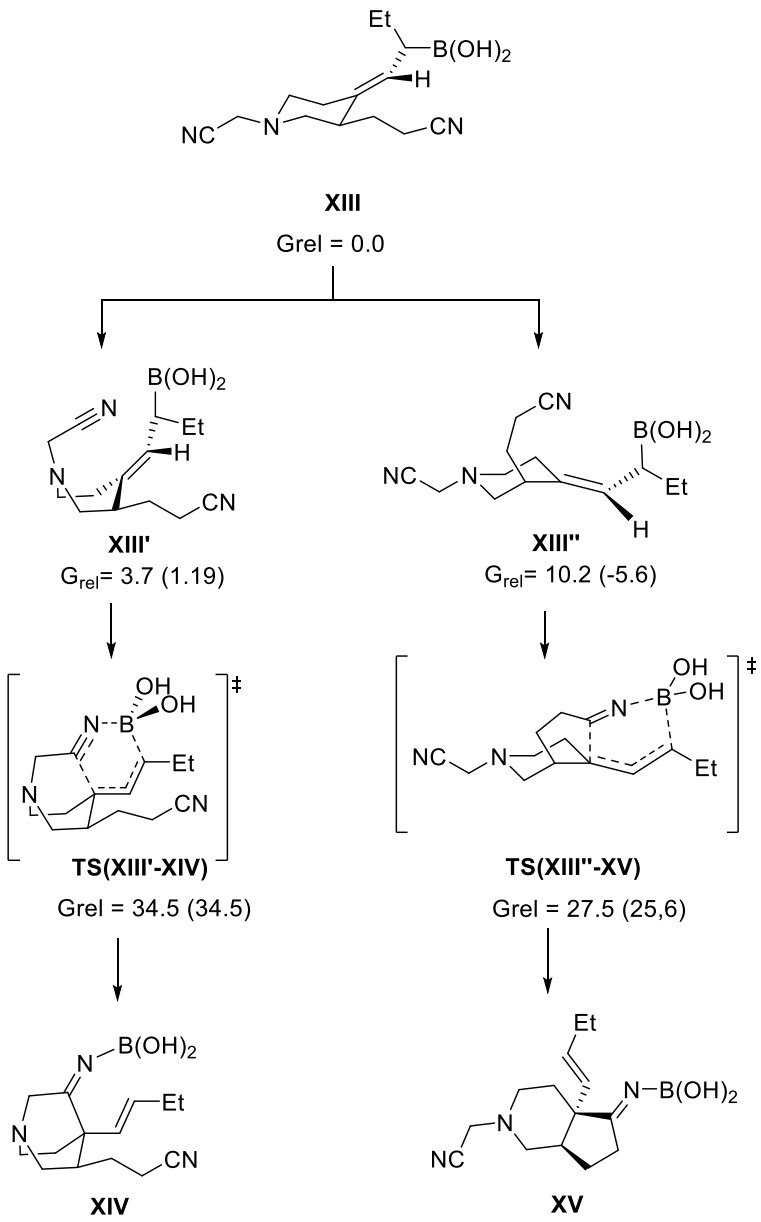
2.B.2.7.2. Chemoselectivity of the transformation: employment of a *N*-tosylhydrazone with two different cyano groups for the cyclization reaction

In order to examine the chemoselectivity of the transannular cyclization, we synthesized the *N*-tosylhydrazone **80**, which presents two cyano groups over which the attack of the allylboronic intermediate could take place. Reaction under the standard conditions provided the exclusive formation of the product **81**, corresponding to the cyclization over the nitrile group attached to the side chain. Therefore, the transannular cyclization got outcompeted by the more favourable cyclization involving the nitrile attached to the side chain; and the formation of the corresponding 3-quinuclidinone was not observed.



Scheme 2.B.11. Reaction of *N*-tosylhydrazone **80** with alkenylboronic acid **3a**.

To justify these observations, a DFT-based modelling was carried out. With this purpose, the transition states for both cyclization pathways were modeled. Given the analogous nature of the diazo-boronic coupling and 1,3-borotropic rearrangement to the previously described calculations; this time it was only considered the bora-aza-ene reaction (Scheme 2.B.12).



Scheme 2.B.12. Relative Gibbs free energy representation for the different cyclization pathways from **XIII** to **XIV** and **XV**.[81]

[81] M06-2x/6-311++G** (PCM, 1,4-dioxane) level. Relative Gibbs free-energies in gas phase are indicated in brackets. Energies are expressed in kcal·mol^{-1}

By this way, once the allylboronic intermediate **XIII** was formed; the cyclizations that would lead to the formation of the fused bicycle **XV** and [2.2.2] bicyclic ketone **XIV** were modeled. For each type of cyclization, previous conformational changes into **XIII'** and **XIII''** are respectively required.

Considering the formation of the fused bicycle **XV**, it must be indicated that depending on the conformation of the six-membered ring, two different saddle points for the cyclization were identified. The saddle point presenting the 2-cyanoethyl substituent in an axial arrangement, TS **(XIII''-XV)**, was the transition state with the lowest energy in the cyclization process (27.5 kcal·mol^{-1}). It was also identified another saddle point for the cyclization, with the cyanoethyl group in an equatorial position, which featured much higher energy and therefore was not considered.

The geometry of TS **(XIII''-XV)** corresponds again to a highly synchronic concerted bora-aza-ene reaction (Figure 2.B.5), in which the bonds that are being formed and broken are very similar to those found for TS **(XII-XI)** described in section 2.B.2.6. The transannular cyclization goes through the saddle point TS **(XIII'-XIV)** practically identical to the one described also in that section. An important conclusion of these calculations is the high energy difference (7 kcal·mol^{-1}) found between TS **(XIII''-XV)** and TS **(XIII'-XIV)**, which is in full agreement with the experimental results and therefore supports the proposed reaction pathway.

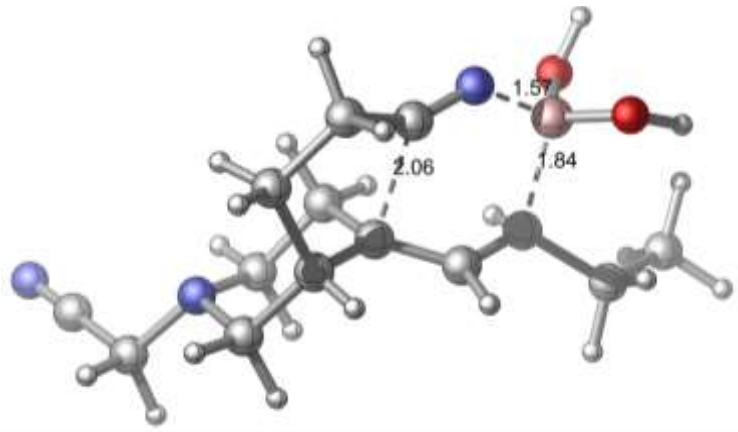


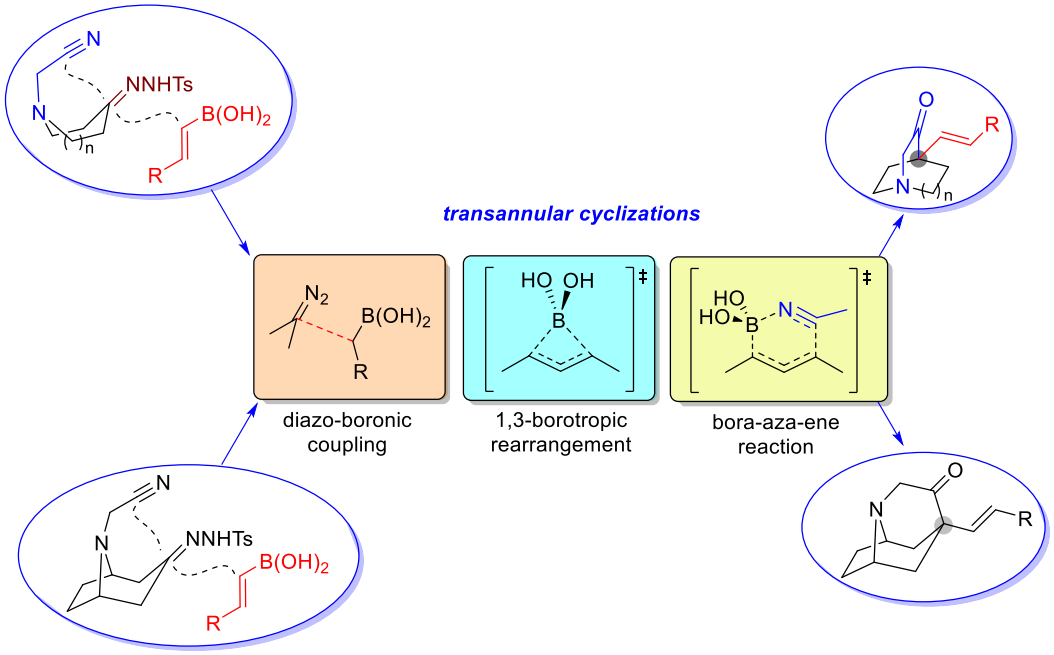
Figure 2.B.5. Representation of the transition state featuring the lowest energy TS **(XIII''-XV)**.

2.B.3. Conclusions

In part B of chapter 2, our new domino carbocyclization reaction was applied in a transannular heterocyclization to build up polycyclic structures of type II. In particular, a new family of 3-quinuclidinones and analogue structures was synthesized. The stereoselectivity of this transformation was examined employing substituted *N*-tosylhydrazones, showing that the reaction proceeded with moderate to high diastereoselectivity. Moreover, the transannular reaction was applied to the synthesis of compounds presenting a novel tricyclic core of the tropane structure.

To provide mechanistic insights of the cyclization process, a DFT-based computational study was carried out. The common reaction steps are the diazo-boronic coupling; followed by a 1,3-borotropic rearrangement; and subsequent bora-aza-ene reaction through a six-centered transition state involving the participation of an allylboronic intermediate.

2.B.4. Graphical summary



Chapter 2. Part C

Spirocyclization reactions based on domino reactions of *N*-tosylhydrazones and functionalized alkylboronic acids through allylborylation of nitriles

2.C.1. Introduction

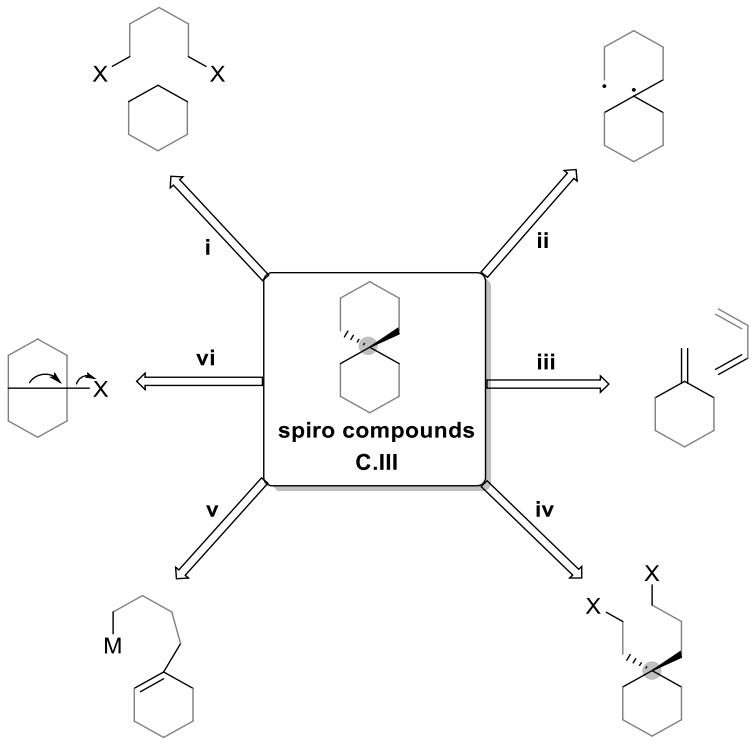
Spirocycles are ring systems in which two different cycles are connected through a single atom, known as the spiro atom. The development of new processes for the rapid assembly of spirocyclic frameworks with high functionalization is always of great importance, given that they are considered privileged structures in drug discovery.[82] This is a highly difficult process, because it involves the creation of a quaternary center that has unique structural features with axial chirality; which is itself considered a challenging undertaking in synthetic organic chemistry. This chirality provides these compounds with an inherent three-dimensional nature, which orientates the functional groups that are present in both cycles of the spiro.

Classical methodologies for the assembly of spirocyclic scaffolds normally implicate one of the processes described in Scheme 2.C.1. These methodologies are normally based on alkylation reactions (**i**), radical cyclizations (**ii**), cycloaddition tactics (**iii**), ring closure of geminally disubstituted compounds (**iv**), transition-metal based processes (**v**) and rearrangement-based approaches (**vi**). Additionally, other synthetic strategies like ring closing/opening methatesis or Pauson-Khand reactions are also important. Some reviews cover all of this kind of processes in detail.[83]

In a general way, all these methods described above normally lack of functional group compatibility at one or more stages, and they are also restricted to a single substitution pattern. Only in a few cases are the newly generated ring systems left with useful functionalities for further derivatization.

[82] For the importance of spirocycles in drug discovery, see: (a) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioor. Med. Chem. Lett.* **2014**, *24*, 3673. (b) Voss, F.; Schunk, S.; Steinhagen, H. Spirocycles as Privileged Structural Motifs in Medicinal Chemistry. In *Privileged Scaffolds in Medicinal Chemistry*; Bräse, S., Ed.; RSC: Cambridge, UK, 2016; pp 439-458. (c) Müller, G.; Berkenbosch, T.; Benningshof, J. C. J; Stumpfe, D.; Bajorath, J. *Chem. Eur. J.* **2017***, 23*, 703.

[83] For reviews covering spirocyclization methodologies, see: (a) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis*. **2009**, *2*, 165. (b) Sannigrahi, M. *Tetrahedron*. **1999**, *55*, 9007.



Scheme 2.C.1. Summary of the most common methodologies to construct spirocyclic scaffolds **C.III**.

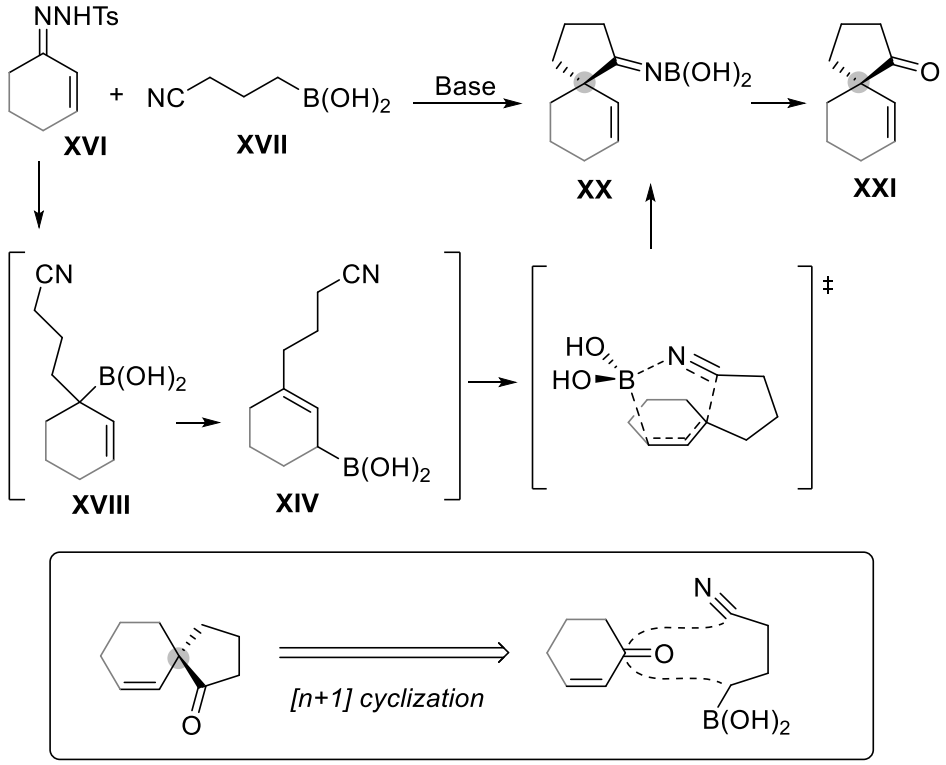
Apart from the previously described methodologies, another appealing family of reactions that give access to spirocyclic frameworks are the ones in which two carbon-carbon bonds are formed on the spiro atom in one single operational step.[84] However, in all of these processes, a transition metal is always needed as a molecular assembler of the starting materials. Therefore, the employment of these methodologies for the construction of complex spirocyclic frameworks based on straightforward transition-metal-free reactions stands as an unexplored task.

[84] Selected examples of metal catalyzed cascade spirocyclizations by formation of two bonds on the same C atom: (a) Barroso, R.; Cabal, M.-P.; Badia-Laino, R.; Valdés, C. *Chem. Eur. J.* **2015**, *21*, 16463. (b) Bai, L.; Yuan, Y.; Liu, J.; Wu, J.; Han, L.; Wang, H.; Wang, Y.; Luan, X. *Angew. Chem. Int. Ed.* **2016**, *55*, 6946. (c) Liu, Y.; Song, R.-J.; Li, J.-H. *Chem. Commun.* **2017**, *53*, 8600. (d) Zuo, Z.; Wang, H.; Fan, L.; Liu, J.; Wang, Y.; Luan, X. *Angew. Chem. Int. Ed.* **2017**, *56*, 2767. (e) Pérez-Gómez, M.; Hernández-Ponte, S.; Bautista, D.; García-López, J.-A. *Chem. Commun.* **2017**, *53*, 2842.

2.C.2. Results and discussion

2.C.2.1. Objective and general considerations

As stated in part B of this chapter, the allylboronic intermediate turned out to be key for the carboborylation of the nitrile to take place. Taking this fact into consideration, we thought of a different combination of the functionalities in the starting materials that would also implicate the formation of an allylboronic acid that could further promote the carbocyclization reaction (Scheme 2.C.2).



Scheme 2.C.2. Synthetic proposal for the construction of carbocycles **XXI** based on the employment of *N*-tosylhydrazones **XVI** and alkylboronic acids **XVII**.

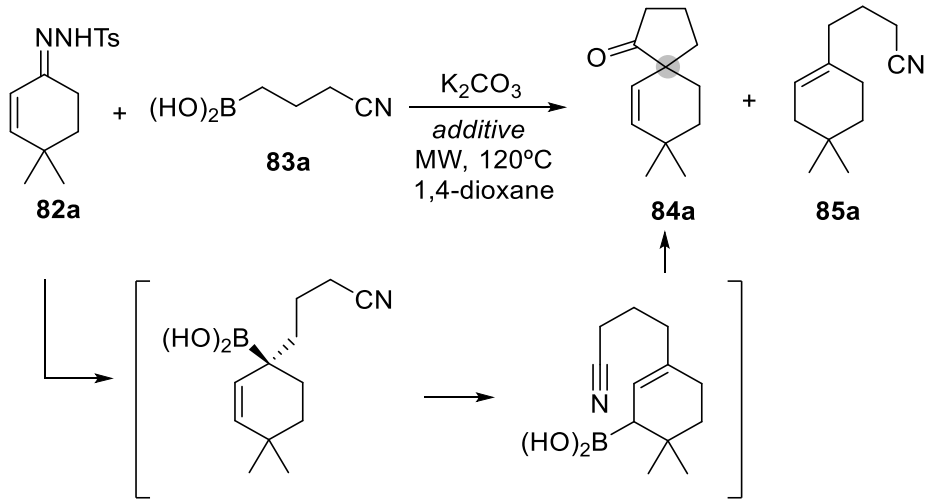
In particular, if a *N*-tosylhydrazone derived of an α,β-unsaturated ketone **XVI** were made to react with an alkylboronic acid containing a cyano functionality **XVII**; the formation of the allylboronic intermediate **XVIII** would be expected. After a 1,3-borotropic rearrangement to form a new allylboronic intermediate **XIV**, subsequent bora-aza-ene reaction could give rise to species **XX**, which after hydrolysis would end up forming the carbocycles **XXI**.

If this reaction were possible, this methodology could give access to spirocyclic structures of type **C.III** described in the general introduction of this chapter. Once again, this process would be based in the construction of two different C-C bonds on the same carbon atom to construct all-carbon quaternary centers in the final products.

All in all, this transformation might represent a conceptually new [n+1] type of spirocyclization, employing extremely simple reaction conditions.

2.C.2.2. Optimization

For the synthetic purpose described in the previous section, we synthesized the *N*-tosylhydrazone **82a** and alkylboronic acid **83a**. Initial attempts under the same reaction conditions as the ones described for our carbocyclization reaction (2 eq K_2CO_3, 1,4-dioxane, microwave heating at 120°C) led to a 6:1 mixture of the desired spirocycle **84a** and protodeboronation product **85a**.



no additive: **84a**: **85a** ratio, 6: 1; Yield, 50 %
$ZnCl_2$ (20 % mol): **84a**: **85a** ratio, 100: 0; Yield, 51 %

Scheme 2.C.3. First attempts in the formation of spirocyclic scaffolds **84a** based in our original [n+1] carbocyclization reaction.

Different temperatures were tested in an attempt to control the exclusive formation of the carbocycle **84a**. However, all the combinations in the range 90-150 °C in both classical and microwave heating failed to completely avoid the formation of the protodeboronation compound **85a**. Additionally, different bases (KOH, CaH_2, DBU, LiO^tBu) were tested at 120 °C under microwave heating, but they also showed no improvement.

At this point, we thought of the employment of a Lewis acid to enhance the electrophilicity of the nitrile group and facilitate the carboborylation of the nitrile. Several compounds were employed as additives ($ZnCl_2$, $Sc(OTf)_3$, $La(OTf)_3$). However, the only one that seemed to work properly was $ZnCl_2$. Gratifyingly, the employment

of 20 % mol of this salt enhanced the chemoselectivity of our reaction and granted access to the spirocyclic compound 84**a** as the exclusive ones in our reaction. After some optimization, it was found that the loading of $ZnCl_2$ could be decreased to a 6 % mol without compromising the yield of the transformation.

Although the role of the $ZnCl_2$ is still unclear, it must be pointed out that this class of zinc salts have been previously reported to enhance the rate of the 1,3-borotropic rearrangement by coordination to the oxygen or nitrogen atoms of boronates or aminoboronates, respectively.[85] This fact facilitates the 1,3-borotropic rearrangement for the subsequent bora-aza-ene to take place.

It must be also indicated that, although this is no longer a transition-metal-free reaction, the addition of the zinc salt is *not essential* for the cyclization to occur. Anyway, an unprecedented [4+1] spirocyclization reaction has taken place upon formation of both a Csp^3-Csp^2 and Csp^3-Csp^3 bonds on the spiro atom in one single step.

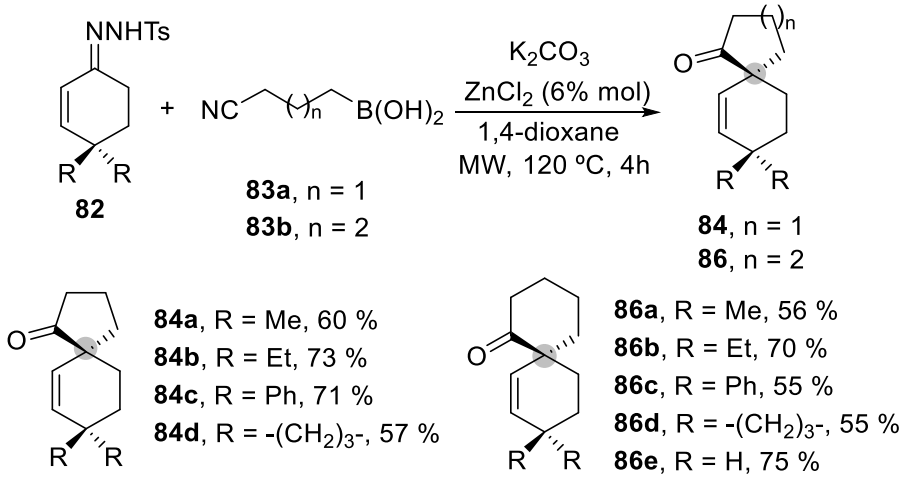
[85] For some key references on 1,3-borotropic rearrangements: (a) Hancock, K. G.; Kramer, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 6463. (b) Miyamoto, H.; Silverio, D. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 4701 and references cited therein.

2.C.2.3. Generalization of the spirocyclization reactions for the [4+1] and [5+1] cyclizations

With the optimized reaction conditions in our hands, we thought of the employment of different starting materials with regard to the *N*-tosylhydrazones derived of α,β-unsaturated ketones and alkylboronic acids containing a cyano group.

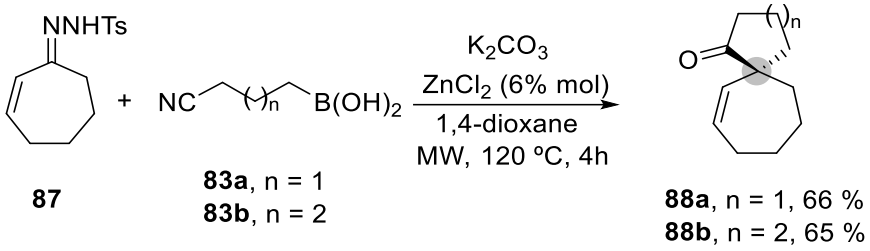
In particular, different *N*-tosylhydrazones derived from 4,4-disubstituted cyclohexenones **82** were tested. The scope of the reaction was examined for the construction of the 5- and 6-membered rings in the newly formed cycle of the spiranes (Scheme 2.C.4).

The domino [4+1] carbocyclization reactions with (3-cyanopropyl)boronic acid **83a** proceeded very well to form the spirocyclic scaffolds **84** with good yields. On the other hand, the construction of the new six-membered ring in the carbocycles **86** was also possible thanks to the employment of (4-cyanobutyl)boronic acid **83b**.



Scheme 2.C.4. Scope of the spirocyclization reaction fo form compounds **84** and **86**.

Next, when the *N*-tosylhydrazone **87** derived from the cycloheptenone was tested, the carbocyclization products **88a** and **88b** were also obtained, which increased the versatility of this transformation (Scheme 2.C.5).



87

83a, n = 1
83b, n = 2

88a, n = 1, 66 %
88b, n = 2, 65 %

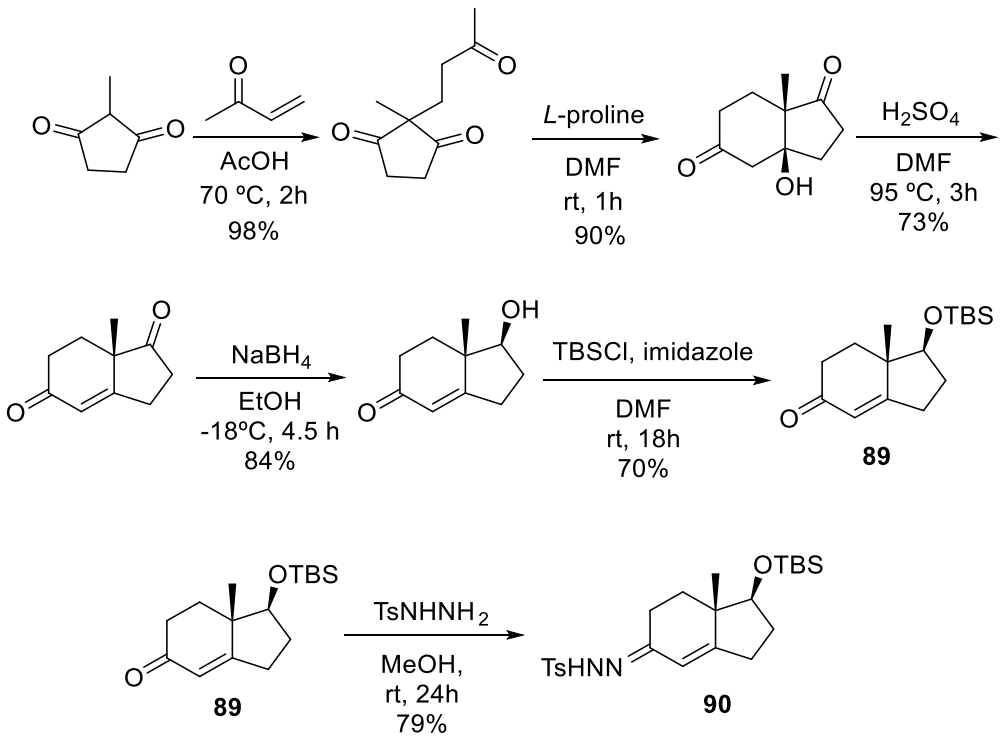
Scheme 2.C.5. Formation of spirocyclic compounds **88** when the *N*-tosylhydrazone derived of the cycloheptenone was utilized.

One important feature of this spirocyclic scaffolds is the double functionalization they present (the double bond, and the newly formed carbonyl group). This could enable orthogonal derivatization of the final products, which increases their synthetic value.

2.C.2.3. Diastereoselectivity of the spirocyclization reactions: structural modification of the Hajos-Parrish ketone

In order to examine the diastereoselectivity of these reactions, we focused our efforts in the synthesis of the enantiomerically pure *N*-tosylhydrazone **90**, derived of the Hajos-Parrish ketone. Moreover, this example would also expand the scope of the reaction to trisubstituted α,β-unsaturated ketones.

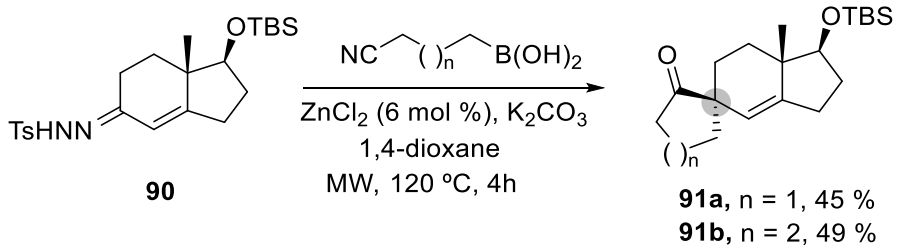
For this purpose, we followed a procedure found in the literature for the synthesis of compound **89**.[86] Reaction under the classical conditions for the formation of the *N*-tosylhydrazones granted the formation of our desired starting material **90**, as a single enantiomer (Scheme 2.C.6).



Scheme 2.C.6. Synthetic route for the construction of the *N*-tosylhydrazone **90**.

[86] (a) Isaacs, R. C. A.; Di Grandi, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 3938. (b) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413

Next, reaction of compound **90** with the alkylboronic acids **83a** and **83b** under the standard conditions proceeded in moderate yields to for the spirocyclic derivatives **91**. Gratifyingly, only one isomer was detected in the final compounds, what increased the synthetical value of this transformation (Scheme 2.C.7). These are very important results, which demonstrate that the quaternary center has been created in a diastereoselective fashion starting from the optically pure *N*-tosylhydrazone. In sections E.5.3 and E.5.4 of the Experimental Part, a careful analysis by NMR techniques was done to stablish the stereochemistry of compounds **91a** and **91b**, respectively.

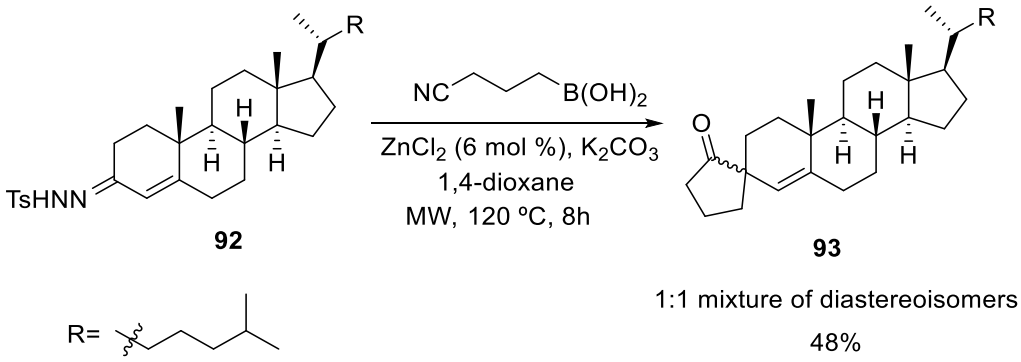


Scheme 2.C.7. Reaction of the enationmerically pure *N*-tosylhydrazone **90** to form the spirocyclic compounds **91**.

Moreover, other research groups encountered useful applications of spirocyclic structures derived of the Hajos-Parrish ketone,[87] what illustrates the potential usefulness these compounds might possess.

[87] For previous spirocyclization reactions of Hajos-Parrish ketone derivatives see: Asim, M.; Klonowska, D.; Choueiri, C.; Korobkov, I.; Carlson, K. E.; Katzenellenbogen, J. A.; Durst, T. *Bioor. Med. Chem. Lett.* **2012**, *22*, 3713.

In an attempt to test our spirocyclization reaction for the structural modification of natural products, we synthesized the enantiomerically pure *N*-tosylhydrazone **92**, which is directly derived from the commercially available 4-cholesten-3-one. The reaction with the functionalized alkylboronic acid worked well to afford the desired spirocyclic scaffold **93**, although as a 1:1 mixture of diastereoisomers. This result shows the potential applicability of our reaction for the modification of steroid-like compounds.



Scheme 2.C.7. Application of the spirocyclization reaction for the structural modification of steroids.

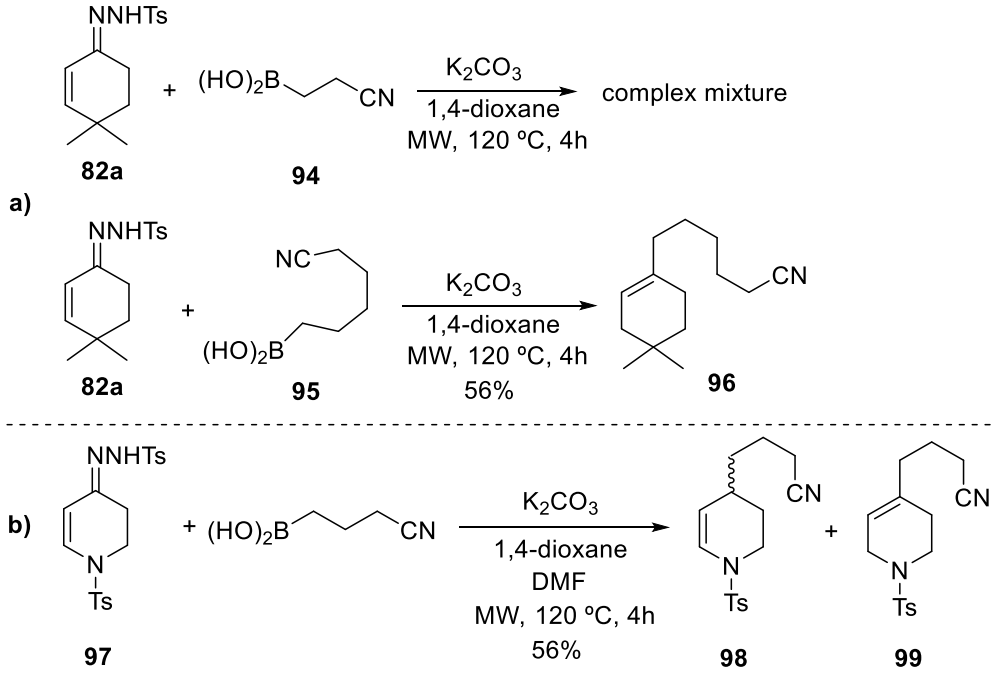
2.C.2.3. Limitations of the spirocyclization reactions

Unfortunately, there were some cases in which the spirocyclization reaction did not take place.

When the carbocyclization reactions for the construction of the 4- and 7-membered rings in the newly formed cycle of the spiranes was examined, in none of these two cases was the cyclization possible (Scheme 2.C.8, a).

In the first case, a complex mixture was detected in the crude of the reaction with no spirocyclization product observed. This might be due to the extremely small size of the alkylboronic acid, which was prone to self-protodeboronate without further reacting with the *N*-tosylhydrazone.

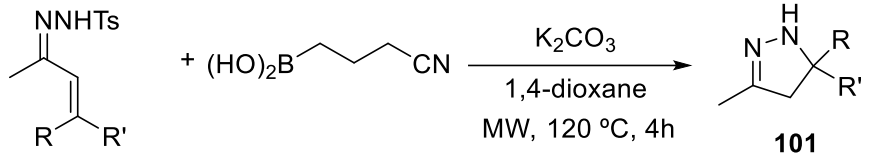
On the other hand, when the alkylboronic acid **95** was employed in the reaction with the *N*-tosylhydrazone **82a**, the protodeboronation product **96** was solely formed in this transformation. Clearly, the formation of the large 7-membered rings is not favoured under these conditions.



Scheme 2.C.8. Summary of the limitations of the spirocyclization reactions.

We also wanted to expand the scope of the reaction for unsaturated ketones presenting heteroatoms. With this idea, we synthesized the *N*-tosylhydrazone **97**. Disappointingly, the reaction under the standard conditions led to a recovery of the starting material untouched. After some experimentation, we decided to add a small amount of DMF to increase the solubility of the *N*-tosylhydrazone. Under these new conditions, the reaction worked well; although not for the formation of the desired spirocycles. In this case, a complex mixture of isomers of the protodeboronation products **98** and **99** was detected (Scheme 2.C.8, b). It must be noticed that in this case, the reactivity of the starting material is not like the one expected for an α,β-unsaturated ketone. This system **97** is a *N*-tosylhydrazone derived from a vinilogous enamide, which reactivity is understandably different from the previous systems; and therefore different reaction outcomes are expected.

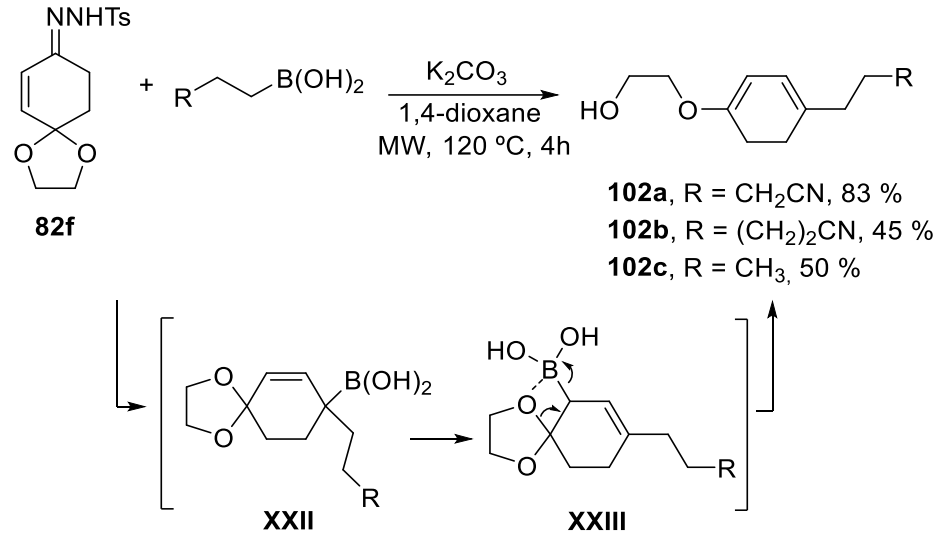
Finally, when trying *N*-tosylhydrazones derived from linear α,β-unsaturated ketones **100**, the formation of a pyrazoline **101** was observed. This reactivity prevented the reaction of the *N*-tosylhydrazones with the boronic acids, given that the intramolecular reaction is prior to the formation of the diazocompounds through the Bamford-Stevens reaction (Scheme 2.C.9). This reactivity had previously been observed in our research group for this kind of *N*-tosylhydrazones and did not take us by surprise.



Scheme 2.C.9. Reaction of *N*-tosylhydrazones **30** end up in the formation of pyrazolines **31**.

2.C.2.3. Deviations of the spirocyclization reactions: a new route for the synthesis of 1,4-disubstituted 1,3-cyclohexadienes

During the development of the scope of the reaction between *N*-tosylhydrazones derived from 4,4-disubstituted cyclohexenones, we found an unexpected deviation of the reaction outcome when the *N*-tosylhydrazone that presents an acetal group **82f** was employed. Instead of the expected spirocyclic products, a 1,3-diene was observed as the unique product of the reaction. This reaction was found to be general for both alkylboronic acids **83a** and **83b**. When the reaction was run employing propylboronic acid, the same reaction outcome was observed, given that the 1,3-diene **102c** was formed in a moderate yield. These results made it clear that the bora-aza-ene reaction did not take place in this reaction, and therefore a different mechanistic route must be proposed.



Scheme 2.C.10. Synthesis of 1,3-dienes **102** starting from the *N*-tosylhydrazone **82f**.

In this regard, the formation of the cyclohexadienes **102** could be explained through the mechanism proposed in Scheme 2.C.10. After formation of the allylboronic intermediate **XXII**, a 1,3-borotropic rearrangement would form a new allylboronic acid **XXIII**. This last intermediate is prone to undergo a boronate-alkoxy β-elimination that would end up forming a new double bond with simultaneous opening of the acetal. This type of β-elimination, which is typical of the well-known bora-Wittig reactions,[88] had been previously observed in our research group, as pointed in chapter 1 of this memory.

This reaction gave additional support for the 1,3-borotropic rearrangement we proposed in our cascade reactions. From a synthetical point of view, this transformation opened the door to an innovative transition-metal-free methodology for the synthesis of substituted 1,4-disubstituted cyclohexadienes. Its scope could be tremendously expanded upon employment of other boronic acids and/or usage of other *N*-tosylhydrazones presenting functional groups to facilitate this kind of reactivity. We are currently working on the development of this methodology based on these last premises.

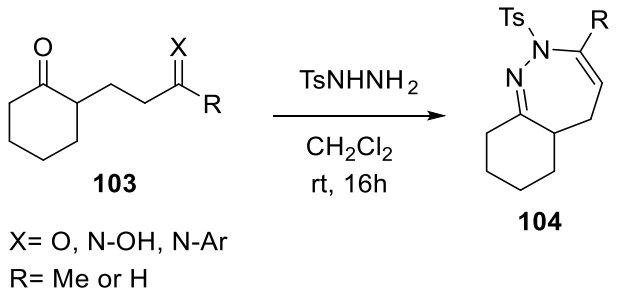
[88] (a) Pelter, A.; Singaram, B.; Wilson, J. W.; *Tetrahedron Lett.* **1983**, *24*, 635. (b) Pelter, A.; Buss, E.; Colclough, E. *J. Chem. Soc. Chem. Commun.* **1987**, 297.

2.C.2.3. Applications of the spirocyclization reactions: extension to other electrophilic functionalities in the alkylboronic acids

All the spirocyclization reactions explored so far involved an alkylboronic acid presenting a cyano group as the electrophilic functionality.

As stated in part A of this chapter, the only electrophilic groups that successfully promoted our carbocyclization reaction were the nitrile and ester functionalities.

However, the reactivity of carbonyl, oxime and imine groups remained unexplored due to the synthetic issues to produce the starting materials needed. Much to our dismay, in all of the conditions we tried, a product of intramolecular cyclization **104** was obtained (Scheme 2.C.11). This overall approach took a long period of time in which we only met with frustration.



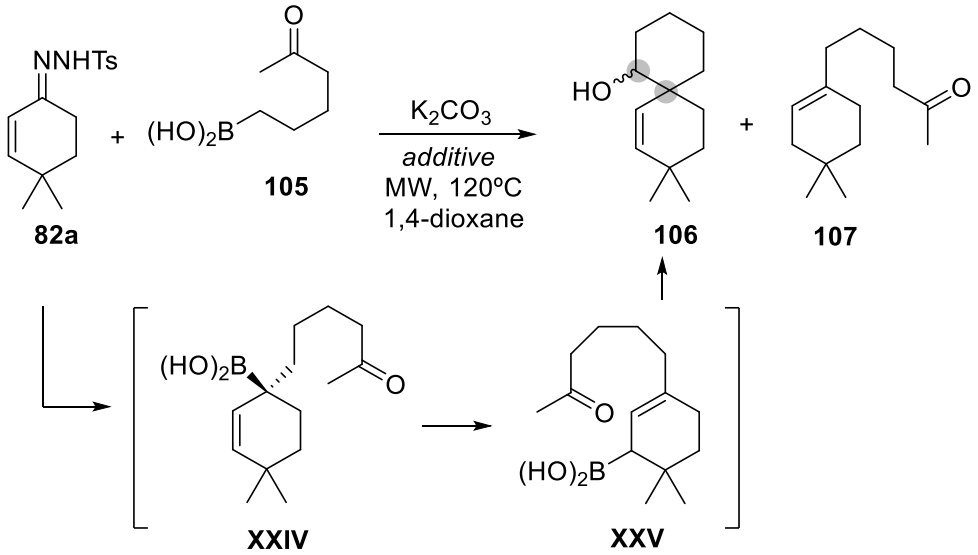
Scheme 2.C.11. Undesired intramolecular cyclization to form compounds **104** in an attempt to synthesyze the *N*-tosylhydrazones derived from carbonyl derivatives **103** tethered with a carbonyl, oxime and imine functionalities.

Nevertheless, a different combination of the functionalities in the starting materials could address this issue, given that the electrophilic functionality does not need to be in the *N*-tosylhydrazone fragment any longer.

In this context, we developed a methodology for the synthesis of the alkylboronic acid **15c**, which presents a carbonyl group in the linear alkylic chain. By this way, reaction of this compound with a *N*-tosylhydrazone derived of an α,β-unsaturated ketone could result in the formation of the allylboronic intermediate **T**. After 1,3-borotropic rearrangement, a new allylboronic acid **U** would be formed, in

which a carboborylation of the ketone could take place to form a new stereogenic center presenting a new hydroxyl functionality.

It must be first of all pointed out the challenge this reaction represents. During this transformations, two contiguous stereogenic centers would be formed in a single operational step. Therefore, any control of the stereoselectivity of this overall proccess would be of great importance.



Scheme 2.C.12. First attempts in the reaction of *N*-tosylhydrazone **14a** with the alkylboronic acid **15c**.

Initial attemps under the metal-free conditions revealed the formation of the desired product **106**, along with the protodeboronation product **107** in a 2.7:1 mixture (Scheme 2.C.12). In order to improve the chemoselectivity, a preliminary reaction was run employing a 20% $ZnCl_2$ mol loading. Under these conditions, the ratio towards the formation of the carbocyclization product **106** was improved, giving rise to a 5:1 mixture of **106**:**107**. Although a 1:1 mixture of diastereoisomers was obtained in the formation of the spirocyclization product, this reaction showed the potential reactivity of a ketone group as the electrophilic functionality in these reactions.

In light of all the above, further experimentation needs to be done to provide in-depth insight into this transformation, based on the employment of other substitution in the boronic acid or other reaction conditions. The exploration of these results is currently ongoing in our research lab.

2.C.3. Conclusions

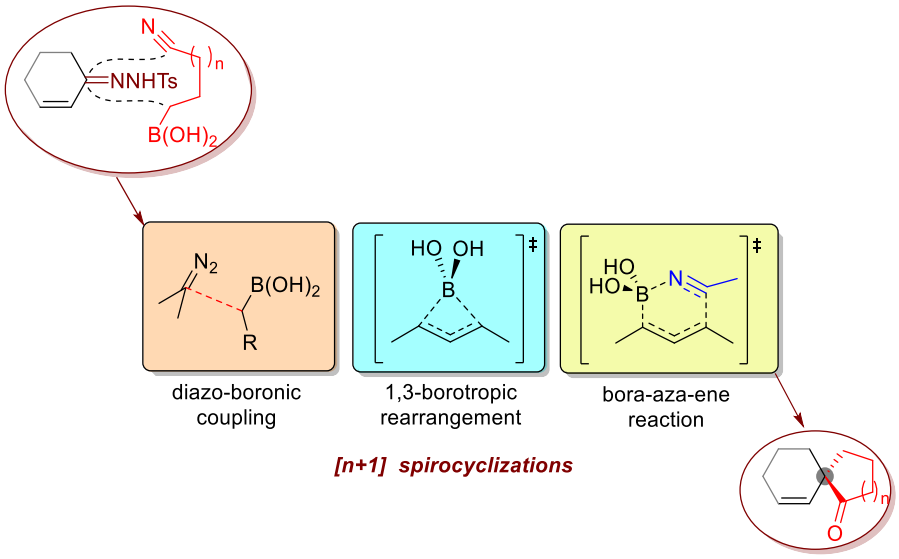
In this part of the chapter, a new spirocyclization reaction was discovered based on the employment of functionalizaed alkylboronic acids and *N*-tosylhydrazones derived of α,β-unsaturated ketones. This reaction represents a novel [n+1] spirocyclization methodology in organic synthesis, based on the creation of two different C-C bonds on the spiro atom in one step. The addition of a catalytic amount of $ZnCl_2$ was found to improve the chemoselectivity of the transformation, affording the carbocyclization products exclusively in this reaction.

The scope of the reaction was examined for the construction of the five and six-membered rings in the newly formed cycle of the spirocyclic compounds. In this regard, different *N*-tosylhydrazones derived from 4,4-disubstituted cyclohexenones and cycloheptenone were employed with good results.

Moreover, an enantiomerically enriched trisubstituted *N*-tosylhydrazone derived of the Hajos-Parrish ketone was employed to examine the stereoselectivity of the spirocyclization reaction. Gratifyingly, the final spirocyclic compounds were obtained in moderate yields and, very importantly, as single stereoisomers.

Finally, a deviation of the reaction outcome opened the gate to the development of a new metal-free methodology for the synthesis of 1,4-disubstituted cyclohexadienes.

2.C.4. Graphical summary



Conclusiones generales

Las reacciones entre diazo compuestos y compuestos de organoboro han sido estudiadas desde hace décadas. Un aumento exponencial en el interés por este tipo de transformaciones ha tenido lugar desde la implementación del uso de *N*-tosilhidrazonas en este tipo de reacciones. A través de la reacción de Bamford-Stevens, estos compuestos se descomponen para generar en el medio de reacción diazo compuestos. En este contexto, particularmente interesante fue la reacción descrita por nuestro grupo de investigación en 2009, basada en el acoplamiento entre ácidos borónicos y *N*-tosilhidrazonas, una metodología versátil para la creación de enlaces C-C.

En el Capítulo 1, se ha descrito una nueva metodología basada en el acoplamiento reductor estereoselectivo entre *N*-tosilhidrazonas y ácidos alquenilborónicos. Esta reacción representa el primer ejemplo descrito en la bibliografía acerca de reacciones estereoselectivas en ausencia de metal empleando diazocompuestos. Las aplicaciones potenciales de esta transformación son evidentes dado el inmenso numero de ciclohexanonas enantiopuras accesibles comercial y sintéticamente.

