Transition-metal-free reactions between boronic acids and *N*-sulfonylhydrazones or diazo compounds: reductive coupling processes and beyond

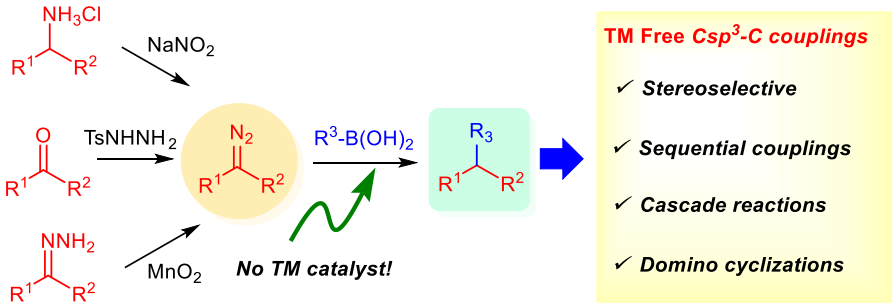
Miguel Paraja[a]
Manuel Plaza[a]
Carlos Valdés*[a]

[a] Departamento de Química Orgánica e Inorgánica. Instituto Universitario de Química Organometálica "Enrique Moles". Universidad de Oviedo. C/ Julián Clavería 8. Oviedo 33006. Spain.

* indicates the main/corresponding author.

acvg@uniovi.es

Click here to insert a dedication.



Received:
Accepted:
Published online:
DOI:

Abstract The metal-free reaction between diazo compounds and boronic acids has established in the recent years as a powerful Csp^3-C bond forming reaction. This account covers the recent advances in this area. First, the various synthetic applications the reactions with *N*-sulfonylhydrazones as convenient source of diazo compounds will be treated. These transformations can be seen as reductive couplings of carbonyl compounds. The incorporation of other mild sources of diazo compounds in these reactions - diazotation of amines and oxidation of hydrazones – will be also covered. Finally, the development of sequential and cascade processes will be presented.

Key words cross-coupling, boronic acid, hydrazone, diazo compound, metal-free.

1. Introduction

Metal catalyzed C-C bond forming reactions are highly reliable methodologies that represent some of the most powerful tools in modern organic synthesis. The presence of the metal catalyst allows the achievement of transformations that would not be possible in the absence of the catalyst, and also enable regio- and stereochemical control of the processes. On the opposite, in the recent years the development of C-C of C-X bond forming processes that may not require the mediation of a transition-metal catalyst (so called transition-metal free reactions) have concentrated a great deal of attention.[1] Among the advantages of these processes environmental and economical reasons could be highlighted, since the employment of expensive and/or toxic metals is avoided. Additionally, many of these processes usually take place under particularly simple experimental conditions, without the need of inert atmosphere or dry solvents. Of course, there are a myriad of C-C bond forming transformations that take place in the absence of any metal catalyst, such as aldol reactions, Michael type additions, pericyclic reactions, radical processes, organocatalytic reactions. However, the controversial terms "metal free" or "transition-metal free" are usually employed to allude those processes that would be expected to proceed with the participation of a metal catalyst, but take place under non-catalyzed conditions, and through unconventional mechanisms.

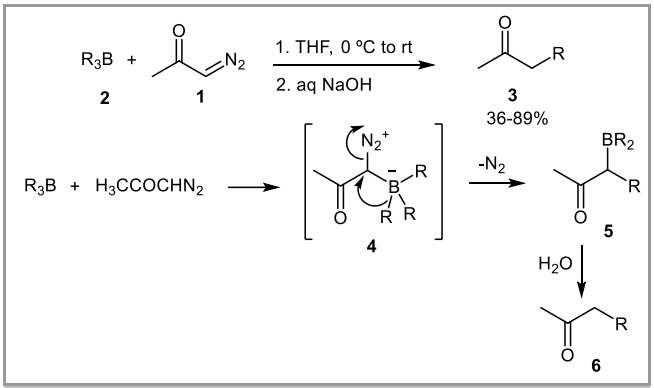
The reactions between organoboron compounds and diazo compounds are typical examples of this class of "transition metal-free" C-C bond forming reactions. These transformations have been known for five decades now, but recent advances in the form of the incorporation of readily available and bench stable boronic acid derivatives, as well as the employment of alternative methods to generate the diazo compounds have taken these methodologies into another level. In particular, the reactions with *N*-sulfonylhydrazones, which can be regarded as reductive coupling reactions of carbonyl compounds, have attracted considerable attention due to their simplicity and synthetic potential. A review on the reactions of diazo compounds and organoboranes written by Wang et al. was published in 2013[2] and is recommended to the interested reader. The remarkable advances have been developed since then are covered this account, which focuses on metal-free C-C bond forming reactions employing in situ generated unstable

diazo compounds and boronic acids. Moreover, recently developed sequential and cascade processes based on this fundamental transformation will be also covered.