En el Capítulo 2, se profundiza sobre un modo de carbociclación sin precedentes en Química Orgánica basado en el empleo de *N*-tosilhidrazonas y ácidos borónicos. La transformación consiste en la creación de dos enlaces C-C en un mismo átomo de carbono en un solo paso, uno para formar un nuevo ciclo, y el otro para incorporar una cadena lateral. En la parte A de este Capítulo, esta metodología es aplicada para la síntesis de carbociclos fusionados, encontrando aplicación en la modificación de productos naturales como la androsterona. En la parte B, se describe la aplicación de esta reacción a través de una heterociclación transanular para formar estructuras bicíclicas y derivados de alcaloides. Por último, en la parte C se resumen los avances en el desarrollo de una metodología para la construcción de esqueletos espirocíclicos basado en una ciclación del tipo n+1 empleando *N*-tosilhidrazonas α,β-insaturadas y ácidos alquilborónicos funcionalizados.

Asímismo, un estudio del mecanismo de reacción a través de cálculos computacionales ha permitido elucidar los pasos de acoplamiento diazo-borónico reagrupamiento 1,3-borotropico y reacción bora-aza-eno como los pasos comunes en todas las transformaciones descritas en el capítulo 2. La formación del intermedio alíl borónico en todos los casos se considera la clave por la que esta reacción tiene lugar.

Experimental Part

E.1. General considerations

E.1.1 Reactions

Unless otherwise indicated, microwave-assisted reactions were conducted using a focused microwave unit (Biotage InitiatorTM 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) or (2-5 mL) glass vials, which were sealed with a cap with septum. The specific reaction time corresponds to the total irradiation time.

E.1.2 Solvents

The solvents employed in the reactions under inert atmosphere were dried and distilled before their use according with the standard techniques[89] or through columns filled with active alumina, Innovative Technology, Pure Solv, model PS-400-7 (adapted system for toluene, acetonitrile, dimethylformamide, dichloromethane, hexane and tetrahydrofuran). The only exception was 1,4-dioxane, which was dried with sodium as dehydrating agent and distilled under nitrogen atmosphere.

E.1.3 Reagents

The majority of the boronic acids employed are commercially available from Aldrich Chemical co., Acros Organics Chemical co. and Alfa Aesar Chemical co. Unless otherwise indicated, the *N*-Tosylhydrazones were prepared from the corresponding carbonyl compounds and through previously described methodologies.[90] The full characterization for the *N*-tosylhydrazones or boronic acids previously undescribed in the literature will be reported in the following sections of the Experimental Part.

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

---

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

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

E.1.4 Separation and purification

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

E.1.5 Analytical and instrumental techniques

- Gas chromatography-mass spectrometry (GC-MS)

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

- Nuclear magnetic resonance spectroscopy (NMR)

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

- Mass spectrometry (HRMS)

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

- Melting points

Melting points were measured in a Gallenkamp apparatus using open capillary tubes.

- Specific rotation

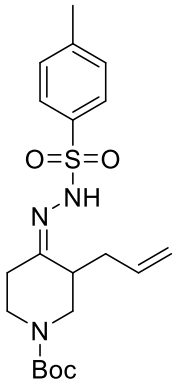
The specific rotation was measured with an automatic polarimeter (Autopol® IV Rudolph Research Analytical) with a sodium lamp and CH_2Cl_2 as solvent (c, g/100 mL).

E.2. Chapter 1: Synthesis of the reductive coupling products

E.2.1. Synthesis of the starting materials

Tosylhydrazone **16** was synthesized in enantiomerically pure form following a previously described procedure.[91] Alkenylboronic acid **3b** was synthesized starting from its commercially available alkenylboronic ester following a procedure found in literature.[92]

tert-Butyl (*Z*)-3-allyl-4-(2-tosylhydrazono)piperidine-1-carboxylate (**9e**)



Tosylhydrazone **9e** was prepared from the corresponding carbonyl compound[93] and tosylhydrazide following the standard procedure.

Some of the signals are broad or splitted due to the presence of rotamers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30-0.02 (bs, 1H), 7.90-7.80 (m, 2H stereoisomer maj+min), 7.37-7.27 (m, 2H stereoisomer maj+min), 5.65-5.48 (m, 1H), 5.07-4.82 (m, 2H), 3.80-3.21 (m, 3H), 2.92-2.73 (m, 1H), 2.43 (s, 3H), 2.40-2.00 (m, 5H), 1.44 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.1 (C), 154.7 (C), 154.6 (C), 144.1 (C), 135.4 (C),

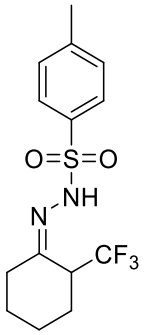
[91] C. M. Gartner, B. C. Mossman and M. E. Prince. *Tetrahedron. Lett.* **1993**, *34*, 4272.

[92] D. Kontokosta, D. S. Mueller, H. Wang, L. L. Anderson. *Org. Lett.* **2013**, *15*, 4830.

[93] J. Zhou, E. L. Campbell-Conroy, A. Silina, J. Uy, F. Pierre, D. J. Hurley, N. Hilgraf, B. A. Frieman, M. P. DeNinno. *J. Org. Chem*. **2015**, *80*, 70.

135.1 (C), 134.0 (CH), 129.5 (CH), 129.4 (CH), 128.1 (CH), 127.9 (CH), 118.6 (CH), 116.7 (CH), 80.1 (C), 47.5 (CH), 42.6 (CH_2), 36.9 (CH_2), 33.5 (CH_2), 31.5 (CH_2), 28.3 (CH_3), 25.9 (CH_2), 21.6 (CH_3) ppm. mp = 151.6-153.4 ºC

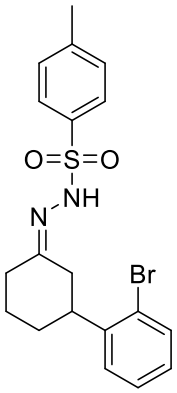
(*Z*)-4-Methyl-*N*'-(2-(trifluoromethyl)cyclohexylidene)benzenesulfonohydrazide (**9k**)



Tosylhydrazone **9k** was prepared from the corresponding carbonyl compound and tosylhydrazide following the standard procedure.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.11-2.98 (m, 1H), 2.44 (s, 3H), 2.34-1.50 (m, 8H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.3 (C), 144.1 (C), 134.9 (C), 129.5 (C, q, $^{2}J_{C-F}$ = 95.4 Hz), 129.4 (CH), 128.0 (CH), 45.1 (CH, q, $^{3}J_{C-F}$ = 105.6 Hz), 25.8 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 21.7 (CH_2), 21.6 (CH_3) ppm. mp = 152.7-154.2 ºC

(*Z*)-*N*'-(3-(2-Bromophenyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (**12b**)



Tosylhydrazone **12b** was prepared from corresponding carbonyl compound[94] and tosylhydrazide following the standard procedure.

Some of the signals are broad or splitted due to the presence of rotamers.

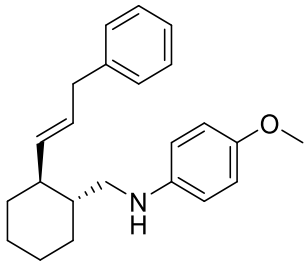
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (bs, 1H), 7.86 (d, *J* = 7.7 Hz, 2H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.40-7.15 (m, 4H), 7.12-7.00 (m, 1H), 3.25-3.00 (m, 1H), 2.92-2.72 (m, 2H), 2.70-2.58 (m, 1H), 2.43 (s, 3H), 2.30-2.11 (m, 1H), 2.10-1.80 (m, 3H), 1.65-1.45 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) 161.2 (C), 160.9 (C), 143.9 (C), 143.4 (C), 142.9 (C), 135.3 (C), 135.2 (C), 133.1 (CH), 129.6 (CH), 129.5 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 126.9 (CH), 124.3 (C), 124.2 (C), 43.0 (CH), 42.1 (CH), 40.8 (CH_2), 34.7 (CH_2), 32.7 (CH_2), 32.0 (CH_2), 31.8 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 24.7 (CH_2), 21.6 (CH_3) ppm. mp = 148.7-149.2 ºC

E.2.2. General procedure for the reductive coupling between *N*-tosylhydrazones and alkenylboronic acids under microwave irradiation and characterization data

General procedure **A**: A microwave vial provided with a triangular stir bar was charged with the tosylhydrazone (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 2.4 mL of dry dioxane. The vial was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at the desired temperature (120 ºC) during the reaction time (4 h) in a Biotage Initiator microwave apparatus. When the reaction finished, it was allowed to reach room temperature, solvents were eliminated and a saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (5 mL) 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, the products were purified by flash chromatography on silica gel.

[94] X. Lu, S. Lin. *J. Org. Chem*. **2005**, *70*, 9651.

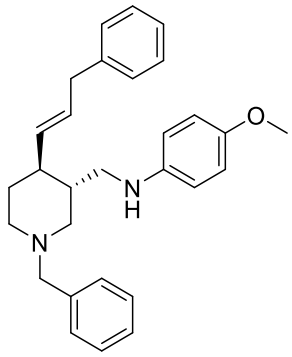
4-Methoxy-*N*-(((1*R**,2*S**)-2-((*E*)-3-phenylprop-1-en-1-yl)cyclohexyl)methyl)aniline (**7a**)



From (*Z*)-*N*'-(2-(((4-methoxyphenyl)amino)methyl)cyclohexylidene)-4-methylben zenesulfonohydrazide (60.2 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.5 mg, 0.3 mmol), **7a** was obtained in 62% isolated yield (31.0 mg) following ***General procedure A*** as a yellow oil. **7a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.27 (m, 2H). 7.25-7.17 (m, 3H), 6.78 (d, *J*= 9.0 Hz), 6.55 (d, 8.7 Hz), 5.65 (dt, *J*= 15.3, 6.9 Hz, 1H), 5.42 (dd, *J* = 15.3, 8.9 Hz, 1H), 3.78 (s, 3H), 3.39 (d, *J* = 6.8 Hz, 2H), 3.27 (dd, J= 12.6, 3.9 Hz, 1H), 2.85-2.75 (m, 1H), 2.00-1.50 (m, 6H), 1.50-1.30 (m, 1H), 1.30-1.14 (m, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.9 (C), 142.5 (C), 140.8 (C), 136.4 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 125.9 (CH), 114.9 (CH), 114.3 (CH), 55.8 (CH_3), 49.8 (CH_2), 45.8 (CH), 41.4 (CH), 39.0 (CH_2), 33.9 (CH_2), 30.7 (CH_2), 25.9 (CH_2), 25.8 (CH_2) ppm. HRMS(EI): calcd. For $[C_{23}H_{29}NO]^+$: 335.2249, found: 335.2240.

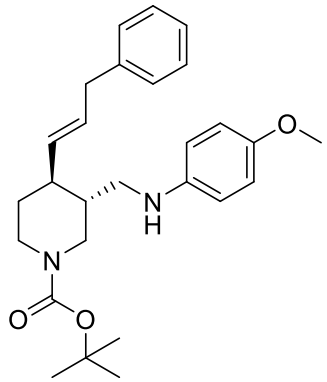
N-(((3*R**,4*S**)-1-Benzyl-4-((*E*)-3-phenylprop-1-en-1-yl)piperidin-3-yl)methyl)-4-methoxyaniline (**7b**)



From (*Z*)-*N*'-(1-benzyl-3-(((4-methoxyphenyl)amino)methyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (147.7 mg, 0.3 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (97.2 mg, 0.6 mmol), **7b** was obtained in 68% isolated yield (84.1 mg) following ***General procedure A*** as an orange oil. **7b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 3:1 as eluent. R_f (hexanes/ethyl acetate 3:1) = 0.15.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.18 (m, 10H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.50 (d, *J* = 9.0 Hz, 2H), 5.67 (dt, *J* = 15.2, 6.7 Hz, 1H), 5.44 (dd, *J* = 15.2, 8.8 Hz, 1H), 3.79 (s, 3 H), 3.63 (d, *J* = 13.1 Hz, 1H), 3.50 (d, *J* = 13.2 Hz, 1H), 3.41 (d, *J* = 6.9 Hz, 2H), 3.29-3.11 (m, 2H), 3.03-2.53 (m, 2H), 2.05-1.95 (m, 2H), 1.90-1.60 (m, 3H), 1.35-1.25 (m, 2H), 1.00-0.89 (m, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.9 (C), 142.7 (C), 140.6 (C), 134.8 (CH), 130.1 (CH), 129.4 (CH), 129.2 (C), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.3 (CH), 126.0 (CH), 114.9 (CH), 114.2 (CH), 63.2 (CH_2), 57.8 (CH_2), 55.9 (CH_3), 53.0 (CH_2), 47.4 (CH_2), 43.5 (CH), 40.5 (CH), 39.0 (CH_2), 32.4 (CH_2) ppm. HRMS(EI): calcd. For $[C_{29}H_{34}NO_2]^+$: 426.2671, found: 426.2672.

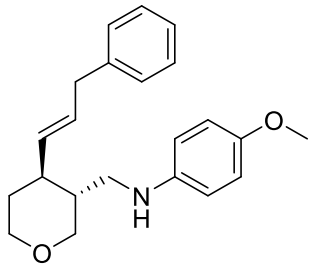
tert-Butyl (3*R**,4*S**)-3-(((4-methoxyphenyl)amino)methyl)-4-((*E*)-3-phenylprop-1-en-1-yl)piperidine-1-carboxylate (**7c**)



From *tert*-butyl (*Z*)-3-(((4-methoxyphenyl)amino)methyl)-4-(2-tosylhydrazono) piperidine-1-carboxylate (75.4 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.6 mg, 0.3 mmol), **7c** was obtained in 56% isolated yield (74.7 mg) following ***General procedure A*** as a colourless oil. **7c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. R_f (hexanes/ethyl acetate 5:1) = 0.22.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 8.5 Hz, 2H), 5.72 (dt, *J* = 15.3, 6.8 Hz, 1H), 5.40 (dd, *J* = 15.2, 8.9 Hz, 1H), 4.35-4.20 (bs, 1 H), 4.10-3.98 (bs, 1 H), 3.77 (s, 3H), 3.39 (d, *J* = 6.8 Hz, 2H), 3.28 (dd, *J* = 12.8, 3.8 Hz, 1H), 2.85 (dd, *J* = 12.8, 8.5 Hz, 1H), 2.80-2.75 (m, 1H), 2.60-2.50 (m, 1H), 1.70-1.65 (m, 1H), 1.65-1.55 (bs, 1H), 1.98 (dddd, *J* = 10.3, 10.1, 8.9, 3.9 Hz, 1H), 1.53-1.49 (m, 1H), 1.45 (s, 9 H), 1.43-1.40 (m, 1H) ppm.**^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.7 (C), 152.1 (C), 142.3 (C), 140.4 (CH), 134.2 (CH), 130.4 (CH), 128.5 (CH), 126.1 (CH), 114.9 (CH), 114.2 (CH), 79.6 (C), 55.9 (CH_3), 46.9 (CH_2), 43.6 (CH), 40.3 (CH), 39.0 (CH_2), 32.2 (CH_2), 28.45 (CH_3) ppm. HRMS(EI): calcd. For $[C_{27}H_{36}N_2O_3]^+$: 436.2776, found: 436.2730.

4-Methoxy-*N*-(((3*R**,4*S**)-4-((*E*)-3-phenylprop-1-en-1-yl)tetrahydro-2*H*-pyran-3-yl) methyl)aniline (**7d**)

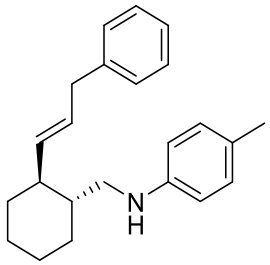


From (*Z*)-*N*'-(3-(((4-methoxyphenyl)amino)methyl)tetrahydro-4*H*-pyran-4-ylidene)-4-methylbenzenesulfonohydrazide (60.5 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.5 mg, 0.3 mmol), **7d** was obtained in 60% isolated yield (30.2 mg) following ***General procedure A*** as a yellow oil. **7d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. R_f (hexanes/ethyl acetate 5:1) = 0.13.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 6.80 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 9.0 Hz, 2H), 5.73 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.45 (dd, *J* = 15.2, 8.7 Hz, 1H), 4.14 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.99 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.78 (s, 3H), 3.42 (d *J* = 6.8 Hz, 2H), 3.27-3.15 (m, 2H), 2.85 (dd, *J* = 12.8, 8.2 Hz, 1H), 2.06 (dddd, *J* = 10.1, 10.0, 8.8, 4.2 Hz, 1H), 1.82-1.72 (m, 2H), 1.66-1.60 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.2 (C), 140.4 (C), 134.2 (C), 130.3 (CH), 128.5 (CH), 126.1 (CH), 114.9 (CH), 114.1 (CH), 71.2 (CH_2), 67.9 (CH_2), 55.9 (CH_3), 45.9 (CH_2), 42.9 (CH), 40.7 (CH_2), 38.9 (CH_2), 32.9 (CH_2) ppm.

HRMS(EI): calcd. For $[C_{22}H_{27}NO_2]^+$: 337.2042, found: 337.2057.

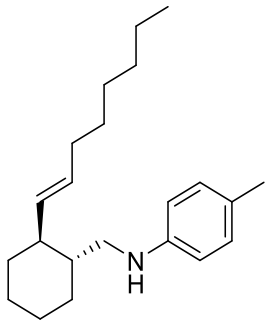
4-Methyl-*N*-(((1*R**,2*S**)-2-((*E*)-3-phenylprop-1-en-1-yl)cyclohexyl)methyl)aniline (**7e**)



From 4-methyl-*N*'-(2-((*p*-tolylamino)methyl)cyclohexylidene)benzene sulfono hydrazide (115.6 mg, 0.3 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (97.2 mg, 0.6 mmol)**, 7e** was obtained in 65% isolated yield (66.7 mg) following ***General procedure A*** as a yellow oil. **7e** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 30:1 as eluent. R_f (hexanes/ethyl acetate 30:1) = 0.24.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.50 (d, *J* = 8.4 Hz, 2H), 5.65 (dt, *J* = 15.2, 6.7 Hz, 1H), 5.42 (dd, *J* = 15.2, 8.9 Hz, 1H), 3.40 (d, *J* = 6.5 Hz, 2H), 3.30 (dd, *J* = 12.6, 4.0Hz, 1H), 2.81 (dd, J = 12.7, 7.8 Hz, 1H), 2.29 (s, 3H), 1.96-1.91 (m, 1H), 1.90-1.66 (m, 5H), 1.37-1.00 (m, 4H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.2 (C), 140.8 (C), 136.4 (C), 129.7 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 125.9 (CH), 113.1 (CH), 113.0 (CH), 49.0 (CH_2), 45.9 (CH), 41.4 (CH), 39.0 (CH_2), 33.9 (CH_2), 30.7 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 20.4 (CH_3) ppm. HRMS(EI): calcd. For $[C_{23}H_{29}N]^+$: 319.2300, found: 319.2307.

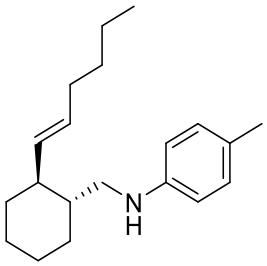
4-Methyl-*N*-(((1R*,2S*)-2-((*E*)-oct-1-en-1-yl)cyclohexyl)methyl)aniline (**7f**)



From 4-methyl-*N*'-(2-((p-tolylamino)methyl)cyclohexylidene)benzenesulfono hydrazide (57.8 mg, 0.15 mmol) and *trans*-1-octen-1-ylboronic acid (46.8 mg, 0.3 mmol), **7f** was obtained in 66% isolated yield (30.9 mg) following ***General procedure A*** as a yellow oil. **7f** 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) = 0.50.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.2 Hz, 2H), 6.53 (d, *J* = 8.3 Hz, 2H), 5.47 (dt, *J*= 15.3, 6.3 Hz, 1H), 5.30 (dd, *J* = 15.4, 8.6 Hz, 1H), 3.26 (dd, *J* = 12.8, 4.2 Hz, 1H), 2.81 (dd, *J* = 12.7, 7.6 Hz, 1H), 2.226 (s, 3H), 2.10-1.98 (m, 2H), 1.96-1.87 (m, 1H), 1.83-1.50 (m, 5H), 1.45-1.15 (m, 8H), 1.10-0.98 (m, 1H), 0.95-0.85 (m, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.2 (C), 134.8 (CH), 130.4 (CH), 129.6 (CH), 113.0 (CH), 49.1 (CH_2), 46.0 (CH), 34,1 (CH_2), 32.6 (CH_2), 31.7 (CH_2), 30.8 (CH_2), 29.6 (CH_2), 28.8 (CH_2), 25.9 (CH_2), 22.6 (CH_2), 20.3 (CH_3), 14.1 (CH_3) ppm. HRMS(EI): calcd. For $[C_{22}H_{35}N]^+$: 313.2770, found: 313.2757.

N-(((1*R**,2*S**)-2-((*E*)-Hex-1-en-1-yl)cyclohexyl)methyl)-4-methylaniline (**7g**)

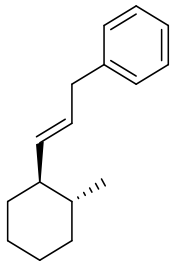


From (*Z*)-4-methyl-*N*'-(2-((*p*-tolylamino)methyl)cyclohexylidene)benzenesulfono hydrazide (57.8 mg, 0.15 mmol) and *trans*-1-hexen-1-ylboronic acid (38.4 mg, 0.3 mmol), **7g** was obtained in 52% isolated yield (21.4 mg) following ***General procedure A*** as a yellow oil. **7g** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 10:1 as eluent. Rf (hexanes/ethyl acetate 10:1) = 0.70.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.3 Hz, 2H), 6.51 (d, *J* = 8.4 Hz, 2H), 5.65 (dt, *J*= 15.3, 6.3 Hz, 1H), 5.30 (dd, *J* = 15.5, 8.7 Hz, 1H), 3.26 (dd, *J* = 12.8, 4.3 Hz, 1H), 2.80 (dd, *J* = 12.8, 7.5 Hz, 1H), 2.25 (s, 3H), 2.10-1.94 (m, 2H), 1.92-1.85 (m, 1H), 1.80-1.56 (m, 4H), 1.45-1.10 (m, 8H), 0.98-0.85 (m, 4H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.3 (C), 134.8 (CH), 130.3 (CH), 129.7 (CH), 126.0 (C), 112.9 (CH), 49.0

(CH_2), 46.0 (CH), 41.4 (CH), 34.1 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 30.8 (CH_2), 25.9 (CH_2), 22.2 (CH_2), 20.3 (CH_3), 13.9 (CH_3) ppm. HRMS(EI): calcd. For $[C_{20}H_{31}N]^+$: 285.2457, found: 285.2457.

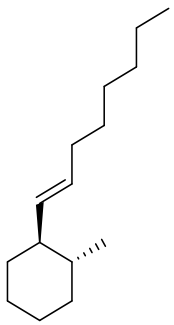
((*E*)-3-((1*R**,2*R**)-2-Methylcyclohexyl)allyl)benzene (**9a**)



From (*Z*)-4-methyl-*N*'-(2-methylcyclohexylidene)benzenesulfonohydrazide (84.1 mg, 0.3 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (97.2 mg, 0.6 mmol), **9a** was obtained in 52% isolated yield (33.3 mg) following ***General procedure A*** as a colourless oil. **9a** was purified by flash chromatography on silica gel using hexane as eluent. R_f (hexane) = 0.80.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.27 (m, 2H), 7.26-7.19 (m, 3H), 5.56 (dt, *J* = 15.2, 6.7 Hz, 1H), 5.37 (dd, *J*=15.1, 9.0 Hz, 1H), 3.38 (d, *J* = 6.7 Hz, 1H), 1.80-1.65 (m, 4H), 1.64-1.51 (m, 1H), 1.33-1.12 (m, 4H), 1.07-0.94 (m, 1H) ,0.90 (d, *J* = 6.5 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.3 (C), 137.3 (CH), 128.5 (CH), 128.3 (CH), 127.8 (CH), 125.8 (CH), 48.8 (CH), 39.1 (CH_2), 37.1 (CH), 35.2 (CH_2), 33.8 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 21.0 (CH_3) ppm. HRMS(EI): calcd. For $[C_{16}H_{23}]^+$: 215.1794, found: 215.1792.

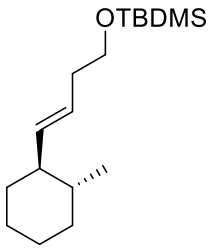
(1*R**,2*R**)-1-Methyl-2-((*E*)-oct-1-en-1-yl)cyclohexane (**9b**)



From (*Z*)-4-methyl-*N*'-(2-methylcyclohexylidene)benzenesulfonohydrazide (42.1 mg, 0.15 mmol) and *trans*-1-octen-1-ylboronic acid (46.8 mg, 0.3 mmol), **9b** was obtained in 56% isolated yield (17.2 mg) following ***General procedure A*** as a colourless oil. **9b** was purified by flash chromatography on silica gel using hexane as eluent. R_f (hexane) = 0.90.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.20 (dd, *J* = 15.4, 8.5 Hz, 1H), 2.04-1.95 (2H), 1.77-1.47 (m, 7H), 1.40-0.95 (m, 13H), 0.90 (t, *J*=6.3 Hz, 3H), 0.84 (d, *J*=6.3 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.4 (CH), 129.5 (CH), 48.8 (CH), 37.0 (CH), 35.2 (CH_2), 33.9 (CH_2), 32.6 (CH_2), 31.7 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 22.6 (CH_2), 20.8 (CH_3), 14.0 (CH_3) ppm. HRMS(EI): calcd. For $[C_{20}H_{31}N]^+$: 208.2191, found: 208.2184.

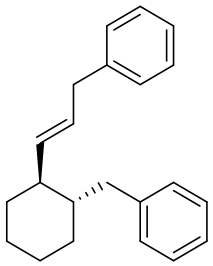
<u>*tert*-Butyldimethyl(((*E*)-4-((1R*,2R*)-2-methylcyclohexyl)but-3-en-1-yl)oxy)silane (**9c**)</u>



From (*Z*)-4-methyl-*N*'-(2-methylcyclohexylidene)benzenesulfonohydrazide (42.0 mg, 0.15 mmol) and (*E*)-(4-((tert-butyldimethylsilyl)oxy)but-1-en-1-yl)boronic acid (69.0 mg, 0.3 mmol) **9c** was obtained in 60% isolated yield (21.9 mg) following ***General procedure A*** as a colourless oil. **9c** 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) = 0.23.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42-5.23 (m, 2H), 3.63 (t, *J* = 6.9 Hz, 2H), 2.22 (q, *J* = 6.6 Hz, 2H), 1.75-1.65 (m, 3H), 1.58-1.43 (m, 1H), 1.35-1.00 (m, 6H), 0.90 (s, 9H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.96 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.5 (CH), 125.5 (CH), 63.5 (CH_2), 48.9 (CH), 36.9 (CH), 36.3 (CH_2), 33.7 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 25.9 (CH_3), 20.9 (CH_3), 18.3 (C), -5.2 (CH_3) ppm. HRMS(EI): calcd. For $[C_{17}H_{35}OSi]^+$: 283.2451, found: 283.2458.

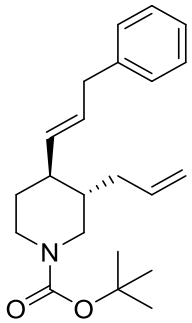
((*E*)-3-((1*R**,2*S**)-2-Benzylcyclohexyl)allyl)benzene (**9d**)



From (*Z*)-*N*'-(2-benzylcyclohexylidene)-4-methylbenzenesulfonohydrazide (105.0 mg, 0.3 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (97.2 mg, 0.6 mmol) **9d** was obtained in 56% isolated yield (48.8 mg) following ***General procedure A*** as an orange oil. **9d** was purified by flash chromatography on silica gel using hexane as eluent. Rf (hexane) = 0.42.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.20 (m, 9H), 7.20-7.12 (m, 2H), 5.67 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.49 (dd, *J* = 15.3, 8.7 Hz, 1H), 3.44 (d, *J* = 6.7 Hz, 1H), 3.09 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.13 (dd, *J* = 13.4, 10.2 Hz, 1H), 1.90-1.60 (m, 5H), 1.45-1-07 (m, 4H), 0.96-0.82 (m, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.7 (C), 141.1 (C), 137.2 (CH), 129,3 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.0 (CH), 125.9 (CH), 125.5 (CH), 47.4 (CH), 44.0 (CH), 41.3 (CH_2), 39.2 (CH_2), 34.3 (CH_2), 31.3 (CH_2), 26.2 (CH_2), 26.1 (CH_2) ppm. HRMS(EI): calcd. For $[C_{22}H_{26}]^{+}$: 290.2035, found: 290.2040.

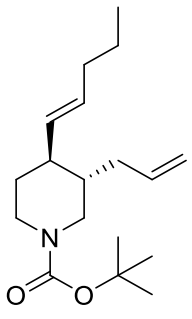
tert-Butyl (3*S**,4*S**)-3-allyl-4-((*E*)-3-phenylprop-1-en-1-yl)piperidine-1-carboxylate (**9e**)



From *tert*-butyl (*Z*)-3-allyl-4-(2-tosylhydrazono)piperidine-1-carboxylate (81.5 mg, 0.2 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (64.7 mg, 0.4 mmol) **9e** was obtained in 58% isolated yield (39.5 mg) following ***General procedure A*** as a colourless oil. **9e** 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) = 0.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.10 (m, 5H), 5.86-5.70 (m, 1H), 5.63 (dt, J= 15.3, 6.6 Hz, 1H), 5.34 (dd, J= 15.3, 8.4 Hz, 1H), 5.10-4.96 (m, 2H), 4.20-4.00 (m, 2H), 3.38 (d, *J* = 6.9 Hz, 2H), 2.80-2.60 (m, 1H), 2.45-2.25 (m, 2H), 2.20-2.05 (m, 1H), 1.92-1.72 (m, 2H), 1.70-1.60 (m, 1H), 1.50-1.20 (m, 10H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.7 (C), 140.6 (C), 135.9 (CH), 134.5 (CH), 130.0 (CH), 128.4 (CH), 128.3 (CH), 125.9 (CH), 116.4 (CH_2), 79.3 (C), 48.0 (CH_2), 44.9 (CH), 43.7 (CH_2), 39.9 (CH), 39.0 (CH_2), 36.2 (CH_2), 35.8 (CH_2), 35.0 (CH_2), 32.5 (CH_2), 28.4 (CH_3) ppm. HRMS(EI): calcd. For $[C_{22}H_{31}NO_2Na]^+$: 364.2247, found: 364.2236.

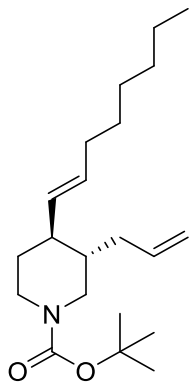
tert-Butyl (3*S**,4*S**)-3-allyl-4-((*E*)-pent-1-en-1-yl)piperidine-1-carboxylate (**9f**)



From *tert*-butyl (*Z*)-3-allyl-4-(2-tosylhydrazono)piperidine-1-carboxylate (61.1 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (34.1 mg, 0.3 mmol) **9f** was obtained 50% isolated yield (25.0 mg) following ***General procedure A*** as a colourless oil. **9f** 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) = 0.35.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86-5.70 (m, 1H), 5.45 (dt, *J*= 15.4, 6.6 Hz, 1H), 5.19 (dd, *J*= 15.4, 8.4 Hz, 1H), 5.10-4.96 (m, 2H), 4.20-4.00 (m, 2H), 2.70 (td, *J* = 12.9, 3.0 Hz, 1H), 2.40-2.28 (m, 2H), 2.08-1.95 (m, 2H), 1.87-1.70 (m, 2H), 1.68-1.63 (m, 1H), 1.60-1.55 (m, 1H), 1.48 (s, 9H), 1.45-1.23 (m, 5H), 0.91 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.5 (C), 136.1 (CH), 133.0 (CH), 131.4 (CH), 116.3 (CH_2), 79.2 (C), 48.1 (CH_2), 45.0 (CH), 43.7 (CH_2), 39.9 (CH), 35.8 (CH_2), 34.6 (CH_2), 32.6 (CH_2), 28.4 (CH_3), 22.6 (CH_2), 13.6 (CH_3). HRMS(EI): calcd. For $[C_{18}H_{32}NO_2]^+$: 294.2427, found: 294.2425.

tert-Butyl (3S*,4S*)-3-allyl-4-((*E*)-oct-1-en-1-yl)piperidine-1-carboxylate (**9g**)

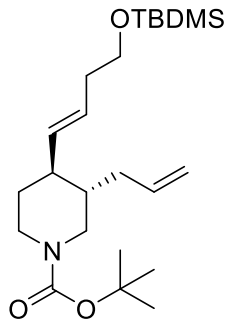


From *tert*-butyl (*Z*)-3-allyl-4-(2-tosylhydrazono)piperidine-1-carboxylate (61.1 mg, 0.15 mmol) and *trans*-1-octen-1-ylboronic acid (46.8 mg, 0.3 mmol) **9g** was obtained 50% isolated yield (23.4 mg) following ***General procedure A*** as a colourless oil. **9g** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 20:1 as eluent. R_f (hexanes/ethyl acetate 20:1) = 0.30.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86-5.70 (m, 1H), 5.45 (dt, *J*= 15.4, 6.6 Hz, 1H), 5.19 (dd, *J*= 15.4, 8.4 Hz, 1H), 5.10-4.96 (m, 2H), 4.20-4.00 (m, 2H), 2.78-2.65 (m, 1H), 2.42-2.28 (m, 2H), 2.10-1.95 (m, 2H), 1.85-1.70 (m, 2H), 1.49 (s, 9H), 1.42-1.22 (m, 9H), 0.90 (t, *J*= 6.0 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.8 (C), 136.1 (CH),

132.8 (CH), 131.6 (CH), 116.3 (CH_2), 79.2 (C), 45.0 (CH), 39.9 (CH), 35.8 (CH_2), 32.5 (CH_2), 31.6 (CH_2), 29.4 (CH_2), 28.7 (CH_2), 28.4 (CH_3), 22.6 (CH_2), 14.0 (CH_3) ppm. HRMS(EI): calcd. For $[C_{21}H_{38}NO_2]^+$: 336.2897, found: 336.2900.

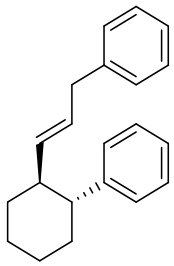
tert-Butyl (3*S**,4*S**)-3-allyl-4-((*E*)-4-((*tert*-butyldimethylsilyl)oxy)but-1-en-1-yl)piperidine-1-carboxylate (**9h**)



From *tert*-butyl (*Z*)-3-allyl-4-(2-tosylhydrazono)piperidine-1-carboxylate (40.7 mg, 0.1 mmol) and (*E*)-(4-((*tert*-butyldimethylsilyl)oxy)but-1-en-1-yl)boronic acid (46.0 mg, 0.2 mmol) **9h** was obtained in 65% isolated yield (25.8 mg) following ***General procedure A*** as a colourless oil. **9h** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 20:1 as eluent. R_f (hexanes/ethyl acetate 20:1) = 0.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86-5.69 (m, 1H), 5.45 (dt, *J*= 15.0, 6.0 Hz, 1H), 5.19 (dd, *J*= 15.6, 8.6 Hz, 1H), 5.10-4.96 (m, 2H), 4.20-4.00 (m, 2H), 3.65 (t, *J* = 6.7 Hz, 2H), 2.71 (dd, *J* = 13.9, 10.9 Hz, 1H), 2.41-2.20 (m, 4H), 1.85-1.70 (m, 2H), 1.58 (s, 9H), 1.43-1.25 (m, 3H), 0.91 (s, 9H), 0.09 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.7 (C), 136.0 (CH), 134.9 (CH), 127.9 (CH), 116.3 (CH_2), 79.2 (C), 63.1 (CH_2), 45.1 (CH), 39.8 (CH), 36.2 (CH_2), 35.8 (CH_2), 32.5 (CH_2), 28.4 (CH_3), 25.9 (CH_3), 18.35 (C), -5.2 (CH_3) ppm. HRMS(EI): calcd. For $[C_{23}H_{44}NO_3Si]^+$: 410.3084, found: 410.3095.

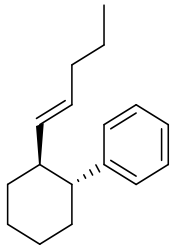
((*E*)-3-((1*S**,2*R**)-2-Phenylcyclohexyl)allyl)benzene (**9i**)



From (*Z*)-4-methyl-*N*'-(2-phenylcyclohexylidene)benzenesulfonohydrazide (51.3 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.5 mg, 0.3 mmol) **9i** was obtained 55% isolated yield (23.0 mg) following ***General procedure A*** as a colourless oil. **9i** 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) = 0.78.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 8H), 6.79-6.72 (m, 2H), 5.34-5.16 (m, 2H), 3.15 (d, *J* = 5.3 Hz, 2H), 2.40-2.20 (m, 2H), 1.95-1.80 (m, 2H), 1.60-1.25 (m, 4H), 0.95-0.85 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.4 (C), 140.8 (C), 136.6 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 125.7 (CH), 125.5 (CH), 50.6 (CH), 46.7 (CH), 38.7 (CH_2), 35.3 (CH_2), 33.6 (CH_2), 26.7 (CH_2), 26.1 (CH_2) ppm. HRMS(EI): calcd. For $[C_{21}H_{24}]^+$: 277.1950, found: 277.1943.

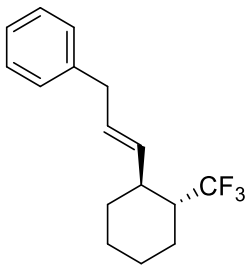
((1*R**,2*S**)-2-((*E*)-Pent-1-en-1-yl)cyclohexyl)benzene (**9j**)



From (*Z*)-4-methyl-*N*'-(2-phenylcyclohexylidene)benzenesulfonohydrazide (51.3 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (34.1 mg, 0.3 mmol), **9j** was obtained in 51% isolated yield (18.0 mg) following ***General procedure A*** as a colourless oil. **9j** 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) = 0.85.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.23 (m, 2H), 7.19-7.11 (m, 3H), 5.13-5.08 (m, 2H), 2.32-2.12 (m, 2H), 1.95-1.65 (m, 5H), 1.60-1.25 (m, 4H), 1.20-1.15 (m, 2H), 0.95-0.80 (m, 1H), 0.65 (t, *J*= 6.0 Hz) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.4 (C), 134.4 (CH), 129.4 (CH), 127.9 (CH), 129.8 (CH), 125.5 (CH), 50.6 (CH), 46.3 (CH), 35.4 (CH_2), 34.5 (CH_2), 33.6 (CH_2), 26.7 (CH_2), 26.2 (CH_2), 22.5 (CH_2), 13.2 (CH_3) ppm. HRMS(EI): calcd. For $[C_{17}H_{23}]^+$: 227.1779, found: 227.1794.

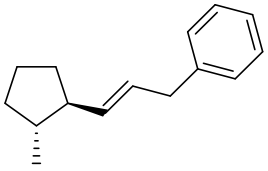
((*E*)-3-((1*S**,2*R**)-2-(Trifluoromethyl)cyclohexyl)allyl)benzene (**9k**)



From (*E*)-4-methyl-*N*'-(2-(trifluoromethyl)cyclohexylidene)benzenesulfono hydrazide (100.3 mg, 0.3 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (97.1 mg, 0.6 mmol), **9k** was obtained in 63% isolated yield (50.0 mg) following ***General procedure A*** as a colourless oil. **9k** 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) = 0.56.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.17 (m, 5H), 5.62 (dt, *J* = 15.0, 6.6 Hz, 1H), 5.44 (dd, *J* = 15.1, 8.6 Hz, 1H), 3.37 (d, *J* = 6.5 Hz, 2H), 2.20-1.70 (m, 6H), 1.39-1.18 (m, 4H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.6 (C), 134.7 (CH), 128.5 (CH), 128.3 (CH), 125.9 (CH), 46.6 (q, $^{3}J_{C\text{-}F}$ = 93.9 Hz), 41.5 (CH), 38.8 (CH_2), 33.7 (CH_2), 25.2 (CH_2), 24.7 (CH_2) ppm. HRMS(EI): calcd. For $[C_{16}H_{19}F_3]^+$: 268.1437, found: 268.1433.

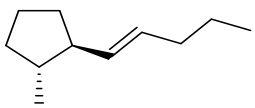
((*E*)-3-((1*R**,2*R**)-2-Methylcyclopentyl)allyl)benzene (**11a**)



From (*Z*)-4-methyl-*N*'-(2-methylcyclopentylidene)benzenesulfonohydrazide (35.7 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.5 mg, 0.3 mmol) **11a** was obtained in 73% isolated yield (22.0 mg) following ***General procedure A*** as a colourless oil. **11a** was purified by flash chromatography on silica gel using hexane as eluent. Rf (hexane) = 0.85.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (m, 2H), 7.24-7.15 (m, 3H), 5.57 (dt, *J*= 15.0, 6.6 Hz, 1H), 5.43 (dd, *J*= 15.3 Hz, 1.8 Hz), 3.38 (d, *J* = 6.6 Hz, 1H), 1.95-1.80 (m, 3H), 1.70-1.35 (m, 4 H), 1.27-1.12 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.2 (C), 135.9 (CH), 128.4 (CH), 128.32 (CH), 128.0 (CH), 125.8 (CH), 51.6 (CH), 41.0 (CH), 39.0 (CH_2), 34.3 (CH_2), 33.1 (CH_2), 23.4 (CH_2), 18.5 (CH_3) ppm. HRMS(EI): calcd. For $[C_{15}H_{20}]^+$: 200.1565, found: 200.1528.

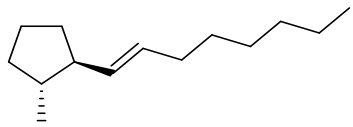
(1*R**,2*R**)-1-Methyl-2-((*E*)-pent-1-en-1-yl)cyclopentane (**11b**)



From (*Z*)-4-methyl-*N*'-(2-methylcyclopentylidene)benzenesulfonohydrazide (71.4 mg, 0.3 mmol) and *trans*-1-penten-1-ylboronic acid (76.7 mg, 0.6 mmol) **11b** was obtained 62% isolated yield (31.0 mg) following ***General procedure A*** as a colourless oil. **11b** was purified by flash chromatography on silica gel using hexane as eluent. R_f (hexane) = 0.88.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (dt, *J* = 15.0, 6.4 Hz, 1H), 5.28 (dd, *J* = 15.4, 6.9 Hz, 1H), 2.10-1.96 (m, 2H), 1.90-1.75 (m, 3H), 1.66-1.58 (m, 1H), 1.50-1.05 (m, 9H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.90-0.84 (m, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.1 (CH), 129.8 (CH), 51.7 (CH), 41.0 (CH), 34.3 (CH_2), 33.2 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 23.3 (CH_2), 22.6 (CH_2), 18.4 (CH_3), 13.0 (CH_3) ppm. HRMS(EI): calcd. For $[C_{12}H_{23}]^+$: 167.1782, found: 167.1794.

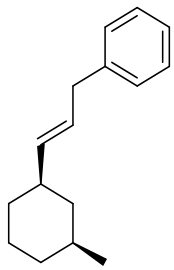
(1*R**,2*R**)-1-Methyl-2-((*E*)-oct-1-en-1-yl)cyclopentane (**11c**)



From (*Z*)-4-methyl-*N*'-(2-methylcyclopentylidene)benzenesulfonohydrazide (71.4 mg, 0.3 mmol) and *trans*-1-octen-1-ylboronic acid (93.6 mg, 0.6 mmol) **14c** was obtained 48% isolated yield (28.0 mg) following ***General procedure A*** as a colourless oil. **14c** was purified by flash chromatography on silica gel using hexane as eluent. R_f (hexane) = 0.90.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (dt, *J* = 15.1, 6.4 Hz, 1H), 5.27 (dd, *J* = 15.3, 7.1 Hz, 1H), 2.05-1.96 (m, 2H), 1.90-1.75 (m, 4H), 1.66-1.58 (m, 1H), 1.45-1.20 (m, 9H), 0.95 (d, *J* = 6.5 Hz, 3H) 0.90 (t, *J* = 6.7 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.1 (CH), 129.8 (CH), 51.7 (CH), 41.0 (CH), 34.3 (CH_2), 33.2 (CH_2), 32.7 (CH_2), 31.7 (CH_2), 29.7 (CH_2), 28.8 (CH_2), 23.3 (CH_2), 22.6 (CH_2), 18.4 (CH_3), 14.2 (CH_3) ppm. HRMS(EI): calcd. For $[C_{14}H_{27}]^+$: 195.2107, found: 195.2102.

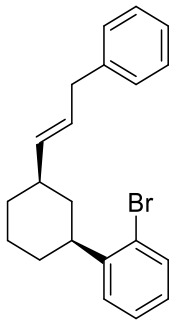
((*E*)-3-((1*R**,3*S**)-3-Methylcyclohexyl)allyl)benzene (**13a**)



From (*Z*)-4-methyl-*N*'-(3-methylcyclohexylidene)benzenesulfonohydrazide (42.1 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.5 mg, 0.3 mmol), **13a** was obtained in 57% isolated yield (18.2 mg) following ***General procedure A*** as a colourless oil. **13a** was purified by flash chromatography on silica gel using hexane as eluent. Rf (hexane) = 0.83.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.28 (m, 2H), 7.24-7.17 (m, 3H), 5.62-5.42 (m, 2H), 3.34 (d, *J* = 5.7 Hz, 1H), 2-06-1.91 (m, 1H), 1.80-1.67 (m, 3H), 1.45-1.26 (m, 2H), 1.07-0.95 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.85-0.68 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.2 (C), 138.0 (CH), 128.4 (CH), 128.3 (CH), 126.1 (CH), 125.8 (CH), 41.9 (CH_2), 40.8 (CH), 39.1 (CH_2), 34.9 (CH_2), 32.7 (CH_2), 32.7 (CH), 26.1 (CH_2), 22.8 (CH_3) ppm. HRMS(EI): calcd. For $[C_{16}H_{22}]^+$: 214.1722, found: 214.1729.

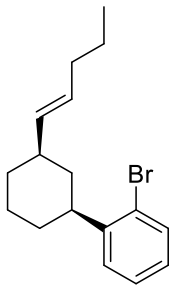
1-Bromo-2-((1*S**,3*R**)-3-((*E*)-3-Phenylprop-1-en-1-yl)cyclohexyl)benzene (**13b**)



From (*Z*)-*N*'-(3-(2-bromophenyl)cyclohexylidene)-4-methylbenzenesulfono hydrazide (63.0 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.5 mg, 0.3 mmol) **13b** was obtained in 58% isolated yield (30.7 mg) following ***General procedure A*** as a colourless oil. **13b** was purified by flash chromatography on silica gel using hexane as eluent. Rf (hexane) = 0.85.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.35-7.17 (m, 7H), 7.10-7.03 (m, 1H), 5.61 (dt, *J* = 15.1, 6.0 Hz, 1H), 5.53 (dd, *J* = 15.5, 5.8 Hz, 1H), 3.36 (d, *J* = 6.0 Hz, 2H), 3.07 (tt, *J* = 12.1, 3.0 Hz, 1H), 2.30-2.16 (m, 1H), 2.03-1.84 (m, 4H), 1.57-1.45 (m, 1H), 1.40-1.09 (m, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.8 (C), 141.0 (C), 137.2 (CH), 132.8 (CH), 128.4 (CH), 128.3 (CH), 127.5 (CH), 127.3 (CH), 126.7 (CH), 125.8 (CH), 124.4 (C), 42.7 (CH), 40.8 (CH), 39.4 (CH_2), 39.1 (CH_2), 32.6 (CH_2), 26.3 (CH_2) ppm. HRMS(EI): calcd. For $[C_{21}H_{22}Br]^+$: 352.0821, found: 352.0834.

1-Bromo-2-((1*S**,3*R**)-3-((*E*)-pent-1-en-1-yl)cyclohexyl)benzene (**13c**)

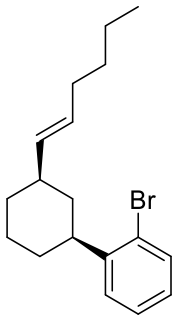


From (*Z*)-*N*'-(3-(2-bromophenyl)cyclohexylidene)-4-methylbenzenesulfono hydrazide (63.0 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (34.1 mg, 0.3

mmol), **13c** was obtained in 50% isolated (23.0 mg) yield following ***General procedure A*** as a colourless oil. **13c** was purified by flash chromatography on silica gel using hexane as eluent. R_f (hexane) = 0.81.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.9 Hz, 1H), 7.30-7.25 (m, 2H), 7.10-7.01 (m, 1H), 5.50-5.36 (m, 2H), 3.07 (tt, *J* = 12.0, 3.1 Hz, 1H), 2.25-2.10 (m, 1H), 2.01-1.80 (m, 6H), 1.60-1.45 (m, 2H), 1.44-1.26 (m, 3H), 1.23-1.07 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.9 (C), 135.7 (CH), 132.8 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 124.4 (C), 42.8 (CH), 40.1 (CH), 39.5 (CH_2), 32.7(CH_2), 32.6 (CH_2), 26.3 (CH_2), 22.7 (CH_2), 13.6 (CH_3) ppm. HRMS(EI): calcd. For $[C_{17}H_{23}Br]^+$: 306.0983, found: 306.0984.

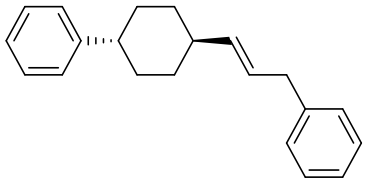
1-Bromo-2-((1S*,3R*)-3-((*E*)-hex-1-en-1-yl)cyclohexyl)benzene (**13d**)



From (*Z*)-*N*'-(3-(2-bromophenyl)cyclohexylidene)-4-methylbenzenesulfono hydrazide (63.0 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (34.1 mg, 0.3 mmol), **13d** was obtained in 52% isolated (25.0 mg) yield following ***General procedure A*** as a colourless oil. **13d** was purified by flash chromatography on silica gel using hexane as eluent. R_f (hexane) = 0.79.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.9 Hz, 1H), 7.30-7.25 (m, 2H), 7.10-7.00 (m, 1H), 5.52-5.36 (m, 2H), 3.07 (tt, *J* = 12.0, 3.1 Hz, 1H), 2.25-1.75 (m, 7H), 1.58-1.05 (m, 8H), 0.91 (t, *J* = 6.8 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.9 (C), 135.5 (CH), 132.8 (CH), 128.2 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 124.4 (C), 42.8 (CH), 40.9 (CH), 39.5 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 32.3 (CH_2), 31.8 (CH_2), 26.3 (CH_2), 22.1 (CH_2), 13.9 (CH_3) ppm. HRMS(EI): calcd. For $[C_{18}H_{26}Br]^+$: 321.1212, found: 321.1204.