2. Early work: Reactions between alkylboranes and diazo compounds or *N*-sulfonylhydrazones

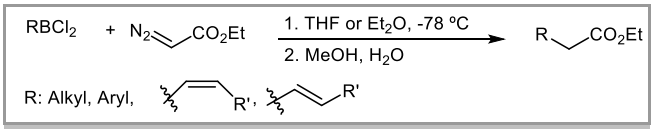
2.1 Reactions between alkylboranes and diazo compounds

The earliest examples of reactions between diazocarbonyl compounds and organoboron reagents dates back to 1968, and was described by Hooz and coworkers.[3] This seminal reaction employed diazoacetone **1** and trialkylboranes **2** and afforded ketones **3** after alkaline hydrolysis (Scheme 1).



Scheme 1 Reactions of organoboranes with stabilized diazo compounds and proposed mechanism.

Over the subsequent years the methodology was expanded to the employment of other stabilized diazo compounds such as diazoacetate, diazoacetonitrile, bisdiazoketones, and diazoacetaldehyde.[4] The proposed mechanism involved the coordination of the borane with the diazo compound through a Lewis acid-Lewis base interaction to generate a boronate intermediate **4**, followed by a 1,2-alkyl shift with simultaneous nitrogen release. Hydrolysis of the α-borylketone **5** under basic conditions afforded the alkylated ketone **6**. From a synthetic perspective, considering that the alkylboranes were obtained by hydroboration of terminal olefins, this reaction could be envisioned as the homologation of olefins into ketones, nitriles or esters. However, the reaction suffered from some limitations, in particular high sensitivity to steric hindrance. The same type of reactions were studied later employing dialkylchloroboranes, as well as alkyldichloroboranes, aryldichloroboranes and 1-alkenyldichloroboranes and ethyl diazoacetate.[5] The reactions took place under very mild conditions (-65 to -78 ^{0}C) and led to the corresponding alkylated, arylated or alkenylated acetates respectively (scheme 2). The higher reactivity of dichloroorganoboranes when compared with the trialkylboranes was rationalized by a combination of the lower steric hindrance and higher electron deficiency at the boron center on chloro- and dichloroboranes that allowed for the very fast formation of the boronate intermediate.

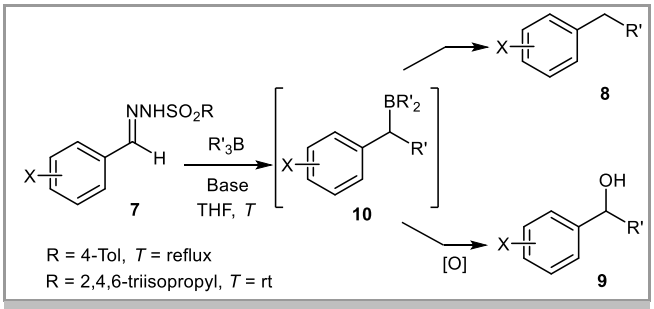


Scheme 2 Reactions of dialkylchloroboranes with stabilized diazo compounds.

The overall transformation consisted on a very original type of C-C bond forming reactions. However, the synthetic impact of these methodologies was really limited, probably due to the scarce availability of the required organoboranes. Moreover, the modest scope regarding the structure of the diazo compounds represented an additional drawback of the reactions.

2.2 Reactions between alkylboranes and N-sulfonylhydrazones

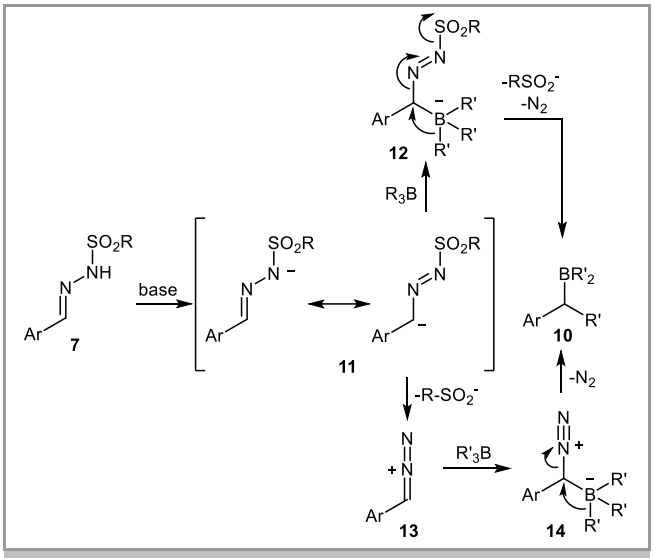
In 1994, Kabalka and coworkers reported the alkylation of arylaldehydes by reaction of *N*-sulfonylhydrazones **7** with trialkylboranes.[6] Depending on the reaction conditions and the subsequent workup, arylalkanes **8** or benzyl alcohols **9** were obtained with excellent yields (Scheme 3). Thus, reactions with the nucleophilic bases NaOH and Bu_4NOH under reflux of THF produced excellent yields of the reductive alkylation products **8**. The reaction was postulated to proceed through the formation of the benzylborane **10**, that would undergo protodeboronation promoted by the nucleophilic base to give **8** (Scheme 3). On the other hand, the employment of non nucleophilic bases such as DBU, minimized the protodeboronation step, and alcohols **9** could be isolated upon oxidation of the benzylborane **10** with sodium perborate or peracetic acid. Importantly, the reactions tolerated the presence of functional groups sensitive to more nucleophilic organometallic reagents, such as organolithium of Grignard reagents, and therefore could represent an alternative for the alkylation of aldehydes in the presence of additional functionality in either the aldehyde or the nucleophile (Scheme 3). Interestingly, the employment of trisylhydrazones led to the obtention of both the alkanes and the alcohols with comparable yields under much milder conditions, as the reactions took place at room temperature.



Scheme 3 Kabalka's reactions between *N*-sulfonylhydrazones and alkylboranes. Base: NaOH, Bu_4NOH or DBU; [O]: $NaBO_3.4H_2O$ of CH_3CO_3H

Two alternative mechanisms could be proposed for these transformations, an anionic mechanism, and a pathway involving the formation of a diazo compound (Scheme 4). The anionic mechanism would consist on 1) the deprotonation of the sulfonylhydrazone **7** by the action of the base to generate anion **11**, 2) reaction of **11** with the trialkylborane, to form a boronate complex **12**, 3) 1,2-migration of one of the R' groups with concomitant release of N_2 and sulfinate, to form the benzylborane **10**. The alternative pathway would comprise 1) the loss of sulfinate from the deprotonated hydrazone through the classical Bamford-Stevens reaction[7] to form a diazo compound **13**, 2) formation of a boronate intermediate **14** by reaction of the diazo compound with the organoborane, 3) 1,2-migration of one of the R' groups with concomitant release of N_2. This second pathway would be similar to that proposed for the reactions described by Hooz commented above. The difference

between both pathways is the particular moment when the sulfinate is released. It was demonstrated that the diazo compound **13** generated independently reacted with the organoborane to provide the expected reaction products, and therefore the diazo compound route could be a feasible mechanism. However, the combination of all the mechanistic studies carried out by Kabalka et al. was more consistent with the anionic mechanism (scheme 4). Nevertheless, in spite of the potential interest of this methodology, it had very little impact in synthetic chemistry in the following years, probably due to the limited scope, only *N*-sulfonylhydrazones derived from aromatic aldehydes could be employed, and the practical inconveniences associated with the use of trialkylboranes.



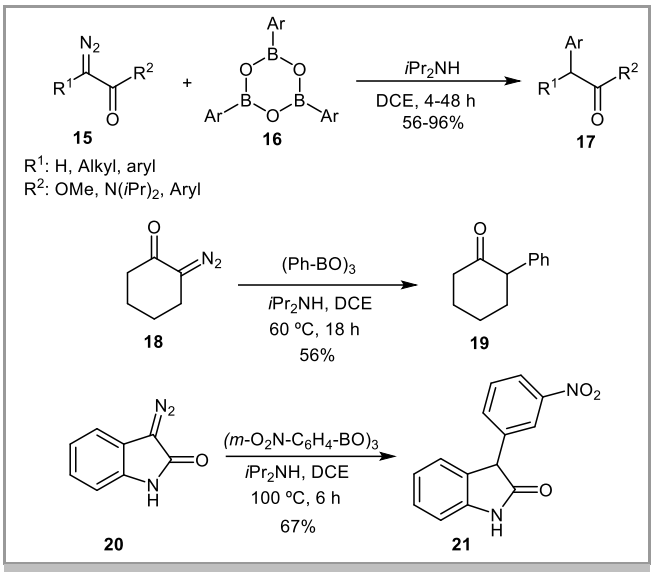
Scheme 4 Mechanism alternatives for the reaction between *N*-sulfonylhydrazones and alkylboranes.

3. Reactions of *N*-sulfonylhydrazones and diazo compounds with aryl and alkyl boronic acids

The year 2009 represented a turning point for the development of the chemistry covered in this review, as a result of the independent work of the groups of Prof. Jianbo Wang and our own research group.

3.1 Reactions of arylboroxines with diazo compounds

In 2009, Wang et al. reported the arylation and vinylation of α-diazocarbonyl compounds by reaction with boroxines.[8] The reactions took place by mixing the diazo compound **15** with the boroxine **16** in DCE in the presence of *i*Pr$_2$NH at a temperature between 60-100 ^{0}C, and led to the α-arylated carbonyl compound or carboxylate **17** (Scheme 5). The transformation featured wide scope regarding both the structure of the diazo compound and the arylboroxine. Moreover, it could be applied to α-diazocarbonyl substrates such as a cyclic α-diazoketone **18** and a cyclic α-diazoamide **20** to provide the α-arylated ketone **19** and amide **20** respectively (Scheme 5). The mechanism proposed for these transformations is similar to the initial proposal of Hooz for the reactions with organoboranes.



Scheme 5 Metal-free cross-coupling between arylboroxines and α-diazo carbonyl compunds.