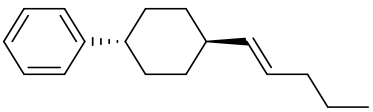
((*E*)-3-((1*r**,4*r**)-4-Phenylcyclohexyl)allyl)benzene (**15a**)



From 4-methyl-*N*'-(4-phenylcyclohexylidene)benzenesulfonohydrazide (102.6 mg, 0.3 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (97.1 mg, 0.6 mmol), **15a** was obtained in 60% isolated yield (48.8 mg) following ***General procedure A*** as a colourless oil. **15a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 40:1 as eluent. Rf (hexanes/ethyl acetate 40:1) = 0.66.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 10H), δ 5.67 (dt, *J* = 15.3, 6.6 Hz, 1H), 5.58 (dd, *J* = 15.6, 5.7 Hz, 1H), 3.41 (d, *J* = 5.8 Hz, 2H), 2.53 (tt, J= 12.0, 3.3 Hz, 1H), 2.20-1.90 (m, 5H), 1.55 (qd, *J* = 12.3, 2.7 Hz, 2H), 1.34 (qd, *J* = 12.3, 3.0 Hz, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.6 (C), 141.1 (C), 137.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 126.8 (CH), 126.6 (CH), 125.9 (CH), 44.1 (CH), 40.4 (CH), 39.1 (CH_2), 34.0 (CH_2), 33.3 (CH_2) ppm. HRMS(EI): calcd. For $[C_{21}H_{24}]^+$: 276.1872, found: 216.1871.

((1r*,4r*)-4-((*E*)-Pent-1-en-1-yl)cyclohexyl)benzene (**15b**)



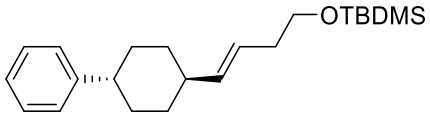
From 4-methyl-*N*'-(4-phenylcyclohexylidene)benzenesulfonohydrazide (102.6 mg, 0.3 mmol) and *trans*-1-penten-1-ylboronic acid (68.3 mg, 0.6 mmol) **15b** was obtained 75% isolated yield (50.7 mg) following ***General procedure A*** as a colourless oil. **15b** was purified by flash chromatography on silica gel using hexane as eluent. Rf (hexane) = 0.81.

This reaction was scaled to a 2 mmol scale employing 4-methyl-*N*'-(4-phenylcyclohexylidene)benzenesulfonohydrazide (684.2 mg, 2 mmol) and *trans*-1-

penten-1-ylboronic acid (455.8 mg, 4 mmol). Compound **15b** was obtained in 70 % isolated yield (319 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.15 (m, 5H), 5.53-5.37 (m, 2H), 2.51 (tt, *J*= 12.0, 3.3 Hz, 1H), 2.10-1.85 (m, 7H), 1.65-1.48 (m, 2H), 1.47-1.36 (m, 2H), 1.35-1.22 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.7 (C), 136.1 (CH), 128.3 (CH), 127.9 (CH), 126.8 (CH), 125.8 (CH), 44.1 (CH), 40.4 (CH), 34.8 (CH_2), 34.0 (CH_2), 33.5 (CH_2), 22.8 (CH_2), 13.6 (CH_3) ppm. HRMS(EI): calcd. For $[C_{17}H_{24}]^+$: 228.1872, found: 228.1872.

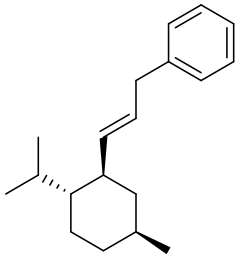
tert-Butyldimethyl(((*E*)-4-((1r,4r)-4-phenylcyclohexyl)but-3-en-1-yl)oxy)silane (**15c**)



From 4-methyl-*N*'-(4-phenylcyclohexylidene)benzenesulfonohydrazide (102.6 mg, 0.3 mmol) and (*E*)-(4-((tert-butyldimethylsilyl)oxy)but-1-en-1-yl)boronic acid (138.1 mg, 0.6 mmol), **15c** was obtained in 51% isolated yield (52.2 mg) following ***General procedure A*** as a colourless oil. **15c** was purified by flash chromatography on silica gel using hexane as eluent. Rf (hexane) = 0.15.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.17 (m, 5H), 5.55-5.37 (m, 2H), 3.66 (t, *J* = 6.8 Hz, 2H), 2.49 (tt, *J* = 12.2, 3.3 Hz, 1H), 2.28 (d, *J* = 6.6 Hz, 1H), 2.24 (d, *J* = 6.7 Hz, 1H), 2.07-1.83 (m, 5H), 1.54 (qd, *J* = 12.9, 2.7 Hz, 2H), 1.27 (qd, *J* = 13.2, 3.3 Hz, 2H), 0.93 (s, 9H), 0.10 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.7 (C), 138.1 (C), 128.2 (CH), 126.8 (CH), 125.9 (CH), 124.2 (CH), 63.4 (CH_2), 44.1 (CH), 40.5 (CH), 36.4 (CH_2), 34.0 (CH_2), 33.3 (CH_2), 26.0 (CH_3), 18.4 (C), -5.2 (CH_3) ppm. HRMS(EI): calcd. For $[C_{22}H_{37}OSi]^+$: 345.2608, found: 345.2614.

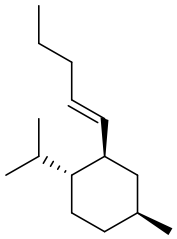
((*E*)-3-((1*R*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl)allyl)benzene (**17a**)



From *N*'-((2*R*,5*S*,E)-2-isopropyl-5-methylcyclohexylidene)-4-methylbenzene sulfonohydrazide (96.6 mg, 0.3 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (97.1 mg, 0.6 mmol), **17a** was obtained in 60% isolated yield (46.0 mg) following ***General procedure A*** as a colourless oil. **17a** was purified by flash chromatography on silica gel using hexane as eluent. R_f (hexane) = 0.85.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 7.23-7.18 (m, 3H), 5.55 (dtd, *J* = 15.2, 6.9, 0.7 Hz, 1H), 5.33 (ddt, *J* = 15.1, 9.1, 1.4 Hz, 1H), 1.95 (m, 2H), 1.97-1.90 (m, 2H), 1.77-1.72 (m, 1H), 1.67-1.62 (m, 2H), 1.43-1.35 (m, 1H), 1.06-0.97 (m, 2H), 0.93-0.85 (m, 8H), 0.74 (d, *J* = 6.9 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.2 (C), 137.1 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 125.8 (CH), 47.2 (CH), 44.6 (CH), 43.4 (CH), 39.0 (CH), 35.2 (CH_2), 32.5 (CH_2), 28.0 (CH_2), 24.1 (CH_2), 22.6 (CH_3), 21.4 (CH_3), 15.3 (CH_3) ppm. HRMS(EI): calcd. For $[C_{19}H_{28}]^+$: 256.2185, found: 256.2189. $[\alpha]_D^{23}$ = -82.9º (c = 0.11).

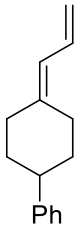
(1*R*,2*R*,4*S*)-1-Isopropyl-4-methyl-2-((*E*)-pent-1-en-1-yl)cyclohexane (**17b**)



From *N*'-((2R,5S,E)-2-isopropyl-5-methylcyclohexylidene)-4-methylbenzene sulfonohydrazide (96.6 mg, 0.3 mmol) and *trans*-1-penten-1-ylboronic acid (68.3 mg, 0.6 mmol), **17b** was obtained in 56% isolated yield (35 mg) following ***General procedure A*** as a colourless oil. **17b** was purified by flash chromatography on silica gel using hexane as eluent. R*f* (hexane) = 0.90.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.18 (dd, *J* = 15.1, 9.0 Hz, 1H), 2.04-1.55 (m, 8H), 1.46-1.28 (m, 3H), 1.00-0.80 (m, 12H), 0.72 (d, *J* = 6.9 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.5 (CH), 129.0 (CH), 47.2 (CH), 44.6 (CH), 43.6 (CH), 35.3 (CH), 34.7 (CH_2), 32.5 (CH_2), 27.9 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 21.5 (CH_3), 15.2 (CH_3), 13.6 (CH_3) ppm. HRMS(EI): calcd. For $[C_{15}H_{23}]^+$: 208.2191, found: 208.2185. $[\alpha]_D^{20}$ = -70.0º (c = 0.11).

(4-allylidenecyclohexyl)benzene (**23**)



From 4-methyl-*N*'-(4-phenylcyclohexylidene)benzenesulfonohydrazide (34.2 mg, 0.1 mmol) and (*E*)-(3-methoxyprop-1-en-1-yl)boronic acid (34.7mg, 0.3 mmol), **23** was obtained in 42% isolated yield (8.0 mg) following ***General procedure A*** as a colourless oil. **23** 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) = 0.80.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.26 (m, 2H), 7.24-7.17 (m, 3H), 6.68 (dt, *J* = 16.8, 10.6 Hz, 1H), 5.91 (d, *J* = 11.0 Hz, 1H), 5.18 (dd, *J* = 16.9, 2.1 Hz, 1H), 5.04 (dd, *J* = 10.2, 2.1 Hz, 1H), 3.10-2.90 (m, 1H), 2.75 (tt, *J* = 12.3, 3.4 Hz, 1H), 2.44-2.25 (m, 2H), 2.11-1.93 (m, 3H), 1.70-1.49 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.6 (C), 142.5 (C), 132.6 (CH), 128.3, 126.8 (CH), 126.0 (CH), 123.3 (CH), 115.0 (CH_2), 44.6 (CH), 36.9 (CH_2), 35.6 (CH_2), 34.8 (CH_2), 28.9 (CH_2). HRMS(EI): calcd. For $[C_{15}H_{18}]^{+}$: 198.1410, found: 198.1409.

E.2.3. Stereochemical assignment of the 1,4-disubstituted cyclohexane 15a

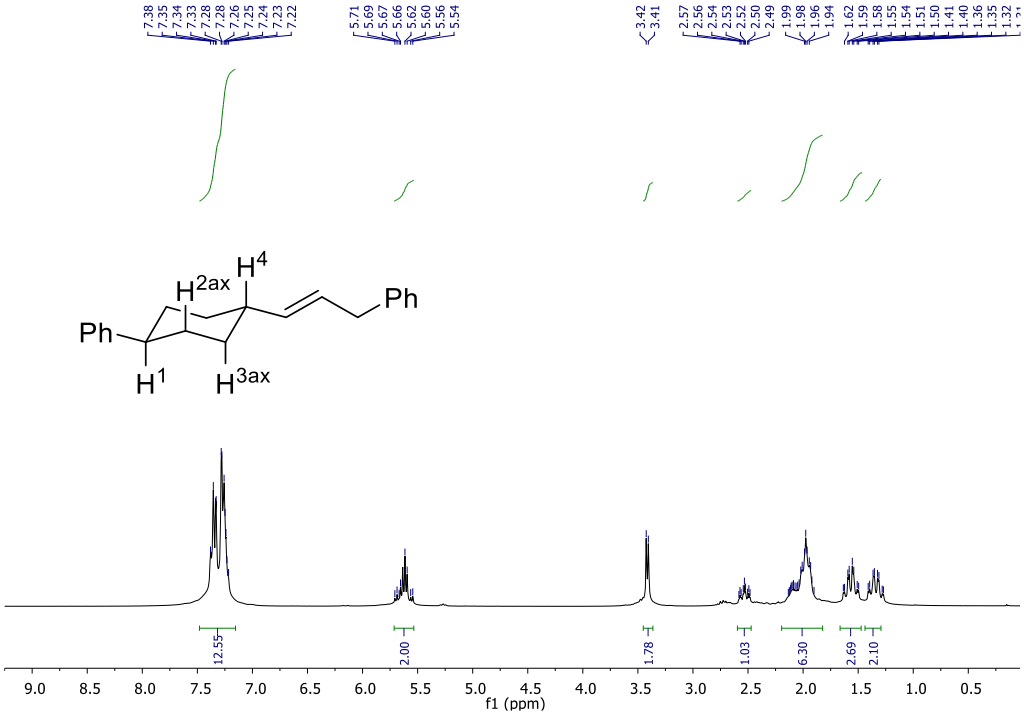


Figure E.1. ^{1}H-NMR spectra of compound **15a**.

The stereochemical assignment of **15a** was based on the analysis of its ^{1}H NMR spectra (300 MHz, $CDCl_3$).

The signal that appears at 2.53 ppm as a tt corresponds to H^1 ($^{3}J_{H1\text{-}H2eq}$= 3.3 Hz, $^{3}J_{H1\text{-}H2ax}$=12.0 Hz).

The signal for H^{2ax} is shown at 1.34 ppm as a qd ($^{3}J_{H2ax\text{-}H3eq}$= 3.0 Hz, $^{3}J_{H1\text{-}H2ax}$=$^{3}J_{H2ax\text{-}H3ax}$ =$^{2}J_{H2eq\text{-}H2ax}$ = 12.2 Hz), determining the axial disposition of H^1 and therefore the equatorial arrangement of the phenyl ring.

The signal for H^{3ax} is set also as a qd ($^{3}J_{H3ax\text{-}H2eq}$= 2.7 Hz, $^{3}J_{H4\text{-}H3ax}$=$^{3}J_{H2ax\text{-}H3ax}$ =$^{2}J_{H3eq\text{-}H3ax}$ = 12.3 Hz) and establishes the axial arrangement of H^4 and therefore the equatorial disposition of the alkenyl substituent.

E.2.4. Stereochemical assignment of the 1,3-disubstituted cyclohexane 13c

The stereochemical assignment of **13c** was based on the analysis of its ^{1}H NMR spectra (400 MHz, $CDCl_3$). The signal that appears at 3.06 ppm as a tt corresponds to H^3 ($^{3}J_{H3\text{-}H2ax} = {}^{3}J_{H3\text{-}H4ax}$ = 12.1 Hz, $^{3}J_{H3\text{-}H2eq} = {}^{3}J_{H3\text{-}H4eq}$ = 3.1 Hz), determining the axial arrangement of H^3 and the equatorial arrangement of the phenyl ring.

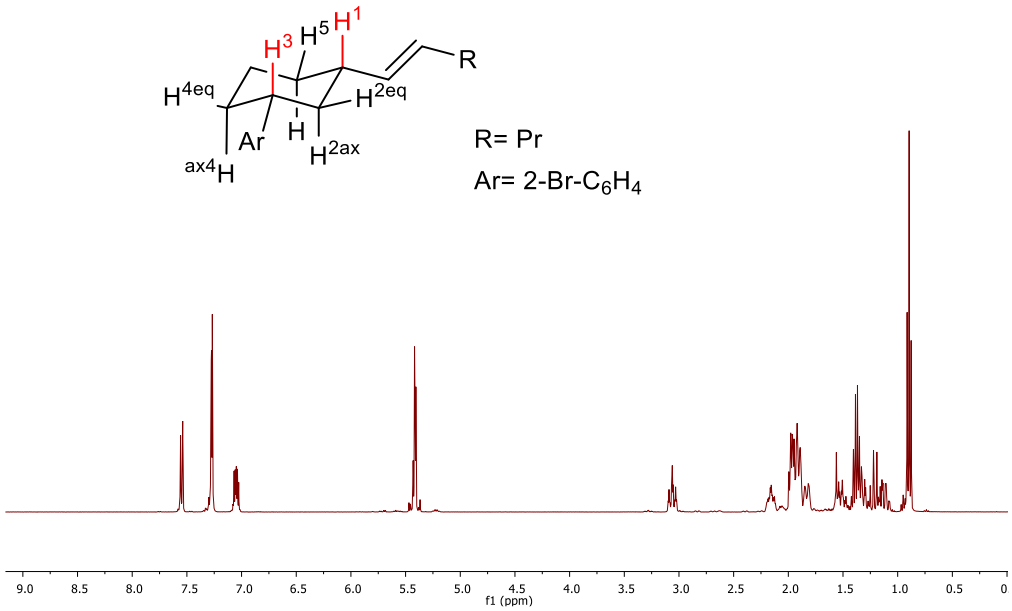


Figure E.2. ^{1}H-NMR spectra of compound **13c**.

In order to determine the stereochemical arrangement of H^1, an Homo-Decoupling experiment was carried out over the olefinic protons. Saturation of the signal at 5.48 ppm led to the simplification of the multiplicity of the signal at 2.16 ppm, which corresponds to H^1 (Figure E.3). In the Homo-Decoupling experiment, the signal at 2.16 ppm appears as tt ($^{3}J_{H1\text{-}H5ax} = {}^{3}J_{H1\text{-}H2ax}$ = 11.7 Hz, $^{3}J_{H1\text{-}H2eq} = {}^{3}J_{H1\text{-}H5eq}$ = 3.4 Hz), establishing the axial arrangement of H^1 and therefore the equatorial disposition of the alkenyl substituent.

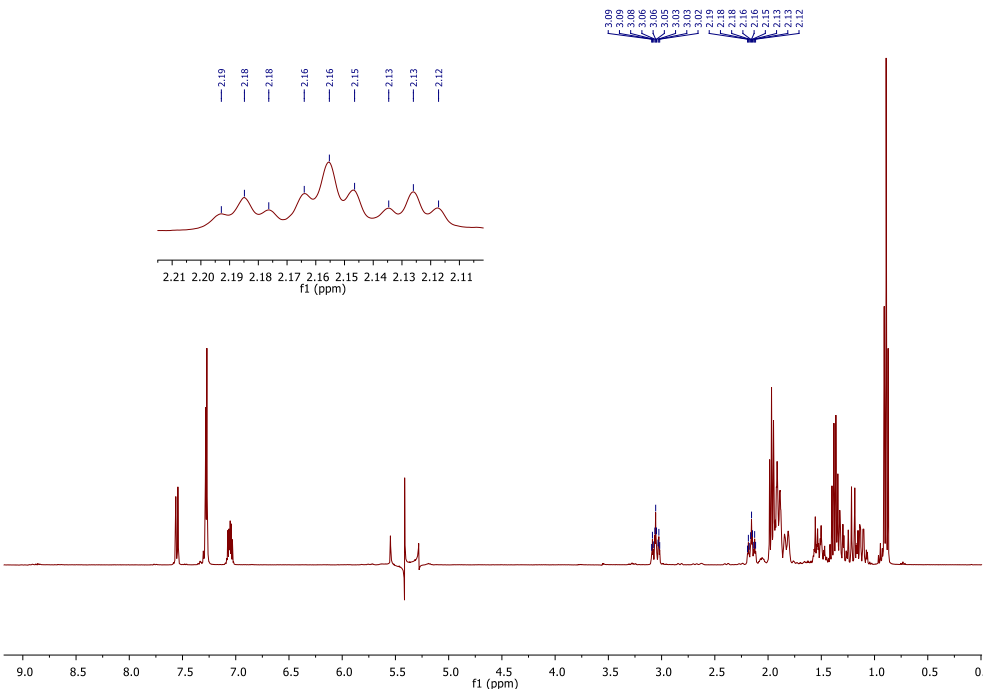


Figure E.3. Homo-Decoupling experiment saturating the signal at 5.58 ppm.

E.2.5. Stereochemical assignment of the 1,2-disubstituted piperidine 7c

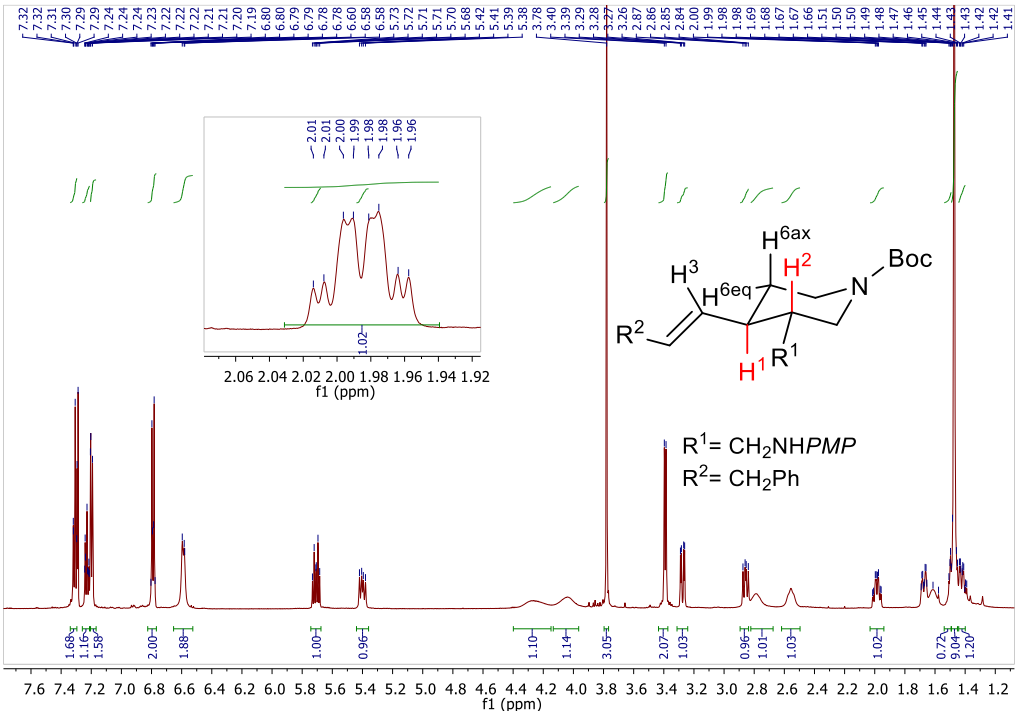


Figure E.4. ^{1}H-NMR spectra of compound **7c**.

The stereochemical assignment of **7c** was based on the analysis of its ^{1}H NMR spectra (600 MHz, $CDCl_3$).

The signal that appears at 1.99 ppm corresponds to H^1 and features the multiplicity pattern of a qd ($^{3}J_{H1\text{-}H2} \approx {}^{3}J_{H1\text{-}H6ax} \approx {}^{3}J_{H1\text{-}H3} \approx 10.6$ Hz, $^{3}J_{H1\text{-}H6eq} = 3.7$ Hz).

The presence of three large coupling constants unambiguously indicates the existence of two characteristic H^{axial}-H^{axial} couplings (H^1-H^{6ax} and H^1-H^2), thus H^1 and H^2 must be both in axial positions, and therefore R^1 and the alkenyl group equatorial arrangement.

E.2.6. Stereochemical assignment of the 1,2,5-trisubstituted cyclohexane 17a

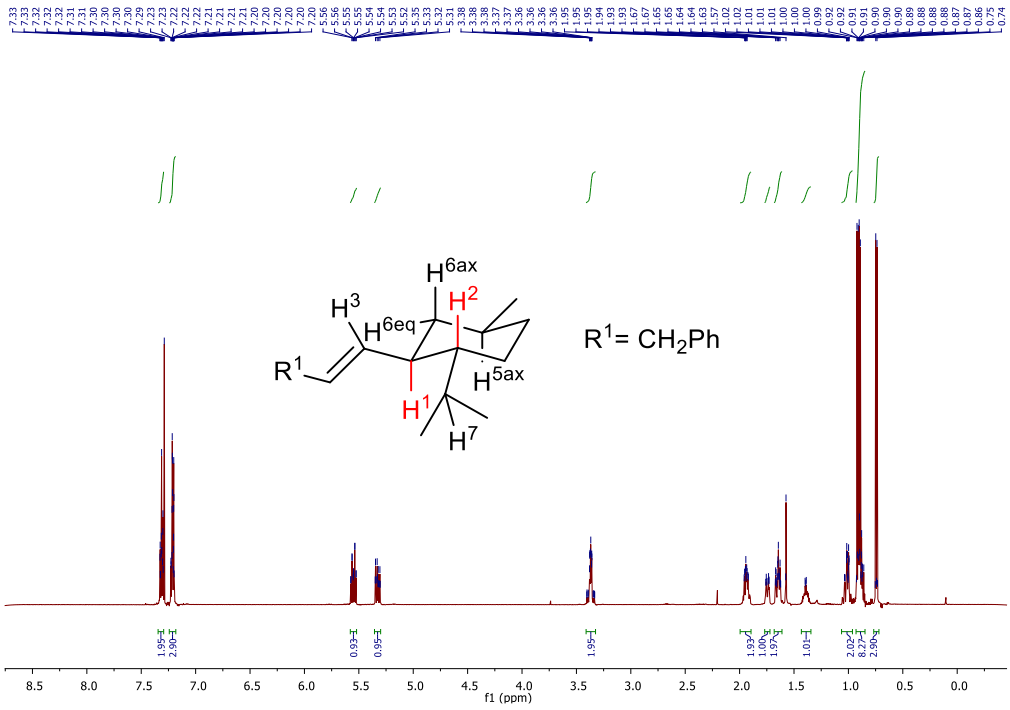


Figure E.5. ^{1}H-NMR spectra of compound **17a**.

The stereochemical assignment of **17a** was based on the analysis of its ^{1}H NMR spectra (600 MHz, $CDCl_3$) and a selective TOCSY experiment.

Analogously to the previous cases, an analysis of H^1 would determine the stereochemistry of this compound. However, the signal corresponding to this hydrogen is overlapped in the range 2.00-1.90 ppm with the signal corresponding to H^7. To address this issue, the signal at 1.38 ppm corresponds to H^{5ax}, was saturated through a selective TOCSY (Figure E.6) using a short-mixing time (the overlapping of the signals of protons H^1 and H^7 is avoided) in order to analyze the signal corresponding to H^1.

The new signal which appears at 1.93 ppm corresponds to H^1 and features the multiplicity pattern of a qd ($^{3}J_{H1\text{-}H2} \approx {}^{3}J_{H1\text{-}H6ax} \approx {}^{3}J_{H1\text{-}H3} \approx 10.8$ Hz, $^{3}J_{H1\text{-}H6eq} = 2.7$ Hz).

The presence of three large coupling constants unambiguously indicates the existence of two characteristic H^{axial}-H^{axial} couplings (H^1-H^{6ax} and H^1-H^2), thus H^1 and

H^2 must be both in axial positions, and therefore R^1 and the alkenyl group in the equatorial positions.

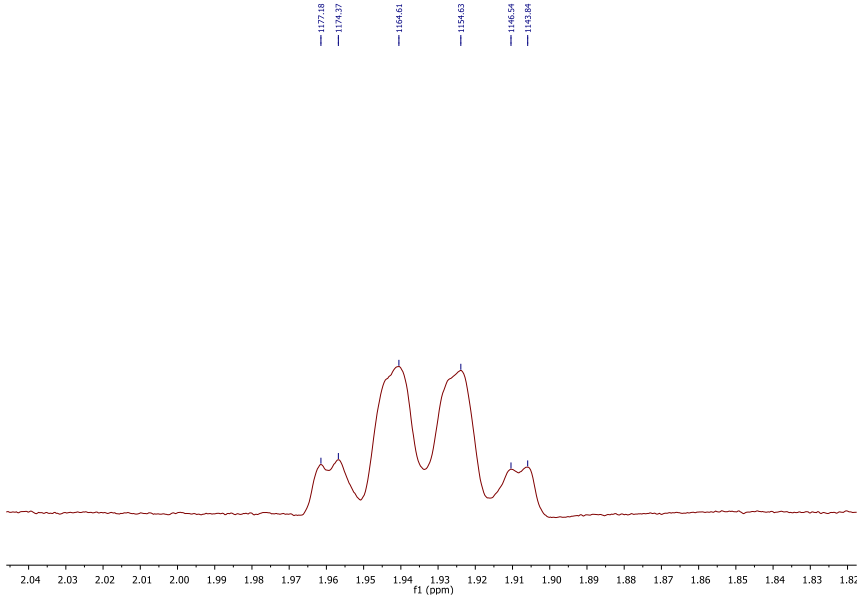


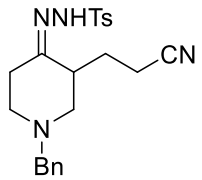
Figure E.6. Expansion of the selective TOCSY experiment upon saturation of the signal of H^{5ax} at 1.38 ppm.

E.3. Chapter 2. Part A: Synthesis of the carbocyclization products

E.3.1. Synthesis of the starting materials and characterization data

Alkenylboronic acids **3c, 3d, 3f** and **3g** were synthesized starting from the commercially available alkenylboronic esters following a procedure found in literature.[95]

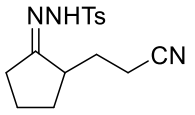
N'-(1-Benzyl-3-(2-cyanoethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (**31**)



Tosylhydrazone **31** was prepared through previously described methodologies indicated in section **E.1**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.42-7.37 (m, 5H), 3.70-3.55 (2H), 2.82-2.65 (2H), 2.64-2.50 (m, 3H), 2.45 (s, 3H), 2.40-2.25 (m, 3H), 2.10-1.95 (m, 3H), 1.65-1.50 (1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.4 (C), 134.8 (C), 129.6 (CH), 129.1 (CH), 128.5 (CH), 128.2 (CH), 119.62 (C), 61.8 (CH_2), 57.8 (CH_2), 51.1 (CH_2), 41.6 (CH), 25.9 (CH_2), 25.8 (CH_2), 21.6 (CH_3), 14.7 (CH_2). m.p.=169.0-170.5 ºC**.**

N'-(2-(2-Cyanoethyl)cyclopentylidene)-4-methylbenzenesulfonohydrazide (**32**)

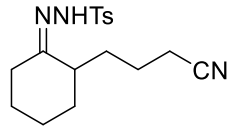


[95] Kontokosta, D.; Mueller, D. S.; Wang, H.; Anderson. L. L. *Org. Lett.* **2013**, *15*, 4830.

Tosylhydrazone **32** was prepared through previously described methodologies indicated in section **E.1**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 2.45 (s, 2H), 2.40.2.20 (m, 4H), 2.15-2.05 (m, 1H), 1.95-1.30 (m, H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.3 (C), 134.9 (C), 129.6 (CH), 128.4 (C), 128.1 (CH), 119.6 (C), 43.3 (CH), 33.3 (CH_2), 30.3 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 23.5 (CH_2), 22.9 (CH_2), 21.6 (CH_3), 17.1 (CH_2). m.p.=117.9-119.1 ºC.

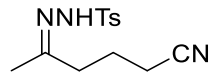
N'-(2-(3-Cyanopropyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (**36**)



Tosylhydrazone **36** was prepared through previously described methodologies indicated in section **E.1**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 2.44 (s, 3H), 2.21 (t, *J* = 6.7 Hz, 2H), 2.05-1.30 (m, 13H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.7 (C), 144.2 (C), 135.1 (C), 129.5 (CH), 128.1 (CH), 119.7 (C), 43.4 (CH), 33.4 (CH_2), 30.2 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 23.8 (CH_2), 22.9 (CH_2), 21.6 (CH_3), 17.1 (CH_2). m.p.=118.5-119.7 ºC.

N'-(5-Cyanopentan-2-ylidene)-4-methylbenzenesulfonohydrazide (**37**)

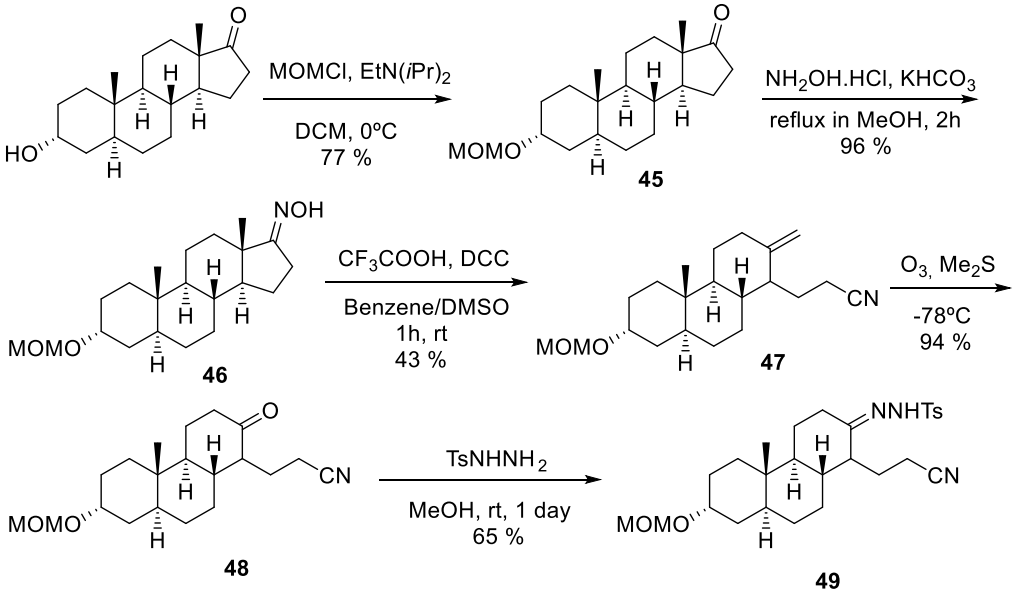


Tosylhydrazone **37** was prepared through previously described methodologies indicated in section **E.1**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.60 (bs, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H), 2.36 (t, *J* = 6.8 Hz, 2H), 2.25 (t, *J* = 7.1 Hz, 2H), 1.97-1.83 (m, 2H), 1.81 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.4 (C), 144.3 (C), 135.1 (C), 129.6 (CH), 128.1 (CH), 119.4 (C), 36.4 (CH_2), 21.6 (CH_2), 21.1 (CH_3), 16.3 (CH_2), 16.0 (CH_3). m.p.=107.5-109.0 ºC.

E.3.1.1. General procedure for the preparation of tosylhydrazone 49.

N-Tosylhydrazone **49** was prepared following previously described procedures found in literature for similar compounds.[96] The synthetic pathway is outlined in Scheme E.1.



Scheme E.1. Synthesis of tosylhydrazone **49**.

(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-3-(Methoxymethoxy)-10,13-dimethylhexadecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (**45**): Chloromethyl methyl ether (1.71 mL, 20 mmol) was added dropwise over 20 minutes to a stirred solution of androsterone (4.85g, 16.7 mmol) and diisipropylehtylamine (6.05 mL, 33.4 mmol) in dichloromethane (34 mL) at 0 ºC. The reaction was allowed to reach room temperature and the stirring was maintained for 12 h. The reaction solution was poured into brine (50 mL). The combined organic solvents were washed with 0.5 N HCl (2x30 mL), brine (2x30 mL) and water (2x30 mL). Solvent removal gave an oil which was purified by flash chromatography in a mixture 10:1 Hexane/EtOAc to yield **45** as colourless crystals (77%, 4.27 g). R_f (hexanes/ethyl acetate 10:1) = 0.15.

[96] (a) Jiang, X.; Wang, C.; Hu, Y.; Hu. H. *J. Org. Chem*. **2000**, *65*, 3555. (b) Han, M.; Covey. D. F. *J. Org. Chem*. **1996**, *61*, 7614.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65-4.60 (m, 2H), 3.85-3.78 (m, 1H), 3.37-3.20 (m, 3H), 2.47-2.35 (m, 1H), 2.10-1.85 (m, 2H), 1.82-1.60 (m, 4H), 1.59-1.35 (m, 8H), 1.34-1.10 (m, 8H), 1.09-0.91 (m, 1H), 0.90-0.70 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.3 (C), 94.5 (CH_2), 71.4 (CH_3), 55.1 (CH), 54.3 (CH), 51.4 (CH), 47.7 (C), 39.7 (CH), 35.9 (C), 35.8 (CH_2), 35.0 (CH), 33.6 (CH_2), 32.7 (CH_2), 31.5 (CH_2), 30.7 (CH_2), 28.2 (CH_2), 26.2 (CH_2), 21.7 (CH_2), 20.0 (CH_2), 13.8 (CH_3), 11.3 (CH_3). m.p.= 120.8-121.2 ºC. $[\alpha]_D^{25}$ = 93.0º (*c* = 0.08).

(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-3-(Methoxymethoxy)-10,13-dimethylhexadecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one oxime (**46**): Compound **45** (4.27g, 12.8 mmol) was added to a stirred mixture of $KHCO_3$ (4.43g, 44.2 mmol) and $NH_2OH{\cdot}HCl$ (3.06, 44.2 mmol) in methanol (42 mL). After cooling to room temperature, the reaction solution was poured into brine (50 mL). The combined organic solvents were washed with 0.5 M HCl (2x30 mL), brine (2x30 mL) and water (2x30 mL). Solvent removal gave a solid which was purified by flash chromatography in a mixture 2:1 Hexane/EtOAc to yield **46** as colourless crystals (96%, 4.09 g). R_f (hexanes/ethyl acetate 2:1) = 0.45.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70-4.65 (m, 2H), 3.85-3.79 (m, 1H), 3.37-3.20 (s, 3H), 2.55-2.45 (m, 1H), 1.95-0.95 (m, 21H), 0.90 (s, 3H), 0.81 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0 (C), 94.4 (CH_2), 71.5 (CH_3), 55.1 (CH), 54.4 (CH), 53.8 (CH), 44.0 (C), 39.7 (CH), 35.9 (C), 34.8 (CH_2), 34.0 (C), 33.6 (CH_2), 32.7 (CH_2), 31.4 (CH_2), 28.3 (CH_2), 26.2 (CH_2), 25.0 (CH_2), 23.1 (CH_2), 20.2 (CH_2), 17.1 (CH_3), 11.3 (CH_3). m.p.= 107.7-108.8 ºC. $[\alpha]_D^{25}$ = 95.2º (*c* = 0.12).

3-((4*aS*,4*bS*,7*R*,8*aS*,10*aS*)-7-(Methoxymethoxy)-4*b*-methyl-2-methylenetetradecahydro phenanthren-1-yl)propanenitrile (**47**): Trifluoroacetic acid (0.61 mL, 8.15 mmol) was added dropwise to a stirred solution of oxime **46** (4.09 g, 11.71 mmol) and DCC (7.24g, 35.12 mmol) dissolved in DMSO (20 mL) and benzene (20 mL) under N_2 at room temperature. After 1 h, the reaction mixture was poured into brine (50 mL) and extracted with EtOAc (3x50 mL). The combined organic solvents were washed with a satured solution of $NaHCO_3$ (50 mL), brine (2x50 mL). Solvent removal gave an oil which was purified by flash chromatography in a mixture 60:35:5 Hexane/$CHCl_3$/EtOAC (to yield **47** as a colourless oil (43%, 1.68 g). R_f (60:35:5 Hexane/$CHCl_3$/EtOAC) = 0.20.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 1H), 4.55 (s, 2H), 4.38 (s, 1H), 3.73 (s, 1H), 3.27 (s, 3H), 2.45-0.90 (m, 19H), 0.63 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.8 (C), 120.0 (C), 104.7 (CH_2), 94.4 (CH_2), 71.2 (CH_3), 54.9 (CH), 53.1 (CH), 47.7 (CH), 41.9 (CH), 38.8 (CH), 36.7 (CH_2), 36.0 (C), 33.3 (CH_2), 32.6 (CH_2), 31.4 (CH_2), 28.2 (CH_2), 27.2 (CH_2), 26.2 (CH_2), 23.6 (CH_2), 14.6 (CH_2), 11.1 (CH_3). $[\alpha]_D^{24}$ = 21.8 º (*c* = 0.07).

3-((4*aS*,4*bS*,7*R*,8*aS*,10*aR*)-7-(Methoxymethoxy)-4*b*-methyl-2-oxotetradecahydro phenanthren-1-yl)propanenitrile (**48**): Ozone was passed through a solution of compound **47** (1.68g, 5.07 mmol) in methanol (32 mL) and dichloromethane (3.6 mL) at -78ºC until a blue colour persisted. The excess ozone was removed by a stream of oxygen. After dimethyl sulfide was added (1.9 mL), the mixture was allowed to reach room temperature and was stirred for 1 h. The solvent was removed, giving an oil which was purified by flash chromatography in a mixture 2:1 Hexane/EtOAc to yield **48** as a colourless oil (94%, 1.58 g). R_f (hexanes/ethyl acetate 2:1) = 0.45.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (d, *J*= 6.9H, 1H), 4.65 (d, *J*= 6.9H, 1H), 3.87-3.83 (m, 1H), 3.37 (s, 3H), 2.50-1.10 (m, 22H), 0.73 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.7 (C), 120.0 (C), 94.5 (CH_2), 71.3 (CH), 55.2 (CH), 54.3 (CH), 52.2 (CH), 42.6 (CH), 41.8 (CH_2), 38.8 (CH), 36.2 (CH_2), 33.1 (CH_2), 32.8 (CH_2), 32.1 (CH_2), 28.0 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 21.7 (CH_2), 15.1 (CH_2), 11.1 (CH_3). $[\alpha]_D^{24}$ = 0.9º (*c* = 0.07).

N'-((4*aS*,4*bS*,7*R*,8*aS*,10*aR*)-1-(2-Cyanoethyl)-7-(methoxymethoxy)-4*b*-methyldodecahy drophenanthren-2(1*H*)-ylidene)-4-methylbenzenesulfonohydrazide (**49**): Compound **48** (1.58 g, 4.76 mmol) was added to a stirred solution of *p*-toluensulfonylhydrazide (0.98g, 5.31 mmol) in MeOH (3 mL). The reaction was stirred for 1 day until total consumption of the starting carbonyl. Then, the solvent was eliminated, giving a colourless solid which was purified by flash chromatography in a mixture 1:1 Hexane/EtOAc to yield **49** as colourless crystals (65%, 1.54 g). R_f (hexanes/ethyl acetate 1:1) = 0.65.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.60 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 4.66 (s, 2H), 3.84 (s, 1H), 3.37 (s, 3H), 2.74 (d, *J* = 13.0 Hz, 1H), 2.46 (s, 3H), 2.25-2.15 (m, 2H), 2.06 (s, 1H), 2.00-1.00 (m, 18H), 0.68 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.1 (C), 144.4 (C), 134.9 (C), 129.73 (CH), 128.2 (CH), 120.3 (C), 94.5 (CH_2), 71.2 (CH_3), 60.4 (C), 55.2 (CH), 52.4 (CH), 48.8 (CH), 41.5 (CH), 38.8 (CH), 36.1 (C), 33.2 (CH_2), 32.7 (CH_2), 31.5 (CH_2), 28.0 (CH_2), 27.1 (CH_2), 26.2 (CH_2), 24.9 (CH_2), 22.6 (CH_2), 21.6 (CH_3), 14.2 (CH_2), 11.1 (CH_3). m.p.= 71.8-73.2 ºC. $[\alpha]_D^{25}$ = 21.3º (c = 0.18).

E.3.2. General procedures for the synthesis of the carbocyclization products and characterization data

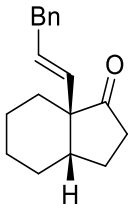
General procedure (**A**) for the carbocyclization reaction of *N*-tosylhydrazones with alkenyl boronic acids under microwave irradiation to form compounds **29**, **33**, **34**, **36**, **38**, **42** and **57**: A microwave vial provided with a triangular stir bar was charged with the tosylhydrazone (0.3 mmol), the alkenyl boronic acid (0.6 mmol) and K_2CO_3 (82.9 mg, 0.6 mmol) in 2.4 mL of dry 1,4-dioxane. The vial was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at the desired temperature (120 ºC) during the reaction time (4h) in a Biotage Initiator microwave apparatus. Once the reaction finished, it was allowed to reach room temperature, and the solvents were eliminated under reduced pressure. A saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (5 mL) were added and the layers were separated. The aqueous phase was extracted three times with dichloromethane (3x5mL). The combined organic layers were washed with $NaHCO_3$, brine, dried over Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Finally, the products were purified by flash chromatography on silica gel.

General procedure (**B**) for the carbocyclization reaction of *N*-tosylhydrazones with alkenyl boronic acids under microwave irradiation to form androsterone derivatives **50**: A microwave vial provided with a triangular stir bar was charged with the tosylhydrazone **49** (0.3 mmol), the alkenyl boronic acid (0.6 mmol), K_2CO_3 (82.9 mg, 0.6 mmol) in 2.4 mL of dry 1,4-dioxane. The vial was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at the desired temperature (120 ºC) during the reaction time (10h) in a Biotage Initiator microwave apparatus. When the reaction finished, it was allowed to reach room temperature, solvents were eliminated and a saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (5 mL) 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 Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Finally, the products were purified by flash chromatography on silica gel.

General procedure (**C**) for the carbocyclization/reduction sequence from *N*-tosylhydrazones and alkenyl boronic acids to form compounds **44**: A microwave vial provided with a triangular stir bar was charged with the tosylhydrazone (0.15 mmol),

the alkenyl boronic acid (0.3 mmol), K_2CO_3 (41.4 mg, 0.3 mmol) in 1.2 mL of dry 1,4-dioxane. The vial was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at the desired temperature (120 ºC) during the reaction time (4h) in a Biotage Initiator microwave apparatus. When the reaction finished, the vial was released from the microwave cavity, cooled to room temperature and then $NaBH_4$ (22.6 mg, 0.6 mmol) was added. After stirring for 1 hour at room temperature, water (5 mL) was added. A saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (5 mL) 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 Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Finally, the products were purified by flash chromatography on silica gel.

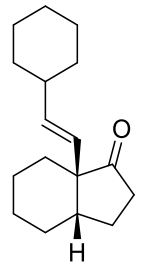
(3*aS**,7*aS**)-7*a*-((*E*)-3-Phenylprop-1-en-1-yl)octahydro-1*H*-inden-1-one (**29a**)



From *N*'-(2-(2-Cyanoethyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (95.8 mg, 0.3 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (97.1 mg, 0.6 mmol), **29a** was obtained in 65% isolated yield (49.0 mg) following ***General procedure A*** as a colourless oil. **29a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.27.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (m, 2H), 7.24-7.14 (m, 3H), 5.63 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.46 (d, *J* = 15.7 Hz, 1H), 3.39 (d, *J* = 6.7 Hz, 2H), 2.40-2.17 (m, 3H), 2.07-1.95 (m, 1H), 1.85-1.15 (m, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.4 (C), 140.2 (C), 133.7 (CH), 129.9 (CH), 128.4 (CH), 128.4 (CH), 126.0 (CH), 55.2 (C), 41.2 (CH), 39.1 (CH_2), 34.9 (CH_2), 29.8 (CH_2), 27.4 (CH_2), 23.5 (CH_2), 22.9 (CH_2), 22.5 (CH_2). HRMS(ESI): calcd. For $[C_{18}H_{22}O]^+$: 254.1671, found: 254.1671.

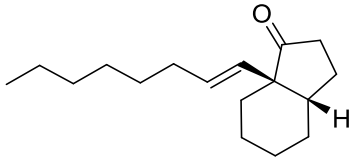
(3*aS**,7*aS**)-7*a*-((*E*)-2-Cyclohexylvinyl)octahydro-1*H*-inden-1-one (**29b**)



From *N*'-(2-(2-Cyanoethyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (47.9 mg, 0.15 mmol) and (*E*)-(2-cyclohexylvinyl)boronic acid (46.2 mg, 0.3 mmol), **29b** was obtained in 51% isolated yield (18.5 mg) following ***General procedure A*** as a colourless oil. **29b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 40:1 as eluent. R_f (hexanes/ethyl acetate 40:1) = 0.20.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (dd, *J* = 16.0, 6.2 Hz, 1H), 5.27 (d, *J* = 16.2 Hz, 1H), 2.35-2.22 (m, 2H), 2.20-2.10 (m, 1H), 1.85-1.40 (m, 11H), 1.35-0.80 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.8 (C), 137.2 (CH), 129.7 (CH), 55.1 (C), 41.3 (CH), 40.8 (CH), 34.7 (CH_2), 33.0 (CH_2), 32.9 (CH_2), 30.2 (CH_2), 27.7 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 23.5 (CH_2), 23.3 (CH_2), 22.6 (CH_2). HRMS(ESI): calcd. For $[C_{17}H_{26}O]^+$: 246.1984, found: 246.1975.

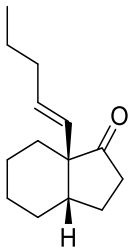
(3*aS**,7*aS**)-7*a*-((*E*)-Oct-1-en-1-yl)octahydro-1*H*-inden-1-one (**29c**)



From (*N*'-(2-(2-Cyanoethyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (47.9 mg, 0.15 mmol) and *trans*-1-octen-1-yl-boronic acid (46.8 mg, 0.3 mmol), **29c** was obtained in 75% isolated yield (28.0 mg) following ***General procedure A*** as a colourless oil. **29c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 30:1 as eluent. R_f (hexanes/ethyl acetate 40:1) = 0.47.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (dt, *J* = 15.7, 6.4 Hz, 1H), 5.31 (d, *J* = 15.9 Hz, 1H), 2.35-2.25 (m, 2H), 2.22-2.13 (m, 1H), 2.07-1.95 (m, 3H), 1.85-1.40 (m, 1H), 1.39-1.12 (12H), 0.89 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.7 (C), 132.1 (CH), 131.6 (CH), 55.2 (C), 41.4 (CH), 34.7 (CH_2), 32.7 (CH_2), 31.6 (CH_2), 30.1 (CH_2), 29.2 (CH_2), 28.7 (CH_2), 27. (CH_2), 23.5 (CH_2), 23.2 (CH_2), 22.6 (CH_2), 14.0 (CH_3). HRMS(ESI): calcd. For $[C_{17}H_{28}O]^+$: 248.2140, found: 248.2139.

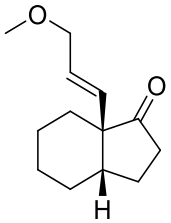
(3*aS**,7*aS**)-7*a*-((*E*)-Pent-1-en-1-yl)octahydro-1*H*-inden-1-one (**29d**)



From *N*'-(2-(2-Cyanoethyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (47.9 mg, 0.15 mmol) and *trans*-1-penten-1-yl-boronic acid (38.4 mg, 0.3 mmol), **29d** was obtained in 58% isolated yield (17.9 mg) following ***General procedure A*** as a colourless oil. **29d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 30:1 as eluent. R_f (hexanes/ethyl acetate 30:1) = 0.45.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (dt, *J* = 15.8, 6.3 Hz, 1H), 5.31 (d, *J* = 16.0 Hz, 1H), 2.31-2.23 (m, 2H), 2.21-2.12 (m, 1H), 2.09-1.95 (m, 3H), 1.85-1.10 (m, 11H), 0.87 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.7 (C), 132.4 (CH), 131.3 (CH), 55.2 (C), 41.4 (CH), 34.8 (CH_2), 34.7 (CH_2), 30.1 (CH_2), 27.6 (CH_2), 23.5 (CH_2), 23.2 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 13.5 (CH_3). HRMS(ESI): calcd. For $[C_{14}H_{22}O]^+$: 206.1671, found: 206.1678.