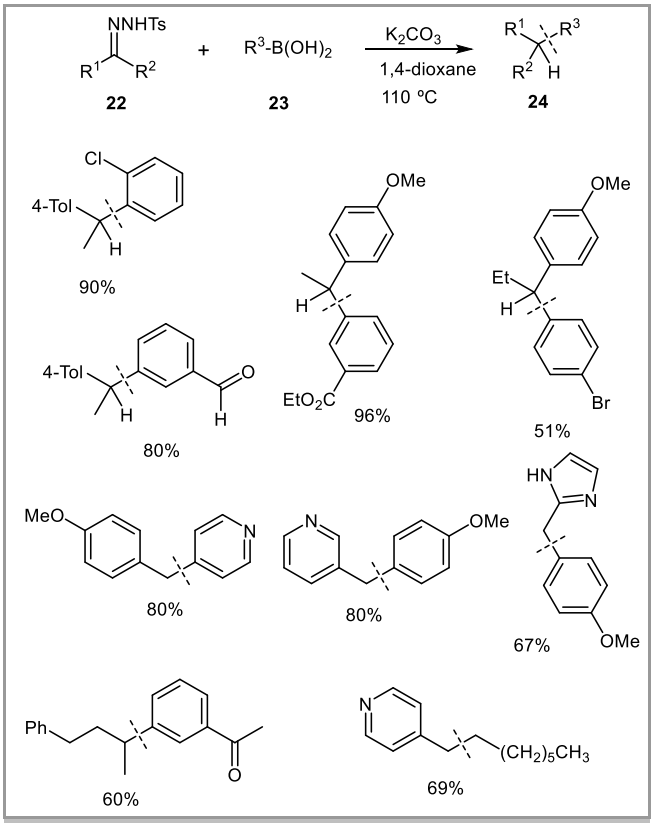
3.2 Reductive couplings of N-sulfonylhydrazones with aryl- and alkylboronic acids

All the reactions that had been described so far between organoboranes and diazo compounds had been limited to diazo compounds stabilized by electronwithdrawing groups, or the non-enolizable diazo compounds derived from *N*-tosylhydrazones of aromatic aldehydes. One of the limitations associated with non stabilized diazo compounds is their tendency to undergo decomposition to give alkenes. In fact, the base promoted thermal decomposition of *N*-tosylhydrazones is a well established method for the preparation of alkenes from ketones- so called Bamford–Stevens reaction. In the early 2000s, Aggarwal's group introduced the use of *N*-tosylhydrazones as a convenient source of diazo compounds, which were employed in a number of transformations. In particular, in transition metal catalyzed reactions involving the generation of metal carbenes from the diazo compounds.[9] Nevertheless, most of this chemistry was still restricted to *N*-tosylhydrazones derived from non enolizable carbonyl compounds, that generate relatively stable diazo compounds.

A few years later, in 2007, in the context of our collaboration with the late Prof. Barluenga, we reported the Pd-catalyzed cross-coupling reaction between arylhalides and *N*-tosylhydrazones.[10] This reaction, which turned out to be a very general method for the synthesis of substituted alkenes, was postulated to proceed through an intermediate Pd-carbene complex, that would be generated from the diazo compound derived from the decomposition of the *N*-tosylhydrazone. Importantly, this reaction showed a very wide scope regarding the structure of the starting *N*-tosylhydrazone, including those derived from enolizable aldehydes or ketones. Therefore, these results sent the message that it was possible to do interesting chemistry with *N*-tosylhydrazones derived from enolizable and aliphatic carbonyls other than the typical Bamford-Stevens olefination.

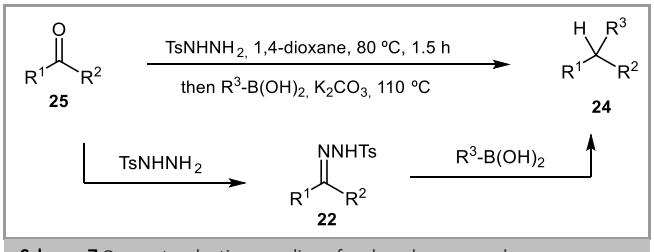
Thus, in the context of our interest on developing new reactions with *N*-tosylhydrazones, in 2009 we reported the metal-free coupling with boronic acids.[11] The reaction led to the corresponding reductive coupling products **24**, in which a C-C

bond had been formed between the former hydrazonic carbon and the carbon attached to the boron center (Scheme 6). The reactions took place under very simple experimental conditions, mixing the *N*-tosylhydrazone **22** and the boronic acid **23** in dioxane as solvent and only the presence of K_2CO_3 as additional reagent. This transformation was an excellent method for the preparation of diarylmethanes by the employment of arylboronic acids and *N*-tosylhydrazones of aromatic aldehydes or ketones, and tolerated the presence of almost any functional group, including unprotected amines, enolizable ketones, esters and N-H azoles. Regarding the boronic acid, both aryl and alkyl boronic acids could participate in the reaction successfully (Scheme 6).