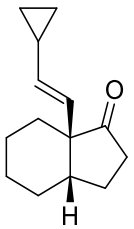
(3*aS**,7*aS**)-7*a*-((*E*)-3-Methoxyprop-1-en-1-yl)octahydro-1*H*-inden-1-one (**29e**)



From *N*'-(2-(2-Cyanoethyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (47.9 mg, 0.15 mmol) and (*E*)-(3-methoxyprop-1-en-1-yl)boronic acid (34.7 mg, 0.3 mmol), **29e** was obtained in 61% isolated yield (19.0 mg) following ***General procedure A*** as a colourless oil. **29e** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, *J* = 16.1 Hz, 1H), 5.57 (dt, *J* = 16.0, 5.1 Hz, 1H), 3.92 (d, *J* = 4.7 Hz, 2H), 3.32 (s, 3H), 2.42-2.19 (m, 3H), 2.05-1.92 (m, 1H), 1.85-1.20 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.1 (C), 135.33 (CH), 127.2 (CH), 73.0 (CH_2), 57.8 (C), 54.9 (CH_3), 40.8 (CH), 35.0 (CH_2), 29.5 (CH_2), 27.1 (CH_2), 23.4 (CH_2), 22.7 (CH_2), 22.3 (CH_2). HRMS(ESI): calcd. For $[C_{13}H_{21}O_2]^+$: 208.1463, found: 208.1464.

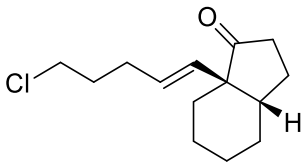
(3*aS**,7*aS**)-7*a*-((*E*)-2-Cyclopropylvinyl)octahydro-1*H*-inden-1-one (**29f**)



From *N*'-(2-(2-Cyanoethyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (31.9 mg, 0.10 mmol) and (*E*)-(2-cyclopropylvinyl)boronic acid (22.3 mg, 0.20 mmol), **29f** was obtained in 70% isolated yield (14.0 mg) following ***General procedure A*** as a colourless oil. **29f** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.48.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (d, *J* = 15.7 Hz, 1H), 4.94 (dd, *J* = 15.8, 8.8 Hz, 1H), 2.35-1.95 (m, 3H), 1.85-1.10 (m, 11H), 0.92-0.85 (m, 1H), 0.74-0.63 (m, 1H), 0.40-0.30 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.6 (C), 135.1 (CH), 129.6 (CH), 55.0 (C), 41.4 (CH), 34.7 (CH_2), 30.1 (CH_2), 27.6 (CH_2), 23.5 (CH_2), 23.2 (CH_2), 22.6 (CH_2), 14.0 (CH), 6.6 (CH_2). HRMS(ESI): calcd. For $[C_{14}H_{21}O]^+$: 205.1586, found: 205.1583.

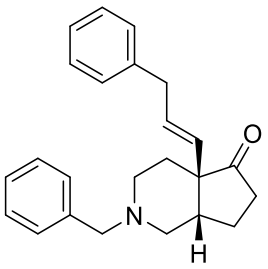
(3*aS**,7*aS**)-7*a*-((*E*)-5-Chloropent-1-en-1-yl)octahydro-1*H*-inden-1-one (**29g**)



From *N*'-(2-(2-Cyanoethyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (31.9 mg, 0.10 mmol) and (*E*)-(5-chloropent-1-en-1-yl)boronic acid (29.6 mg, 0.20 mmol), **29g** was obtained in 90% isolated yield (21.5 mg) following ***General procedure A*** as a yellow oil. **29g** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.30.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47-5-32 (m, 2H), 3.52 (t, *J* = 6.5 Hz, 2H), 2.40-2.10 (m, 4H), 2.90-1.10 (m, 15H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.4 (C), 133.8 (CH), 129.3 (CH), 55.1 (CH), 44.2 (CH_2), 41.4 (CH_2), 34.8 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 27.4 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 22.5 (CH_2). HRMS(ESI): calcd. For $[C_{14}H_{21}ClNaO]^+$: 263.1173, found: 263.1167.

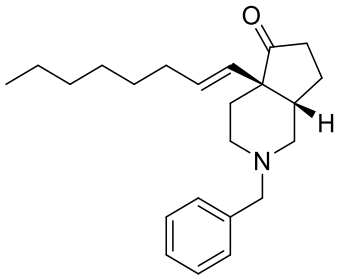
(4*aR**,7*aS**)-2-Benzyl-4*a*-((*E*)-3-phenylprop-1-en-1-yl)octahydro-5*H*-cyclopenta[*c*]pyri din-5-one (**33a**)



From *N*'-(1-Benzyl-3-(2-cyanoethyl)piperidin-4-ylidene)-4-methylbenzenesulfono hydrazide (61.5 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.6 mg, 0.30 mmol), **33a** was obtained in 50% isolated yield (25.3 mg) following ***General procedure A*** as a yellow oil. **33a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. R_f (hexanes/ethyl acetate 5:1) = 0.26.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 6.40 (m, 10H), 5.64 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.44 (d, *J* = 15.9 Hz, 1H), 3.47 (s, 2H), 3.38 (d, *J* = 6.7 Hz, 2H), 2.70 (dd, *J* = 12.2, 5.0 Hz, 1H), 2.55-2.48 (m, 1H), 2.44-2.36 (m, 1H), 2.32 (t, *J* = 7.8 Hz, 2H), 2.12-1.92 (m, 3H), 1.91-1.81 (m, 1H), 1.70-1.51 (m, 1H), 0.95-0.85 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.7 (C), 140.0 (C), 132.6 (C), 130.6 (CH), 129.0 (CH), 128.4 (CH), 128.2 (CH), 127.0 (CH), 126.0 (CH), 63.2 (CH_2), 54.8 (CH_2), 53.6 (C), 50.7 (CH_2), 41.2 (CH), 39.1 (CH_2), 34.9 (CH_2), 29.9 (CH_2), 22.1 (CH_2). HRMS(ESI): calcd. For $[C_{24}H_{28}NO]^+$: 346.2165, found: 346.2165.

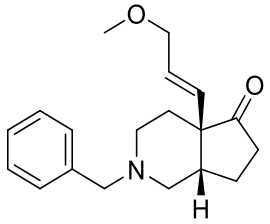
(4*aR**,7*aS**)-2-Benzyl-4a-((*E*)-oct-1-en-1-yl)octahydro-5*H*-cyclopenta[*c*]pyridin-5-one (**33b**)



From *N*'-(1-Benzyl-3-(2-cyanoethyl)piperidin-4-ylidene)-4-methylbenzenesulfono hydrazide (61.5 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (46.8 mg, 0.30 mmol), **33b** was obtained in 50% isolated yield (25.0 mg) following ***General procedure A*** as a yellow oil. **33b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.23.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H), 5.45 (dt, *J* = 15.7, 6.5 Hz, 1H), 5.31 (d, *J* = 15.9 Hz, 1H), 3.46 (d, *J* = 2.7 Hz, 2H), 2.71 (dd, *J* = 12.1, 5.1 Hz, 1H), 2.57-2.45 (m, 1H), 2.41-2.15 (m, 3H), 2.09-1.81 (m, 4H), 1.80-2.68 (m, 1H), 1.65-1.50 (m, 1H), 1.40-1.10 (m, 10H), 0.90 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.0 (C), 138.3 (C), 132.3 (CH), 131.0 (CH), 129.0 (CH), 128.2 (CH), 127.0 (CH), 63.2 (CH_2), 55.0 (CH_2), 53.6 (C), 50.8 (CH_2), 41.3 (CH), 34.8 (CH_2), 32.7 (CH_2), 31.6 (CH_2), 30.0 (CH_2), 29.1 (CH_2), 28.6 (CH_2), 22.6 (CH_2), 22.0 (CH_2), 14.08 (CH_3). HRMS(ESI): calcd. For $[C_{23}H_{34}NO]^+$: 340.2621, found: 340.2633.

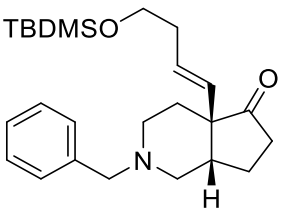
(4*aR**,7*aS**)-2-Benzyl-4*a*-((*E*)-3-methoxyprop-1-en-1-yl)octahydro-5*H*-cyclopenta[*c*]pyridin-5-one (**33c**)



From *N*'-(1-Benzyl-3-(2-cyanoethyl)piperidin-4-ylidene)-4-methylbenzenesulfono hydrazide (61.5 mg, 0.15 mmol) and (*E*)-(3-methoxyprop-1-en-1-yl)boronic acid (34.7 mg, 0.3 mmol), **33c** was obtained in 68% isolated yield (30.0 mg) following ***General procedure A*** as a colourless oil. **33c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 3:1 as eluent. R_f (hexanes/ethyl acetate 3:1) = 0.20.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.19 (m, 5H), 5.71-5.53 (m, 2H), 3.92 (d, *J* = 4.1 Hz, 2H), 3.46 (s, 2H), 3.33 (s, 3H), 2.67 (dd, *J* = 11.6, 4.9 Hz, 1H), 2.55-2.27 (m, 4H), 2.20-1.85 (m, 5H), 1.67-1.55 (m, 1H). **^{13}C NMR (**75 MHz, $CDCl_3$) δ 218.4 (C), 138.3 (C), 134.1 (CH), 128.91 (CH), 128.2 (CH), 127.9 (CH), 127.0 (CH), 72.8 (CH_2), 63.1 (CH_2), 57.8 (CH_3), 54.5 (CH_2), 53.3 (C), 50.5 (CH_2), 41.0 (CH), 35.1 (CH_2), 29.6 (CH_2), 22.1 (CH_2). HRMS(ESI): calcd. For $[C_{19}H_{26}NO_2]^+$: 300.1958, found: 300.1958.

(4*aR**,7*aS**)-2-Benzyl-4*a*-((*E*)-4-((tert-butyldimethylsilyl)oxy)but-1-en-1-yl)octahydro-5*H*-cyclopenta[*c*]pyridin-5-one (**33d**)

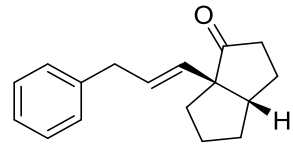


From *N*'-(1-Benzyl-3-(2-cyanoethyl)piperidin-4-ylidene)-4-methylbenzenesulfono hydrazide (61.5 mg, 0.15 mmol) and (*E*)-(4-((tert-butyldimethylsilyl)oxy)but-1-en-1-yl)boronic acid (69.0 mg, 0.3 mmol), **33d** was obtained in 50% isolated yield (31.2 mg) following ***General procedure A*** as a

colourless oil. **33d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H), 5.47 (dt, *J* = 15.9, 5.9 Hz, 1H), 5.39 (d, *J* = 16.0 Hz, 1H), 3.62 (t, *J* = 6.7 Hz, 2H), 3.45 (d, *J* = 2.2 Hz, 2H), 2.69 (dd, *J* = 11.7, 4.9 Hz, 1H), 2.55-2.45 (m, 1H), 2.40-2.20 (m, 5H), 2.09-1.91 (m, 4H), 1.85-1.75 (m, 1H), 1.65-1.52 (1H), 0.90 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.8 (C), 138.3 (C), 133.0 (CH), 128.9 (CH), 128.6 (CH), 128.2 (CH), 127.0 (CH), 63.2 (CH_2), 62.78 (CH_2), 54.8 (CH_2), 53.7 (C), 50.7 (CH_2), 41.2 (CH), 36.4 (CH_2), 34.9 (CH_2), 30.0 (CH_2), 25.9 (CH_3), 22.0 (CH_2), 18.3 (C), -5.2 (CH_3). HRMS(ESI): calcd. For $[C_{25}H_{40}NO_2Si]^+$: 414.2822, found: 414.2803.

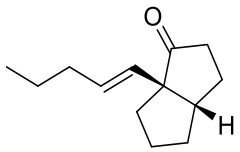
(3*aS**,6*aS**)-6*a*-((*E*)-3-Phenylprop-1-en-1-yl)hexahydropentalen-1(2*H*)-one (**34a**)



From *N*'-(2-(2-Cyanoethyl)cyclopentylidene)-4-methylbenzenesulfonohydrazide (45.8 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.6 mg, 0.30 mmol), **34a** was obtained in 67% isolated yield (24.0 mg) following ***General procedure A*** as a colourless oil. **34a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.46.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.02 (m, 5H), 5.60-5.56 (m, 2H), 3.38 (d, *J* = 4.5 Hz, 2H), 2.66 (ddd, *J* = 12.7, 8.1, 4.9 Hz, 1H), 2.46-2.22 (m, 2H), 2.21-1.85 (m, 3H), 1.82-1.36 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.7 (C), 140.3 (CH), 132.8 (CH), 128.4 (CH), 128.4 (CH), 128.2 (CH), 126.0 (CH), 63.1 (C), 46.8 (CH_2), 39.0 (CH), 37.1 (CH_2), 36.8 (CH_2), 32.9 (CH_2), 25.2 (CH_2), 24.9 (CH_2). HRMS(ESI): calcd. For $[C_{17}H_{20}NaO]^+$: 263.1406, found: 263.1405.

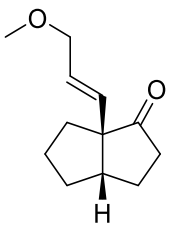
(3*aS**,6*aS**)-6*a*-((*E*)-Pent-1-en-1-yl)hexahydropentalen-1(2*H*)-one (**34b**)



From *N*'-(2-(2-Cyanoethyl)cyclopentylidene)-4-methylbenzenesulfonohydrazide (91.6 mg, 0.30 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (68.3 mg, 0.60 mmol), **34b** was obtained in 70% isolated yield (40.0 mg) following ***General procedure A*** as a colourless oil. **34b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.47.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52-5.37 (m, 2H), 2.66-2.55 (m, 1H), 2.46-2.22 (m, 2H), 2.21 – 1.85 (m, 5H), 1.82 – 1.36 (m, 8H), 0.87 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 222.1 (C), 131.3 (CH), 129.6 (CH), 63.1 (C), 46.9 (CH), 37.0 (CH_2), 36.7 (CH_2), 34.7 (CH_2), 32.8 (CH_2), 25.2 (CH_2), 24.8 (CH_2), 22.4 (CH_2), 13.5 (CH_3). HRMS(ESI): calcd. For $[C_{13}H_{20}NaO]^+$: 215.1406, found: 215.1407.

(3*aS**,6*aS**)-6*a*-((*E*)-3-Methoxyprop-1-en-1-yl)hexahydropentalen-1(2*H*)-one (**34c**)

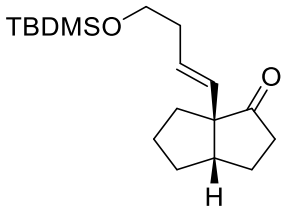


From (*E*)-*N*'-(2-(2-Cyanoethyl)cyclopentylidene)-4-methylbenzenesulfono hydrazide (45.8 mg, 0.15 mmol) and (*E*)-(3-Methoxyprop-1-en-1-yl)boronic acid (34.7 mg, 0.3 mmol), **34c** was obtained in 52% isolated yield (15.0 mg) following ***General procedure A*** as a colourless oil. **34c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 4:1 as eluent. R_f (hexanes/ethyl acetate 4:1) = 0.28.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, *J* = 15.8 Hz, 1H), 5.58 (dt, *J* = 15.8, 5.8 Hz, 1H), 3.90 (dd, *J* = 5.8, 1.4 Hz, 2H), 3.32 (s, 3H), 2.74-2.62 (m, 1H), 2.40.2.31 (m, 2H),

2.20-1.95 (m, 3H), 1.79-1.42 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.2 (C), 134.7 (CH), 125.3 (CH), 72.9 (CH_2), 62.9 (C), 57.9 (CH_2), 46.6 (CH), 37.1 (CH_2), 36.8 (CH_2), 32.9 (CH_2), 25.2 (CH_2), 24.9 (CH_2). HRMS(ESI): calcd. For $[C_{12}H_{18}NaO_2]^+$: 217.1196, found: 217.1196.

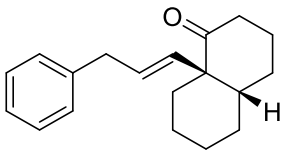
(3*aS**,6*aS**)-6*a*-((*E*)-4-((tert-butyldimethylsilyl)oxy)but-1-en-1-yl)hexahydropentalen-1(2*H*)-one (**34d**)



From *N*'-(2-(2-Cyanoethyl)cyclopentylidene)-4-methylbenzenesulfonohydrazide (91.6 mg, 0.30 mmol) and (*E*)-(4-((tert-butyldimethylsilyl)oxy)but-1-en-1-yl)boronic acid (69.0 mg, 0.3 mmol), **7d** was obtained in 50% isolated yield (46.0 mg) following ***General procedure A*** as a colourless oil. **7d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.36.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (d, *J* = 15.9 Hz, 1H), 5.45 (dt, *J* = 15.7, 6.4 Hz, 1H), 3.62 (t, *J* = 6.7 Hz, 2H), 2.69-2.57 (m, 1H), 2.39-1.40 (m, 7H), 1.75-1.40 (m, 5H), 0.9 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.8 (C), 133.1 (CH), 126.0 (CH), 63.2 (C), 62.9 (CH_2), 46.7 (CH), 37.0 (C), 36.8 (CH_2), 36.2 (CH_2), 32.9 (CH_2), 25.9 (CH_3), 25.2 (CH_2), 24.8 (CH_2), 18.3 (CH_2), -5.2 (CH_3). HRMS(ESI): calcd. For $[C_{18}H_{32}NaO_2Si]^+$: 331.2063, found: 331.2065.

(4*aS**,8*aS**)-8*a*-((*E*)-3-Phenylprop-1-en-1-yl)octahydronaphthalen-1(2*H*)-one (**36a**)

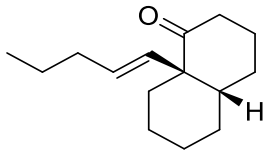


From *N*'-(2-(3-cyanopropyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (38.1 mg, 0.11 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (32.3 mg, 0.22 mmol), **36a** was obtained in 60% isolated

yield (17.4 mg) following ***General procedure A*** as a colourless oil. **36a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.51.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.1 (m, 5H), 5.68 (d, *J* = 15.9 Hz, 1H), 5.44 (dt, *J* = 15.9, 6.7 Hz, 1H), 3.37 (d, *J* = 6.8 Hz, 2H), 2.60 (ddd, *J* = 14.9, 12.4, 7.5 Hz, 1H), 2.30-2.11 (m, 3H), 2.05-1.65 (m, 5H), 1.59-1.20 (m, 6H), 1.07 (td, *J* = 12.9, 4.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.1 (C), 140.1 (CH), 138.1 (CH), 129.5 (CH), 128.4 (CH), 126.0 (CH), 55.6 (C), 44.4 (CH), 39.1 (CH_2), 38.9 (CH_2), 34.7 (CH_2), 28.7 (CH_2), 27.3 (CH_2), 25.9 (CH_2), 23.2 (CH_2), 22.3 (CH_2). HRMS(ESI): calcd. For $[C_{15}H_{24}NaO]^+$: 269.1899, found: 269.1896.

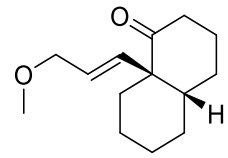
(4*aS**,8*aS**)-8*a*-((*E*)-Pent-1-en-1-yl)octahydronaphthalen-1(2*H*)-one (**36b**)



From *N*'-(2-(3-Cyanopropyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (50.0 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (34.1 mg, 0.30 mmol), **36b** was obtained in 57% isolated yield (18.8 mg) following ***General procedure A*** as a colourless oil. **36b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.45.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (d, *J* = 15.9 Hz, 1H), 5.24 (dt, *J* = 15.9, 6.8 Hz, 1H), 2.63 (ddd, *J* = 14.9, 12.6, 7.6 Hz, 1H), 2.30-2.10 (m, 3H), 2.05-1.70 (m, 6H), 1.60-1.15 (m, 8H), 1.07 (td, *J* = 12.9, 4.2 Hz, 1H), 0.88 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.5 (C), 136.9 (CH), 130.9 (CH), 55.6 (C), 44.5 (CH), 38.8 (CH_2), 34.9 (CH_2), 34.8 (CH_2), 28.8 (CH_2), 27.2 (CH_2), 26.0 (CH_2), 23.2 (CH_2), 22.3 (CH_2), 22.3 (CH_2), 13.5 (CH_3). HRMS(ESI): calcd. For $[C_{15}H_{24}NaO]^+$: 243.1719, found: 243.1715.

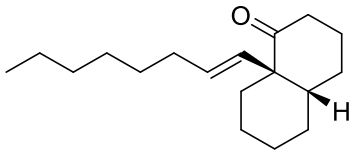
(4*aS**,8*aS**)-8*a*-((*E*)-3-Methoxyprop-1-en-1-yl)octahydronaphthalen-1(2*H*)-one (**36c**)



From *N*'-(2-(3-cyanopropyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (50.0 mg, 0.15 mmol) and (*E*)-(3-methoxyprop-1-en-1-yl)boronic acid (34.7 mg, 0.3 mmol), **36c** was obtained in 63% isolated yield (21.0 mg) following ***General procedure A*** as a colourless oil. **36c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.20.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (d, *J* = 16.1 Hz, 1H), 5.39 (dt, *J* = 16.1, 5.8 Hz, 1H), 3.89 (dd, *J* = 5.8, 1.4 Hz, 2H), 3.32 (s, 3H), 2.58 (ddd, *J* = 14.9, 12.4, 7.5 Hz, 1H), 2.30-2.05 (m, 3H), 2.02-1.65 (m, 4H), 1.60-1.15 (m, 6H), 1.04 (td, *J* = 12.9, 4.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.7 (C), 139.5 (CH), 126.8 (CH), 72.9 (CH_2), 57.8 (CH_3), 55.5 (C), 44.2 (CH), 38.9 (CH_2), 34.3 (CH_2), 28.6 (CH_2), 27.2 (CH_2), 25.8 (CH_2), 23.0 (CH_2), 22.2 (CH_2). HRMS(ESI): calcd. For $[C_{14}H_{22}NaO_2]^+$: 245.1512, found: 245.1507.

(4*aS**,8*aS**)-8*a*-((*E*)-Oct-1-en-1-yl)octahydronaphthalen-1(2*H*)-one (**36d**)

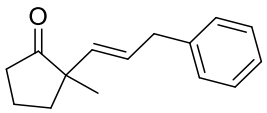


From *N*'-(2-(3-Cyanopropyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (25.0 mg, 0.07 mmol) and *trans*-1-octen-1-ylboronic acid (23.4 mg, 0.15 mmol), **11d** was obtained in 57% isolated yield (11.0 mg) following ***General procedure A*** as a colourless oil. **11d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.67.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (d, *J* = 15.9 Hz, 1H), 5.24 (dt, *J* = 15.9, 6.8 Hz, 1H), 2.62 (ddd, *J* = 14.9, 12.6, 7.6 Hz, 1H), 2.25-2.10 (m, 3H), 2.09-1.70 (m, 7H), 1.55-

1.15 (m, 13H), 1.01 (td, *J* = 13.1, 4.4 Hz, 1H), 0.89 (t, *J* = 6.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.5 (C), 136.7 (CH), 131.1 (CH), 55.6 (C), 44.5 (CH), 38.8 (CH_2), 34.9 (CH_2), 32.7 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 27.2 (CH_2), 26.0 (CH_2), 23.2 (CH_2), 22.6 (CH_2), 22.3 (CH_2), 14.0 (CH_3). HRMS(ESI): calcd. For $[C_{18}H_{30}NaO]^+$: 285.2188, found: 285.2197.

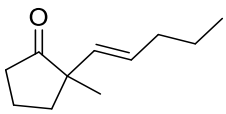
(*E*)-2-Methyl-2-(3-phenylprop-1-en-1-yl)cyclopentan-1-one (**38a**)



From *N*'-(5-Cyanopentan-2-ylidene)-4-methylbenzenesulfonohydrazide (41.8 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.6 mg, 0.30 mmol), **38a** was obtained in 67% isolated yield (21.2 mg) following ***General procedure A*** as a colourless oil. **38a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.36.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.10 (m, 5H), 5.65 (dt, *J* = 15.6, 6.5 Hz, 1H), 5.55 (d, *J* = 1.6 Hz, 1H), 3.38 (d, *J* = 6.6 Hz, 2H), 2.40-2.00 (m, 3H), 1.98-1.75 (m, 3H), 1.17 (3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 220.7 (C), 140.2 (C), 133.7 (CH), 128.8 (CH), 128.4 (CH), 128.4 (CH), 126.0 (CH), 51.2 (C), 39.0 (CH_2), 37.1 (CH_2), 36.8, 22.7 (CH_3), 18.7 (CH_2). HRMS(ESI): calcd. For $[C_{15}H_{18}O]^+$: 214.1358, found: 214.1357.

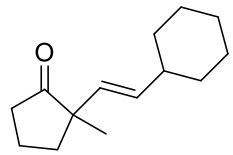
(*E*)-2-Methyl-2-(pent-1-en-1-yl)cyclopentan-1-one (**38b**)



From *N*'-(5-Cyanopentan-2-ylidene)-4-methylbenzenesulfonohydrazide (41.8 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (48.6 mg, 0.30 mmol), **38b** was obtained in 70% isolated yield (15.9 mg) following ***General procedure A*** as a colourless oil. **38b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.46.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.38 (d, *J* = 15.8 Hz, 1H), 2.35-1.74 (m, 5H), 1.45-1.23 (m, 4H), 1.12 (s, 3H), 0.95-0.80 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.0 (C), 132.3 (CH), 130.2 (CH), 51.2 (C), 37.1 (CH_2), 36.9 (CH_2), 34.7 (CH_2), 22.8 (CH_3), 22.4 (CH_2), 18.6 (CH_2), 13.5 (CH_3). HRMS(ESI): calcd. For $[C_{11}H_{18}O]^+$: 166.1359, found: 166.1359.

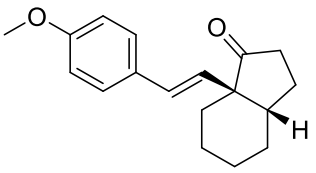
(*E*)-2-(2-Cyclohexylvinyl)-2-methylcyclopentan-1-one (**38c**)



From *N*'-(5-Cyanopentan-2-ylidene)-4-methylbenzenesulfonohydrazide (41.8 mg, 0.15 mmol) and (*E*)-(2-cyclohexylvinyl)boronic acid (46.2 mg, 0.3 mmol), **38c** was obtained in 57% isolated yield (17.0 mg) following ***General procedure A*** as a colourless oil. **38c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.40.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (dd, *J* = 15.9, 5.8 Hz, 1H), 5.33 (d, *J* = 15.9 Hz, 1H), 2.35-1.64 (m, 12H), 1.35-1.19 (m, 2H), 1.12 (s, 3H), 1.10-0.90 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.1 (C), 136.1 (CH), 129.6 (CH), 51.0 (C), 40.7 (CH_3), 37.1 (CH_2), 36.9 (CH_2), 32.9 (CH_2), 32.9 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 22.9 (CH_3), 18.6 (CH_2). HRMS(ESI): calcd. For $[C_{14}H_{22}O]^+$: 206.1671, found: 206.1640.

(3*aS**,7*aS**)-7*a*-((*E*)-4-methoxystyryl)octahydro-1*H*-inden-1-one (**42a**)

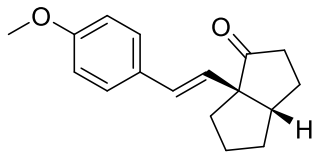


From *N*'-(2-(2-Cyanoethyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (47.9 mg, 0.15 mmol) and *trans*-2-(4-methoxyphenyl)vinylboronic acid (53.4 mg, 0.3 mmol), **42a** was obtained in 49% isolated yield (19.6 mg) following ***General procedure A*** as a colourless oil. **42a** was

purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.30.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.34 (d, *J* = 16.3 Hz, 1H), 5.99 (d, *J* = 16.3 Hz, 1H), 3.82 (s, 3H), 2.40-2.25 (m, 3H), 2.10-1.20 (m, 10H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 219.2 (C), 159.1 (C), 129.9 (CH), 129.7 (C), 127.3 (CH), 113.9 (CH), 55.3 (CH), 55.3 (CH_3), 41.4 (CH_2), 34.8 (CH_2), 30.1 (CH_2), 27.6 (CH_2), 23.6 (CH_2), 23.1 (CH_2), 22.6 (CH_2). HRMS(ESI): calcd. For $[C_{18}H_{23}O_2]^+$: 271.1692, found: 271.1691.

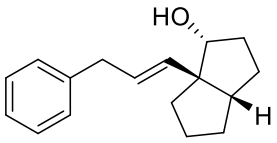
(3*aS**,6*aS**)-6*a*-((*E*)-4-Methoxystyryl)hexahydropentalen-1(2*H*)-one (**42b**)



From *N*'-(2-(2-Cyanoethyl)cyclopentylidene)-4-methylbenzenesulfonohydrazide (45.8 mg, 0.15 mmol) and *trans*-2-(4-Methoxyphenyl)vinylboronic acid (53.4 mg, 0.3 mmol), **42b** was obtained in 52% isolated yield (19.7 mg) following ***General procedure A*** as a colourless oil. **42b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.24.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.35 (d, *J* = 16.2 Hz, 1H), 6.13 (d, *J* = 16.2 Hz, 1H), 3.82 (s, 3H), 2.83-2.63 (m, 1H), 2.49-2.31 (m, 2H), 2.25-2.19 (m, 3H), 1.85-1.45 (m, 3H), 1.35-1.22 (m, 1H), 0.95-0.85 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.5 (C), 159.0 (C), 129.7 (CH), 129.0 (CH), 128.1 (CH), 127.3 (CH), 113.9 (CH), 63.3 (CH), 55.2 (CH_3), 46.8 (CH_2), 37.1 (CH_2), 33.0 (CH_2), 25.3 (CH_2), 24.9 (CH_2). HRMS(ESI): calcd. For $[C_{17}H_{21}O_2]^+$: 257.1536, found: 257.1542.

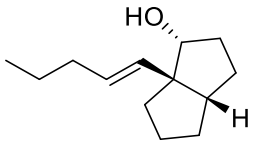
(1*R**,3*as**,6*aS**)-6*a*-((*E*)-3-Phenylprop-1-en-1-yl)octahydropentalen-1-ol (**44a**)



From *N*'-(2-(2-Cyanoethyl)cyclopentylidene)-4-methylbenzenesulfonohydrazide (45.8 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.6 mg, 0.30 mmol), **44a** was obtained in 70% isolated yield (25.0 mg) following ***General procedure C*** as a colourless oil. **44a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.20.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.15 (m, 5H), 5.71 (d, *J* = 15.5 Hz, 1H), 5.60 (dt, *J* = 15.5, 6.3 Hz, 1H), 4.02 (dd, *J* = 9.5, 5.8 Hz, 1H), 3.39 (d, *J* = 6.2 Hz, 2H), 2.32-2.20 (m, 1H), 2.05-1.50 (m, 7H), 1.36-1.20 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.0 (C), 140.1 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 125.9 (CH), 124.7 (CH), 80.3 (CH), 58.4 (C), 48.6 (CH), 39.1 (CH_2), 35.3 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 28.0 (CH_2), 26.5 (CH_2). HRMS(ESI): calcd. For $[C_{17}H_{22}NaO]^+$: 265.1568, found: 265.1567.

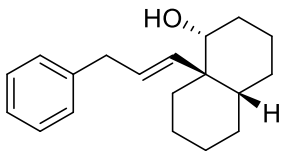
(1*R**,3*aS**,6*aS**)-6*a*-((*E*)-Pent-1-en-1-yl)octahydropentalen-1-ol (**44b**)



From *N*'-(2-(2-Cyanoethyl)cyclopentylidene)-4-methylbenzenesulfonohydrazide (45.8 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (34.1 mg, 0.30 mmol), **44b** was obtained in 78% isolated yield (22.0 mg) following ***General procedure C*** as a colourless oil. **44b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.10.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (d, *J* = 15.5 Hz, 1H), 5.42 (dt, *J* = 15.5, 6.5 Hz, 1H), 3.98 (dd, *J* = 9.5, 5.8 Hz, 1H), 2.28-2.15 (m, 1H), 2.10-1.20 (m, 14H), 0.90 (t, *J* = 7.3 Hz, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.5 (CH), 126.0 (CH), 80.4 (CH), 58.2 (C), 48.6 (CH), 35.3 (CH_2), 34.8 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 28.0 (CH_2), 26.4 (CH_2), 22.7 (CH_2), 13.6 (CH_3). HRMS(ESI): calcd. For $[C_{11}H_{20}NaO]^+$: 217.1549, found: 217.1562.

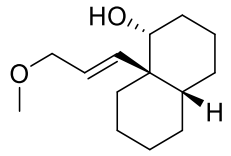
(1*R**,4*aS**,8*aS**)-8a-((*E*)-3-phenylprop-1-en-1-yl)decahydronaphthalen-1-ol (**44c**)



From *N*'-(2-(3-Cyanopropyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (50.0 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.6 mg, 0.30 mmol), **44c** was obtained in 55% isolated yield (22.0 mg) following ***General procedure C*** as a colourless oil. **44c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.12.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 5H), 5.72 (dt, *J* = 15.9, 6.8 Hz, 1H), 5.37 (d, *J* = 16.0 Hz, 1H), 3.48 (d, *J* = 6.8 Hz, 2H), 3.27 (dd, *J* = 11.1, 4.3 Hz, 1H), 1.85-1.20 (m, 15H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.7 (C), 139.1 (CH), 130.0 (CH), 128.5 (CH), 128.3 (CH), 126.0 (CH), 75.6 (CH), 45.2 (C), 40.9 (CH), 39.6 (CH_2), 28.1 (CH_2), 27.7 (CH_2), 26.0 (CH_2), 24.0 (CH_2), 21.7 (CH_2), 20.9 (CH_2), 20.3 (CH_2). HRMS(ESI): calcd. For $[C_{19}H_{26}NaO]^+$: 293.1875, found: 293.1880.

(1*R**,4*aS**,8*aS**)-8*a*-((*E*)-3-Methoxyprop-1-en-1-yl)decahydronaphthalen-1-ol (**44d**)

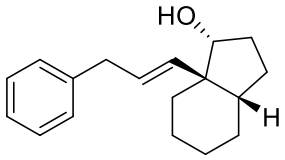


From *N*'-(2-(3-cyanopropyl)cyclohexylidene)-4-methylbenzenesulfonohydrazide (50.0 mg, 0.15 mmol) and (*E*)-(3-methoxyprop-1-en-1-yl)boronic acid (34.7 mg, 0.30 mmol), **44d** was obtained in 60% isolated yield (20.0 mg) following ***General procedure C*** as a yellow oil. **44d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 4:1 as eluent. R_f (hexanes/ethyl acetate 4:1) = 0.15.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (dt, *J* = 16.2, 5.8 Hz, 1H), 5.53 (d, *J* = 16.2 Hz, 1H), 4.07-3.93 (m, 2H), 3.36 (s, 3H), 3.26 (dd, *J* = 11.3, 4.3 Hz, 1H), 2.39-2.32 (m, 1H), 1.85-1.20 (m, 14H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.4 (CH), 127.1 (CH), 75.5 (CH), 73.5

(CH_2), 57.8 (CH_3), 45.1 (C), 40.6 (CH), 28.0 (CH_2), 27.9 (CH_2), 26.0 (CH_2), 23.9 (CH_2), 21.6 (CH_2), 20.8 (CH_2), 20.3 (CH_2). HRMS(ESI): calcd. For $[C_{14}H_{24}NaO_2]^+$: 247.1668, found: 247.1668.

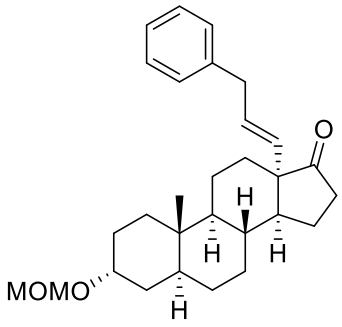
(1*R**,3*aS**,7*aS**)-7*a*-((*E*)-3-Phenylprop-1-en-1-yl)octahydro-1*H*-inden-1-ol (**44e**)



From *N*'-(2-(2-Cyanoethyl)cyclohexylidene-4-methylbenzenesulfonohydrazide (47.9 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.6 mg, 0.30 mmol), **44e** was obtained in 74% isolated yield (28.1 mg) following ***General procedure C*** as a colourless oil. **44e** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.10.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 5H), 5.70 (dt, *J* = 15.9, 6.8 Hz, 1H), 5.48 (d, *J* = 15.7 Hz, 1H), 3.88 (t, *J* = 8.6 Hz, 1H), 3.44 (d, *J* = 6.7 Hz, 2H), 2.20-1.20 (m, 13H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.9 (C), 137.9 (CH), 128.4 (CH), 128.3 (CH), 125.9 (CH), 81.5 (CH), 48.1 (C), 41.1 (CH), 39.5 (CH_2), 29.4 (CH_2), 24.8 (CH_2), 23.5 (CH_2), 23.1 (CH_2), 21.6 (CH_2), 20.6 (CH_2). HRMS(ESI): calcd. For $[C_{18}H_{24}NaO]^+$: 279.1723, found: 279.1719.

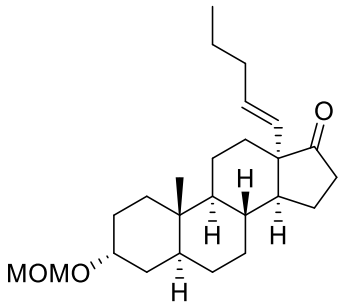
(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-3-(Methoxymethoxy)-10-methyl-13-((*E*)-3-phenylprop-1-en-1-yl)hexadecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (**50a**)



From (4*aS*,4*bS*,7*R*,8*aS*,10*aR*)-1-(2-Cyanoethyl)-7-(methoxymethoxy)-4*b*-methyl dodecahydrophenanthren-2(1*H*)-ylidene)-4-methylbenzenesulfonohydrazide (75.2 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.6 mg, 0.30 mmol), **20a** was obtained in 68% isolated yield (44.0 mg) following ***General procedure B*** as a colourless oil. **20a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 4:1 as eluent. R_f (hexanes/ethyl acetate 4:1) = 0.10.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.03 (m, 5H), 5.45 (dt, *J* = 15.3, 6.3 Hz, 1H), 5.35 (d, *J* = 15.7 Hz, 1H), 4.67 (s, 2H), 3.84 (s, 1H), 3.38 (s, 3H), 3.31 (d, *J* = 6.2 Hz, 2H), 7.37-7.09 (m, 6H), 2.01-0.69 (m, 16H), 0.63 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.8 (C), 140.3 (C), 137.4 (CH), 129.6 (CH), 128.3 (CH), 128.2 (CH), 125.9 (CH), 94.5 (CH_2), 71.4 (CH_3), 55.1 (CH), 54.8 (C), 51.8 (CH), 51.7 (CH), 39.1 (CH), 38.8 (C), 36.2 (CH), 35.9 (CH_2), 33.5 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 28.41 (CH_2), 26.20 (CH_2), 22.3 (CH_2), 21.1 (CH_2), 11.2 (CH_3). HRMS(ESI): calcd. For $[C_{29}H_{40}NaO_3]^+$: 459.2869, found: 459.2862. $[\alpha]_D^{25}$ = 0.2º (c = 0.44).

(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-3-(Methoxymethoxy)-10-methyl-13-((*E*)-pent-1-en-1-yl)hexadecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (**50b**)

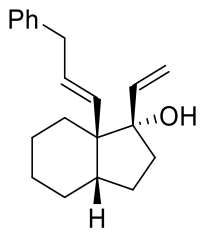


From (4*aS*,4*bS*,7*R*,8*aS*,10*aR*)-1-(2-Cyanoethyl)-7-(methoxymethoxy)-4*b*-methyldodecahydrophenanthren-2(1*H*)-ylidene)-4-methylbenzenesulfonohydrazide (75.2 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (34.1 mg, 0.30 mmol), **20b** was obtained in 60% isolated yield (35.0 mg) following ***General procedure B*** as a yellow oil. **20b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. R_f (hexanes/ethyl acetate 2:1) = 0.30.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35-5.18 (m, 2H), 4.68-4.62 (m, 2H), 3.85-3.80 (m, 1H), 3.37 (s, 3H), 2.55-2.40 (m, 1H), 2.10-1.10 (m, 22H), 1.00-0.87 (m, 2H), 0.84

(t, *J* = 7.3 Hz, 3H), 0.80-0.67 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 191.3 (C), 136.0 (CH), 129.6 (CH), 94.5 (CH_2), 71.5 (CH_3), 55.1 (CH), 54.8 (C), 51.8 (CH), 39.2 (CH), 36.2 (CH), 35.9 (C), 34.5 (CH_2), 33.5 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 28.4 (CH_2), 26.1 (CH_2), 22.4 (CH_2), 22.2 (CH_2), 21.1 (CH_2), 13.5 (CH_3), 11.2 (CH_3). HRMS(ESI): calcd. For $[C_{25}H_{40}NaO_3]^+$: 411.2869, found: 411.2874. $[\alpha]_D^{25}$ = 2.7º (c = 0.50).

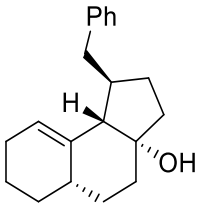
(1*S**,3*aS**,7*aS**)-7*a*-((*E*)-3-phenylprop-1-en-1-yl)-1-vinyloctahydro-1*H*-inden-1-ol (**51a**)



To a solution in a sealed vial under a nitrogen atmosphere of (3*aS**,7*aS**)-7*a*-((*E*)-3-phenylprop-1-en-1-yl)octahydro-1*H*-inden-1-one (**29a**) (66.0 mg, 0.26 mmol) in THF (4mL) was added vinyl magnesium bromide (1.06 mL from a 1.0 M solution in THF) at 0°C. The solution was stirred at 40°C for two days until total consumption of the starting material **29a** followed by TLC. The reaction is quenched with a saturated solution of $NH_4Cl_{(aq)}$ (5 mL) and extracted with Et_2O (3x10 mL). After purification by flash chromatpgraphy (8:1 mixture of hexane/AcOet), **51a** was obtained as a colourless oil (52.8 mg, 72%). R_f (hexanes/AcOEt) = 0.34.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.28 (m, 2H), 7.25-7.16 (m, 3H), 6.02 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.58 (dt, *J* = 15.9, 6.8 Hz, 1H), 5.30 (d, *J* = 15.9 Hz, 1H), 5.15 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.05 (dd, *J* = 10.8, 1.3 Hz, 1H), 3.42 (d, *J* = 6.8 Hz, 2H), 2.27-2.16 (m, 1H), 2.10-1.76 (m, 3H), 1.75-1.65 (m, 2H), 1.60-1.25 (m, 7H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.4 (CH), 141.0 (C), 135.4 (CH), 129.1 (CH), 128.5 (CH), 128.3 (CH), 125.8 (CH), 110.7 (CH_2), 85.9 (C), 51.0 (C), 39.6 (CH), 39.5 (CH_2), 35.1 (CH_2), 27.0 (CH_2), 25.2 (CH_2), 23.4 (CH_2), 21.8 (CH_2), 20.6 (CH_2). HRMS(ESI): calcd. For $[C_{20}H_{27}O]^+$: 283.2-62, found: 283.2061.

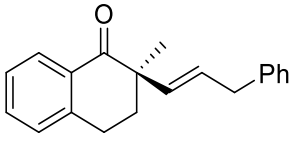
(1*R**,3*aR**,5*aR**,9*bS**)-1-benzyl-1,2,3,4,5,5a,6,7,8,9b-decahydro-3*aH*-cyclopenta [a]naphthalen-3*a*-ol (**53a**)



In a Schlenk tube under an argon atmosphere, (1*S**,3*aS**,7*aS**)-7*a*-((*E*)-3-phenylprop-1-en-1-yl)-1-vinyloctahydro-1*H*-inden-1-ol (**51a**) (36 mg, 0.12 mmol) in THF (6.5 mL) were added. To this solution, another solution of LiHDMS (0.33 mL from a 1M solution in THF) was added. The mixture was stirred at 65°C overnight. The reaction mixture was cooled down to r.t.; quenched with a saturated solution of $NH_4Cl_{(aq)}$ (5 mL) and extracted with Et_2O (3x10 mL). After purification by flash chromatography (8:1 mixture of hexane/AcOet), **53a** was obtained as a colourless oil (22.0 mg, 65%). R_f (hexanes/AcOEt) = 0.38.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.21-7.17 (m, 1H), 7.17-7.14 (m, 2H), 5.55 (t, *J* = 6.0 Hz), 2.88 (dd, *J* = 13.7, 4.0 Hz, 2H), 2.33 (dd, *J* = 13.6, 10.1 Hz, 2H), 2.20-2.09 (m, 2H), 2.08-1.95 (m, 3H), 1.90-1.82 (m, 1H), 1.81-1.77 (m, 1H), 1.75-1.60 (m, 5H), 1.54-1.48 (m, 1H), 1.45-1.32 (m, 2H), 1.27-1.20 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.6 (C), 137.6 (C), 128.8 (CH), 128.1 (CH), 125.6 (CH), 125.6 (CH), 80.0 (C), 62.1 (CH), 42.1 (CH), 41.3 (CH_2), 38.4 (CH_2), 34.7 (CH_2), 33.0 (CH), 30.8 (CH_2), 30.6 (CH_2), 27.3 (CH_2), 25.9 (CH_2), 21.8 (CH_2). HRMS(ESI): calcd. For $[C_{20}H_{27}O]^+$: 283.2062, found: 283.2064.

(*R*,E*)-2-methyl-2-(3-phenylprop-1-en-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one (**57a**)

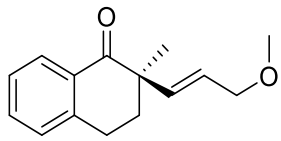


From (*E*)-*N*'-(4-(2-cyanophenyl)butan-2-ylidene)-4-methylbenzenesulfonohydra zide (51.2 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (34.1 mg, 0.30 mmol), **57a** was obtained in 78% isolated yield (31.9

mg) following ***General procedure A*** as a colourless oil. **57a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.53.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.48 (td, *J* = 7.5, 1.5 Hz, 1H), 7.36-7.15 (m, 5H), 7.12-7.05 (m, 2H), 5.73 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.56 (dt, *J* = 15.8, 6.6 Hz, 1H), 3.35 (dd, *J* = 6.5, 1.2 Hz, 2H), 3.09 (ddd, *J* = 15.7, 9.9, 5.4 Hz, 1H), 2.91 (dt, *J* = 17.1, 4.9 Hz, 1H), 2.20-2.01 (m, 2H), 1.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.5 (C), 143.5 (C), 140.1 (CH), 133.9 (CH), 133.0 (C), 131.9 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 126.6 (CH), 125.9 (CH), 47.8 (C), 39.0 (CH_2), 35.6 (CH_2), 26.0 (CH_2), 24.0 (CH_3). HRMS(ESI): calcd. For $[C_{20}H_{21}O]^+$: 277.1586, found: 277.1584.

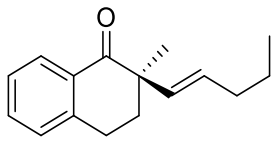
(*R**,*E*)-2-(3-methoxyprop-1-en-1-yl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**57b**)



From (*E*)-*N*'-(4-(2-cyanophenyl)butan-2-ylidene)-4-methylbenzenesulfonohydra zide (51.2 mg, 0.15 mmol) and (*E*)-(3-methoxyprop-1-en-1-yl)boronic acid (34.7 mg, 0.30 mmol), **57b** was obtained in 88% isolated yield (30.0 mg) following ***General procedure A*** as a colourless oil. **57b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 5:1 as eluent. R_f (hexanes/ethyl acetate 5:1) = 0.33.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.1 Hz, 1H), 7.47 (td, *J* = 7.4, 1.6 Hz, 1H), 7.31 (dd, *J* = 13.0, 5.5 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 5.92 (d, *J* = 15.9 Hz, 1H), 5.53 (dt, *J* = 16.0, 5.8 Hz, 1H), 3.89 (dd, *J* = 5.8, 1.5 Hz, 2H), 3.29 (s, 3H), 3.08 (ddd, *J* = 15.4, 9.6, 5.2 Hz, 1H), 2.92 (dt, *J* = 17.2, 5.1 Hz, 1H), 2.20-2.05 (m, 2H), 1.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.1 (C), 143.4 (C), 135.5 (C), 133.1 (CH), 131.8 (CH), 128.6 (CH), 127.9 (CH), 126.6 (CH), 126.5 (CH), 72.9 (CH_2), 57.8 (CH_3), 47.6 (C), 35.4 (CH_2), 25.9 (CH_2), 23.7 (CH_3). HRMS(ESI): calcd. For $[C_{15}H_{18}NaO_2]^+$: 253.1199, found: 253.1200.

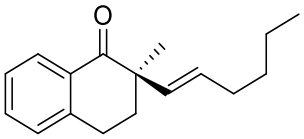
(*R**,*E*)-2-methyl-2-(pent-1-en-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one (**57c**)



From (*E*)-*N*'-(4-(2-cyanophenyl)butan-2-ylidene)-4-methylbenzenesulfonohydra zide (51.2 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (34.1 mg, 0.30 mmol), **57c** was obtained in 70% isolated yield (24.0 mg) following ***General procedure A*** as a colourless oil. **57c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.53.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 2H), 7.37-7.25 (m, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 5.59 (d, *J* = 15.8 Hz, 1H), 5.36 (dt, *J* = 15.9, 6.7 Hz, 1H), 3.09 (ddd, *J* = 16.2, 9.8, 5.9 Hz, 1H), 2.87 (dt, *J* = 17.0, 4.6 Hz, 1H), 2.20-1.90 (m, 3H), 1.41-1.22 (m, 6H), 0.82 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.7 (C), 143.6 (C), 132.9 (C), 132.1 (CH), 132.0 (CH), 130.8 (CH), 128.5 (CH), 127.8 (CH), 126.5 (CH), 47.8 (C), 35.9 (CH_2), 34.8 (CH_2), 26.0(CH_2), 24.2 (CH_3), 22.3 (CH_2), 13.4 (CH_3). HRMS(ESI): calcd. For $[C_{16}H_{20}NaO]^+$: 251.1392, found: 251.1405.

(*R**,*E*)-2-(hex-1-en-1-yl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**57d**)

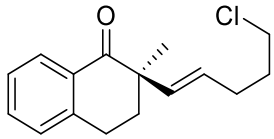


From (*E*)-*N*'-(4-(2-cyanophenyl)butan-2-ylidene)-4-methylbenzenesulfonohydra zide (51.2 mg, 0.15 mmol) and *trans*-1-hexen-1-ylboronic acid (38.3 mg, 0.30 mmol), **57d** was obtained in 50% isolated yield (18.2 mg) following ***General procedure A*** as a colourless oil. **57d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.55.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 2H), 7.37-7.25 (m, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 5.58 (d, *J* = 15.9 Hz, 1H), 5.36 (dt, *J* = 15.8, 6.7 Hz, 1H), 3.09 (ddd, *J* = 16.1, 9.7, 6.0 Hz, 1H), 2.87 (dt, *J* = 17.0, 4.6 Hz, 1H), 2.12-1.90 (m, 4H), 1.32 (s, 3H), 1.30-1.10 (m, 5H), 1.00-0.87 (m, 2H), 0.85 (t, *J* = 7.0

Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.8 (C), 143.6 (C), 132.9 (CH), 132.0 (C), 131.9 (CH), 131.0 (CH), 128.5 (CH), 127.8 (CH), 126.5 (CH), 47.7 (C), 35.9 (CH_2), 32.4 (CH_2), 31.3 (CH_2), 26.0 (CH_2), 24.2 (CH_3), 22.5 (CH_2), 13.8 (CH_3). HRMS(ESI): calcd. For $[C_{17}H_{23}O]^+$: 243.1743, found: 243.1742.

(*R**,*E*)-2-(5-chloropent-1-en-1-yl)-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**57e**)



From (*E*)-*N*'-(4-(2-cyanophenyl)butan-2-ylidene)-4-methylbenzenesulfonohydra zide (51.2 mg, 0.15 mmol) and (*E*)-(5-chloropent-1-en-1-yl)boronic acid (44.5 mg, 0.30 mmol), **57e** was obtained in 60% isolated yield (24.0 mg) following ***General procedure A*** as a colourless oil. **57e** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 6:1 as eluent. R_f (hexanes/ethyl acetate 6:1) = 0.60.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.9 Hz, 1H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H),), 5.58 (d, *J* = 15.9 Hz, 1H), 5.31 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.50-3.35 (m, 2H), 3.07 (ddd, *J* = 16.0, 9.7, 5.8 Hz, 1H), 2.89 (dt, *J* = 17.0, 4.7 Hz, 1H), 2,20-1.99 (m, 4H), 1.78 (p, *J* = 6.9 Hz, 2H), 1.32 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.5 (C), 143.4 (C), 133.8 (CH), 133.0 (CH), 131.9 (C), 128.7 (CH), 128.6 (CH), 127.8 (CH), 126.5 (CH), 47.8 (C), 44.2 (CH_2), 35.8 (CH_2), 31.7 (CH_2), 29.7 (CH_2), 26.0 (CH_2), 24.1 (CH_3). HRMS(ESI): calcd. For $[C_{16}H_{19}ClNaO]^+$: 285.1016, found: 285.1015.

E.3.3. Stereochemical assignment of compound 36c

In order to determine the stereochemistry of compounds **36**, some high field NMR experiments were carried out. Taking **36c** as model system, the signal corresponding to H1 could be assigned through a HSQC experiment (Figure E.7), featuring a chemical shift of 1.99 ppm in the ^{1}H-RMN.

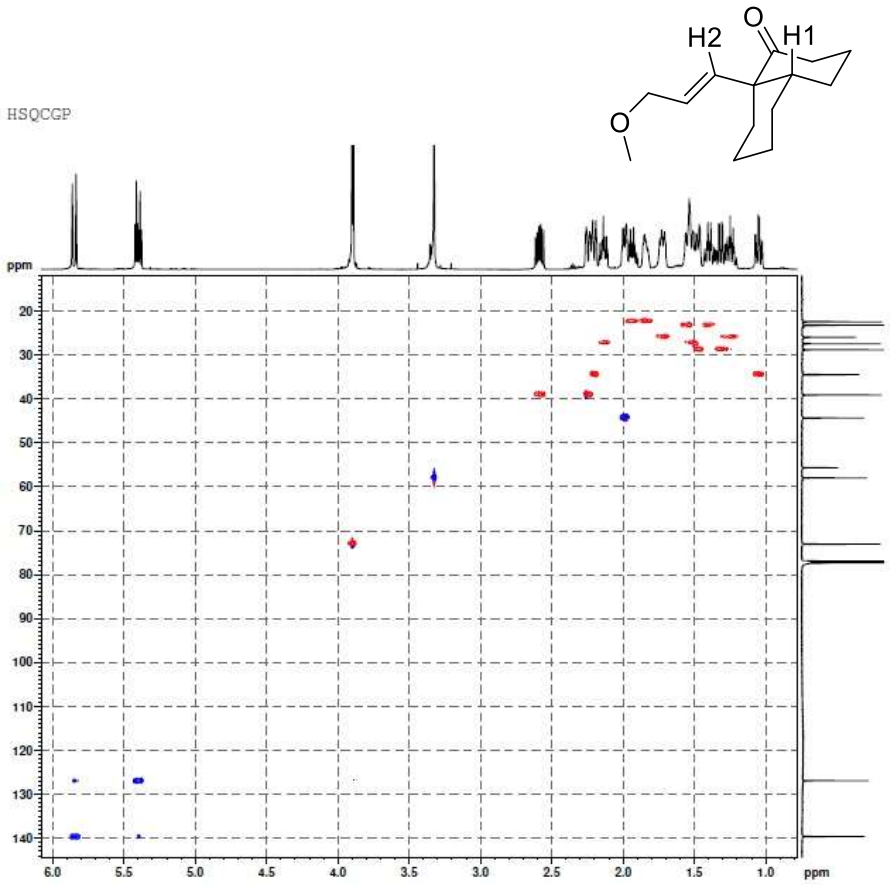


Figure E.7. HSQC experiment carried out in compound **36c.**

The *cis*-decaline arrangement was established through selective nOe experiments. Thus, when the signal characteristic of H2 (δ= 5.40 pm) was saturated (Figure E.8), a strong nOe was detected between H1 and H2. This observation can only be explained if these two hydrogens are in a *cis* arrangement.

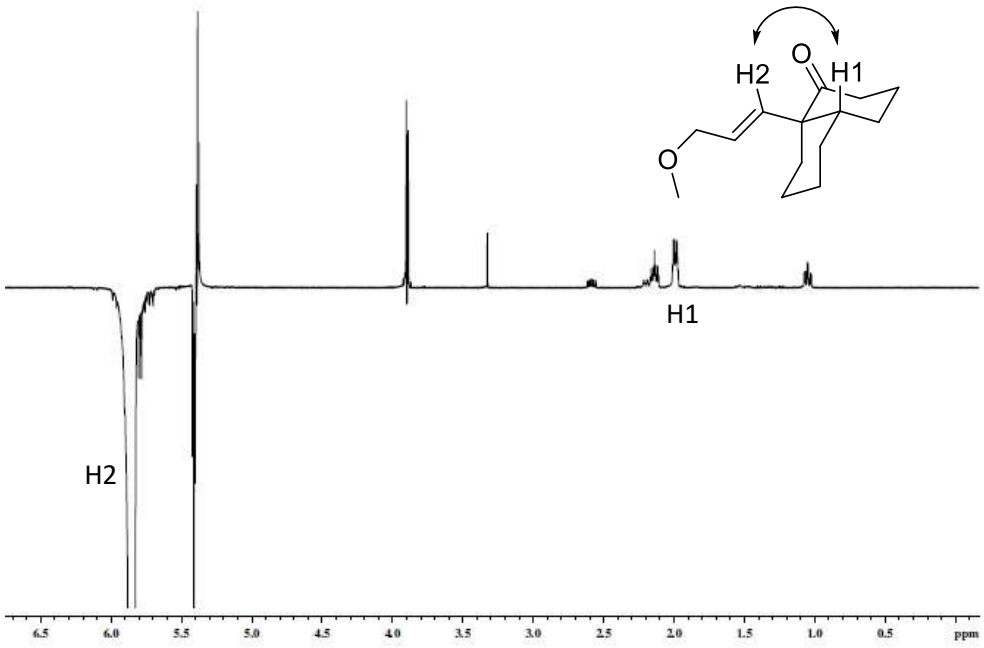


Figure E.8. Selective nOe over the signal of H2.

E.3.4. Stereochemical assignment of compound 29a

The relative stereochemistry of the compound **29a** could be determined through NMR experiments analogous to those described above for compound **36c**.

In this case, the signal corresponding to H1 could be assigned (Figure E.9) through a HSQC experiment, featuring a chemical shift of 2.22 ppm in the ^{1}H-RMN spectrum.

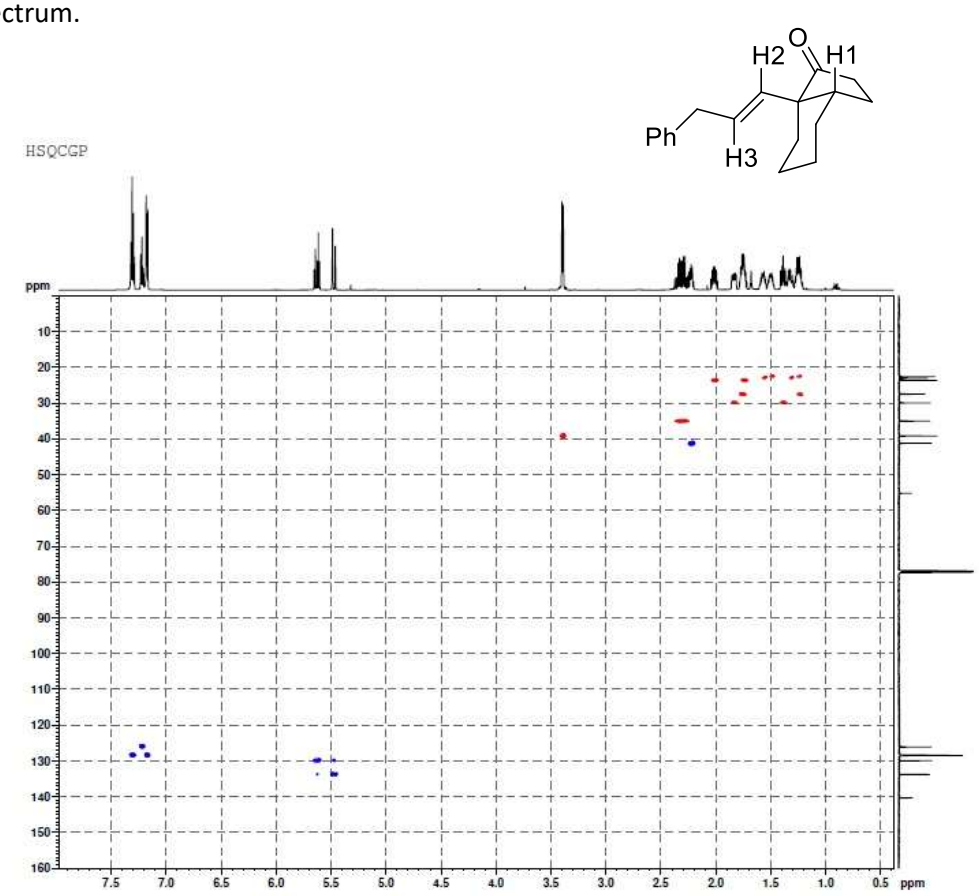


Figure E.9. HSQC experiment carried out in compound **29a**.

When the signal characteristic of H1 (δ= 2.22 pm) was saturated (Figure E.10) in a selective nOe experiment, the olefinic protons H2 and H3 showed a strong nOe. These observations establish the *cis* arrangement between the five and six membered rings.

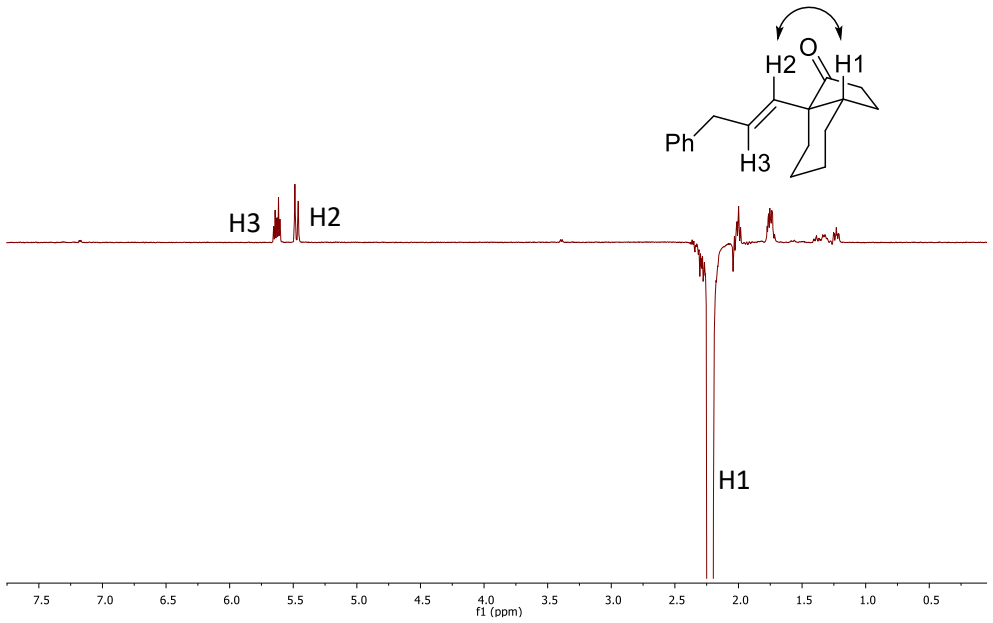


Figure E.10. Selective nOe over the signal of H1.

E.3.5. Stereochemical assignment of compound 44a

The relative stereochemistry of the compound **44a** was determined by analysis of NMR experiments. First, the signals corresponding to H1, H2, H3 and H4 were assigned (5.71, 5.60, 4.02 and 2.25 ppm respectively) in the ^{1}H-NMR.

Selective irradiation over H3 resulted in a strong nOe with the olefinic protons H1 and H2 (Figure E.11), establishing the *trans* arrangement between the OH group and the alkenyl substituent.

Moreover, an intense nOe was detected between both H2 and H3 with H4 in the NOESY experiment (Figure E.12), confirming the *cis* fusion of both rings in the [5,5] fused compounds. This observation also helps in determining the stereochemistry of compounds **11**, where the alkenyl moiety and the side chain display a *trans* arrangement.

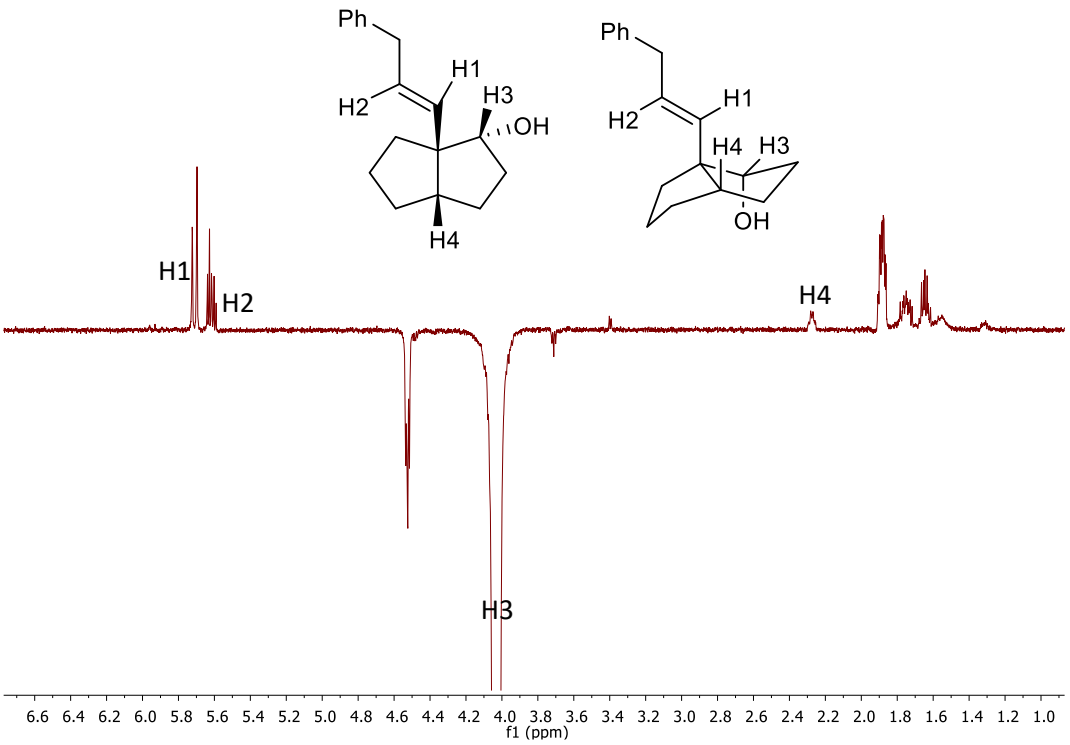


Figure E.11. Selective nOe over the signal of H3.

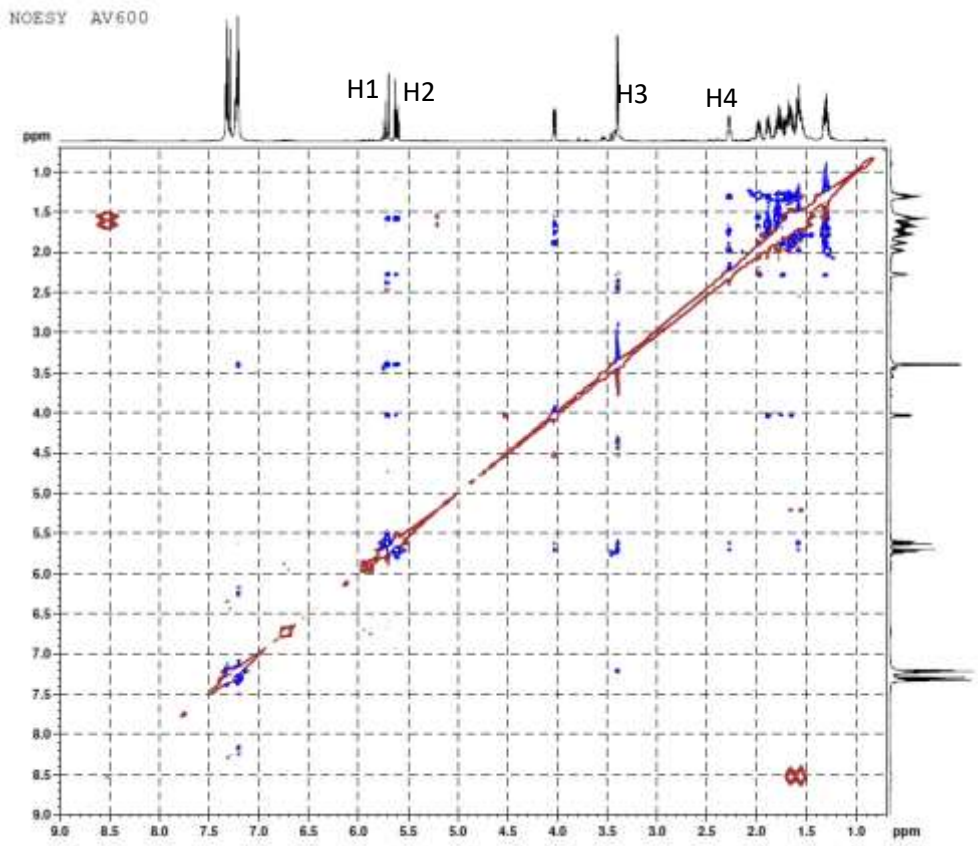
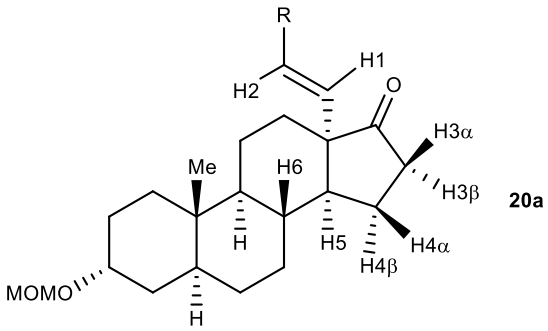


Figure E.12. NOESY experiment of the compound **44a**.

E.3.6. Stereochemical assignment of compound 50a

The stereochemical assignment of compounds **50** was carried out through a series of NMR experiments, using compound **50a** as the model system. In figure S6 is shown the molecular model obtained for **50a** upon a PM3 geometry optimization.[97,98] Dotted lines show critical nOes observed that establish the stereochemistry proposed.



20a

[97] The molecular modeling was carried out with the Gaussian 09 package of programs. Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

[98] The three dimensional models have been rendered employing CYLview. C. Legault, www.cylview.org

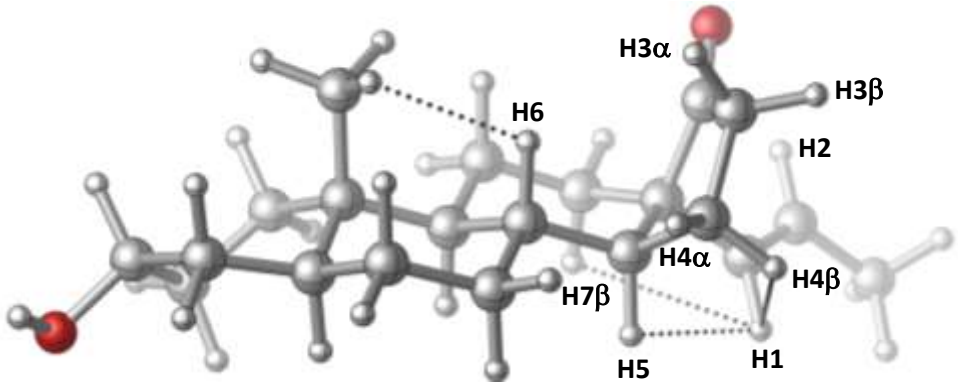


Figure E.13: Molecular model obtained for **50a** (MOM and Ph groups have been replaced by a H atoms) upon a PM3 geometry optimization. Dotted lines show critical nOes observed that establish the stereochemistry proposed.

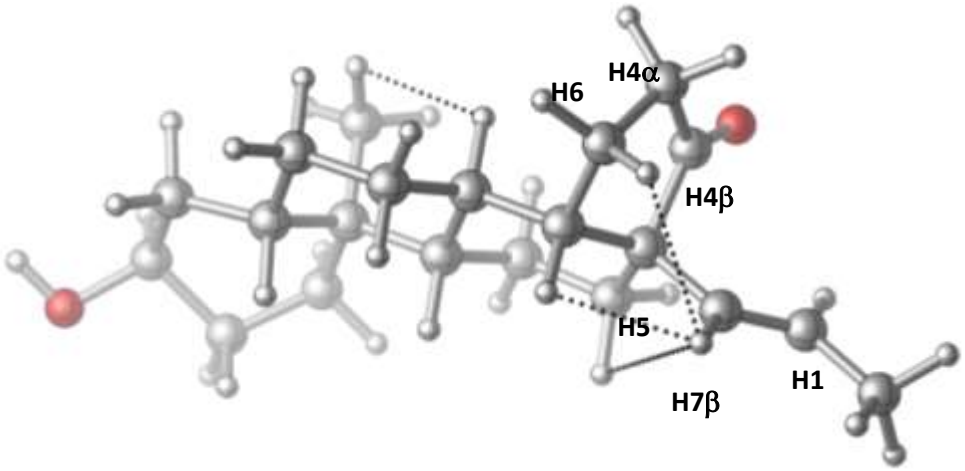


Figure E.13 (cont.)

First of all, the assignment of the signals corresponding to the different hydrogens was achieved by performing a selective TOCSY over hydrogens H3. By adjusting a short mixing time, it was possible to isolate the signals corresponding to the nucleus H4α, H4β and H5. Moreover, when the mixing time was increased, it was also possible to identify the signal corresponding to H6, as depicted in Figure E.14. In this figure, the spectra corresponding to the different mixing times performed are overlapped.

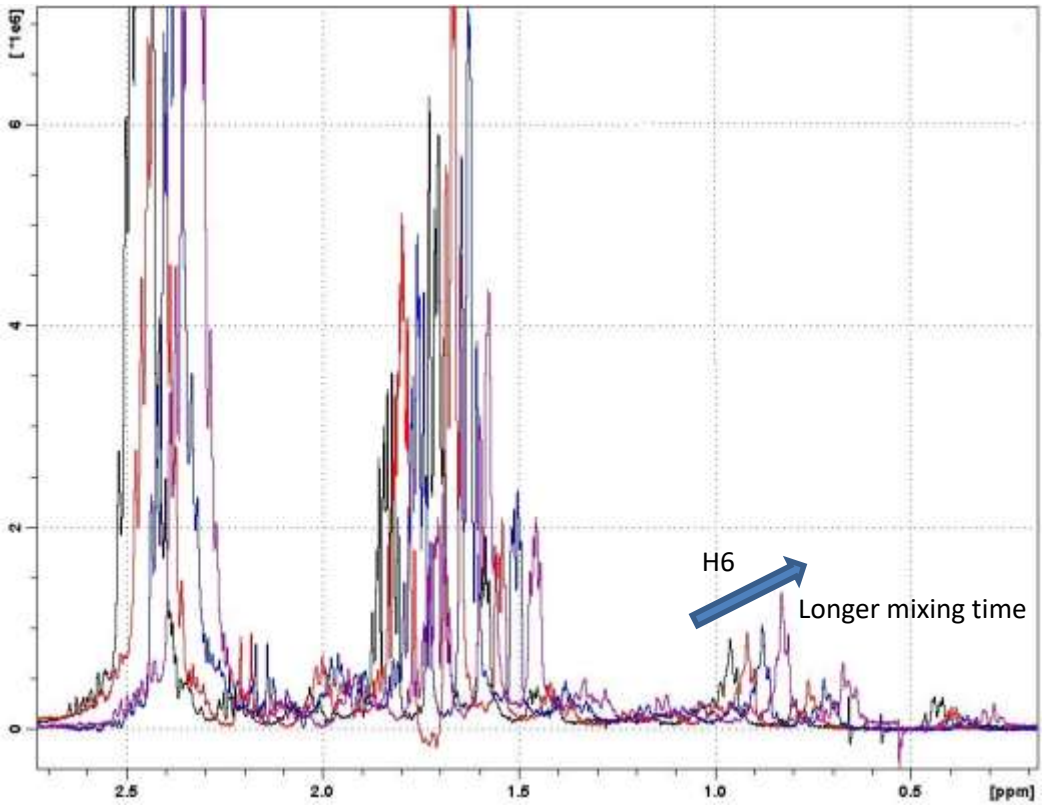


Figure E.14. Overlapping of the TOCSY experiments varying the mixing time.

This experiment made possible the analysis of the multiplicity of the signal corresponding to H_5, that appears at 1.60 ppm. This hydrogen features the multiplicity pattern of a *dd* ($^3J_{H5\text{-}H6}$ = 9.5, $^3J_{H5\text{-}H4\beta}$ = 6.5 Hz), showing a lack of coupling with H4α. This observation is confirmed by the analysis of the COSY experiment (Figure E.15). In this figure, a selective TOCSY over H4β (blue line) and selective nOe over H4β (red line) are also represented. The large value of the coupling constant between H5 and H6 (9.5 Hz) points to a *trans* axial arrangement of both hydrogens. Moreover, the molecular modelling experiments (Figure E.13) predict a torsion angle of 86º between H5 and H4α, and that supports the lack of coupling between these two hydrogens.

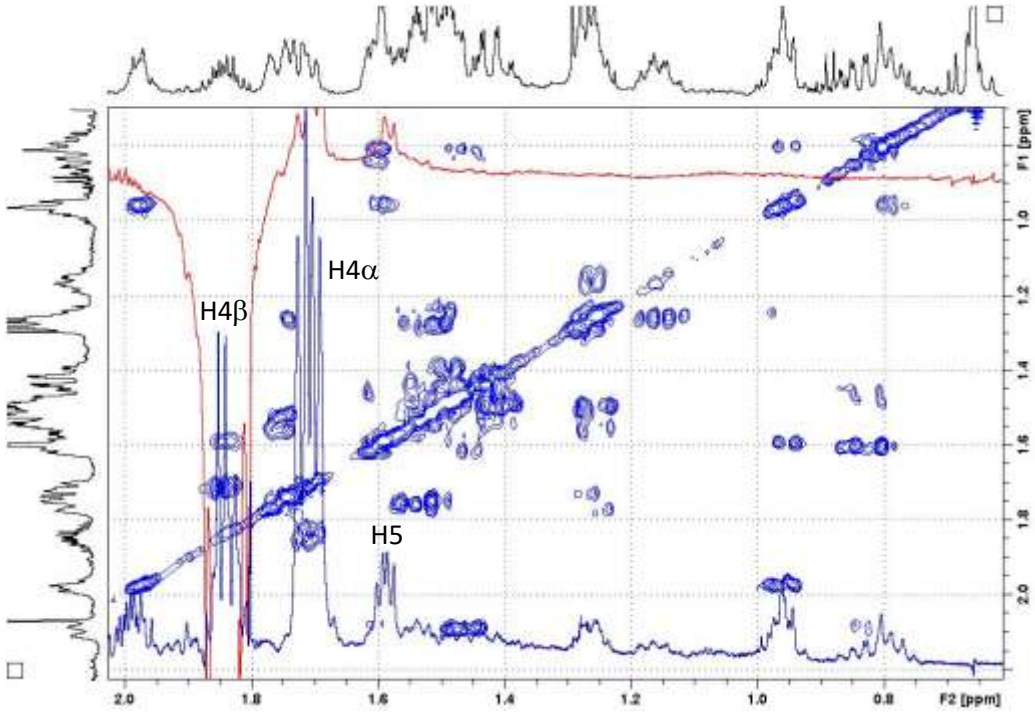


Figure E.15. COSY, selective TOCSY and nOe experiments saturating H4β.

Then, to establish the sterochemistry of the alkenyl group, selective nOe experiments over H1 (black line), and over the methyl group (blue line) were conducted (Figure E.16). The ^{1}H-NMR spectra is also depicted in red in the figure.

Irradiation of H1 resulted in a strong nOe with H5. This observation settles the *cis* arrangement between H5 and the alkenyl group in compound **50a**. This experiment also granted the assignment of H7β (td, $^{2}J_{H7\alpha\text{-}H7\beta}$ = 13.6, $^{3}J_{ax\text{-}ax}$ = 13.6, $^{3}J_{ax\text{-}eq}$ = 4.0 Hz) in the ^{1}H-RMN. An additional nOe with H4β provides additional support for the sterochemical assignment, confirming the *cis* arrangement of H5, H4β and the alkenyl substituent.

It is also worth noting the lack of nOe between H1 and H6 which would be expected if the other epimer had been obtained in the alkenylation reaction.

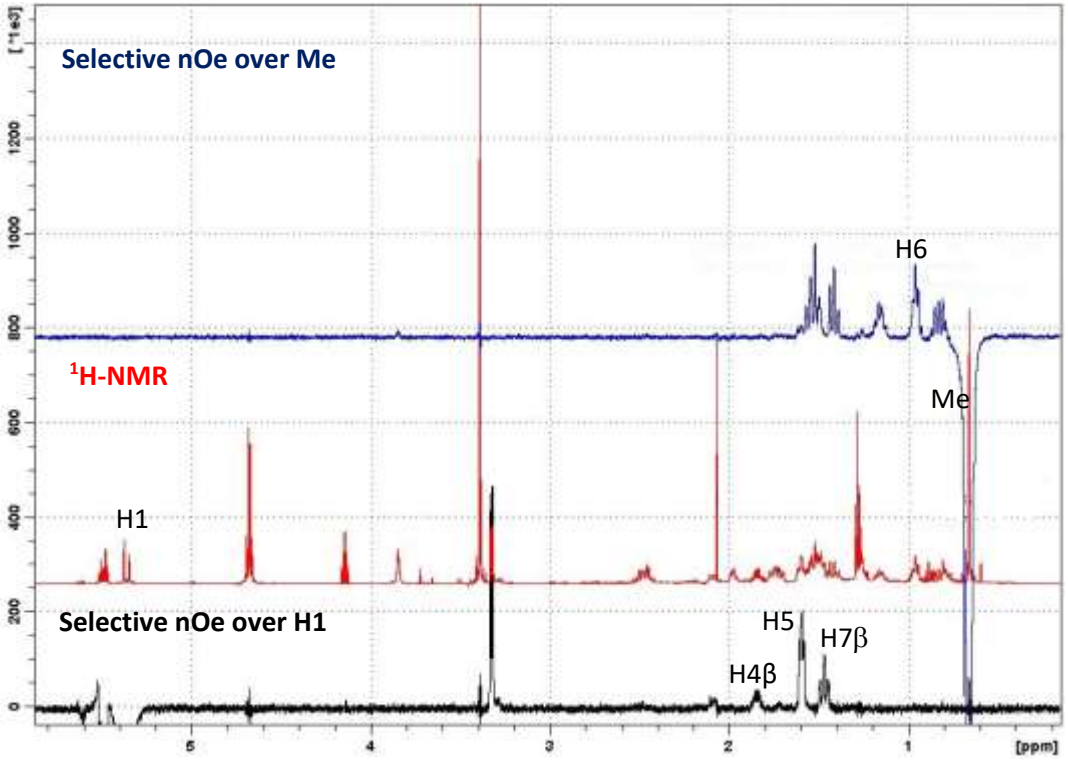


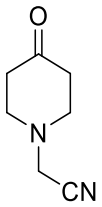
Figure E.16. ^{1}H-NMR, selective nOe over H1 and Me.

Thus, all these experiments unambiguously establish the stereochemistry proposed for **50a**. Interestingly, this stereochemistry is consistent with the expected stereochemical course for the reaction.

E.4. Chapter 2. Part B: Synthesis of the cyclization products

E.4.1. Synthesis of the starting materials and characterization data

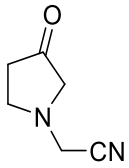
2-(4-Oxopiperidin-1-yl)acetonitrile (**68a**)



In a 100 mL round-bottom flask, 4-piperidone monohydrate hydrochloride (6.45 g, 42.15 mmol) was dissolved in 27 mL of water. When the salt was entirely dissolved, a 37% commercial aqueous solution of formaldehyde (4.2 mL) was added and the reaction was stirred at r.t. for five minutes. Then, a solution of KCN (2.74 g, 42.12 mmol) in water (27 mL) was added to the initial flask. The reaction was stirred for 24 hours at r.t. The reaction was extracted several times with $CHCl_3$. The organic extracts were dried with Na_2SO_4. The solvents were eliminated under reduced pressure, affording the final compound as a white solid in a pure form (4.00 g, 68% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 2H), 2.90 (t, *J* = 5.5 Hz, 4H), 2.51 (t, *J* = 5.5 Hz, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 206.5 (C), 114.3 (C), 51.8 (CH_2), 45.6 (CH_2), 40.6 (CH_2). m.p. 93.2-93.5 ºC

2-(3-oxopyrrolidin-1-yl)acetonitrile (**68b**)

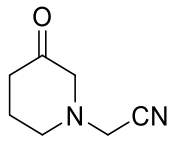


N-Boc-3-pyrrolidinone (2.00 g, 10.79 mmol) was dissolved in dichloromethane (14.4 mL). A commercial solution of 2N HCl in diethyl ether (27 mL) was then added and the reaction mixture was stirred at room temperature for 3 hours. In this time, the precipitation of a brown solid is observed. The solid (pyrrolidine-3-one hydrochloride salt) is filtrated and used for the next step without further purification.

In a 25 mL round-bottom flask, pyrrolidine-3-one hydrochloride salt (0.51 g, 4.18 mmol) was dissolved in 3 mL of water. When the salt was entirely dissolved, a 37% commercial aqueous solution of formaldehyde (0.41 mL) was added and the reaction was stirred at r.t. for five minutes. Then, a solution of KCN (0.27 g, 4.18 mmol) in water (3 mL) was added to the initial flask. The reaction was stirred for 24 hours at r.t. The reaction was extracted several times with $CHCl_3$. The organic extracts were dried with Na_2SO_4. The solvents were eliminated under reduced pressure, affording the final compound as a colourless oil in a pure form (0.33 g, 64% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 2H), 3.09 (s, 2H), 3.06 (t, *J* = 7.0 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.5 (C), 114.0 (C), 58.7 (CH_2), 49.8 (CH_2), 42.2 (CH_2), 37.9 (CH_2).

2-(3-Oxopiperidin-1-yl)acetonitrile (**68c**)

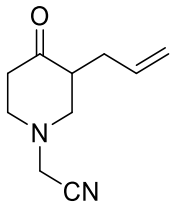


1-Boc-3-piperidone (1.47 g, 7.41 mmol) was dissolved in dichloromethane (10 mL). A commercial solution of 2N HCl in diethyl ether (18 mL) was then added and the reaction mixture was stirred at room temperature for 3 hours. In this time, the precipitation of a brown solid is observed. The solid (piperidin-3-one hydrochloride salt) is filtrated and used for the next step without further purification. In a 25 mL round-bottom flask, pyrrolidine-3-one hydrochloride salt (0.67 g, 5.00 mmol) was dissolved in 3.7 mL of water. When the salt was entirely dissolved, a 37% commercial aqueous solution of formaldehyde (0.58 mL) was added and the reaction was stirred at r.t. for five minutes. Then, a solution of KCN (0.32 g, 5.00 mmol) in water (3.7 mL) was added to the initial flask. The reaction was stirred for 24 hours at

r.t. The reaction was extracted several times with $CHCl_3$. The organic extracts were dried with Na_2SO_4. The solvents were eliminated under reduced pressure, affording the final compound as a colourless oil in a pure form (0.40 g, 57% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58 (s, 2H), 3.10 (s, 2H), 2.89-2.67 (m, 2H), 2.35 (t, *J* = 6.9 Hz, 2H), 2.02-1.92 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.9 (C), 114.0 (C), 62.6 (CH_2), 50.5 (CH_2), 45.6 (CH_2), 37.8 (CH_2), 23.4 (CH_2).

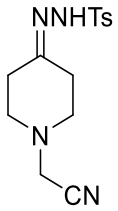
2-(3-Allyl-4-oxopiperidin-1-yl)acetonitrile (**73**)



In an oven-dried 50 mL Schlenk tube under nitrogen atmosphere, 2-(4-oxopiperidin-1-yl)acetonitrile (1.01 g, 7.35 mmol), allylic alcohol (0.16 mL, 2.44 mmol), Xantphos (0.07 g, 0.12 mmol), $[PdCl(allyl)]_2$ (0.02 g, 0.06 mmol) and *D,L*-proline (0,08 g, 0.73 mmol) were dissolved in 15 mL of DMSO. The reaction mixture was stirred at 70 ºC overnight. The reaction mixture was cooled down and extracted with EtOAc/H_2O. The organic layer was washed several times with brine. The organic extracts were collected, dried over Na_2SO_4, and the solvents eliminated under reduced pressure. The crude was purified by flash chromatography (1:1 mixture of Hexane/EtOAc as eluents), affording the final product as a yellow oil (0.40 g, 31% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75-5.60 (m, 1H), 5.05-4.94 (m, 2H), 3.61 (s, 2H), 3.05-2.95 (m, 2H), 2.71 (td, *J* = 10.9, 3.8 Hz, 1H), 2.64-2.46 (m, 3H), 2.45-2.34 (m, 2H), 2.06-1.94 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 207.5 (C), 135.1 (CH), 117.2 (CH), 114.3 (C), 56.8 (CH_2), 52.3 (CH_2), 48.5 (CH), 45.5 (CH_2), 40.3 (CH_2), 31.4 (CH_2).

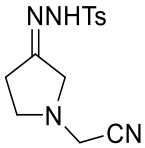
N'-(1-(Cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (**69a**)



Compound **68a** (1.60 g, 11.63 mmol) was added to a stirred solution of *p*-toluensulfonylhydrazide (2.41 g, 12.98 mmol) in MeOH (7.3 mL). The reaction was stirred for 3 h at r.t. (until total consumption of the starting carbonyl). Then, the solvent was eliminated, giving a white solid which was purified by flash chromatography in a mixture 1:2:0.5 Hexane/EtOAc/DCM to yield **69a** as white crystals (76%, 2.40 g). R_f (hexanes/ethyl acetate/dichloromethane 1:2:0.5) = 0.28.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.00 (bs, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.55 (s, 2H), 2.67 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.0 Hz, 2H), 2.48-2.40 (m, 7H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.8 (C), 144.2 (C), 135.0 (C), 129.6 (CH), 128.0 (CH), 114.3 (C), 52.2 (CH_2), 50.8 (CH_2), 45.7 (CH_2), 34.0 (CH_2), 26.5 (CH_2), 21.6 (CH_3). m.p. 148.4-149.3 ºC.

(*E*)-*N*'-(1-(Cyanomethyl)pyrrolidin-3-ylidene)-4-methylbenzenesulfonohydrazide (**69b**)

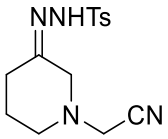


Compound **68b** (0.32 g, 2.61 mmol) was added to a stirred solution of *p*-toluensulfonylhydrazide (0.54 g, 2.91 mmol) in MeOH (1.6 mL). The reaction was stirred for 1 day at r.t. (until total consumption of the starting carbonyl). Then, the solvent was eliminated, giving a white solid which was purified by flash chromatography in a mixture 1:2:0.5 Hexane/EtOAc/DCM to yield **69b** as a white solid (66%, 0.50 g). R_f (hexanes/ethyl acetate/dichloromethane 1:2:0.5) = 0.27.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.46 (bs, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 3.70 (s, 2H), 3.36 (s, 2H), 2.94 (t, *J* = 6.7 Hz, 2H), 2.47 (m, 5H). **^{13}C NMR**

(75 MHz, $CDCl_3$) δ 160.0 (C), 144.4 (C), 135.0 (C), 129.7 (CH), 127.96 (CH), 113.97 (C), 55.6 (CH_2), 50.9 (CH_2), 41.6 (CH_2), 27.7 (CH_2), 21.6 (CH_3). m.p. 146.1-147.0 ºC

(*E*)-*N*'-(1-(Cyanomethyl)piperidin-3-ylidene)-4-methylbenzenesulfonohydrazide (**69c**)

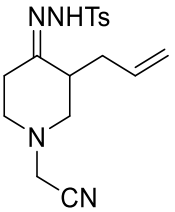


Compound **68c** (0.33 g, 2.38 mmol) was added to a stirred solution of *p*-toluensulfonylhydrazide (0.49 g, 2.66 mmol) in MeOH (1.5 mL). The reaction was stirred for 1 day at r.t. (until total consumption of the starting carbonyl). Then, the solvent was eliminated, giving a white solid which was purified by flash chromatography in a mixture 1:1 Hexane/EtOAc to yield **69c** as a white solid (55%, 0.40 g). R_f (hexanes/ethyl acetate 1:1) = 0.17.

Compound **69c** is observed in the NMR as a mixture of the Z/E isomers:

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.80 (m, 3H), 7.37 (m, isom. min.), 7.33 (d, *J* = 8.0 Hz, 2H), 3.57 (s, isom. min.), 3.54 (s, 2H), 3.24 (s, isom. min.), 3.12 (s, 2H), 2.69-2.62 (m, 2H), 2.47 (s, isom. min), 2.45 (s, 3H), 2.32-2.23 (m, 2H), 1.82-1.74 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.8 (C), 144.3 (C), 135.0 (C), 129.6 (CH), 128.0 (CH), 114.0 (C), 57.9 (CH_2), 51.5 (CH_2), 45.7 (CH_2), 23.8 (CH_2), 23.3 (CH_2), 21.6 (CH_3). m.p. 49.8-50.6 ºC.

(*E*)-*N*'-(3-allyl-1-(Cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfono hydrazide (**74**)

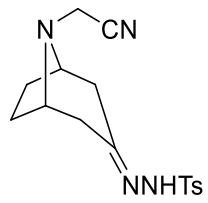


Compound **73** (0.40 g, 2.28 mmol) was added to a stirred solution of *p*-toluensulfonylhydrazide (0.47 g, 2.55 mmol) in MeOH (2 mL). The reaction was stirred for 1 day at r.t. (until total consumption of the starting carbonyl). Then, the solvent was eliminated, giving a white solid which was purified by flash

chromatography in a mixture 1:2:0.5:0.1 Hexane/EtOAc/DCM/MeOH to yield **74** as a white solid (76%, 0.60 g). R_f (hexanes/ethyl acetate/dichloromethane/methanol 1:2:0.5:0.1) = 0.35.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.48 (bs, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 5.70-5.54 (m, 1H), 5.05-4.87 (m, 1H), 3.54 (s, 2H), 2.84-2.49 (m, 4H), 2.47 (s, 3H), 2.45-2.05 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.1 (C), 144.2 (C), 135.7 (CH), 134.9 (C), 129.5 (CH), 128.2 (CH), 116.8 (CH_2), 114.3 (C), 56.5 (CH_2), 51.0 (CH_2), 45.8 (CH_2), 42.5 (CH), 33.8 (CH_2), 25.3 (CH_2), 21.6 (CH_3). m.p. 158.4-159.2 ºC.

N'-((1*R*,5*S*,*Z*)-8-(Cyanomethyl)-8-azabicyclo[3.2.1]octan-3-ylidene)-4-methyl benzenesulfonohydrazide (**76**)

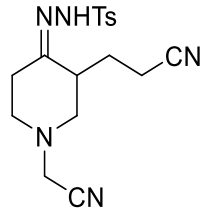


In a 25 mL round-bottom flask, nortropinone hydrochloride salt (1.63 g, 10.11 mmol) was dissolved in 7.5 mL of water. When the salt was entirely dissolved, a 37% commercial aqueous solution of formaldehyde (1.00 mL) was added and the reaction was stirred at r.t. for five minutes. Then, a solution of KCN (0.66 g, 10.11 mmol) in water (7.5 mL) was added to the initial flask. The reaction was stirred for 24 hours at r.t. The reaction was extracted several times with $CHCl_3$. The organic extracts were dried with Na_2SO_4. The solvents were eliminated under reduced pressure, affording the final carbonyl compound as a colourless oil in a pure form (1.60 g, 96% yield), which was used without further purification in a the reaction with *p*-toluensulfonylhydrazide (2.14 g, 11.50 mmol) in MeOH (6.5 mL). The reaction was stirred for 1 day at r.t. (until total consumption of the starting carbonyl). Then, the solvent was eliminated, giving a white solid which was purified by flash chromatography in a mixture 1:2:0.5 Hexane/EtOAc/DCM to yield **8** as a white solid (90%, 3.10 g). R_f (hexanes/ethyl acetate/dichloromethane 1:2:0.5) = 0.26.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.79 (bs, 1H), 3.49-3.40 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.39 (s, 2H), 2.49-2.47 (m, 1H), 2.45 (s, 3H), 2.34-2.15 (m, 2H), 2.03-1.91 (m, 1H), 1.62-1.53 (m, 1H), 1.43-1.33 (m, 1H). **^{13}C NMR** (75 MHz,

$CDCl_3$) δ 155.9 (C), 144.1 (C), 135.1 (C), 129.5 (CH), 127.9 (CH), 117.1 (C), 59.7 (CH), 58.6 (CH), 40.7 (CH_2), 40.2 (CH_2), 34.0 (CH_2), 27.3 (CH_2), 26.2 (CH_2), 21.6 (CH_3). m.p. 162.4-163.2 ºC

(*E*)-*N*'-(3-(2-Cyanoethyl)-1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfono hydrazide (**80**)



To a solution of 2-(4-oxopiperidin-1-yl)acetonitrile (1.00g, 7.23 mmol) in toluene (1 mL) was added pyrrolidine (0.67 mL, 8.24 mmol) and the reaction was heated to reflux employing a Dean-Stark trap overnight. The trap is removed, and the reaction flask is cooled with an external ice bath. Then, acrylonitrile (0.59 mL, 9.0 mmol) was added. The reaction mixture was heated in an oil bath at 60ºC overnight. The flask was cooled down with an external ice bath and 0.52 mL of acetic acid and 0.4 mL of water are added. The brown mixture was stirred for one hour at r.t. The reaction crude was then extracted with diethyl ether and water, washed with brine, dried over Na_2SO_4 and the solvents eliminated under reduced pressure. The obtained dark oil was diluted with MeOH (2 mL) and *p*-toluensulfonylhydrazide was added (1.53 g, 8.24 mmol). The reaction was stirred at r.t. for 3 days. The obtained crude was purified with flash chromatography (1:2 mixture of hexane/AcOEt), affording **80** in a 60% yield (1.55 g). R_f (hexanes/ethyl acetate 1:2) = 0.19.

Compound **80** is observed in the NMR as a mixture of the Z/E isomers:

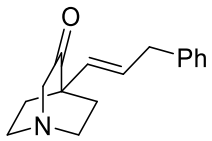
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.40-7.32 (m, 2H), 3.55 (s, 2H), 2.85-2.51 (m, 4H), 2.50-2.42 (m, 5H), 2.40-2.00 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.8 (C), 156.5 (C), 144.6 (C), 144.2 (C), 135.0 (C), 134.7 (C), 129.7 (CH), 129.6 (CH), 128.1 (CH), 128.0 (CH), 119.5 (C), 114.3 (C), 57.3 (CH_2), 52.2 (CH_2), 51.0 (CH_2), 50.8 (CH_2), 45.7 (CH_2), 45.6 (CH_2), 41.7 (CH_2), 34.0 (CH), 26.5 (CH_2), 25.7 (CH_2), 21.6 (CH_2), 14.8 (CH_3). m.p. 115.5-116.4 ºC

E.4.2. General procedures for the synthesis of the cyclization products and characterization data

General procedure (**A**) for the reaction of *N*-tosylhydrazones with alkenylboronic acids under microwave irradiation to form compounds **70**, **71**, **72**, **77**, **78**, **79** and **81**: A microwave vial provided with a triangular stir bar was charged with the corresponding tosylhydrazone (0.15 mmol), the alkenyl boronic acid (0.30 mmol), K_2CO_3 (41.4 mg, 0.30 mmol) in 1.2 mL of dry 1,4-dioxane and 200 µL of dry DMF. The vial was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at the desired temperature (120 ºC) during the reaction time (4 h) in a Biotage Initiator microwave apparatus. When the reaction finished, it was allowed to reach room temperature, solvents were eliminated and a saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (5 mL) 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 Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Finally, the products were purified by flash chromatography on silica gel.