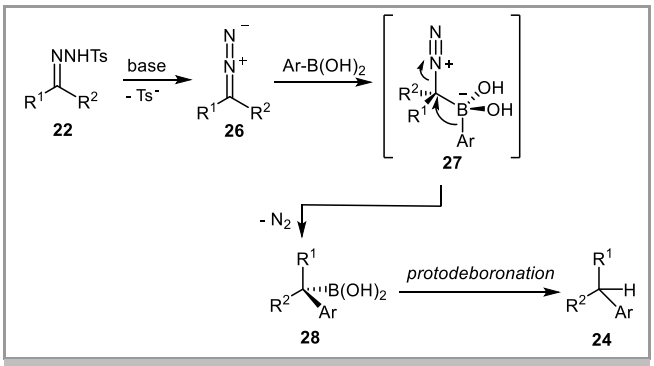
Scheme 6 Reductive coupling of *N*-tosylhydrazones with aryl and alkylboronic acids and selected examples.

Notably, the coupling reaction could be conducted in a one pot fashion directly from the carbonyl compound **25**, by mixing the carbonyl and the tosylhydrazide, and after the time required for the condensation reaction, the boronic acid (Scheme 7). Thus, the overall reaction consists in the reductive coupling of carbonyl compounds, a process that would require several steps through alternative mechanisms.



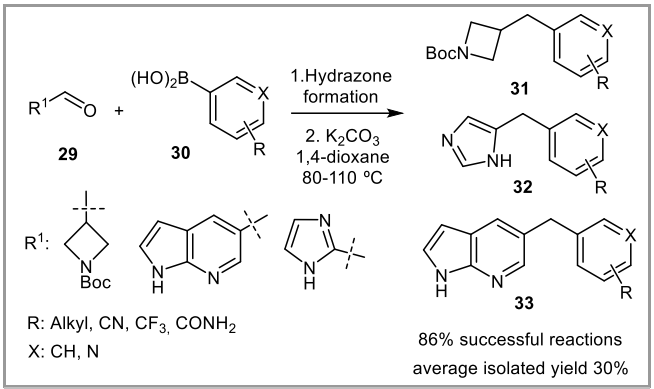
Scheme 7 One-pot reductive coupling of carbonyl compounds

It is important to highlight the differences of this reaction when compared with the previous examples based on diazo compounds and organoboranes. On one side, the employment of boronic acids is an important advantage. First of all, due to their stability, that allows the reactions to be conducted under very simple experimental conditions – no inert atmosphere or dry solvents are needed. Additionally, there is an enormous variety of commercially available boronic acids, mainly due to their constant employment in Suzuki reactions, and therefore the scope of the reaction regarding the boronic acid is almost unlimited. On the other side, the employment of *N*-tosylhydrazones **22** is not restricted to those derived from aromatic aldehydes, but aliphatic aldehydes and ketones can also participate in the reaction. Therefore, this initial report already showed the great potential and wide scope of this new C-C bond forming reaction. Again, a mechanism reminiscent of those previously suggested by Hooz and Kabalka was proposed (Scheme 8). In a first step, the *N*-tosylhydrazone **22** would undergo base promoted decomposition to give the diazo compound **26** under thermal conditions. Then, reaction with the boronic acid would form the boronate intermediate **27**, that would experiment 1,2-migration of the organic rest from boron to carbon, with release of the nitrogen molecule to provide an intermediate boronic acid **28**. Finally, protodeboronation of **28** under the reaction conditions furnishes the final product **24**.



Scheme 8 Mechanism proposed for the reductive coupling of *N*-tosylhydrazones and boronic acids

This reaction has been the object of further studies and found some applications in medicinal and materials chemistry. In 2012, Ryckmans et al. evaluated the applicability of this reaction in parallel synthesis for the preparation of drug-like molecules.[12] Thus, a set of challenging heterocycle-containing aldehydes **29** and functionalized boronic acids **30** were examined in the C-C bond forming reaction. The coupling products **31-33** could be isolated in 86 % of the examples (18 out of 21) with yields ranging from 62 to 2 % (average yield 30 %) (Scheme 9). It is noteworthy that the reactions were conducted in the one pot version and that no further optimization was carried out. Thus, the authors concluded that the reaction was indeed appropriate for the synthesis of high polar, functionalized molecules with drug-like or drug-fragment physicochemical properties.



Scheme 9 Application of the reductive coupling on the one pot the parallel synthesis of drug-like molecules from heterocyclic aldehydes **29** and functionalized boronic acids **30**.

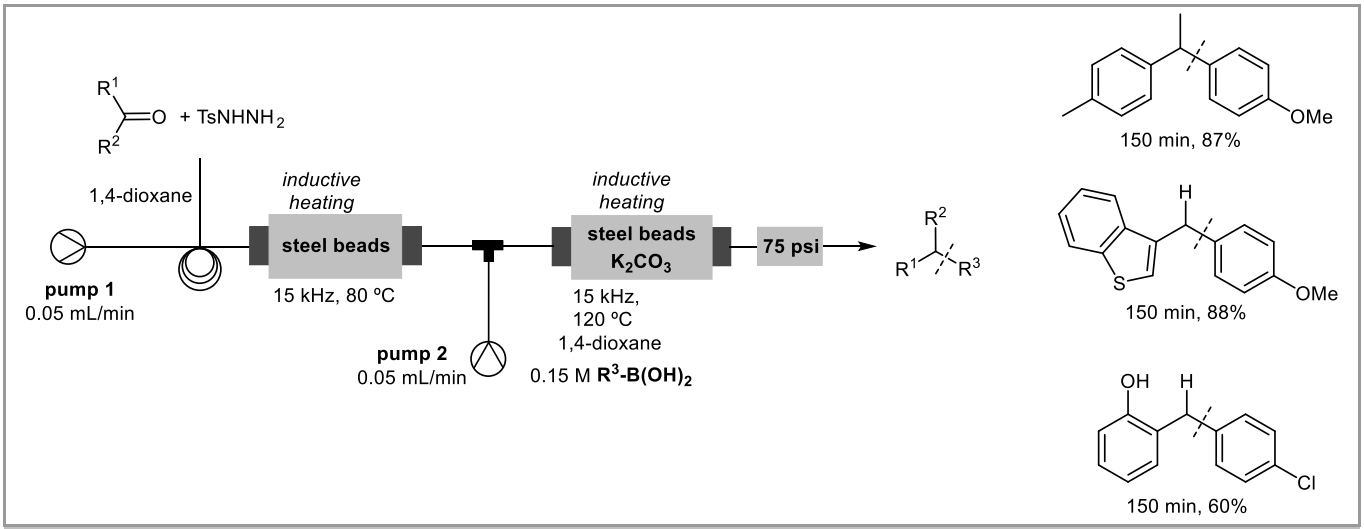
Also in 2012, Kirsching developed a flow protocol for the reductive coupling reaction of *N*-tosylhydrazones with aryl boronic acids. In the optimized operative procedure, the heating was generated inside the reactor by the induce heating of steel beads. High yields were reported for reductive couplings with both *N*-tosylhydrazones of aldehydes and ketones, thus the authors concluded that the reaction was ideally suited to be operated under continuos flow. To enhance the practical applicability of the reaction, a two-steps continuos flow protocol, starting from the carbonyl compounds and tosylhydrazide was also developed (Scheme 10).[13]

The reductive coupling with *N*-tosylhydrazones was also studied employing arylborinic acids - $Ar_2B(OH)$ - instead of arylboronic acids. Under the standard reaction conditions good yields were reported for the synthesis of diarylmethanes. Although the authors suggest advantages related with atom economy, the lack of commercial availability of arylborinic acids when compared with the analogous boronic derivatives might limit the applicability of these reactions.[14]

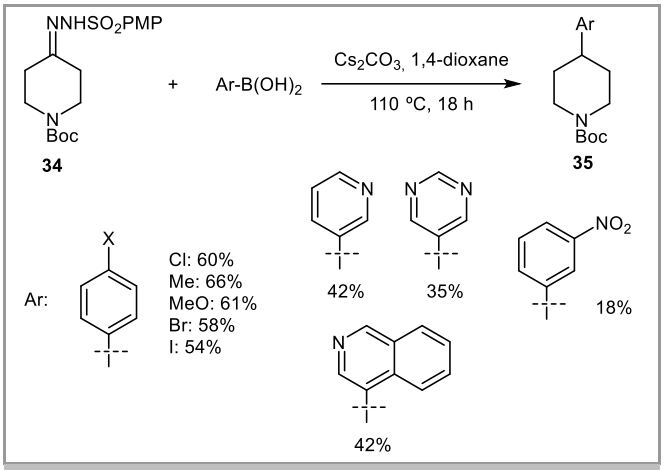
Our original publication had been restricted to acyclic tosylhydrazones. In 2013, Allwood et al. adapted the methodology to *N*-sulfonylhydrazones derived from saturated heterocyclic ketones.[15] After some detailed optimization work, it was discovered that Cs_2CO_3 provided better yield in the model substrate than K_2CO_3. Additionally, a screening on the influence of the substitution of the sulfonylhydrazone showed that *p*-methoxyphenylsulfonylhydrazones produced consistently slightly higher yields than the standard *p*-toluenesulfonylhydrazones. These conditions were applied to the preparation of 4-aryl-*N*-Boc-piperidines **35** from the *N*-sulfonylhydrazone of *N*-Boc-4-piperidone **34** (Scheme 11).

The same conditions were also applied for hydrazones of other six-, five- and four-membered heterocycles leading to the corresponding arylated saturated heterocycles. Again, the employment of *N*-PMP-sulfonylhydrazones turned out to be key for the success of the reactions. Thus, 4-aryltetrahydropyranes **36** and 4-aryltetrahydrothiins **37** were prepared from tetrahydropyran-4-one and tetrahydrothiopyran-4-one respectively, and 3-arylpyrrolidines **38** and 3-aryltetrahydrofurans **39** from the sulfonylhydrazones of *N*-Boc-pyrrolidin-3-one and dihydrofuran-3-one respectively. Finally, the sulfonylhydrazones of 3-oxetanone and *N*-Boc-3-azetidinone gave 3-aryloxetane3, and 3-arylazetidines **41** respectively (scheme 12). The latter reaction was applied for the preparation of a biologically relevant azetidine.