General procedure (**B**) for the reaction of *N*-tosylhydrazones with alkenylboronic acids under microwave irradiation to form compounds **75**: A microwave vial provided with a triangular stir bar was charged with the tosylhydrazone **74** (0.15 mmol), the alkenyl boronic acid (0.30 mmol), K_2CO_3 (41.4 mg, 0.30 mmol) in 1.2 mL of dry 1,4-dioxane. The vial was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at the desired temperature (120 ºC) during the reaction time (4 h) in a Biotage Initiator microwave apparatus. When the reaction finished, it was allowed to reach room temperature, solvents were eliminated and a saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (5 mL) 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 Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Finally, the products were purified by flash chromatography on silica gel.

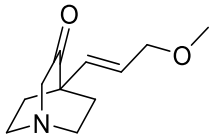
(1*s*,4*s*)-4-((*E*)-3-Phenylprop-1-en-1-yl)quinuclidin-3-one (**70a**)



From *N*'-(1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (45.9 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.6 mg, 0.30 mmol), **70a** was obtained in 50% isolated yield (18.0 mg) following ***General procedure A*** as a colourless oil. **70a** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2H), 7.23-7.17 (m, 3H), 5.87 (d, *J* = 15.8 Hz, 1H), 5.55 (dt, *J* = 15.9, 6.9 Hz, 1H), 3.44 (d, *J* = 6.9 Hz, 2H), 3.33 (s, 2H), 3.16-2.95 (m, 4H), 1.98 (t, *J* = 7.8 Hz, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 217.7 (C), 140.3 (C), 130.7 (CH), 129.3 (CH), 128.5 (CH), 128.4 (CH), 126.0 (CH), 62.4 (CH_2), 47.5 (CH_2), 44.9 (C), 39.3 (CH_2), 30.4 (CH_2). HRMS(ESI): calcd. For $[C_{10}H_{20}NO]^+$: 242.1539, found: 242.1539. IR (Nujol, cm^{-1}) = 1721, 1375, 1303, 1160, 1048, 972, 737, 709.

(1*s*,4*s*)-4-((*E*)-3-Methoxyprop-1-en-1-yl)quinuclidin-3-one (**70b**)

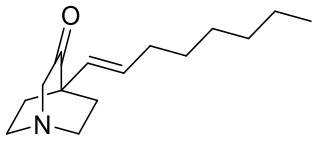


From *N*'-(1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (45.9 mg, 0.15 mmol) and (*E*)-(3-Methoxyprop-1-en-1-yl)boronic acid (34.7 mg, 0.3 mmol), **3a** was obtained in 70% isolated yield (20.5 mg) following ***General procedure A*** as a colourless oil. **3a** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.15.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (d, *J* = 16.1 Hz, 1H), 5.53 (dt, *J* = 16.1, 6.0 Hz, 1H), 3.96 (dd, *J* = 5.9, 1.5 Hz, 2H), 3.34 (s, 3H), 3.32 (s, 2H), 3.17-2.95 (m, 4H), 1.98 (t, *J* = 7.8 Hz, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 217.4 (C), 132.7 (CH), 126.7 (CH), 73.1 (CH_2), 62.4 (CH_2), 57.9 (CH_3), 47.4 (CH_2), 44.8 (C), 30.3 (CH_2). HRMS(ESI): calcd. For

$[C_{11}H_{18}NO_2]^+$: 196.1332, found: 193.1336. IR (Nujol, cm^{-1}) = 1723, 1647, 1375, 1193, 1112, 972, 717.

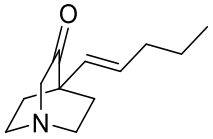
(1*s*,4*s*)-4-((*E*)-Oct-1-en-1-yl)quinuclidin-3-one (**70c**)



From *N*'-(1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (45.9 mg, 0.15 mmol) and *trans*-1-octen-1-ylboronic acid (23.4 mg, 0.15 mmol), **70c** was obtained in 58% isolated yield (20.3 mg) following ***General procedure A*** as a colourless oil. **70c** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.26.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, *J* = 16.0 Hz, 1H), 5.40 (dt, *J* = 15.9, 6.7 Hz, 1H), 3.33 (s, 2H), 3.17-2.95 (m, 4H), 2.15-2.00 (m, 3H), 1.45-1.20 (m, 7H), 1.96 (t, *J* = 7.8 Hz, 4H), 0.89 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.0 (C), 130.9 (CH), 128.9 (CH), 62.5 (CH_2), 47.6 (CH_2), 44.8 (C), 32.9 (CH_2), 31.6 (CH_2), 30.5 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3). HRMS(ESI): calcd. For $[C_{15}H_{16}NO]^+$: 236.2008, found: 236.2005. IR (Nujol, cm^{-1}) = 1730, 1662, 1379, 1123, 1048, 967, 722.

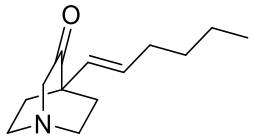
(1*s*,4*s*)-4-((*E*)-Pent-1-en-1-yl)quinuclidin-3-one (**70d**)



From *N*'-(1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (45.9 mg, 0.15 mmol) and *trans*-1-penten-1-ylboronic acid (34.1 mg, 0.30 mmol), **70d** was obtained in 51% isolated yield (14.0 mg) following ***General procedure A*** as a colourless oil. **70d** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, *J* = 15.9 Hz, 1H), 5.40 (dt, *J* = 15.9, 6.8 Hz, 1H), 3.32 (s, 2H), 3.17-2.95 (m, 4H), 2.06 (q, *J* = 6.7 Hz, 2H), 1.95 (t, *J* = 7.8 Hz, 4H), 1.41 (h, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.0 (C), 130.6 (CH), 129.1 (CH), 62.4 (CH_2), 47.5 (CH_2), 44.8 (C), 34.9 (CH_2), 30.5 (CH_2), 22.4 (CH_2), 13.5 (CH_3). HRMS(ESI): calcd. For $[C_{12}H_{20}NO]^+$: 194.1539, found: 194.1539. IR (Nujol, cm^{-1}) = 1730, 1651, 1374, 1191, 1053, 969, 720.

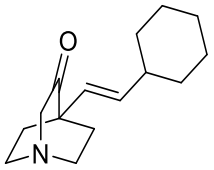
(1*s*,4*s*)-4-((*E*)-Hex-1-en-1-yl)quinuclidin-3-one (**70e**)



From *N*'-(1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (45.9 mg, 0.15 mmol) and *trans*-1-hexen-1-ylboronic acid (38.3 mg, 0.30 mmol), **70e** was obtained in 58% isolated yield (19.0 mg) following ***General procedure A*** as a colourless oil. **70e** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.24.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, *J* = 16.0 Hz, 1H), 5.40 (dt, *J* = 16.0, 6.7 Hz, 1H), 3.32 (s, 2H), 3.06 (m, 4H), 2.15-2.05 (m, 2H), 1.95 (t, *J* = 7.8 Hz, 4H), 1.42-1.25 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.1 (C), 130.8 (CH), 128.9 (CH), 62.5 (CH_2), 47.6 (CH_2), 44.8 (CH_2), 32.5 (CH_2), 31.5 (CH_2), 30.5 (CH_2), 22.1 (CH_2), 13.9 (CH_3). HRMS(ESI): calcd. For $[C_{13}H_{22}NO]^+$: 208.1696, found: 208.1695. IR (Nujol, cm^{-1}) = 1734, 1654, 1369, 1190, 1050, 971, 724.

(1*s*,4*s*)-4-((*E*)-2-Cyclohexylvinyl)quinuclidin-3-one (**70f**)

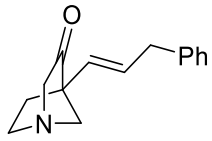


From *N*'-(1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (45.9 mg, 0.15 mmol) and (*E*)-(2-cyclohexylvinyl)boronic acid (46.2 mg, 0.3 mmol), **70f** was obtained in 57% isolated yield (20.0 mg) following ***General procedure A*** as a colourless oil. **70f** was purified by

flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.23.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (d, *J* = 16.1 Hz, 1H), 5.33 (dd, *J* = 16.1, 6.8 Hz, 1H), 3.31 (s, 2H), 3.19-2.95 (m, 4H), 2.05-1.85 (m, 4H), 1.78-1.62 (m, 3H), 1.35-0.80 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.1 (C), 136.5 (CH), 126.6 (CH), 62.53 (CH_2), 47.64 (CH_2), 44.6 (CH_2), 40.9 (CH), 33.0 (CH_2), 30.5 (CH_2), 26.1 (CH_2), 26.0 (CH_2). HRMS(ESI): calcd. For $[C_{15}H_{24}NO]^+$: 234.1852, found: 234.1847

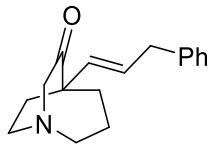
(1*S*,4*S*)-4-((*E*)-3-Phenylprop-1-en-1-yl)-1-azabicyclo[2.2.1]heptan-3-one (**71**)



From (*E*)-*N*'-(1-(cyanomethyl)pyrrolidin-3-ylidene)-4-methylbenzenesulfono hydrazide (37.5 mg, 0.13 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (41.4 mg, 0.26 mmol), **71** was obtained in 51% isolated yield (15.0 mg) following ***General procedure A*** as a colourless oil. **71** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.26.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H), 7.26-7.18 (m, 3H), 5.90-5.75 (m, 2H), 3.46 (d, *J* = 5.1 Hz, 2H), 3.31-3.15 (m, 2H), 3.05-3.00 (m, 1H), 2.99-2.95 (m, 1H), 2.88 (dd, *J* = 10.2, 4.1 Hz, 1H), 2.84-2.73 (m, 1H), 2.16-2.05 (m, 1H), 1.92-1.82 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 217.8 (C), 139.9 (C), 132.6 (CH), 128.5 (CH), 128.4 (CH), 126.1 (CH), 124.2 (CH), 65.5 (CH_2), 64.2 (CH_2), 58.8 (C), 53.8 (CH_2), 39.3 (CH_2), 32.0 (CH_2). HRMS(ESI): calcd. For $[C_{15}H_{18}NO]^+$: 228.1382, found: 228.1377. IR (Nujol, cm^{-1}) = 1750, 1669, 1149, 1375, 1158, 1070, 972, 814, 750, 698.

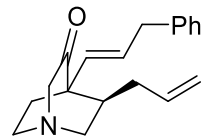
(1*R*,5*S*)-5-((*E*)-3-Phenylprop-1-en-1-yl)-1-azabicyclo[3.2.2]nonan-6-one (**72**)



From (*E*)-*N*'-(1-(cyanomethyl)piperidin-3-ylidene)-4-methylbenzenesulfono hydrazide (45.9 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.5 mg, 0.30 mmol), **72** was obtained in 40% isolated yield (14.0 mg) following ***General procedure B*** as a colourless oil. **72** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H), 7.26-7.16 (m, 3H), 5.64-5.57 (m, 2H), 3.43-3.36 (m, 3H), 3.35-3.27 (m, 2H), 3.26-3.22 (m, 1H), 3.18-3.13 (m, 1H), 3.12-3.02 (m, 2H), 2.04-1.93 (m, 2H), 1.82-1.74 (m, 2H), 1.66-1.58 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 218.5 (C), 140.0 (C), 130.5 (CH), 129.8 (CH), 128.5 (CH), 128.4 (CH), 126.1 (CH), 63.4 (CH_2), 61.6 (CH_2), 53.5 (CH_2), 50.8 (C), 39.2 (CH_2), 35.3 (CH_2), 19.2 (CH_2). HRMS(ESI): calcd. For $[C_{16}H_{20}NO]^+$: 242.1539, found: 242.1539. IR (Nujol, cm^{-1}) = 1745, 1660, 1375, 1167, 1068, 969, 717, 695.

(1*S*,4*S*,5*R**)-5-Allyl-4-((*E*)-3-phenylprop-1-en-1-yl)quinuclidin-3-one (**75a**)



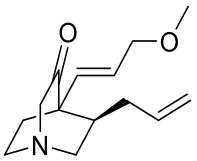
From (*E*)-*N*'-(3-allyl-1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzene sulfonohydrazide (51.9 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.5 mg, 0.30 mmol), **75a** was obtained in 57% isolated yield (24.0 mg) following ***General procedure B*** as a colourless oil. **75a** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.22.

Compound **75a** was obtained as a 7:1 mixture of diastereoisomers (**75a** major isomer, **75a´** minor isomer).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.28 (m, 2H), 7.24-7.17 (m, 3H), 6.17 (d, *J* = 16.1 Hz, 1H), 5.72-5.59 (m, 2H), 5.52 (dt, *J* = 15.9, 6.9 Hz, isom **75a'**), 5.10-4.99 (m, 2H), 3.50 (d, *J* = 7.2 Hz, isom **75a'**), 3.47 (d, *J* = 7.0 Hz, 2H), 3.31 (d, *J* = 20.0 Hz, 1H), 3.24 (d, *J* = 18.6 Hz, 1H), 3.22-3.15 (m, 1H), 3.12-3.05 (m, 1H), 3.04-2.97 (m, 1H), 2.71 (ddd, *J* = 14.0, 5.8, 2.5 Hz, 1H), 2.47-2.42 (m, 1H), 2.21-2.14 (m, 1H), 2.09 (ddd, *J* = 13.5, 10.4, 5.3 Hz, 1H), 1.92 (ddd, *J* = 13.6, 10.5, 5.3 Hz, 1H), 1.68 (ddd, *J* = 14.3, 11.4, 7.7 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 216.8 (C), 140.3 (C), 135.7 (C, isom **75a'**),

135.3 (CH), 130.9 (CH, isom **75a'**), 130.3 (CH), 129.6 (CH, isom **75a'**), 128.8 (CH), 128.5 (CH, isom **75a'**), 128.4 (CH), 128.3 (CH), 126.1 (CH), 117.1 (CH_2), 116.8 (CH_2, isom **75a'**), 62.5 (CH_2), 61.6 (CH_2, isom **75a'**), 54.1 (CH_2, isom **75a'**), 53.8 (CH_2), 48.6 (C, isom **75a'**), 48.2 (C), 47.5 (CH_2), 43.1 (CH), 39.6 (CH_2), 39.4 (CH_2, isom **75a'**), 37.5 (CH_2), 37.1 (CH_2, isom **75a'**), 34.8 (CH, isom **75a'**), 31.1 (CH_2), 21.6 (CH_2, isom **75a'**). HRMS(ESI): calcd. For $[C_{19}H_{24}NO]^+$: 282.1852, found: 282.1851. IR (Nujol, cm^{-1}) = 1723, 1642, 1378, 976, 917, 746, 698.

(1*S*,4*S*,5*R**)-5-Allyl-4-((*E*)-3-methoxyprop-1-en-1-yl)quinuclidin-3-one (**75b**)

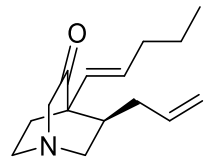


From (*E*)-*N*'-(3-allyl-1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydra zide (51.9 mg, 0.15 mmol) and (*E*)-(3-methoxyprop-1-en-1-yl)boronic acid (34.7 mg, 0.3 mmol), **75b** was obtained in 55% isolated yield (19.0 mg) following ***General procedure B*** as a yellow oil. **75b** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.20.

Compound **75b** was obtained as a 7:1 mixture of diastereoisomers (**75b** major isomer, **75b´** minor isomer).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (d, *J* = 16.4 Hz, 1H), 5.51-5.54 (m, 2H), 5.49 (dt, *J* = 16.1, 5.9 Hz, isom **75b'**), 5.07-4.97 (m, 2H), 3.98 (dd, *J* = 6.0, 1.5 Hz, 2H), 3.35 (s, isom **75b'**), 3.34 (s, 3H), 3.27-3.19 (m, 2H), 3.18-2.95 (m, 4H), 2.69 (ddd, *J* = 14.0, 5.5, 2.3 Hz, 1H), 2.46-2.36 (m, 1H), 2.24-2.00 (m, 2H), 1.91 (ddd, *J* = 13.6, 10.2, 5.6 Hz, 1H), 1.64 (ddd, *J* = 14.1, 11.2, 7.8 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 216.9 (C, isom **75b'**), 216.4 (C), 135.5 (CH, isom **75b'**), 135.1 (CH), 131.4 (CH, isom **75b'**), 130.9 (CH), 128.4 (CH, isom **75b'**), 127.72 (CH), 117.2 (CH), 116.9 (CH, isom **75b'**), 73.3 (CH_2), 73.1 (CH_2, isom **75b'**), 69.9 (CH_2, isom **75b'**), 62.4 (CH_2), 61.5 (CH_2, isom **75b'**), 57.9 (CH_3), 54.0 (CH_2, isom **75b'**), 53.7 (CH_2), 48.54 (C, isom **75b'**), 48.2 (C), 47.4 (CH_2), 42.7 (CH), 37.3 (CH_2), 36.8 (CH, isom **75b'**), 34.7 (CH_2, isom **75b'**), 30.8 (CH_2), 21.51 (CH_2, isom **75b'**). HRMS(ESI): calcd. For $[C_{14}H_{22}NO_2]^+$: 236.1645, found: 236.1638. IR (Nujol, cm^{-1}) = 1726, 1640, 1373, 1186, 1116, 974, 910, 717.

(1*S*,4*S*,5*R**)-5-Allyl-4-((*E*)-pent-1-en-1-yl)quinuclidin-3-one (**75c**)



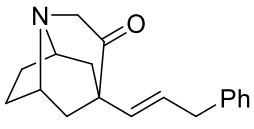
From (*E*)-*N*'-(3-allyl-1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzene sulfonohydrazide (51.9 mg, 0.15 mmol) and (*trans*-1-penten-1-ylboronic acid (34.1 mg, 0.30 mmol), **75c** was obtained in 45% isolated yield (15.0 mg) following ***General procedure B*** as a colourless oil. **75c** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.22.

Compound **75c** was obtained as a 4.5:1 mixture of diastereoisomers (**75c** major isomer, **75c´** minor isomer).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (dt, *J* = 16.1, 1.4 Hz, 1H), 5.72-5.57 (m, 1H), 5.51 (dt, *J* = 16.2, 6.8 Hz, 1H), 5.36 (dt, *J* = 16.0, 6.7 Hz, isom **75c'**), 5.10-4.97 (m, 2H), 3.34-3.30 (m, isom **75c'**), 3.28-3.22 (m, 2H), 3.20-2.93 (m, 3H), 2.69 (ddd, *J* = 14.0, 5.7, 2.4 Hz, 1H), 2.47-2.37 (m, 1H), 2.20-2.00 (m, 5H), 1.63 (ddd, *J* = 14.0, 11.3, 7.8 Hz, 1H), 1.42 (h, *J* = 7.3 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, isom **75c'**), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 217.3 (C), 135.9 (CH, isom **75c'**), 135.4 (CH), 132.2 (CH, isom **75c'**), 131.61 (CH), 127.9 (CH, isom **75c'**), 127.3 (CH), 116.9 (CH_2), 116.7 (CH_2, isom **75c'**), 62.5 (CH_2), 61.7 (CH_2, isom **75c'**), 54.1 (CH_2, isom **75c'**), 53.9 (CH_2), 48.4 (C, isom **75c'**), 48.1 (C), 47.6 (CH_2), 43.1 (CH), 37.4 (CH_2), 37.0 (CH, isom **75c'**), 35.1 (CH_2), 35.0 (CH_2, isom **75c'**), 34.8 (CH_2, isom **75c'**), 31.2 (CH_2), 22.6 (CH_2, isom **75c'**), 22.4 (CH_2), 21.6 (CH_2, isom **75c'**), 13.7 (CH_3, isom **75c'**), 13.62 (CH_3). HRMS(ESI): calcd. For $[C_{15}H_{24}NO]^+$: 234.1852, found: 234.1851. IR (Nujol, cm^{-1}) = 1728, 1633, 1378, 976, 917, 746, 698.

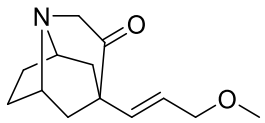
(*E*)-7-(3-Phenylprop-1-en-1-yl)hexahydro-3,7-methanoindolizin-6(5*H*)-one (**77a**)



From *N*'-((1*R*,5*S*,*Z*)-8-(cyanomethyl)-8-azabicyclo[3.2.1]octan-3-ylidene)-4-methyl benzenesulfonohydrazide (49.8 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.5 mg, 0.30 mmol), **77a** was obtained in 50% isolated yield (20.0 mg) following ***General procedure A*** as a colourless oil. **77a** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.23.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H), 7.25-7.19 (m, 3H), 5.74 (dt, *J* = 11.8, 7.6 Hz, 1H), 5.41 (d, *J* = 11.6 Hz, 1H), 3.57 (s, 2H), 3.53-3.45 (m, 2H), 3.40 (d, *J* = 7.5 Hz, 2H), 2.47-2.37 (m, 2H), 2.30-2.20 (m, 2H), 1.90 (d, *J* = 14.2 Hz, 2H), 1.76-1.70 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 215.6 (C), 140.2 (C), 132.8 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 126.1 (CH), 55.0 (CH_2), 54.5 (CH), 43.3 (C), 40.4 (CH_2), 35.8 (CH_2), 32.6 (CH_2). HRMS(ESI): calcd. For $[C_{18}H_{22}NO]^+$: 268.1695, found: 268.1694.

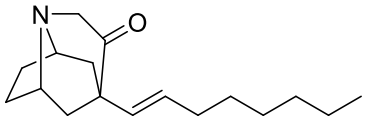
(*E*)-7-(3-Methoxyprop-1-en-1-yl)hexahydro-3,7-methanoindolizin-6(5*H*)-one (**77b**)



From *N*'-((1*R*,5*S*,*Z*)-8-(cyanomethyl)-8-azabicyclo[3.2.1]octan-3-ylidene)-4-methyl benzenesulfonohydrazide (49.8 mg, 0.15 mmol) and (*E*)-(3-methoxyprop-1-en-1-yl)boronic acid (34.7 mg, 0.3 mmol), **77b** was obtained in 52% isolated yield (16.0 mg) following ***General procedure A*** as a yellow oil. **77b** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.26.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (dt, *J* = 12.5, 6.4 Hz, 1H), 5.41 (dt, *J* = 12.1, 1.7 Hz, 1H), 3.91 (dd, *J* = 6.4, 1.7 Hz, 2H), 3.53 (s, 2H), 3.51-3.43 (m, 2H), 3.35 (s, 3H), 2.40-2.29 (m, 2H), 2.27-2.19 (m, 2H), 1.81 (dd, *J* = 14.4, 2.5 Hz, 2H), 1.75-1.64 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 215.4 (C), 130.9 (CH), 129.6 (CH), 69.6 (CH_2), 58.2 (CH_3), 54.9 (CH_2), 54.4 (CH), 43.5 (C), 40.2 (CH_2), 32.6 (CH_2). HRMS(ESI): calcd. For $[C_{13}H_{20}NO_2]^+$: 222.1488, found: 222.1490. IR (Nujol, cm^{-1}) = 1730, 1645, 1372, 1265, 1161, 720.

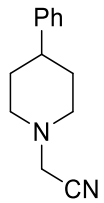
(*E*)-7-(Oct-1-en-1-yl)hexahydro-3,7-methanoindolizin-6(5*H*)-one (**77c**)



From *N*'-((1*R*,5*S*,*Z*)-8-(cyanomethyl)-8-azabicyclo[3.2.1]octan-3-ylidene)-4-methyl benzenesulfonohydrazide (49.8 mg, 0.15 mmol) and *trans*-1-octen-1-ylboronic acid (23.4 mg, 0.15 mmol), **9c** was obtained in 40% isolated yield (15.0 mg) following ***General procedure A*** as a yellow oil. **9c** was purified by flash chromatography on silica gel using a gradient of eluents (Hex/EtOAc 1:1 -> DCM/MeOH 95:5). R_f (DCM/MeOH 95:5) = 0.27.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (dt, *J* = 11.8, 7.5 Hz, 1H), 5.28 (dt, *J* = 11.8, 1.5 Hz, 1H), 3.53 (s, 2H), 3.51-3.43 (m, 2H), 2.39-2.29 (m, 2H), 2.27-2.20 (m, 2H), 2.07-1.95 (m, 2H), 1.84 (dd, *J* = 14.9, 2.1 Hz, 1H), 1.74 (d, *J* = 6.1 Hz, 1H), 1.69 (d, *J* = 6.4 Hz, 1H), 1.40-1.19 (m, 9H), 0.90 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 215.7 (C), 134.9 (CH), 126.4 (CH), 55.0 (CH_2), 54.5 (CH), 43.3 (C), 40.1 (CH_2), 32.6 (CH_2), 31.7 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3). HRMS(ESI): calcd. For $[C_{17}H_{28}NO]^+$: 262.2165, found: 262.2161. IR (Nujol, cm^{-1}) = 1736, 1649, 1375, 1259, 1158, 717.

2-(4-Phenylpiperidin-1-yl)acetonitrile (**78**)

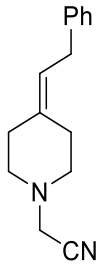


From *N*'-(1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (45.9 mg, 0.15 mmol) and phenylboronic acid (36.5 mg, 0.30 mmol), **78** was obtained in 67% isolated yield (20.0 mg) following ***General procedure A*** as a colourless oil. **78** was purified by flash chromatography on silica gel using a mixture of Hex/EtOAc 4:1 R_f (Hex/EtOAc 4:1) = 0.14.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.30 (m, 2H), 7.22-7.20 (m, 3H), 3.60 (s, 2H), 2.99-2.90 (m, 2H), 2.62-2.46 (m, 3H), 1.99-1.75 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ

145.5 (C), 128.5 (CH), 126.7 (CH), 126.3 (CH), 114.7 (C), 52.8 (CH_2), 46.5 (CH_2), 41.45 (CH_2), 33.05 (CH_2). HRMS(ESI): calcd. For $[C_{13}H_{17}N_2]^+$: 201.1386, found: 201.1388.

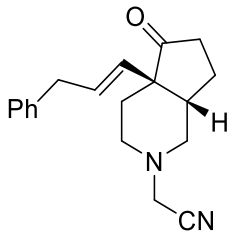
2-(4-(2-Phenylethylidene)piperidin-1-yl)acetonitrile (**79**)



From *N*'-(1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzenesulfonohydrazide (45.9 mg, 0.15 mmol) and *trans*-2-phenylvinylboronic acid (44.3 mg, 0.30 mmol), **79** was obtained in 73% isolated yield (24.0 mg) following ***General procedure A*** as a colourless oil. **79** was purified by flash chromatography on silica gel using a mixture of Hex/EtOAc 1:1 R_f (Hex/EtOAc 1:1) = 0.46.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.29 (m, 2H), 7.25-7.17 (m, 3H), 5.43 (t, *J* = 7.6 Hz, 1H), 3.58 (s, 2H), 3.40 (d, *J* = 7.4 Hz, 2H), 2.67-2.56 (m, 4H), 2.49-2.40 (m, 2H), 2.36-2.28 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.0 (C), 134.5 (C), 128.4 (CH), 128.3 (CH), 125.9 (CH), 122.6 (CH), 114.7 (CH), 53.9 (CH_2), 53.2 (CH_2), 46.2 (CH_2), 35.5 (CH_2), 33.4 (CH_2), 27.9 (CH_2). HRMS(ESI): calcd. For $[C_{15}H_{19}N_2]^+$: 227.1542, found: 227.1543.

2-((4a*R**,7a*S**)-5-oxo-4a-((*E*)-3-Phenylprop-1-en-1-yl)octahydro-2*H*-cyclopenta[*c*]pyridin-2-yl)acetonitrile (**81**)



From (*E*)-*N*'-(3-(2-cyanoethyl)-1-(cyanomethyl)piperidin-4-ylidene)-4-methylbenzene sulfonohydrazide (53.9 mg, 0.15 mmol) and *trans*-3-phenyl-1-propen-1-ylboronic acid (48.5 mg, 0.30 mmol), **81** was obtained in 50% isolated yield

(22.0 mg) following ***General procedure B*** as a colourless oil. **81** was purified by flash chromatography on silica gel using a mixture of Hex/EtOAc 1:1 R_f (Hex/EtOAc 1:1) = 0.26.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.29 (m, 2H), 7.24-7.14 (m, 3H), 5.67 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.43 (d, *J* = 15.8 Hz, 1H), 3.50 (s, 1H), 3.49 (s, 1H), 3.40 (d, *J* = 6.7 Hz, 2H), 2.80 (dd, *J* = 11.4, 5.0 Hz, 1H), 2.60-2.52 (m, 1H), 2.50-2.21 (m, 4H), 2.12-1.97 (m, 1H), 1.92-1.83 (m, 1H), 1.70-1.60 (m, 1H), 0.90 (t, *J* = 6.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 217.6 (C), 139.8 (C), 131.8 (CH), 131.4 (CH), 128.4 (CH), 128.4 (CH), 126.1 (CH), 114.5 (C), 53.3 (CH_2), 52.5 (C), 49.4 (CH_2), 46.4 (CH_2), 40.8 (CH), 39.0 (CH_2), 34.9 (CH_2), 34.1, 29.3 (CH_2), 22.3, 22.0 (CH_2). HRMS(ESI): calcd. For $[C_{12}H_{18}NaO]^+$: 201.1249, found: 201.1254.

E.4.3. Stereochemical assignment of compound 75a

As a model to illustrate the assignment of the stereochemistry of the compounds **7**, we describe the NMR based stereochemical assignment for compound **75a** (Figure E.17).

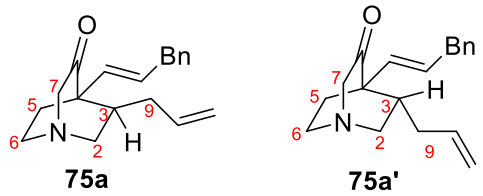


Figure E.17. Possible diastereoisomers **75a** and **75a'**.

First of all, all the hydrogens of the compound **75a** were assigned. This could be achieved by means of the ^{1}H and ^{13}C experiments, in combination with a HSQC and COSY (Figures E.18 and E.19, respectively).

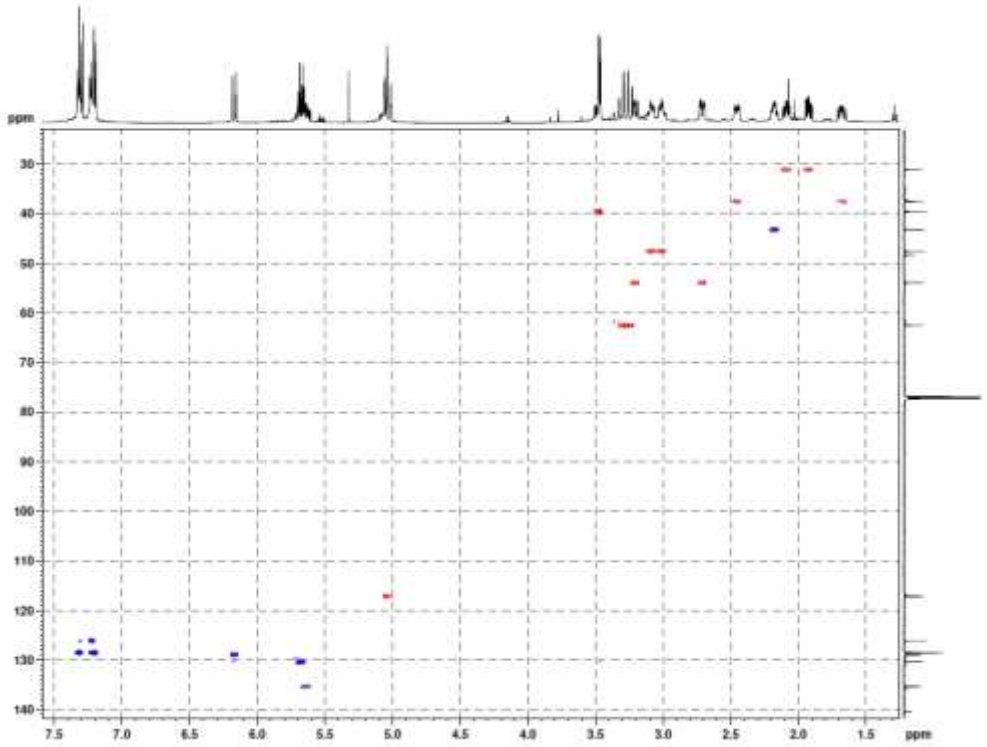


Figure E.18. HSQC experiment of the compound **75a**.

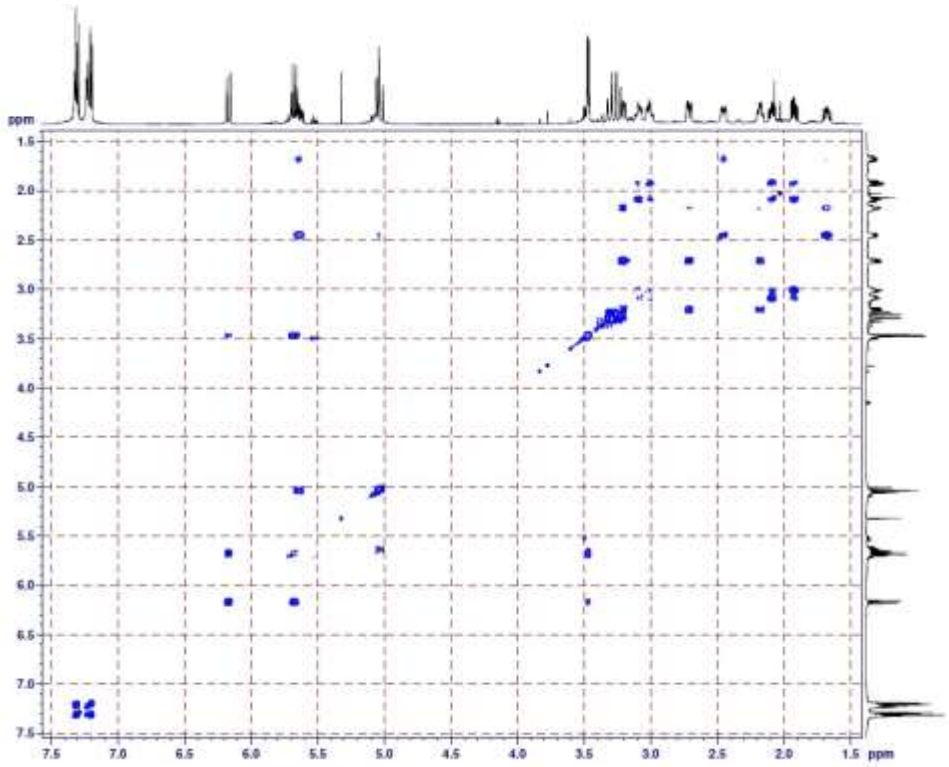


Figure E.19. COSY experiment of the compound **75a**.

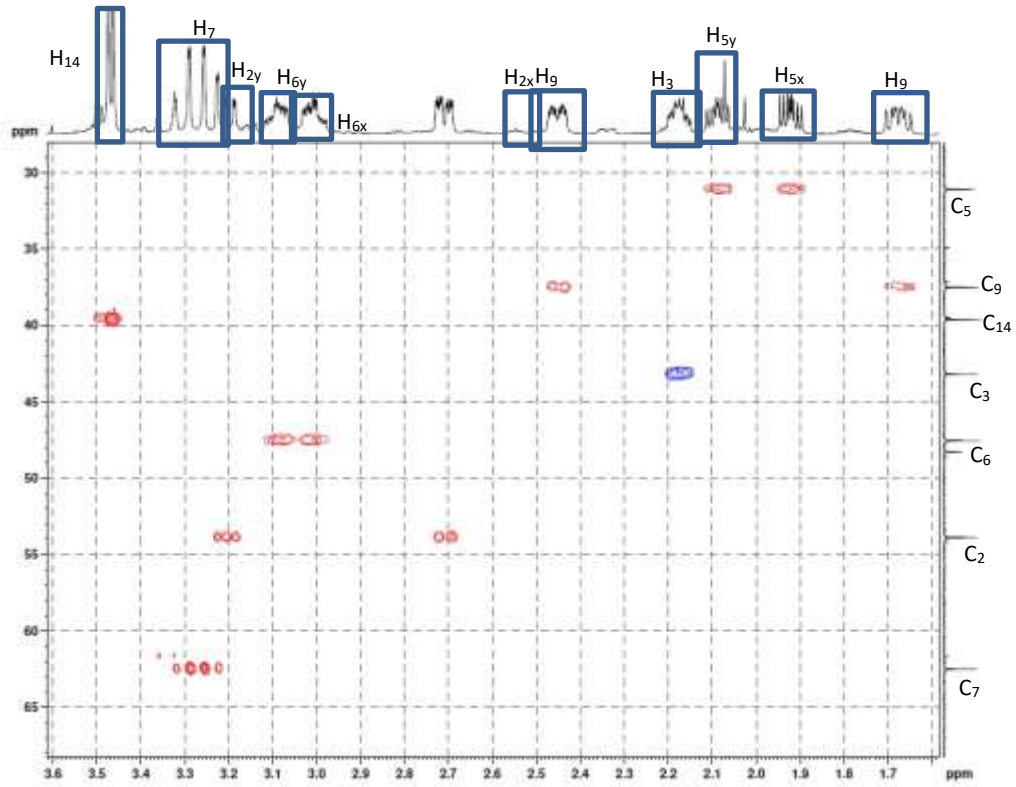


Figure E.20. Expansion of an area of the HSQC experiment of the compound **75a**.

Examining these two experiments, the hydrogens H_{2y} (3.20 ppm, $^{2}J_{gem}$ = 14.2 Hz, $^{3}J_{cis}$ = 9.7 Hz, ^{4}J = 2.5 Hz), H_{2x} (2.71 ppm, $^{2}J_{gem}$ = 14.2 Hz, $^{3}J_{trans}$ = 5.8 Hz, ^{4}J = 2.5 Hz), H_3 (2.20-2.15 ppm, m), H_{5y} (1.68 ppm, ddd, *J* = 14.1, 11.2, 7.7 Hz), H_{5x} (1.68 ppm, ddd, *J* = 14.1, 11.2, 7.7 Hz), H_{6y} (3.00 ppm, dddd, *J* = 13.4, 10.6, 5.5, 2.4 Hz) and H_{6x} (3.09 ppm, dddd, *J* = 12.6, 10.3, 5.3, 2.0 Hz) were assigned.

Then, a selective nOe experiment with saturation of H_3 was conducted. Through this experiment, the stereochemistry of the major isomer was unambiguously assigned. The critical nOes observed between H_3 and H_{5y}/H_{6y} exclude the possibility of the isomer **75a'** as the major one in our reaction, therefore undeniably pointing at the isomer **75a** as the one being predominantly formed. These nOes are depicted in figure E.21, where the ^{1}H spectra (red) and the selective nOe irradiating H_3 (blue) are overlapped. Apart from the critical nOes described before, the nOes between H_3 and its vicinal hydrogens H_{2x}, H_{2y} and H_9 were also

detected, and are understandably more intense than those commented above, where the distance between H_3 and H_{5y}/H_{6y} is much longer. Another observation that supports this stereochemistry is the lack of nOe between H_3 and H_7. See figure E.22 for the three-dimensional model of **75a** where the critical nOes have been highlighted.

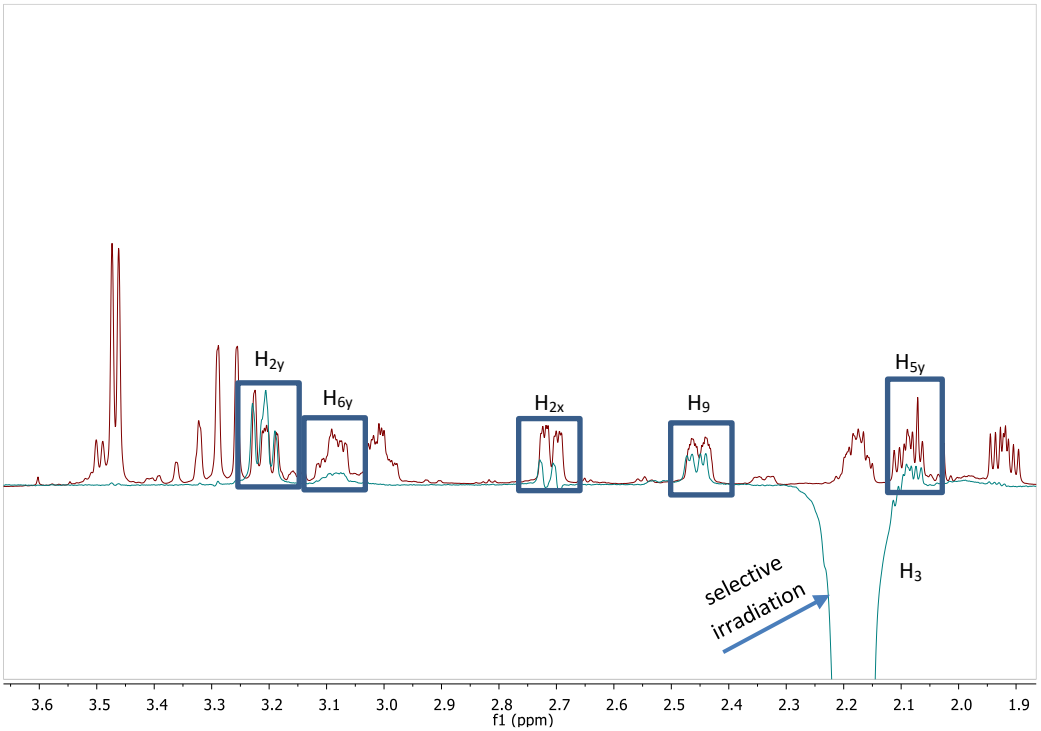


Figure E.21. Overlapping of the ^1H spectra (red) and the selective nOe irradiating H_3 (blue).

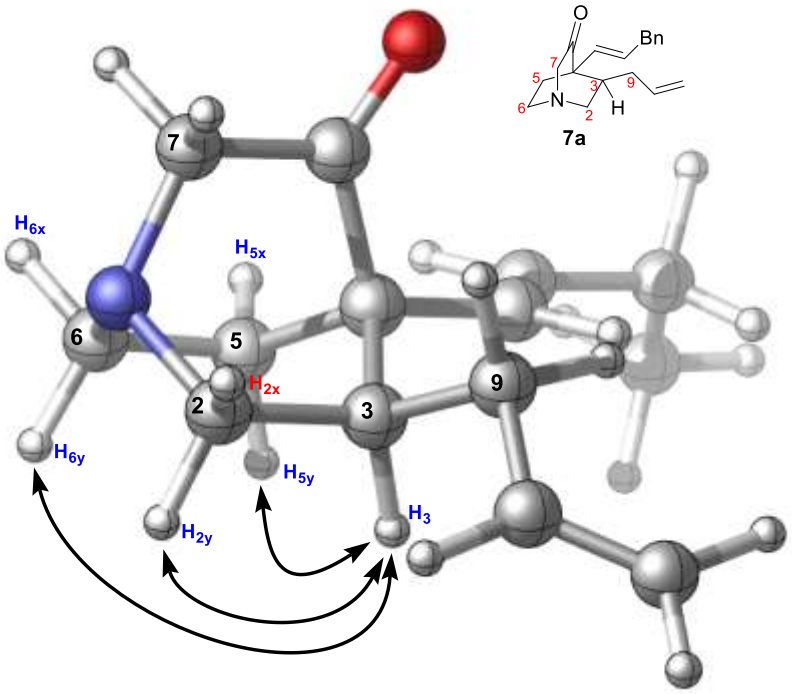


Figure E.22. 3D model (PM3 geometry optimization) of the structure determined for **75a** with critical nOes indicated.

E.5. Chapter 2. Part C: Synthesis of the spirocyclization products

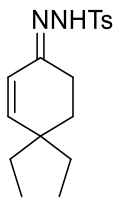
E.5.1. Synthesis of the starting materials and characterization data

Tosylhydrazone precursors of **82b**,[99] **82c**,[100] **82d**,[101] **82f**,[102] and **89**[103] were prepared employing previously described methodologies.

Tosylhydrazones **82a**,[104] **82c**,[105] **82e**,[106] and **87**[107] were prepared from the corresponding carbonyl compounds through previously described procedures.

Boronic acid **83b**[108] was synthesized starting from the corresponding boronic ester following a procedure found in the literature.

(*Z*)-*N*'-(4,4-Diethylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfonohydrazide (**82b**)



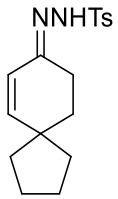
4,4-diethylcyclohex-2-en-1-one (1.58 g, 10.42 mmol) was added to a stirred solution of *p*-toluensulfonylhydrazide (2.16 g, 11.63 mmol) in MeOH (6.5 mL). The reaction was stirred for 1 day at r.t. (until total consumption of the starting carbonyl).

[99] M. Bolli et al. *J. Med. Chem*. **2014**, *57*, 78.
[100] J. C. Amedio et al. *Synthetic Comm*. **1998**, *28*, 3895.
[101] J. Wang et al. *J. Am. Chem. Soc*. **2011**, *133*, 12834.
[102] J. J. Crawford et al. *Tetrahedron*. **2006**, *62*, 11360.
[103] S. Yamashita et al. *Org. Lett*. **2008**, *10*, 3413.
[104] Y. Huang et al. *J. Org. Chem*. **2017**, *82*, 7621.
[105] K. Csatayeva et al. *Tetrahedron*, **2010**, *66*, 8420.
[106] T.-T. Dang et al. *ChemCatChem*. **2011**, *3*, 1491.
[107] J. Barluenga et al. *Adv. Synth. Catal*. **2010**, *352*, 3235.
[108] Y. Zhang et al. *Org. Biomol. Chem*. **2016**, *14*, 4585.

Then, the crude white solid was recrystallized from MeOH to yield **82b** as a white crystals (69%, 2.30 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.64 (bs, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.08 (d, *J* = 10.3 Hz, 1H), 6.03 (d, *J* = 10.3 Hz, 1H), 2.44 (s, 3H), 2.30 (t, *J* = 6.7 Hz, 2H), 1.60 (t, *J* = 6.8 Hz, 2H), 1.44-1.28 (m, 4H), 0.81 (t, *J* = 7.5 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.2 (C), 146.0 (CH), 144.0 (C), 135.4 (C), 129.5 (CH), 128.0 (CH), 125.6 (CH), 37.5 (C), 29.7 (CH_2), 28.8 (CH_2), 21.6 (CH_3), 20.6 (CH_2), 8.1 (CH_3). m.p. 172.5-173.3 ºC

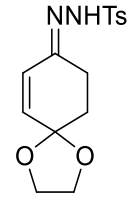
(*Z*)-4-Methyl-*N*'-(spiro[4.5]dec-6-en-8-ylidene)benzenesulfonohydrazide (**82d**)



spiro[4.5]dec-6-en-8-one (0.29 g, 1.96 mmol) was added to a stirred solution of *p*-toluensulfonylhydrazide (0.40 g, 2.18 mmol) in MeOH (1.3 mL). The reaction was stirred for 1 day at r.t. (until total consumption of the starting carbonyl). Then, the solvent was eliminated, giving a white solid which was purified by flash chromatography in a mixture 4:1 Hexane/EtOAc to yield **82d** as a white solid (80%, 0.50 g). R_f (hexanes/ethyl acetate 4:1) = 0.18.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.68 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.08 (d, *J* = 10.1 Hz, 1H), 5.99 (d, *J* = 10.1 Hz, 1H), 2.44 (s, 3H), 2.30 (t, *J* = 6.6 Hz, 2H), 1.75-1.60 (m, 6H), 1.59-1.43 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.4 (C), 146.9 (CH), 144.0 (C), 135.4 (C), 129.5 (CH), 128.0 (CH), 124.3 (CH), 43.4 (C), 38.5 (CH_2), 32.2 (CH_2), 24.3 (CH_2), 21.8 (CH_2), 21.6 (CH_3). m.p. 139.3-140.1 ºC

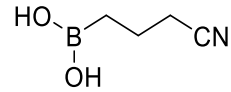
(*Z*)-4-methyl-N'-(1,4-dioxaspiro[4.5]dec-6-en-8-ylidene)benzenesulfonohydrazide (**82f**)



1,4-dioxaspiro[4.5]dec-6-en-8-one (1.19 g, 7.72 mmol) was added to a stirred solution of *p*-toluensulfonylhydrazide (1.60 g, 8.62 mmol) in MeOH (5 mL). The reaction was stirred for 3 hours at r.t. (until total consumption of the starting carbonyl). Then, the solvent was eliminated, giving a brown solid which was purified by flash chromatography in a mixture 2:1 Hexane/EtOAc to yield **82f** as an orange solid (75%, 1.86 g). R_f (hexanes/ethyl acetate 2:1) = 0.28.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.23 (d, *J* = 10.2 Hz, 1H), 6.01 (d, *J* = 10.1 Hz, 1H), 4.02-3.96 (m, 4H), 2.47 (t, *J* = 6.6 Hz, 2H), 2.45 (s, 3H), 1.95 (t, *J* = 6.6 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.8 (C), 144.3 (C), 135.1 (C), 134.9 (CH), 130.0 (CH), 129.6 (CH), 128.0 (CH), 104.4 (C), 64.8 (CH_2), 30.8 (CH_2), 21.6 (CH_2), 21.5 (CH_3). m.p. 127.9-128.1 ºC

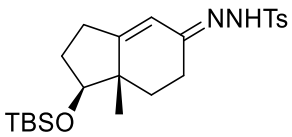
3-Cyanopropylboronic acid (**83a**)



In a 100 mL bottom-round flask, 3-cyano-1-propylboronic acid pinacol ester (1.00 g, 5.12 mmol) and $NaIO_4$ (3.70 g, 17.44 mmol) were dissolved in a mixture of 40 mL of THF and 10 mL of water. The mixture was vigorously stirred at r.t. for five minutes. Then, a 2N HCl solution (1.91 mL) was added, and the reaction was stirred for 3 hours at r.t. The THF was eliminated under reduced pressure and the crude was extracted with EtOAc several times. The organic layer was washed with water (2x50 mL) and brine (2x50 mL). The solvents were eliminated under reduced pressure. The crude yellow oil was crushed out with cold pentane, and the solid was washed several times with cold pentane and the pentane was discarded. The white solid obtained was dried in rotatory pump is compound **83a** in a pure form (65%, 0.37 g).

^{1}H NMR (300 MHz, Acetone-d6) δ 2.44 (t, *J* = 7.1 Hz, 2H), 1.74 (q, *J* = 7.2 Hz, 2H), 0.88 (t, *J* = 7.9 Hz, 2H). **^{13}C NMR** (75 MHz, Acetone-d6) δ 119.9 (C), 20.9 (CH_2), 18.5 (CH_2). m.p. 75.7-75.9 ºC

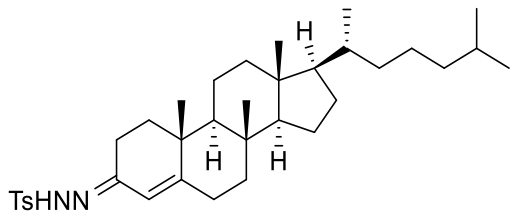
N'-((1*S*,7*aS*)-1-((tert-Butyldimethylsilyl)oxy)-7a-methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-ylidene)-4-methylbenzenesulfonohydrazide (**89**)



(1*S*,7*aS*)-1-((tert-butyldimethylsilyl)oxy)-7a-methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one (0.97 g, 3.46 mmol) was added to a stirred solution of *p*-toluensulfonylhydrazide (0.77 g, 4.16 mmol) in MeOH (3 mL). The reaction was stirred for 1 day at r.t. (until total consumption of the starting carbonyl). Then, the solvent was eliminated, giving **21** as a white solid which was used in the next step without further purification (79%, 1.22 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.89 (s, 1H), 3.63 (dd, *J* = 10.0, 7.4 Hz, 1H), 1.59-2.45 (m, 2H), 2.43 (s, 3H), 2.32-2.09 (m, 2H), 1.95-1.84 (m, 2H), 1.80-1.64 (m, 1H), 1.34 (td, *J* = 13.3, 5.4 Hz, 1H), 0.90 (s, 12H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.3 (C), 143.9 (C), 135.5 (C), 129.5 (CH), 128.0 (CH), 119.7 (CH), 110.3 (C), 81.0 (CH), 44.6 (C), 32.9 (CH_2), 29.7 (CH_2), 25.9 (CH_2), 25.7 (CH_3), 21.6 (CH_3), 20.9 (CH_2), 18.0 (C), 15.4 (CH_3), -4.4 (CH_3), -4.8 (CH_3). m.p. 148.5-149.2 ºC. $[\alpha]_D^{18}$ = 7.0º (c = 0.30).

4-methyl-*N*'-((8*S*,9*S*,10*R*,13*R*,14*R*,17*R*)-8,10,13-trimethyl-17-((*R*)-6-methylheptan-2-yl)-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthren-3-ylidene)benzenesulfonohydrazide (**92**)



4-cholesten-3-one (1.00 g, 2.60 mmol) was added to a stirred solution of *p*-toluensulfonylhydrazide (0.54 g, 2.90 mmol) in MeOH (2 mL) and DCM (1 mL). The reaction was stirred for 16 h at r.t. (until total consumption of the starting carbonyl). Then, the solvents were eliminated. The crude oil was crushed out with hexane forming a white solid, which was recrystallized from EtOH to yield **21** as white crystals (72%, 1.03 g).

Compound **21** is observed in the NMR as a mixture of the Z/E isomers:

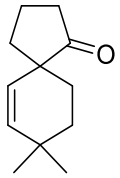
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.00 (s, isom. min.), 5.81 (s, 1H), 2.60-2.45 (m, 1H), 2.43 (s, 3H), 2.40-1.65 (m, 8H), 1.64-1.03 (m, 19H), 1.01 (s, 3H), 0.97-0.73 (m, 12H), 0.69 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.1 (C), 143.8 (C), 135.5 (C), 129.5 (CH), 128.0 (CH), 120.1 (CH), 110.2 (C), 56.1 (CH), 56.0 (CH), 55.9 (CH), 53.5 (CH), 42.3 (C), 39.7 (CH_2), 39.4 (CH_2), 37.6 (C), 36.1 (CH_2), 35.7 (CH), 34.4 (CH_2), 32.4 (CH_2), 32.1 (CH_2), 28.1 (CH_2), 28.0 (CH_3), 24.1 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.6 (CH_3), 21.3 (CH_2), 20.6 (CH_2), 18.6 (CH_3), 17.6 (CH_3), 11.9 (CH_3). m.p. 139.0-139.5 ºC. $[\alpha]_D^{17}$ = 124.1º (c = 0.34).

E.5.2. Synthesis of the spirocyclization products and characterization data

General procedure (**A**) for the spirocyclization reaction of *N*-tosylhydrazones with alkylboronic acids under microwave irradiation to form compounds **84**, **86**, **88**, **91** and **93**: A microwave vial provided with a triangular stir bar was charged with the corresponding tosylhydrazone (0.15 mmol), the alkylboronic acid (0.30 mmol), K_2CO_3 (41.4 mg, 0.30 mmol) in 1.2 mL of dry 1,4-dioxane. To this vial was also added 100 µL of a commercial 0.1 M solution of $ZnCl_2$ in dioxane. The vial was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at the desired temperature (120 ºC) during the reaction time (4 h) in a Biotage Initiator microwave apparatus. When the reaction finished, it was allowed to reach room temperature, solvents were eliminated and a saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (5 mL) 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 Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Finally, the products were purified by flash chromatography on silica gel.

General procedure (**B**) for the reaction of *N*-tosylhydrazones with alkylboronic acids under microwave irradiation to form compounds **102**: A microwave vial provided with a triangular stir bar was charged with the tosylhydrazone **82f** (0.15 mmol), the alkenyl boronic acid (0.30 mmol), K_2CO_3 (41.4 mg, 0.30 mmol) in 1.2 mL of dry 1,4-dioxane. The vial was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at the desired temperature (120 ºC) during the reaction time (4 h) in a Biotage Initiator microwave apparatus. When the reaction finished, it was allowed to reach room temperature, solvents were eliminated and a saturated solution of $NaHCO_3$ (10 mL) and dichloromethane (5 mL) 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 Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Finally, the products were purified by flash chromatography on silica gel.

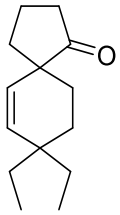
8,8-Dimethylspiro[4.5]dec-6-en-1-one (**84a**)



From (*E*)-*N*'-(4,4-dimethylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfono hydrazide (43.9 mg, 0.15 mmol) and 3-cyanopropylboronic acid (33.9 mg, 0.3 mmol), **16a** was obtained in 60% isolated yield (15.0 mg) following ***General procedure A*** as a colourless oil. **16a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.23.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, *J* = 9.9 Hz, 1H), 5.22 (d, *J* = 10.0 Hz, 1H), 2.45-2.2 (m, 2H), 2.05-1.85 (m, 4H), 1.81-1.60 (m, 2H), 1.57-1.35 (m, 2H), 1.05 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.6 (C), 140.2 (CH), 122.5 (CH), 50.8 (C), 37.5 (CH_2), 37.3 (CH_2), 33.4 (CH_2), 31.5 (C), 29.6 (CH_3), 29.2 (CH_3), 27.4 (CH_2), 18.8 (CH_2). HRMS(ESI): calcd. For $[C_{12}H_{18}NaO]^+$: 201.1249, found: 201.1254. IR (Nujol, cm^{-1}) = 1730, 1592, 1367, 1150, 973, 742, 697.

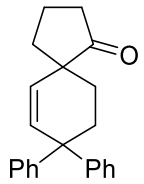
8,8-Diethylspiro[4.5]dec-6-en-1-one (**84b**)



From (*E*)-*N*'-(4,4-diethylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfono hydrazide (48.0 mg, 0.15 mmol) and 3-cyanopropylboronic acid (33.9 mg, 0.3 mmol), **84b** was obtained in 73% isolated yield (22.0 mg) following ***General procedure A*** as a colourless oil. **84b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.22.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, *J* = 10.1 Hz, 1H), 5.33 (d, *J* = 10.1 Hz, 1H), 2.45-2.20 (m, 2H), 2.10-1.79 (m, 4H), 1.80-1.55 (m, 2H), 1.53-1.19 (m, 6H), 0.85 (t, *J* = 7.5 Hz, 3H) 0.82 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.6 (C), 138.2 (CH), 126.8 (CH), 50.9 (C), 37.5 (CH_2), 37.3 (CH_2), 36.9 (C), 30.9 (CH_2), 30.8 (CH_2), 27.8 (CH_2), 27.0 (CH_2), 18.7 (CH_2), 8.2 (CH_3), 8.1 (CH_3). HRMS(ESI): calcd. For $[C_{14}H_{23}O]^+$: 207.1743, found: 207.1743.

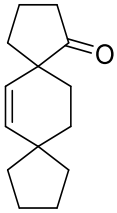
8,8-Diphenylspiro[4.5]dec-6-en-1-one (**84c**)



From (*E*)-*N*'-(2',3'-dihydro-4'*H*-[1,1':1',1''-terphenyl]-4'-ylidene)-4-methylbenzene sulfonohydrazide (62.4 mg, 0.15 mmol) and 3-cyanopropylboronic acid (33.9 mg, 0.3 mmol), **84c** was obtained in 71% isolated yield (32.0 mg) following ***General procedure A*** as a colourless oil. **84c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.15.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.05 (m, 10H), 6.28 (d, *J* = 10.1 Hz, 1H), 5.64 (d, *J* = 10.0 Hz, 1H), 2.59 (ddd, *J* = 12.8, 9.8, 2.7 Hz, 1H), 2.50-2.24 (m, 3H), 2.09-1.89 (m, 3H), 1.77 (ddd, *J* = 13.2, 8.3, 2.5 Hz, 1H), 1.48 (ddd, *J* = 13.2, 9.7, 2.6 Hz, 1H), 0.96-0.85 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 220.3 (C), 148.4 (C), 148.0 (C), 137.1 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 126.0 (CH), 125.9 (CH), 50.6 (C), 48.6 (C), 37.5 (CH_2), 37.2 (CH_2), 32.5 (CH_2), 27.2 (CH_2), 18.7 (CH_2). HRMS(ESI): calcd. For $[C_{22}H_{22}NaO]^+$: 325.1562, found: 325.1561. IR (Nujol, cm^{-1}) = 1734, 1594, 1379, 1151, 969, 746, 698.

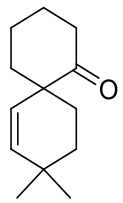
Dispiro[4.2.4^8.2^5]tetradec-13-en-1-one (**84d**)



From (*E*)-4-methyl-N'-(spiro[4.5]dec-6-en-8-ylidene)benzenesulfonohydrazide (47.7 mg, 0.15 mmol) and 3-cyanopropylboronic acid (33.9 mg, 0.3 mmol), **84d** was obtained in 57% isolated yield (17.0 mg) following ***General procedure A*** as a colourless oil. **84d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.18.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, *J* = 9.7 Hz, 1H), 5.24 (d, *J* = 9.8 Hz, 1H), 2.42-2.20 (m, 2H), 2.03-1.83 (m, 4H), 1.80-1.35 (m, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.6 (C), 139.6 (CH), 125.6 (CH), 50.9 (C), 43.2 (C), 40.0 (CH_2), 39.5 (CH_2), 37.5 (CH_2), 37.3 (CH_2), 31,2 (CH_2), 28.4 (CH_2), 24.4 (CH_2), 24.3 (CH_2), 18.7 (CH_2). HRMS(ESI): calcd. For $[C_{14}H_{20}NaO]^+$: 227.1406, found: 227.1405.

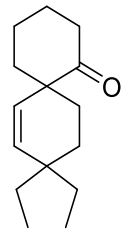
9,9-Dimethylspiro[5.5]undec-7-en-1-one (**86a**)



From (*E*)-*N*'-(4,4-dimethylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfono hydrazide (43.9 mg, 0.15 mmol) and 4-cyanobutylboronic acid (38.0 mg, 0.3 mmol), **86a** was obtained in 56% isolated yield (18.0 mg) following ***General procedure A*** as a colourless oil. **86a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (d, *J* = 10.1 Hz, 1H), 5.58 (d, *J* = 10.1 Hz, 1H), 2.52-2.36 (m, 2H), 2.10-2.01 (m, 1H), 1.98-1.68 (m, 5H), 1.58, 1.45 (m, 4H), 0.98 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.8 (C), 139.8 (CH), 126.7 (CH), 50.54 (C), 40.2 (CH_2), 39.0 (CH_2), 33.7 (CH_2), 31.9 (C), 29.5 (CH_3), 29.1 (CH_3), 28.3 (CH_2), 27.9 (CH_2), 20.9 (CH_2). HRMS(ESI): calcd. For $[C_{13}H_{20}NaO]^+$: 215.1406, found: 215.1406.

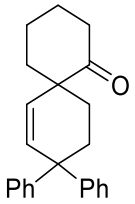
9,9-Diethylspiro[5.5]undec-7-en-1-one (**86b**)



From (*E*)-*N*'-(4,4-diethylcyclohex-2-en-1-ylidene)-4-methylbenzenesulfono hydrazide (48.0 mg, 0.15 mmol) and 4-cyanobutylboronic acid (38.0 mg, 0.3 mmol), **86b** was obtained in 70% isolated yield (23.0 mg) following ***General procedure A*** as a colourless oil. **86b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.35.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (d, *J* = 10.3 Hz, 1H), 5.57 (d, *J* = 10.3 Hz, 1H), 2.55-2.35 (m, 2H), 2.10-1.70 (m, 7H), 1.60-1.21 (m, 7H), 0.85 (t, *J* = 7.4 Hz, 3H) 0.81 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.8 (C), 137.7 (CH), 128.0 (CH), 50.6 (C), 40.2 (CH_2), 39.0 (CH_2), 37.3 (C), 30.9 (CH_2), 30.8 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 20.9 (CH_2), 8.3 (CH_3), 8.1 (CH_3). HRMS(ESI): calcd. For $[C_{15}H_{24}NaO]^+$: 243.1719, found: 243.1713.

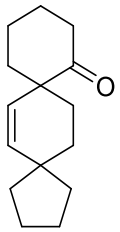
9,9-Diphenylspiro[5.5]undec-7-en-1-one (**86c**)



From (*E*)-*N*'-(2',3'-dihydro-4'*H*-[1,1':1',1''-terphenyl]-4'-ylidene)-4-methylbenzene sulfonohydrazide (62.4 mg, 0.15 mmol) and 4-cyanobutylboronic acid (38.0 mg, 0.3 mmol), **86c** was obtained in 55% isolated yield (26.0 mg) following ***General procedure A*** as a colourless oil. **86c** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 15:1 as eluent. R_f (hexanes/ethyl acetate 15:1) = 0.14.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.15 (m, 10H), 6.23 (d, *J* = 10.2 Hz, 1H), 6.05 (d, *J* = 10.2 Hz, 1H), 2.55-2.30 (m, 4H), 2.09-1.89 (m, 1H), 1.88-1.70 (m, 6H), 1.46 (ddd, *J* = 13.3, 8.6, 4.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.1 (C), 148.3 (C), 147.9 (C), 136.4 (CH), 129.7 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 125.9 (CH), 50.6 (C), 48.9 (C), 40.0 (CH_2), 38.9 (CH_2), 32.9 (CH_2), 27.9 (CH_2), 27.8 (CH_2), 20.9 (CH_2). HRMS(ESI): calcd. For $[C_{23}H_{24}NaO]^+$: 339.1719, found: 339.1721. IR (Nujol, cm^{-1}) = 1708, 1592, 1370, 1127, 926, 748, 695.

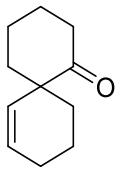
Dispiro[4.2.5^8.2^5]pentadec-6-en-9-one (**86d**)



From (E)-4-methyl-N'-(spiro[4.5]dec-6-en-8-ylidene)benzenesulfonohydrazide (47.7 mg, 0.15 mmol) and 4-cyanobutylboronic acid (38.0 mg, 0.3 mmol), **86d** was obtained in 55% isolated yield (18.0 mg) following ***General procedure A*** as a colourless oil. **86d** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.48.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71-5.58 (m, 2H), 2.55-2.35 (m, 2H), 2.10-1.97 (m, 2H), 1.95-1.60 (m, 9H), 1.55-1.35 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.9 (C), 139.1 (CH), 126.7 (CH), 50.6 (C), 43.6 (C), 40.3 (CH_2), 39.8 (CH_2), 39.3 (CH_2), 39.0 (CH_2), 31,5 (CH_2), 29.4 (CH_2), 28.0 (CH_2), 24.3 (CH_2), 20.9 (CH_2). HRMS(ESI): calcd. For $[C_{15}H_{12}NaO]^+$: 241.1549, found: 241.1562.

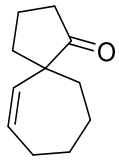
Spiro[5.5]undec-7-en-1-one (**86e**)



From (E)-N'-(cyclohex-2-en-1-ylidene)-4-methylbenzenesulfonohydrazide (39.6 mg, 0.15 mmol) and 4-cyanobutylboronic acid (38.0 mg, 0.3 mmol), **86e** was obtained in 75% isolated yield (18.0 mg) following ***General procedure A*** as a colourless oil. **86e** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 8:1 as eluent. R_f (hexanes/ethyl acetate 8:1) = 0.48. The high volatility of this compound must be pointed out. For this reason, during all the work-up and after the flash chromatography, all the solvents were eliminated carefully in the rotavapour.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (dt, *J* = 10.2, 3.6 Hz, 1H), 5.76 (d, *J* = 10.3 Hz, 1H), 2.52-2.35 (m, 2H), 2.10-1.95 (m, 3H), 1.94-1.61 (m, 8H), 1.51-1.40 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 214.0 (C), 129.4 (CH), 50.4 (C), 40.3 (CH_2), 38.9 (CH_2), 31.3 (CH_2), 27.9 (CH_2), 25.2 (CH_2), 20.8 (CH_2), 19.0 (CH_2). HRMS(ESI): calcd. For $[C_{11}H_{17}O]^+$: 165.1274, found: 165.1358. IR (Nujol, cm^{-1}) = 1715, 1664, 1375, 1259, 1158, 717.

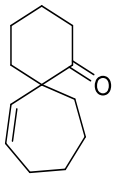
Spiro[4.6]undec-6-en-1-one (**88a**)



From (*E*)-*N*'-(cyclohept-2-en-1-ylidene)-4-methylbenzenesulfonohydrazide (41.7 mg, 0.15 mmol) and 3-cyanopropylboronic acid (33.9 mg, 0.3 mmol), **20a** was obtained in 66% isolated yield (16.0 mg) following ***General procedure A*** as a colourless oil. **20a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 25:1 as eluent. R_f (hexanes/ethyl acetate 25:1) = 0.58. The high volatility of this compound must be pointed out. For this reason, during all the work-up and after the flash chromatography, all the solvents were eliminated carefully in the rotavapour.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 11.7, 6.0 Hz, 1H), 5.43 (d, *J* = 11.5 Hz, 1H), 2.40-2.21 (m, 3H), 2.20-2.05 (m, 2H), 2.00-1.83 (m, 4H), 1.76-1.59 (m, 4H), 1.57-1.47 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 221.6 (C), 133.6 (CH), 133.0 (CH), 55.2 (C), 36.5 (CH_2), 35.7 (CH_2), 31.9 (CH_2), 27.9 (CH_2), 27.5 (CH_2), 25.3 (CH_2), 18.9 (CH_2). HRMS(ESI): calcd. For $[C_{11}H_{16}NaO]^+$: 187.1093, found: 187.1094. IR (Nujol, cm^{-1}) = 1739, 1651, 1368, 1303, 1151, 720.

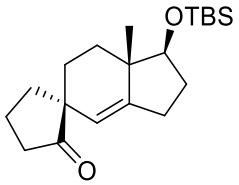
Spiro[5.6]dodec-7-en-1-one (**88b**)



From (*E*)-*N*'-(cyclohept-2-en-1-ylidene)-4-methylbenzenesulfonohydrazide (41.7 mg, 0.15 mmol) and 4-cyanobutylboronic acid (38.0 mg, 0.3 mmol), **88b** was obtained in 65% isolated yield (17.0 mg) following ***General procedure A*** as a colourless oil. **88b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 25:1 as eluent. R_f (hexanes/ethyl acetate 25:1) = 0.28. The high volatility of this compound must be pointed out. For this reason, during all the work-up and after the flash chromatography, all the solvents were eliminated carefully in the rotavapour.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 11.9, 6.0 Hz, 1H), 5.60 (d, *J* = 11.7 Hz, 1H), 2.52-2.41 (m, 2H), 2.16-1.97 (m, 3H), 1.96-1.70 (m, 9H), 1.69-1.60 (m, 1H), 1.57-1.46 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.9 (C), 134.4 (CH), 132.5 (CH), 55.4 (C), 39.8 (CH_2), 38.9 (CH_2), 34.0 (CH_2), 27.9 (CH_2), 27.7 (CH_2), 27.0 (CH_2), 24.9 (CH_2), 21.0 (CH_2). HRMS(ESI): calcd. For $[C_{12}H_{19}O]^+$: 179.1430, found: 179.1436. IR (Nujol, cm^{-1}) = 1704, 1647, 1375, 1303, 1153, 1303, 1153, 717.

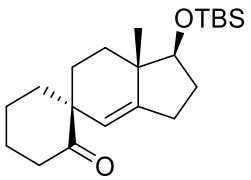
(1*S*,1'*S*,7a'*S**-1'-((tert-Butyldimethylsilyl)oxy)-7*a*'-methyl-1',2',3',6',7',7*a*'-hexahydrospiro[cyclopentane-1,5'-inden]-2-one (**91a**)



From *N*'-((1*S*,7*aS*)-1-((tert-butyldimethylsilyl)oxy)-7*a*-methyl-1,2,3,6,7,7*a*-hexahydro-5*H*-inden-5-ylidene)-4-methylbenzenesulfonohydrazide (67.3 mg, 0.15 mmol) and 3-cyanopropylboronic acid (33.9 mg, 0.3 mmol), **91a** was obtained in 45 % isolated yield (22.0 mg) following ***General procedure A*** as a colourless oil. **91a** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 25:1 as eluent. R_f (hexanes/ethyl acetate 25:1) = 0.10

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.03 (s, 1H), 3.56 (dd, *J* = 9.7, 7.8 Hz, 1H), 2.53 (ddt, *J* = 17.3, 12.1, 2.8 Hz, 1H), 2.38-2.28 (m, 2H), 2.09 (dddd, $^{2}J_{gem}$=17.3 Hz, $^{3}J_{cis}$=9.6 Hz, $^{3}J_{trans}$= 7.7 Hz, ^{4}J=1.5 Hz), 2.03-1.96 (m, 1H), 1.93-1.82 (m, 4H), 1.81-1.73 (m, 2H), 1.66 (dddd, $^{2}J_{gem}$=12.5 Hz, $^{3}J_{cis}$=9.7 Hz, $^{3}J_{trans}$= 7.7 Hz, ^{4}J=1.9 Hz), 1.53 (dtd, $^{2}J_{gem}$=14.0 Hz, $^{3}J_{ax\text{-}eq}$=$^{3}J_{eq\text{-}eq}$ 4.0 Hz, ^{4}J=1.3 Hz), 1.15 (td, $^{2}J_{gem}$=$^{3}J_{ax\text{-}ax}$=13.9 Hz, $^{3}J_{ax\text{-}eq}$=3.8 Hz), 1.00 (s, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 223.3 (C), 147.6 (C), 120.2 (CH), 81.8 (CH), 52.5 (C), 43.9 (C), 37.5 (CH_2), 37.3 (CH_2), 32.5 (CH_2), 29.7 (CH_2), 27.1 (CH_2), 26.0 (CH_2), 25.8 (CH_3), 19.0 (CH_2), 18.0 (C), 16.9 (CH_3), -4.4 (CH_3), -4.7 (CH_3). HRMS(ESI): calcd. For $[C_{20}H_{35}O_2Si]^+$: 335.2400, found: 335.2401. $[\alpha]_D^{25.3}$ = -42.11º (c = 0.29)

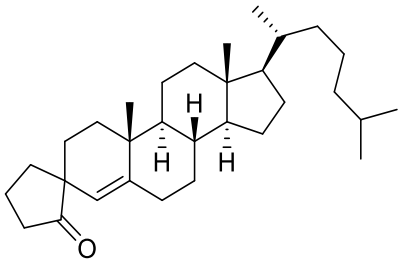
(1*S*,1'*S*,7*a*'*S*)-1'-((tert-butyldimethylsilyl)oxy)-7*a*'-methyl-1',2',3',6',7',7*a*'-hexahydrospiro[cyclohexane-1,5'-inden]-2-one (**91b**)



From *N*'-((1*S*,7*aS*)-1-((tert-butyldimethylsilyl)oxy)-7*a*-methyl-1,2,3,6,7,7*a*-hexahydro-5*H*-inden-5-ylidene)-4-methylbenzenesulfonohydrazide (67.3 mg, 0.15 mmol) and 4-cyanobutylboronic acid (38.0 mg, 0.3 mmol), **22b** was obtained in 49% isolated yield (25.0 mg) following ***General procedure C*** as a colourless oil. **22b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 25:1 as eluent. R_f (hexanes/ethyl acetate 25:1) = 0.40

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.40 (s, 1H), 3.56 (dd, *J* = 9.6, 7.8 Hz, 1H), 2.54 (ddt, *J* = 17.4, 12.1, 2.7 Hz, 1H), 2.50-2.40 (m, 2H), 2.54 (ddt, *J* = 17.4, 12.1, 2.7 Hz, 1H), 1.94 (td, *J* = 14.0, 3.5 Hz, 1H), 1.90-1.57 (m, 10H), 1.26 (td, *J* = 13.4, 3.1 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 12H), 0.05 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 214.7 (C), 146.6 (C), 122.0 (CH), 81.8 (CH), 51.4 (C), 44.2 (C), 39.2 (CH_2), 38.8 (CH_2), 31.5 (CH_2), 29.7 (CH_2), 27.4 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 25.8 (CH_3), 21.2 (CH_2), 18.0 (C), 16.6 (CH_3), -4.4 (CH_3), -4.7 (CH_3). HRMS(ESI): calcd. For $[C_{21}H_{37}O_2Si]^+$: 349.2557, found: 349.2563. IR (Nujol, cm^{-1}) = 1712, 1638, 1375, 1303, 1162, 717. $[\alpha]_D^{20.5}$ = 41.76º (c = 0.17)

(8'S,9'S,10'R,13'R,14'S,17'R)-10',13'-dimethyl-17'-((R)-6-methylheptan-2-yl)-1',2',6',7',8',9',10',11',12',13',14',15',16',17'-tetradecahydrospiro[cyclopentane-1,3'-cyclopenta[a]phenanthren]-2-one (**93**)



From 4-methyl-*N*'-((8*S*,9*S*,10*R*,13*R*,14*R*,17*R*)-8,10,13-trimethyl-17-((*R*)-6-methyl heptan-2-yl)-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phe nanthren-3-ylidene)benzenesulfonohydrazide (82.9 mg, 0.15 mmol) and 3-cyanopropylboronic acid (33.9 mg, 0.3 mmol), ***General procedure A*** was followed. **93** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 25:1 as eluent. Compound **93** was obtained as a mixture 1:1 of diastereoisomers:

Isomer 1 R_f (hexanes/ethyl acetate 25:1) = 0.32. Obtained as a colourless oil. Yield after flash chromatography = 24% (15.7 mg)

Isomer 2 R_f (hexanes/ethyl acetate 25:1) = 0.30. Obtained as a colourless oil. Yield after flash chromatography = 24% (15.7 mg)

After separation by flash chromatography, full characterizations for each of the isomers will be shown in this section:

Isomer 1

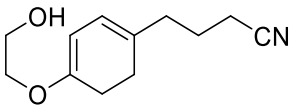
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 1H), 2.41-2.12 (m, 4H), 2.05-1.65 (m, 9H), 1.62-1.08 (m, 18H), 1.02 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.89 (d, *J* = 1.3 Hz, 3H), 0.87 (d, *J* = 1.4 Hz, 3H), 0.70 (t, *J* = 3.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 220.6 (C), 148.8 (C), 119.9 (CH), 56.1 (CH), 55.8 (CH), 53.6 (CH), 50.4 (C), 42.4 (C), 39.7 (CH_2), 39.5 (CH_2), 39.2 (CH_2), 37.0 (CH_2), 36.1 (CH_2), 35.9 (CH), 35.8 (CH), 33.1 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 28.2 (CH_2), 28.0 (CH), 27.6 (CH_2), 24.2 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5

(CH_3), 21.4 (CH_2), 19.1 (CH_3), 18.6 (CH_3), 18.3 (CH_2), 11.9 (CH_3). HRMS(ESI): calcd. For $[C_{31}H_{50}NaO]^+$: 461.3754, found: 461.3763. $[\alpha]_D^{19.6}$ = 145.00º (c = 0.18)

Isomer 2

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (s, 1H), 2.49-2.19 (m, 4H), 2.20-1.77 (m, 7H), 1.76-1.67 (m, 2H), 1.66-1.24 (m, 13H), 1.22-1.10 (m, 5H), 1.07 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.89 (d, *J* = 1.1 Hz, 3H), 0.87 (d, *J* = 1.1 Hz, 3H), 0.73-0.68 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 223.4 (C), 147.3 (C), 120.0 (CH), 56.2 (CH), 56.1 (CH), 54.4 (CH), 51.7 (C), 42.5 (C), 39.9 (CH_2), 39.5 (CH_2), 37.7 (CH_2), 37.2 (CH_2), 36.6 (CH_2), 36.1 (CH), 35.9 (CH), 35.7 (CH_2), 34.2 (CH_2), 33.0 (CH_2), 32.5 (CH_2), 28.2 (CH), 28.0 (CH_2), 26.4 (CH_2), 24.2 (CH_2), 23.8 (CH_3), 22.8 (CH_3), 22.5 (CH_3), 21.5 (CH_2), 19.1 (CH_3), 18.9 (CH_2), 18.6 (CH_3), 11.9 (CH_3). HRMS(ESI): calcd. For $[C_{31}H_{50}NaO]^+$: 461.3754, found: 461.3762. $[\alpha]_D^{20.5}$ = 36.41º (c = 0.20)

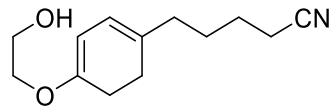
4-(4-(2-hydroxyethoxy)cyclohexa-1,3-dien-1-yl)butanenitrile (**102a**)



From (*Z*)-4-methyl-*N*'-(1,4-dioxaspiro[4.5]dec-6-en-8-ylidene)benzenesulfonohydrazide (48.3 mg, 0.15 mmol) and 3-cyanopropylboronic acid (33.9 mg, 0.3 mmol), **102a** was obtained in 83% isolated yield (26.0 mg) following ***General procedure B*** as a colourless oil. **102b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. R_f (hexanes/ethyl acetate 2:1) = 0.18.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (d, *J* = 6.1 Hz, 1H), 4.93 (d, *J* = 6.1 Hz, 1H), 3.97-3.77 (m, 4H), 2.40-2.27 (m, 4H), 2.26-2.15 (m, 3H), 2.00 (t, *J* = 6.0 Hz), 1.82 (q, *J* = 7.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.2 (C), 128.2 (C), 120.0 (C), 119.7 (C), 93.2 (CH), 68.2 (CH_2), 61.2 (CH_2), 35.1 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 23.4 (CH_2), 16.4 (CH_2). HRMS(ESI): calcd. For $[C_{12}H_{17}NNaO_2]^+$: 230.1157, found: 230.1158.

5-(4-(2-hydroxyethoxy)cyclohexa-1,3-dien-1-yl)pentanenitrile (**102b**)



From (*Z*)-4-methyl-*N*'-(1,4-dioxaspiro[4.5]dec-6-en-8-ylidene)benzene sulfonohydrazide (48.3 mg, 0.15 mmol) and and 4-cyanobutylboronic acid (38.0 mg, 0.3 mmol), **102b** was obtained in 40% isolated yield (13.0 mg) following ***General procedure B*** as a colourless oil. **102b** was purified by flash chromatography on silica gel using a mixture of hexanes/ethyl acetate 2:1 as eluent. R_f (hexanes/ethyl acetate 2:1) = 0.11.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (d, *J* = 6.0 Hz, 3H), 4.91 (d, *J* = 6.0 Hz, 6H), 3.92-3.80 (m, 4H), 2.37 (t, *J* = 6.7 Hz, 2H) 2.34-2.28 (m, 2H), 2.26-2.16 (m, 2H), 2.11 (t, *J* = 6.9 Hz, 2H), 1.97 (t, *J* = 5.7 Hz, 1H),1.72-1.54 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.8 (C), 130.0 (C), 119.7 (C), 118.8 (CH), 93.2 (CH), 68.1 (CH_2), 61.2 (CH_2), 35.5 (CH_2), 27.2 (CH_2), 26.6 (CH_2), 24.8 (CH_2), 17.0 (CH_2). HRMS(ESI): calcd. For $[C_{13}H_{19}NNaO_2]^+$: 244.1308, found: 244.1309.

E.5.3. Stereochemical assignment of compound 91a

The stereochemical assignment of the compound **91a** was achieved based on a series of NMR experiments which are described below. Two possible epimers could be formed depending on the stereochemistry of the newly formed quaternary stereocenter. These isomers are denoted as **91a*S*** and **91a*R*** (figure E.23). For a better understanding of the assignment, the labelling shown in the figures below will be followed. As presented in the molecular models of **91a*S*** (figure E.24) and **91a*R*** (figure E.25) along the discussion the diastereotopic hydrogens for each methylene group will be referred as α or β to indicate their relative position below or above the plane respectively.

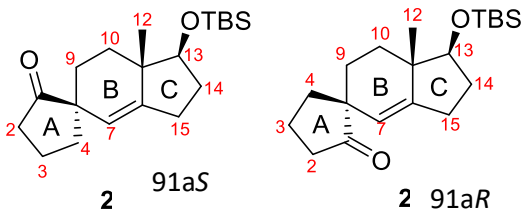


Figure E.23. Stereoisomers that could be formed in the reaction.

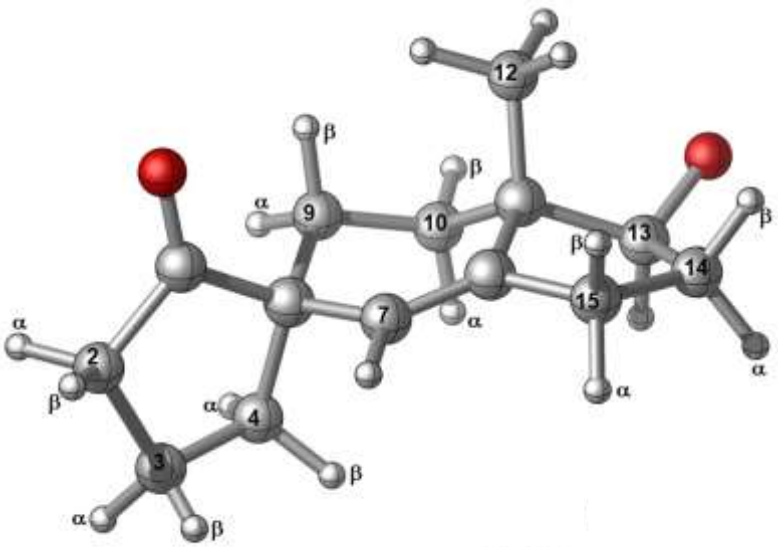


Figure E.24. Three-dimensional model for **91a*S*** optimized at the PM3 level. The TBDMS group has been hidden for clarity.

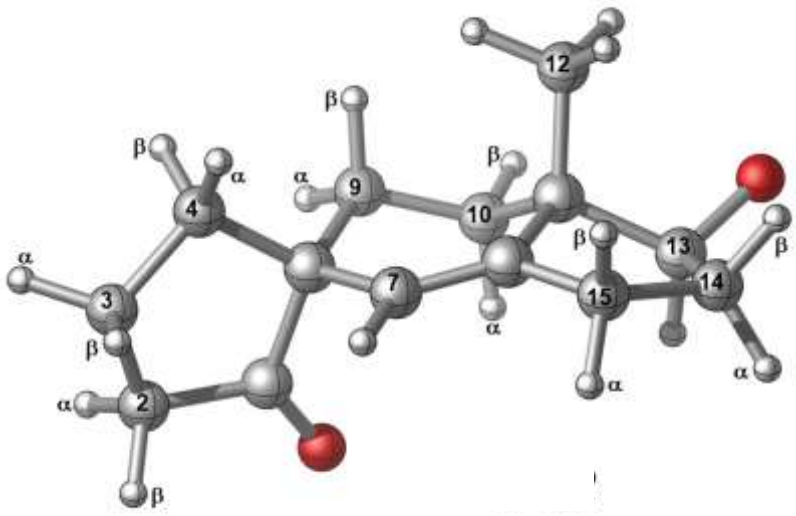


Figure E.25. Three-dimensional model for **91a*R*** optimized at the PM3 level. The TBDMS group has been hidden for clarity.

First, all the signals for the hydrogens of compound **91a** were assigned. To this purpose, we carried out the following NMR experiments: ^{1}H and ^{13}C (section E.5.2, compound **91a**), DEPT-135 (Figure E.26), HSQC (Figure E.27), NOESY (Figure E.28), TOCSY (Figure E.29) and COSY (Figure E.30).

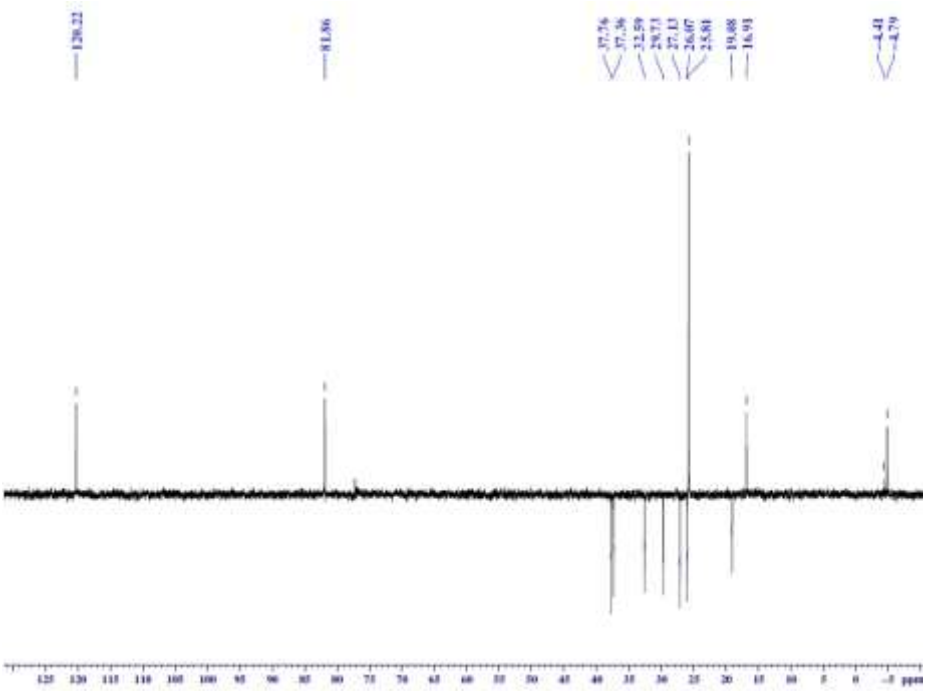


Figure E.26. DEPT-135 experiment of compound **91a**.

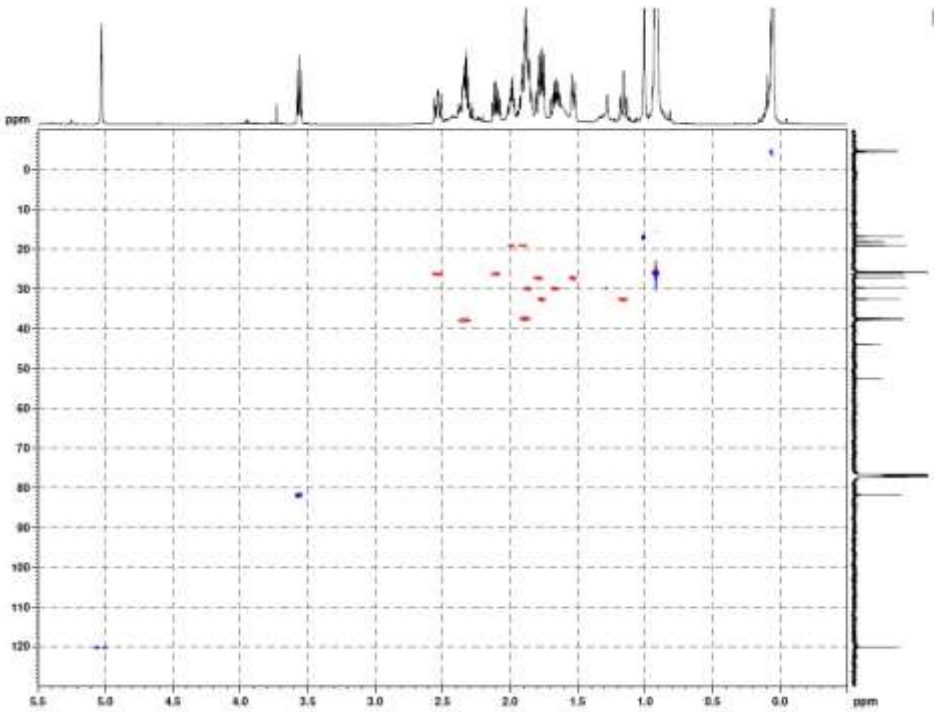


Figure E.27. HSQC experiment of compound **91a**.

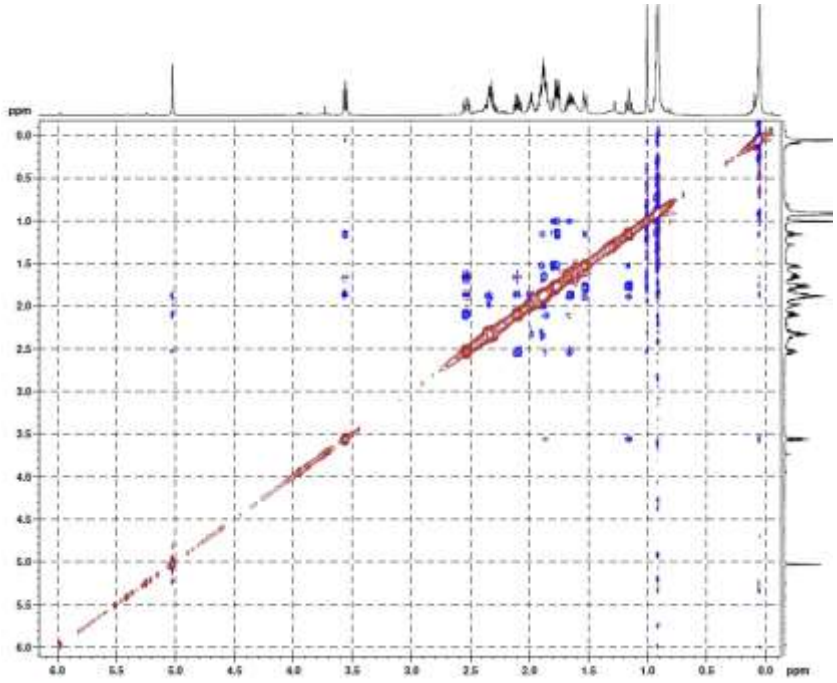


Figure E.28. NOESY experiment of compound **91a**.

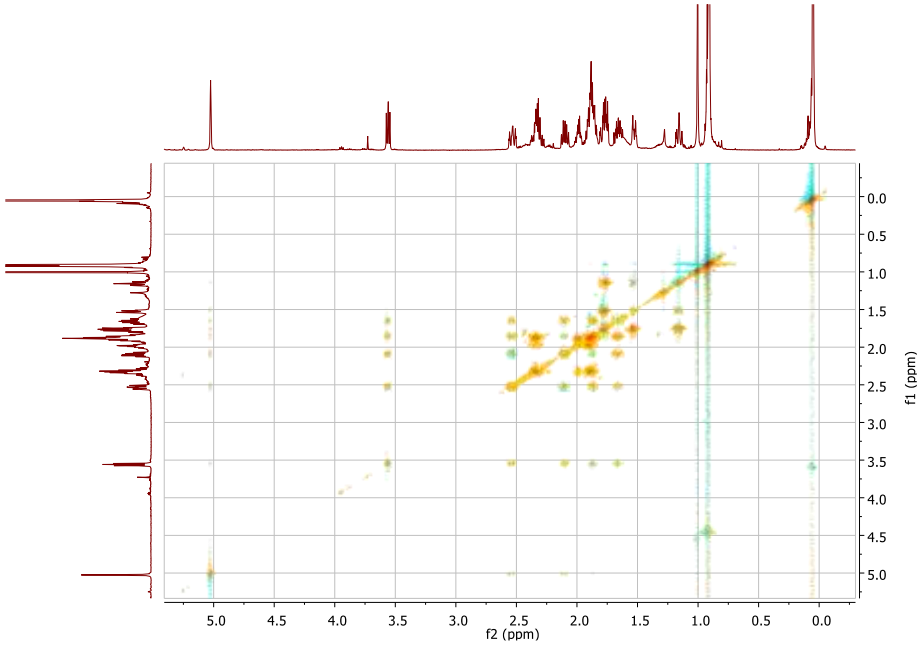


Figure E.29. TOCSY experiment of compound **91a**.

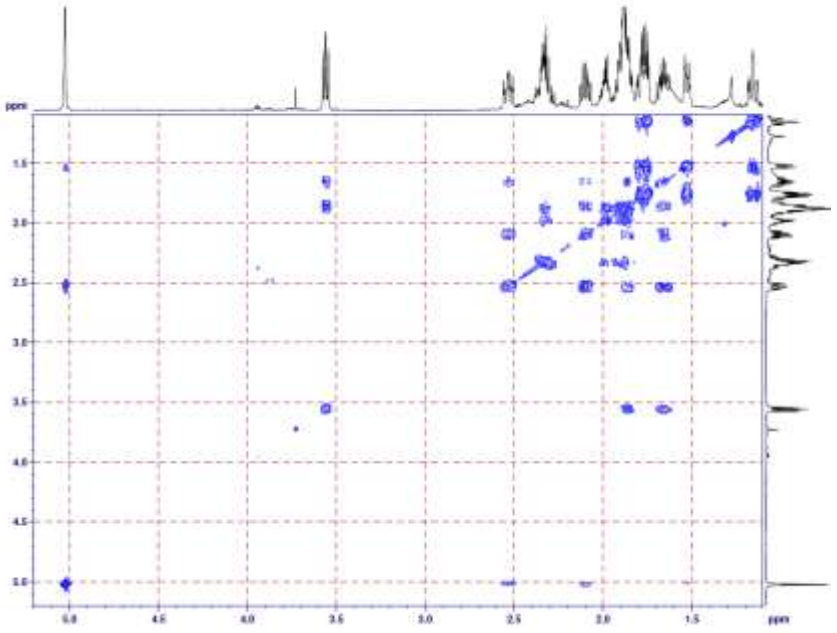


Figure E.30. COSY experiment of compound **91a**.

In combination with all the experiments shown above, some additional experiments were conducted to assign unambiguously all the hydrogens in the compound **91a**:

- In order to assign the hydrogens of ring C, a selective TOCSY (Figure E.31) was carried out irradiating the signal at 3.56 ppm (which corresponds to H13). This experiment, in combination the COSY experiment, enabled to identify both H15α (2.09 ppm, dddd, $^{2}J_{gem}$=17.3 Hz, $^{3}J_{cis}$=9.6 Hz, $^{3}J_{trans}$= 7.7 Hz, ^{4}J=1.5 Hz), H15β (2.53 ppm, ddt, $^{2}J_{gem}$= 17.3 Hz, $^{3}J_{cis}$=12.2 Hz, $^{3}J_{trans}$=$^{4}J_{HH}$=2.8 Hz), H14α (within the multiplet at 1.95-1.83 ppm), and H14β (1.66 ppm, dddd, $^{2}J_{gem}$=12.5 Hz, $^{3}J_{cis}$=9.7 Hz, $^{3}J_{trans}$= 7.7 Hz, ^{4}J=1.9 Hz).

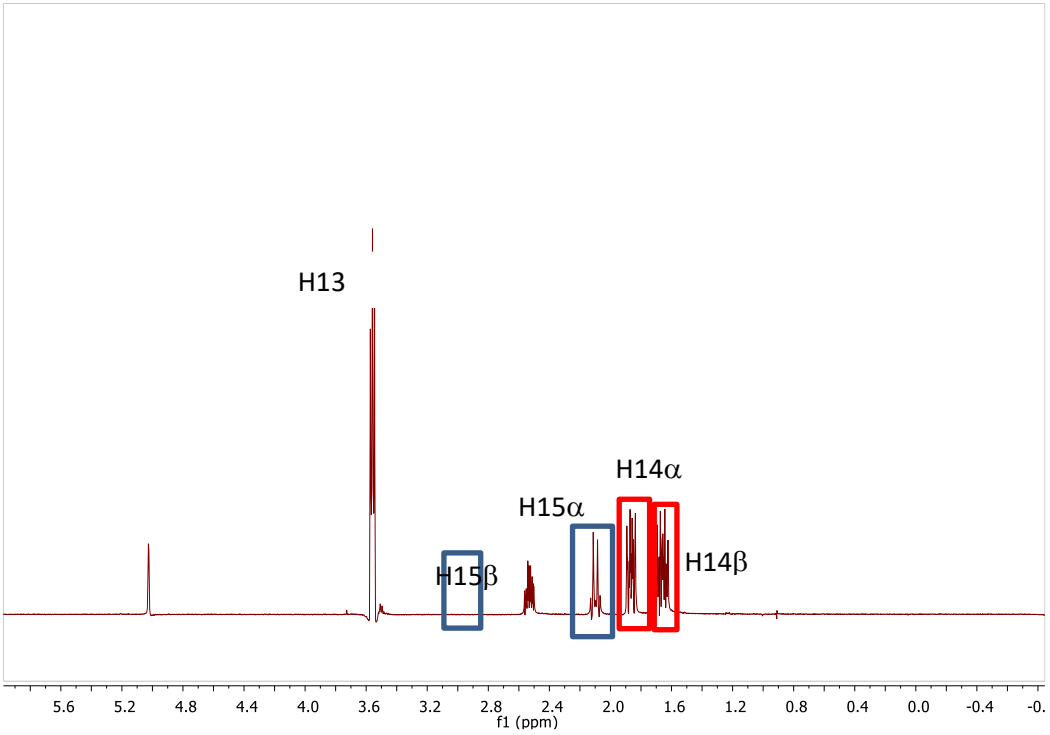


Figure E.31. Selective TOCSY irradiating H13 that assigns the hydrogens of ring C.

- The identification of the remaining hydrogens was possible through a combination between the HMBC experiment (Figure E.32) and the COSY experiment. The hydrogens at C2 appear as a multiplet (2.37-2.28 ppm). With the aid of the COSY,

the identification of both hydrogens of C3 was also possible: one hydrogen appears as a multiplet (2.03-1.95 ppm), and the other within the multiplet at 1.95-1.83 ppm, overlapped with H14 and also with both hydrogens at C4.