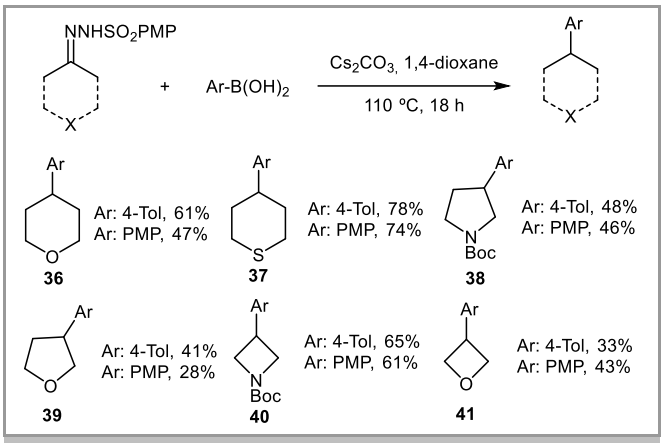
The reductive coupling reaction has been also useful in the area of materials chemistry, in particular for the synthesis of 9-arylfluorenes.[16] Thus, a large variety 9-arylfluorenes **43** were prepared in a one pot process from 9-fluorenone **42** by treatment with *N*-tosylhydrazide, followed by the addition of the boronic acid and K_2CO_3 in toluene (Scheme 13). The reaction was carried out employing aryl, heteroaryl and even alkylboronic acids, and provided high yields in most of the cases. A similar protocol was applied also for the synthesis of triarylmethanes **45** from diaryl ketones **44**.[17] The latter systems turned out to be less reactive, as in order to achieve useful yields, higher temperatures (150 °C) were required in the reductive coupling step (Scheme 13).



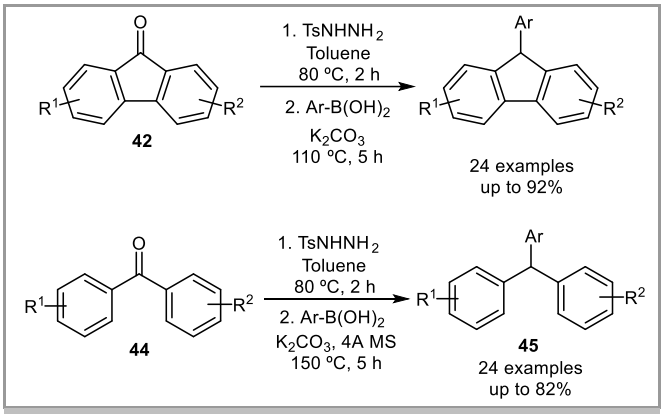
Scheme 10 Two-step protocol for the reductive coupling of carbonyl compounds and arylboronic acids under continuous flow conditions. Selected examples are shown.



Scheme 11 Synthesis of 4-aryl-*N*-Boc-piperidines from 4-piperidone *N*-sulfonylhydrazones. PMP = *p*-C_6H_4



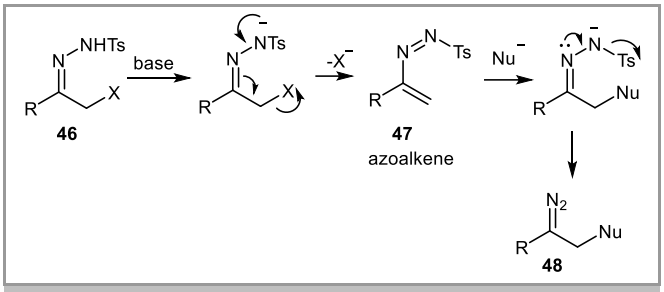
Scheme 12 Synthesis of aryl-substituted saturated heterocycles by reaction of the corresponding sulfonylhydrazones with arylboronic acids.



Scheme 13 Synthesis of 9-arylfluorenes and triarylmethane derivatives.

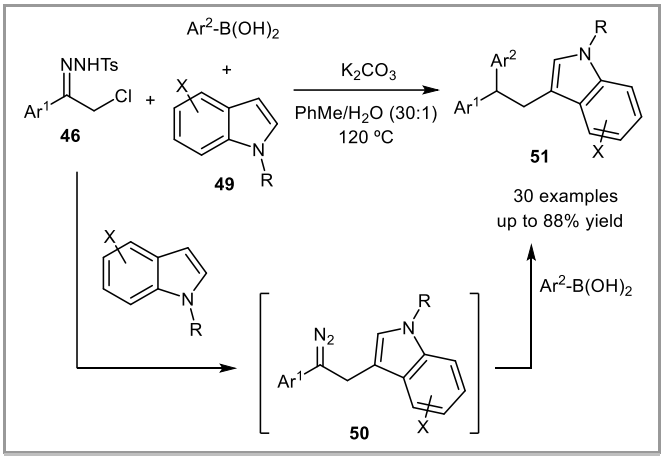
3.3 Three components reactions between α-halotosylhydrazones, boronic acids and indoles.