- The only hydrogens remaining to identify are those of C9 and C10. Through the analysis of the HSQC and COSY experiments, it was possible to assign H10α (1.15 ppm, td, $^{2}J_{gem}=^{3}J_{ax\text{-}ax}$=13.9 Hz, $^{3}J_{ax\text{-}eq}$=3.8 Hz) as the more shielded hydrogen of them. Then, the identification of H9α (1.53 ppm, dtd, $^{2}J_{gem}$=14.0 Hz, $^{3}J_{ax\text{-}eq}=^{3}J_{eq\text{-}eq}$ 4.0 Hz, ^{4}J=1.3 Hz) was achieved. The remaining H10β and H9β are partially overlapped at the multiplet within 1.82-1.73 ppm.

Once all the hydrogens of the compound **91a** were assigned, some experiments to look for critical nOes that would enable the distinction between both isomers were conducted.

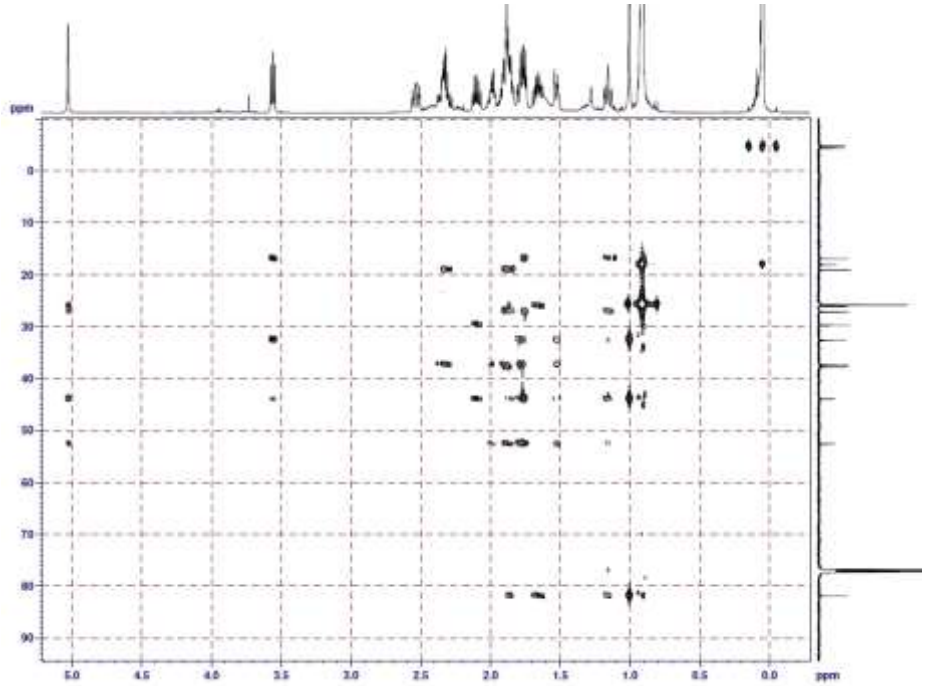


Figure E.32. HMBC experiment of compound **91a**.

With this aim, a selective nOe experiment was carried out by saturating the signal corresponding to H10β and H9β (Figure E.33). Importantly, no nOe was detected with any of the hydrogens at C4. This fact stands as a major evidence for the identification of the compound as isomer **91a*S***, since **91a*R*** should feature an intense nOe between the hydrogens at C4 and H9β.

This stereochemistry assignment is also in agreement with a selective nOe experiment conducted by irradiating H9α (Figure S18). In this experiment, the nOes between this hydrogen and H9β (geminal), H10α (*cis* arrangement) and H4α also point to **91a*S*** as the isomer formed in the reaction.

To get further support to the proposed stereochemistry a careful examination of an overlay of the prior experiment with an expansion of the NOESY (from 1.96 to 1.73 ppm) was conducted. In this superposition (Figure E.35), it was clearly identified a critical nOe between H10α and the hydrogens at C4 (highlighted in purple). This nOe undeniably excludes the **22a*R*** and confirms the previously described evidence for the presence of **22a*S***. Moreover, in the NOESY experiment it was also confirmed the lack of nOe between both hydrogens at C4 and H9β (the exact zone in which this nOe would appear is outlined in orange).

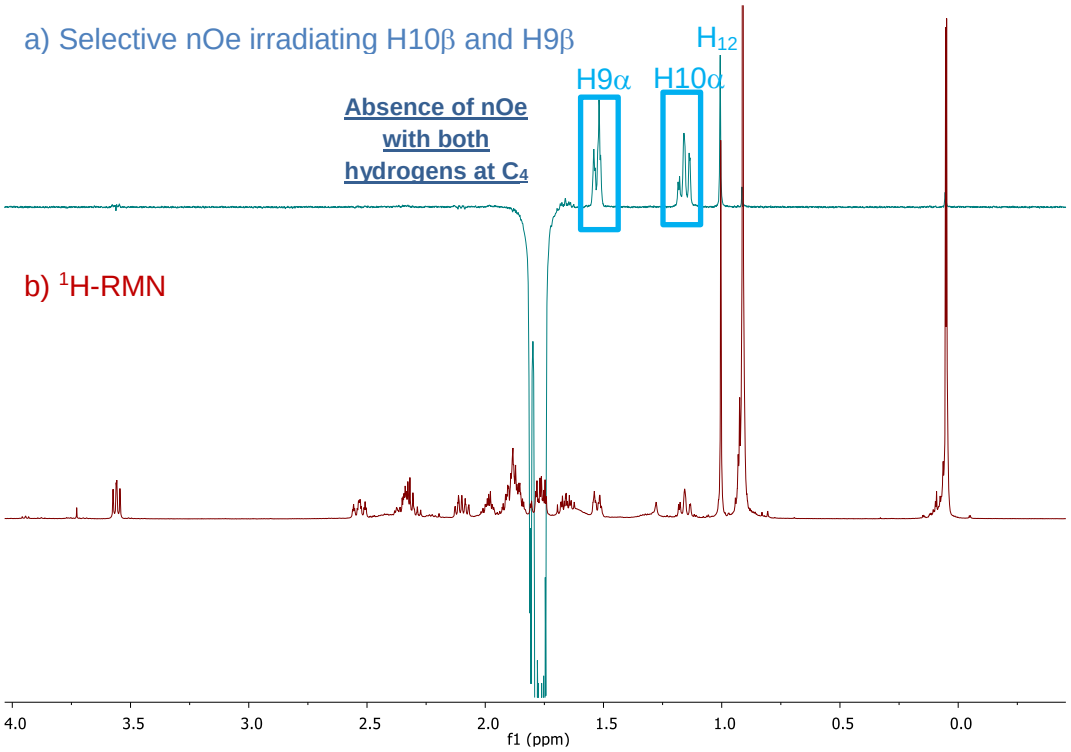


Figure E.33. Superposition of a) Selective nOe by saturation of the signals of H10β and H9β (blue), b) ^{1}H NMR spectra (red).

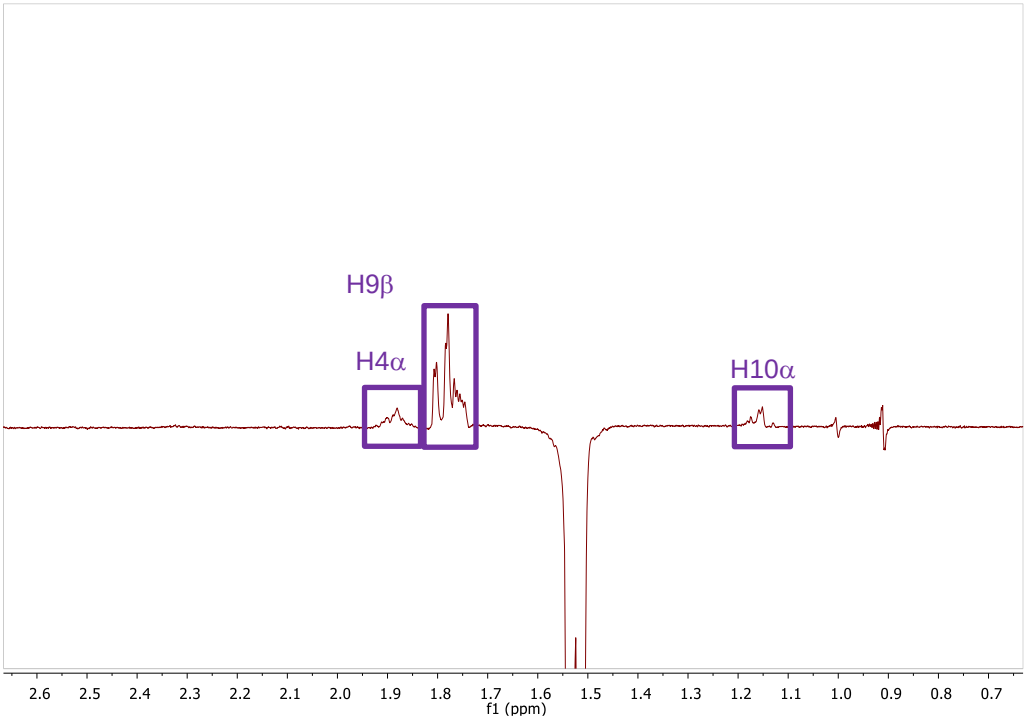


Figure E.34. Selective nOe by saturation of H9α.

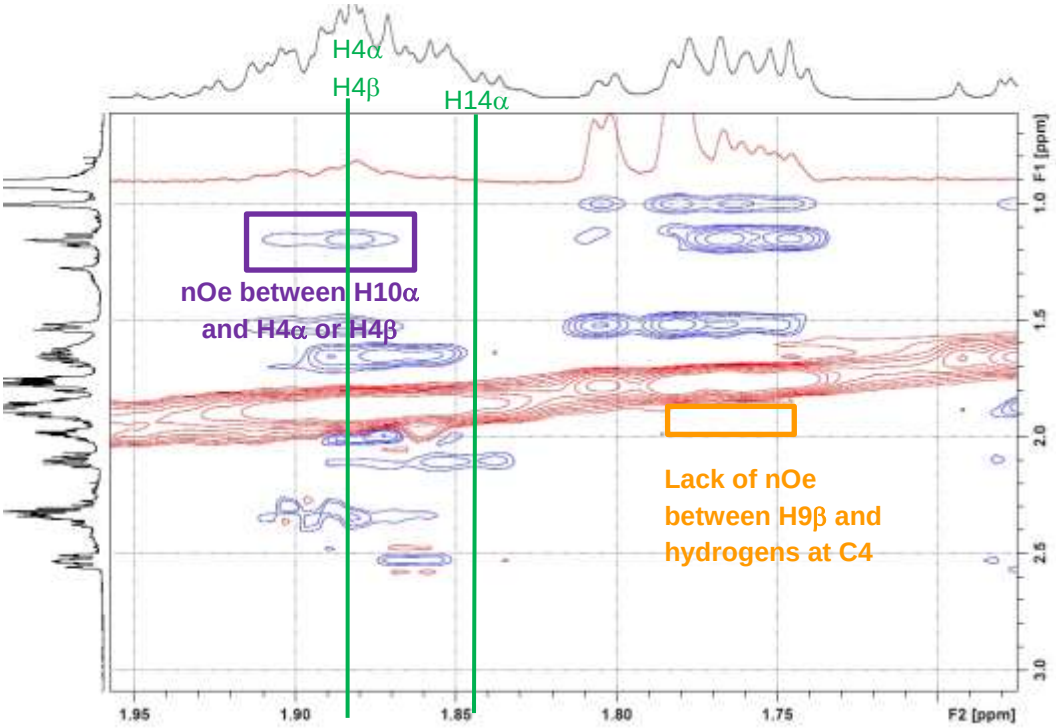


Figure E.35. Superposition of an expansion of the NOESY and the selective nOe experiment irradiating H9α (red line).

In summary, the experiments described indicate unambiguously that the isomer formed in the spirocyclization reaction corresponds to **91aS**. In the figure E.36, the critical nOes that establish the stereochemistry are represented.

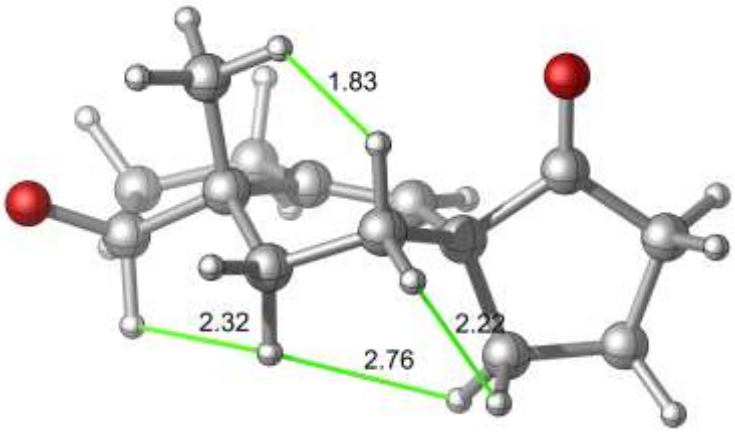
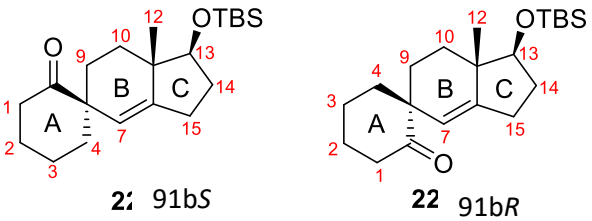


Figure E.36. Three-dimensional structure (PM3) of **91a*S***. The distances highlighted (Å) correspond to critical nOes or NOESY cross-points that establish the stereochemistry of the quaternary center. The TBDMS group has been hidden for clarity.

E.5.4. Stereochemical assignment of compound 91b

The stereochemistry of **91b** could be proposed based on the stereochemistry determined for **91a**, considering that both compounds are formed through the same mechanism. Anyway, an independent NMR study of conducted following a parallel strategy than that described for **91a**. Importantly, the study led to the same epimer as above.

The two possible isomers could be formed depending on the stereochemistry of the newly formed quaternary sterocenter are denoted as **91b*R*** and **91b*S*** (figures E.37, E.38 and E.39). Like in the discussion of **91a**, the diastereotopic hydrogens for each methylene group will be referred as α or β to indicate their relative position below or above the plane, respectively.



2 91b*S* **22** 91b*R*

Figure E.37: Steroisomers that could be formed in the reaction.

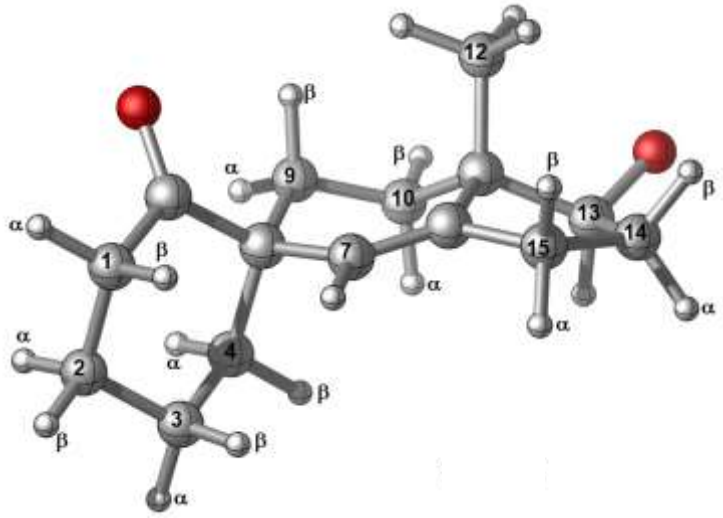


Figure E.38. Three-dimensional model for **91b*S*** optimized at the PM3 level. The TBDMS group has been hidden for clarity.

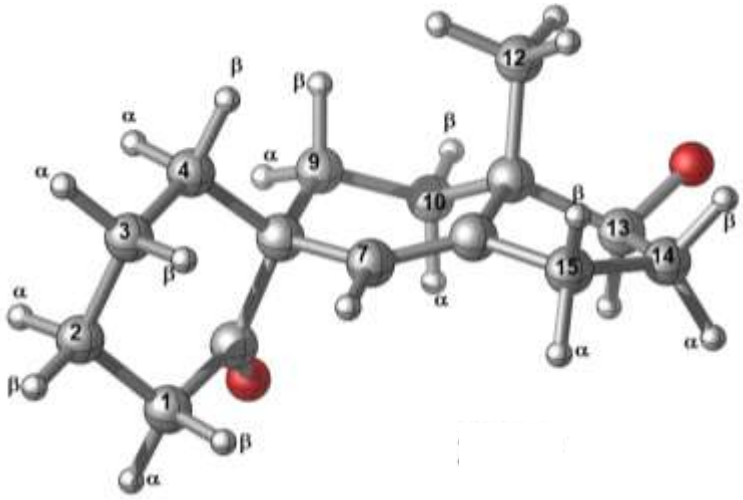


Figure E.39. Three-dimensional model for **23b*R*** optimized at the PM3 level. The TBDMS group has been hidden for clarity.

First of all, all the signals for the hydrogens of compound **91b** were assigned. To this purpose, the following NMR experiments were carried out: ^{1}H and ^{13}C (section

E.5.2, compound **91b**), DEPT-135 (Figure E.40), HSQC (Figure E.41), NOESY (Figure E.42), TOCSY (Figure E.43) and COSY (Figure E.44).

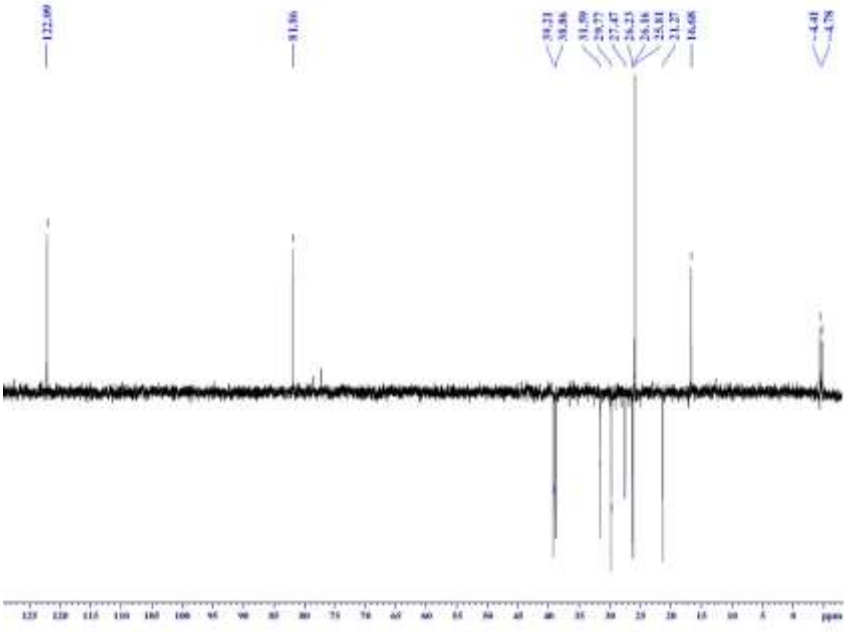


Figure E.40. DEPT-135 experiment of compound **91b**.

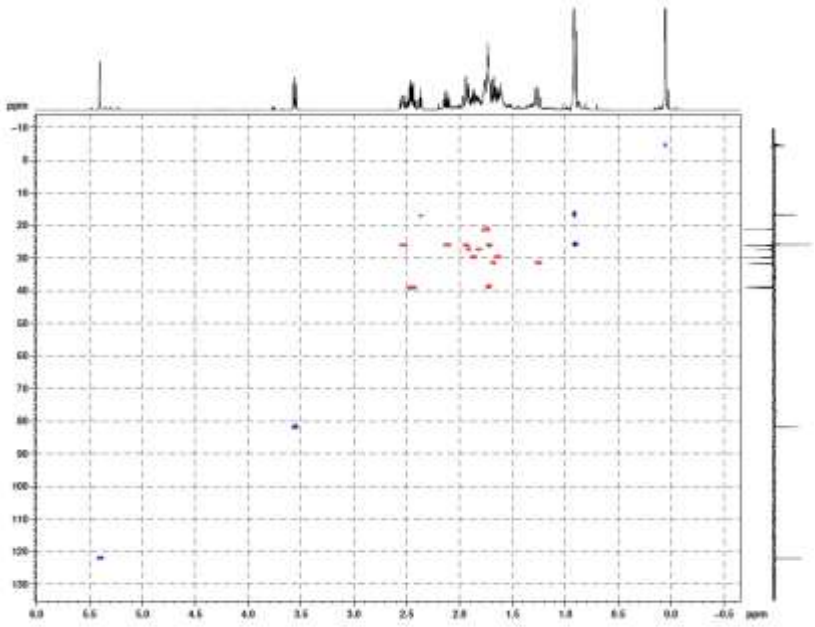


Figure E.41. HSQC experiment of compound **91b**.

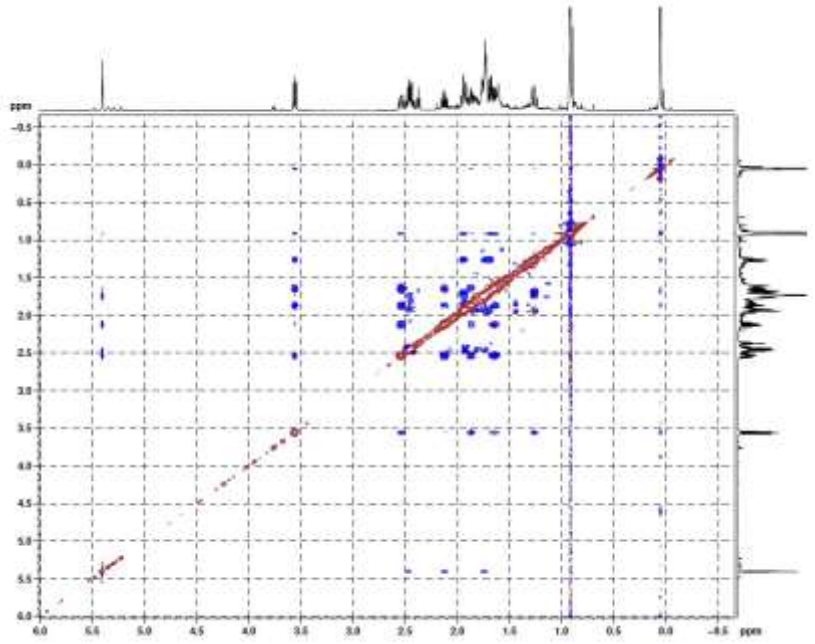


Figure E.42. NOESY experiment of compound **91b**.

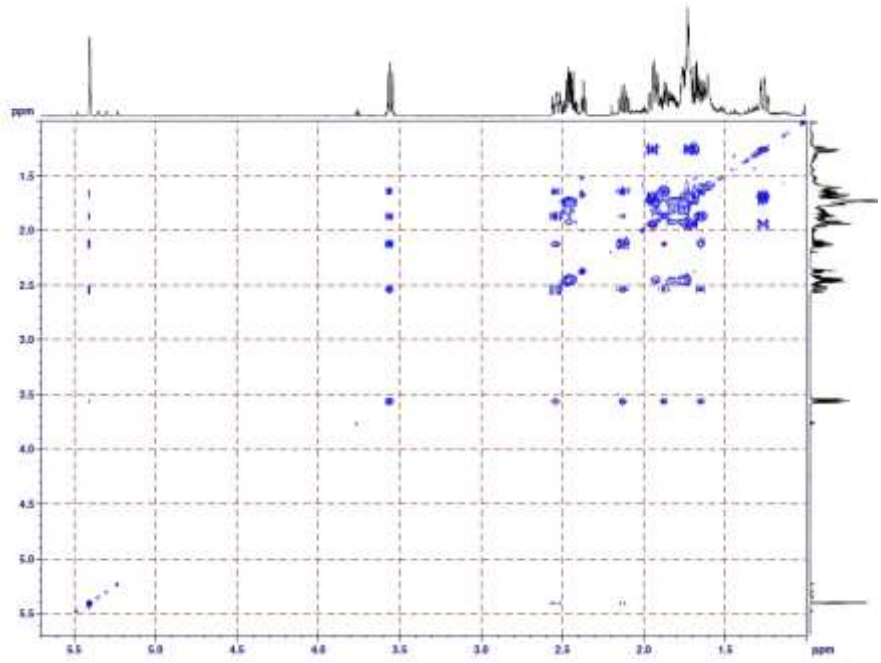


Figure E.43. TOCSY experiment of compound **91b**.

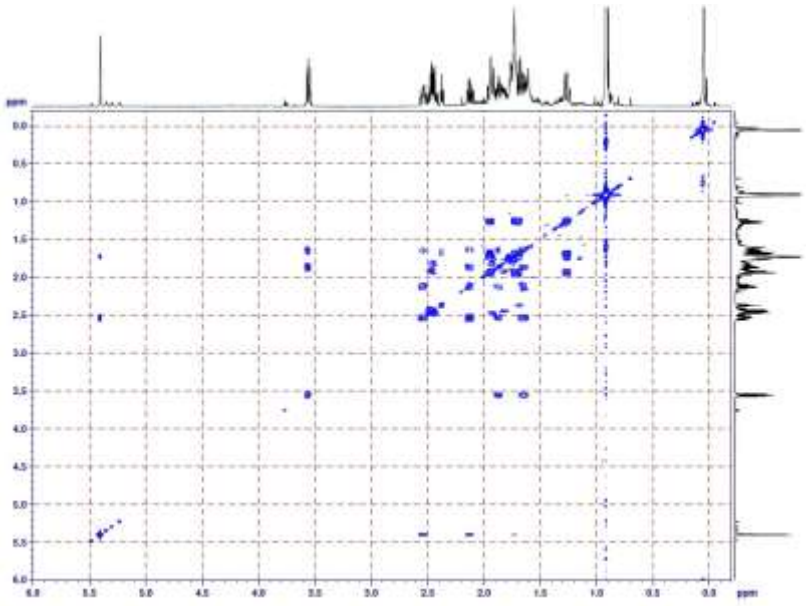


Figure E.44. COSY experiment of compound **91b**.

In combination with all the experiments shown above, some additional experiments were needed to assign unambiguosly all the hydrogens in the compound **91b**:

- In order to assign the hydrogens of ring C, a selective TOCSY (Figure E.45) was carried out irradiating the signal at 3.56 ppm (which corresponds to H13). This experiment, in combination with selective nOe experiments irradiating both H15α (Figure E.46) and H15β (Figure E.47), enabled the assignment of: H15α (2.12 ppm, $^{2}J_{gem}$= $^{3}J_{ax}$=16.5 Hz, $^{3}J_{trans}$= 8.7 Hz), H15β (2.53 ppm, $^{2}J_{gem}$= 16.5 Hz, $^{3}J_{cis}$=12.3 Hz, $^{3}J_{trans}$=$^{4}J_{HH}$=2.7 Hz), H14α (1.86 ppm; $^{2}J_{gem}$ =12.7 Hz, $^{3}J_{cis}$ 8.4 Hz, $^{3}J_{trans}$=3.0 Hz) and H14β (1.63 ppm, $^{2}J_{gem}$= $^{3}J_{ax14\text{-}15}$=$^{3}J_{ax14\text{-}13}$=12.6 Hz, $^{3}J_{trans}$=3.7 Hz).

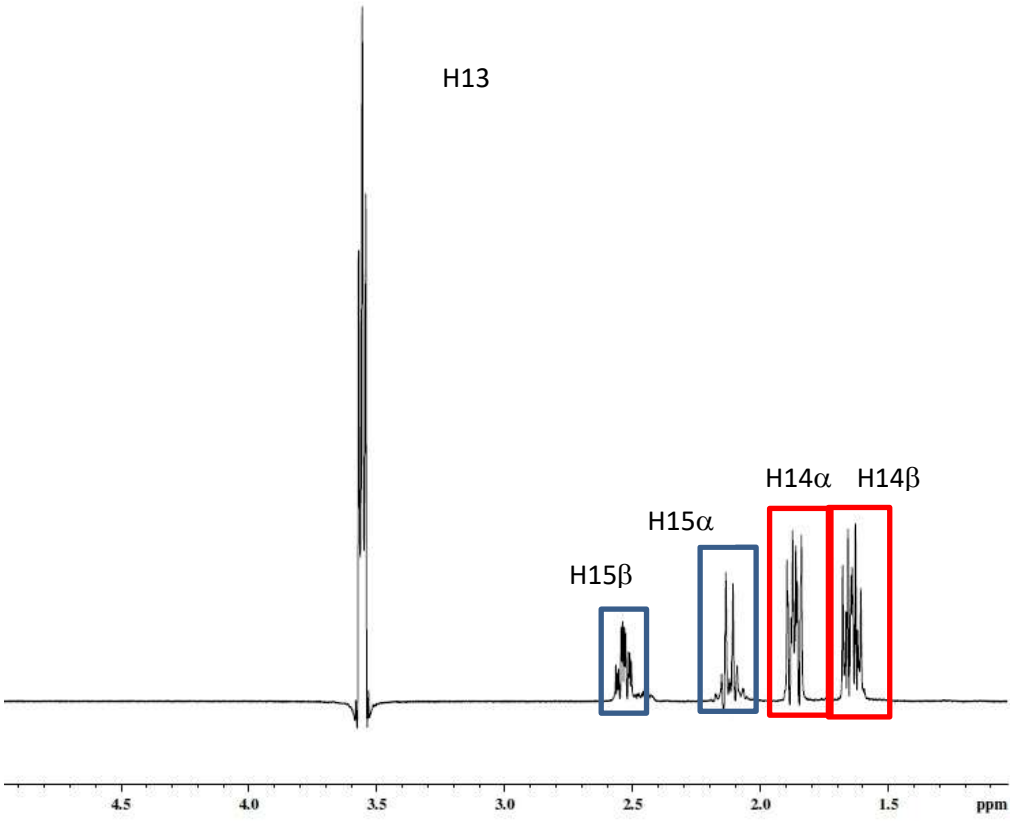


Figure E.45. Selective TOCSY irradiating the signal corresponding to H13 that assigns the hydrogens of ring C

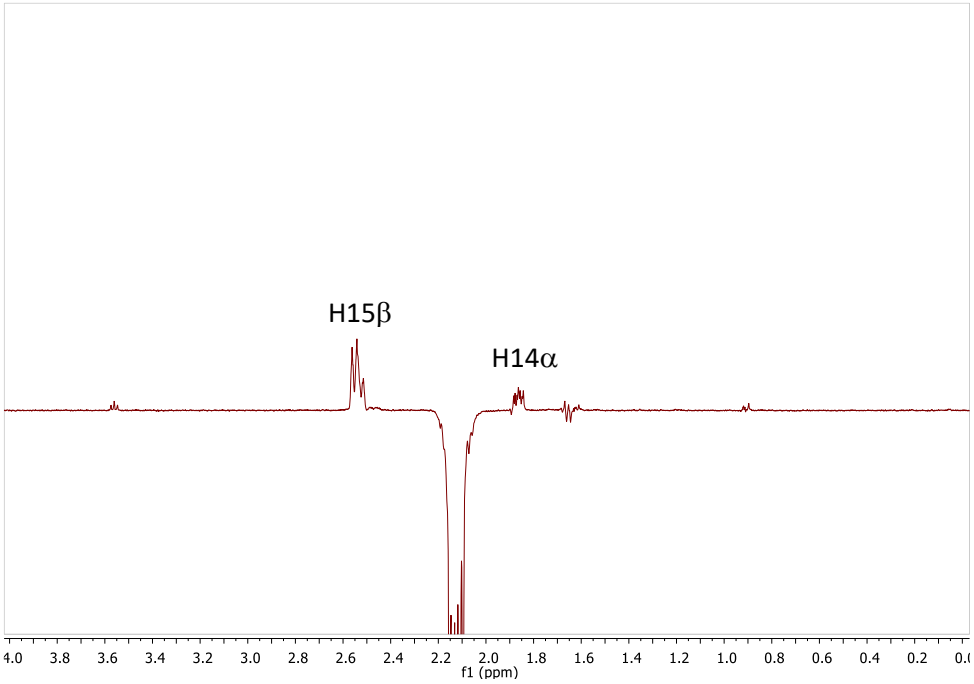


Figure E.46. Selective nOe irradiating the signal corresponding to H15α

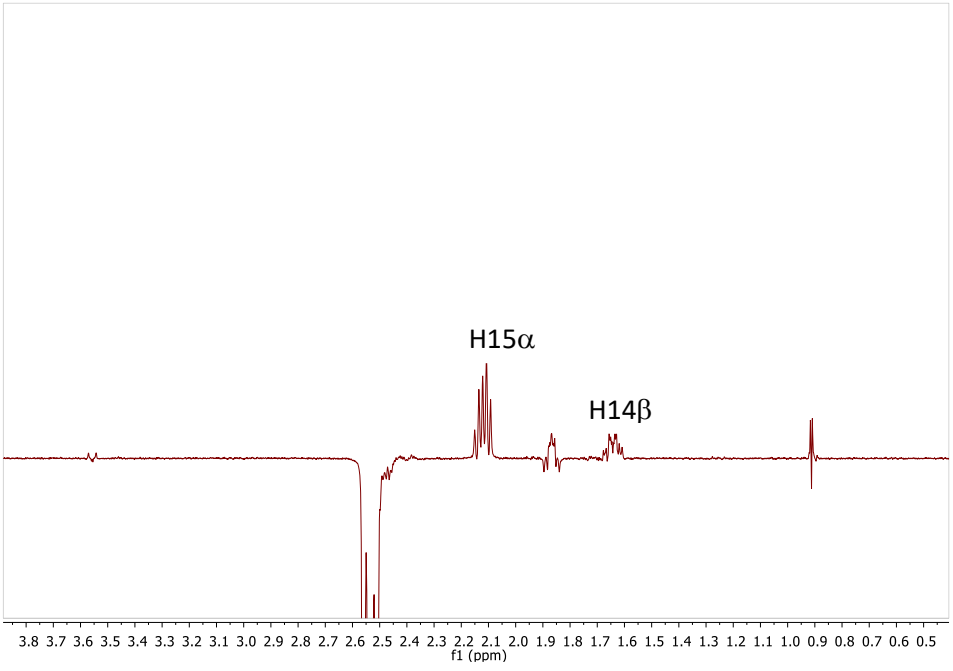


Figure E.47. Selective nOe irradiating the signal of H15β

- Next, the identification of the hydrogens at C9, C4 and C10 was possible by means of a combination between a HMBC experiment (Figure E.48) and a selective TOCSY over the hydrogens at C1 (Figure E.49). In this last experiment, both hydrogens at C1 were irradiated, and that enabled the identification (in combination with the COSY experiment) of both hydrogens at C2, C3 and finally, both hydrogens at C4. Then, the TOCSY (Figure E.50, amplified zone) of H10α (1.26 ppm, td, $^{2}J_{gem}$=13.4 Hz, $^{3}J_{ax\text{-}eq}$=$^{3}J_{eq\text{-}eq}$=3.1 Hz) enabled the assignment of the remaining hydrogens H9β (1.94 ppm, td, $^{2}J_{gem}$=$^{3}J_{ax\text{-}ax}$=13.5 Hz, $^{3}J_{ax\text{-}eq}$=3.2 Hz), H10β (1.68 ppm, m) and H9α (overlapped with both hydrogens at C4 around 1.73 ppm). If the **91b*R*** isomer was present, an intense nOe between H9β and H4β should be observed. On the contrary, in the case of the **91b*S*** isomer, no nOe should not be observed between H9β and the hydrogens at C4, due to the long distance between these hydrogens (see molecular models).

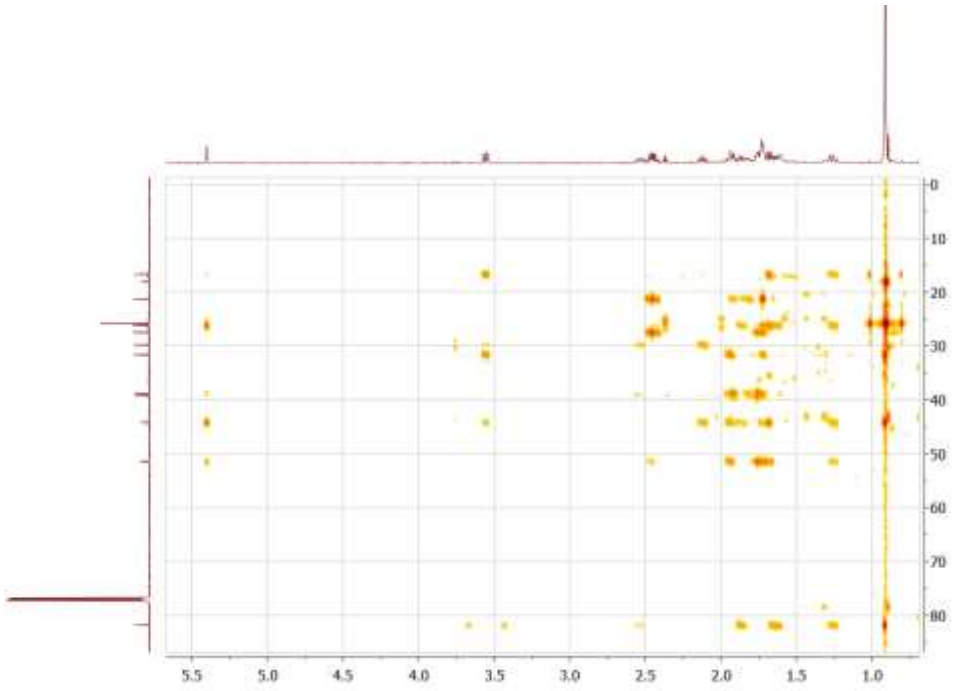


Figure E.48. HMBC experiment (expansion).

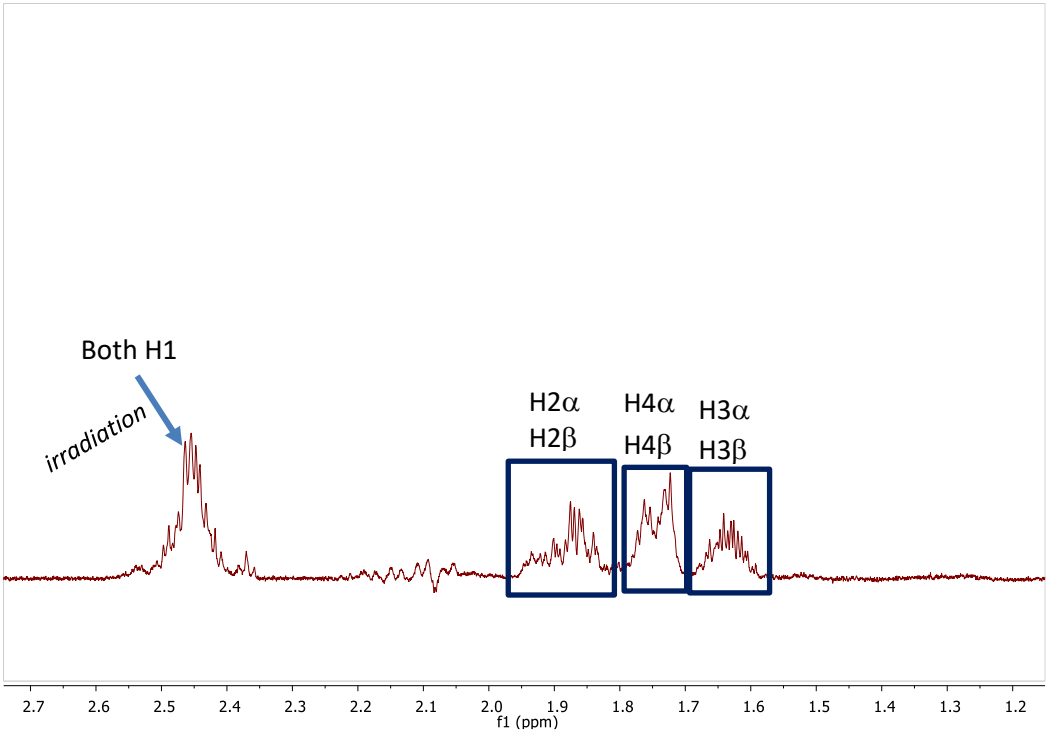


Figure E.49. Selective TOCSY irradiating H1 that identifies the spin system of ring A.

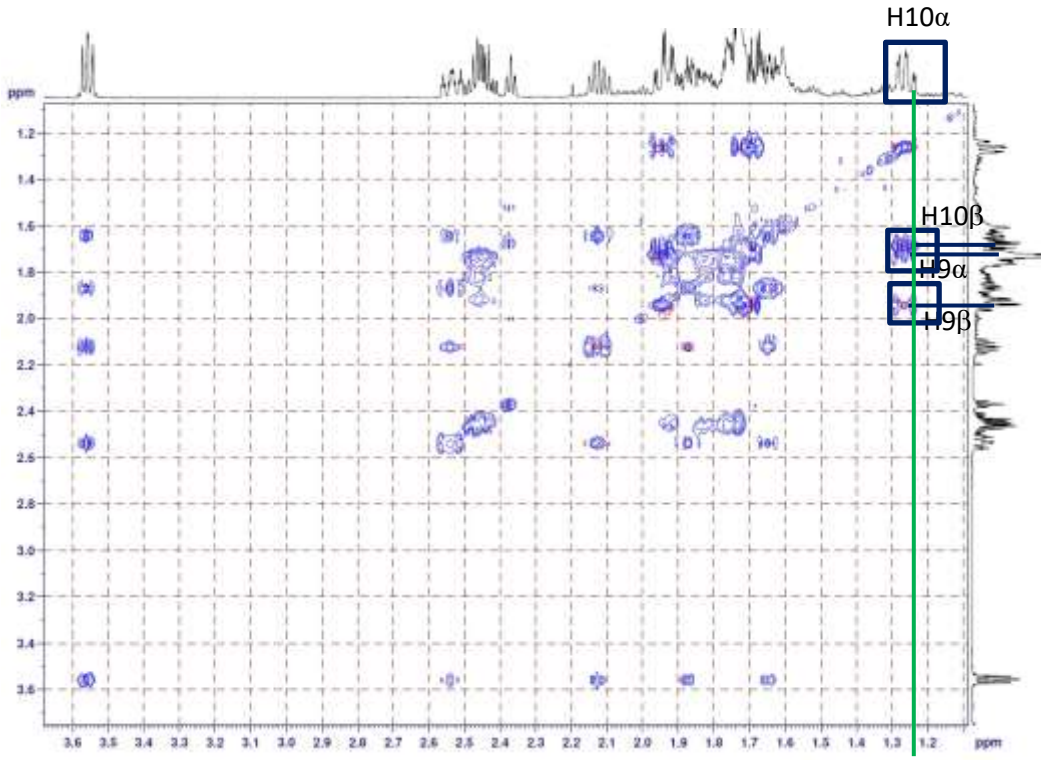


Figure E.50. TOCSY of H10α(amplified zone).

With this purpose, a selective nOe over H9β was carried out. In this experiment, the nOe between H9β and H9α (1.73 ppm, dt, $^{2}J_{gem}$=13.8 Hz, $^{3}J_{ax-eq}$= $^{3}J_{eq-eq}$=3.4 Hz) is clearly detected. The enhanced signal of H9α shows perfectly the pattern of the doublet of triplets (figure E.51, b). This is only possible due to the absence of nOe between H9β and both hydrogens at C4, that appear at the same chemical shift as H9α. Indeed, the lack of nOe between H9β and C4, evident in this experiment, is critical for the assignment of the stereochemistry, and was also observed in **91a*S***.

This observation is showed in figure E.51, which combines: the ^{1}H spectra (purple), the selective nOe irradiating H9 (blue), the selective TOCSY irradiating both hydrogens at C1(red) and the selective nOe irradiating H7 (black). In the last two experiments, the signal corresponding to H9α is not observed in the NMR, enabling the identification of both hydrogens at C4 (overlapped in 1.73 ppm). These

observations point at the isomer **91b*S*** as the one being formed during our transformation.

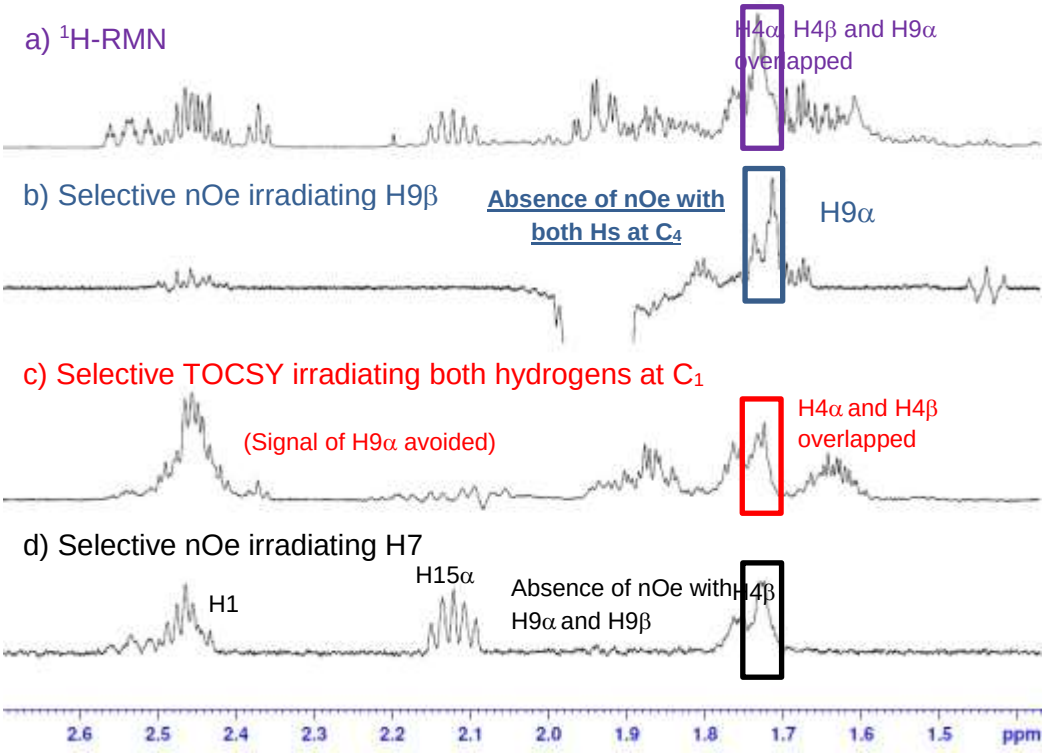


Figure E.51. a) ^{1}H spectra (purple), b) Selective nOe irradiating H9β (blue), c) Selective TOCSY irradiating both hydrogens at C1 (red), d) Selective nOe irradiating H7 (black).

An additional back-up reason that supports the presence of isomer **91b*S*** is the highly deshielded chemical shift observed for H9β (1.94 ppm) in comparison with the expected shift for an axial hydrogen in a cyclohexane ring. Noteworthy, H9β is placed in the deshielding area of the carbonyl group in **91b*S***, and in fact is the only axial hydrogen in the molecule that appears more deshielded than its geminal equatorial hydrogen. Additionally, H9α is also slightly deshielded (1.73 ppm) for the same reason.

Unfortunately, in this example, the critical nOe between H10α and the hydrogens at C4 cannot be unambiguously detected due to the overlap of the signals

of H4α, H4β and H9α. However, in the NOESY experiment (Figure E.52, expanded zone) a very intense cross-peak can be identified between H10α and the hydrogens located around 1.73 ppm. Due to our previous rationale, this nOe should be due to the proximity in space of H10α with H4α, H4β, H9α; fact that would point again as the isomer **91b*S*** as the one being formed in our reaction.

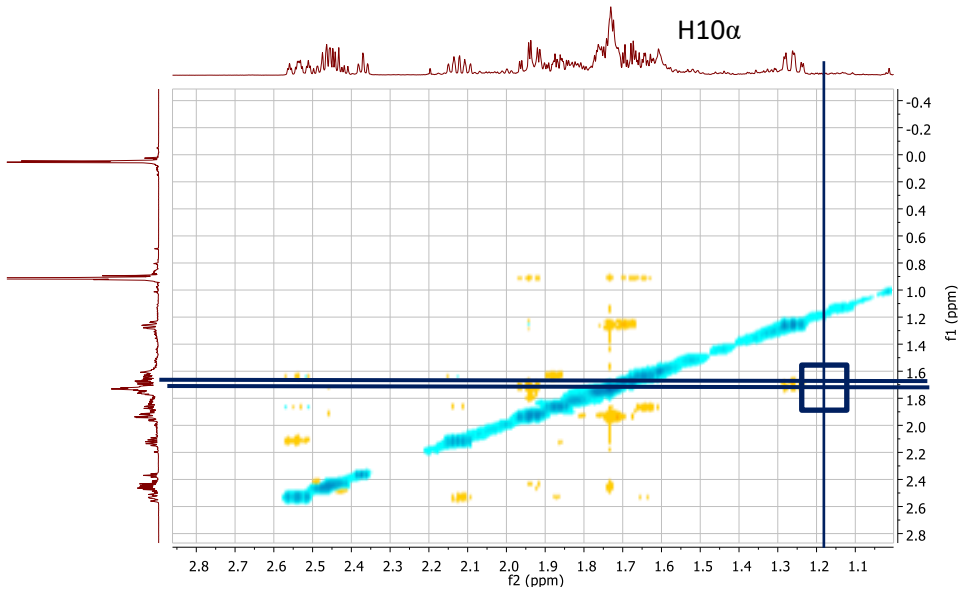


Figure E.52. Expanded area of the NOESY experiment.

List of publications

Part of the results collected in this Memory have been published in the following academic articles:

Communications

- "Stereoselective Csp^3-Csp^2 Bond Forming Reactions by Transition-Metal-Free Reductive Coupling of Cyclic Tosylhydrazones with Boronic Acids". M. Plaza, M. C. Pérez-Aguilar, C. Valdés. *Chem. Eur. J*. **2016**, *22*, 2653-2657.
- "Stereoselective Domino Carbocyclizations of *γ*- and *δ*-Cyano-*N*-tosylhydrazones with Alkenylboronic Acids with Formation of Two Different $C(sp^3)$-$C(sp^2)$ Bonds on a Quaternary Stereocenter". M. Plaza, C. Valdés. *J. Am. Chem. Soc*. **2016**, *138*, 12061-12064.

Full papers

- "Heterocyclization and spirocyclization processes based on domino reactions of *N*-tosylhydrazones and boronic acids involving intramolecular allylborylation of nitriles". M. Plaza, S. Parisotto, C. Valdés. *Chem. Eur. J*. **2018**, 10.1002/chem.201803309.

Education is not something you can finish

- Isaac Asimov -