The particular reactivity of α-halo-*N*-tosylhydrazones was exploited by Wang et al. to develop a very elegant three components reaction combining these functionalized reagents with indoles and arylboronic acids. Unlike typical tosylhydrazones, α-halo *N*-tosylhydrazones **46** in the presence of a base do not decompose to give diazo compounds, but instead, elimination of the halogen takes place to give azoalkenes **47**. Thus, Wang's group developed a methodology to generate a transient diazo compound **48** by reaction of the azoalkene with a nucleophile, that eventually could participate in a subsequent reaction (Scheme 14).[18]



Scheme 14 In situ generation of α–functionalized diazo compounds **48** from α–halo-*N*-tosylhydrazones **46**.

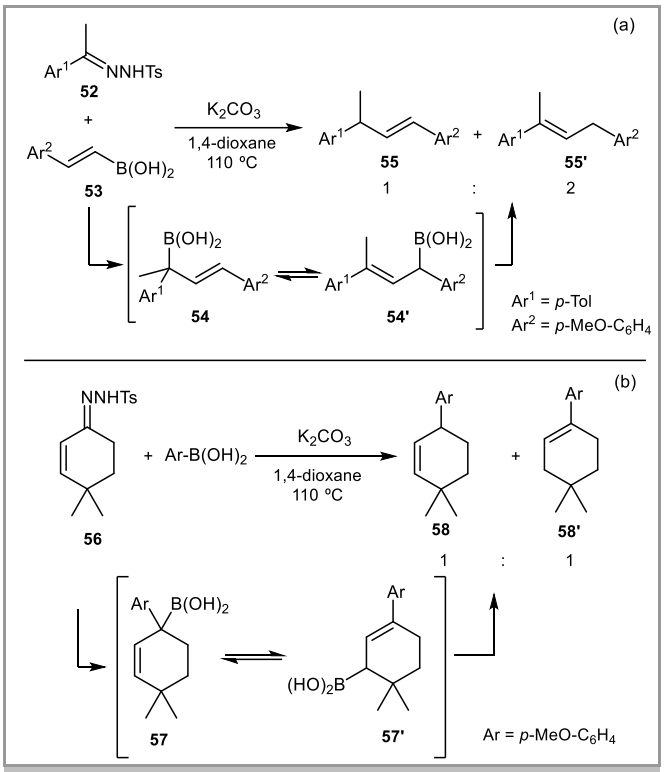
This strategy was applied employing indoles as nucleophiles. The reaction of the α-chloro-*N*-tosylhydrazone **46** with a *N*-alkylindole **49** leads to the diazo intermediate **50**. In the presence of an arylboronic acid, the reductive arylation takes place to give the corresponding 3-substitued indoles **51**. Proper reaction conditions were developed to perform the three-components reaction efficiently, allowing for the generation of a molecular diversity of substituted indoles **51** (Scheme 15).



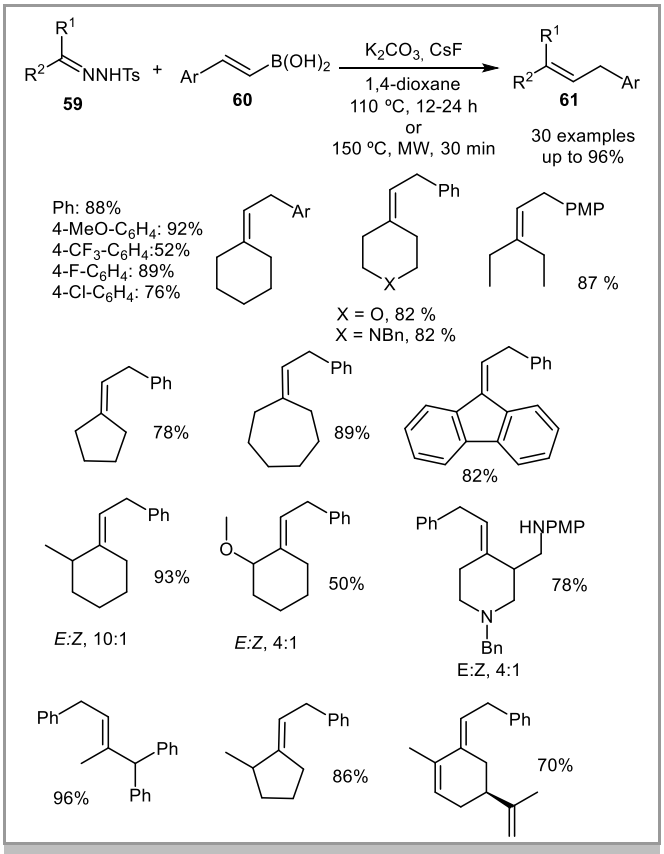
Scheme 15 Three-components synthesis of 3-substituted indoles **51**

4. Reactions of *N*-tosylhydrazones with alkenyl boronic acids

In our initial studies in the reductive coupling reactions,[11] we observed that the reactions of *N*-tosylhydrazones of acetophenones **52** with alkenylboronic acids **53** led to a mixture of two regioisomers, the expected reductive coupling product **55** and a new alkene derived from the migration of the double bond **55'** (Scheme 16, eq a). The formation of the regioisomers might be explained considering the intermediate allylboronic acid **54** , that might undergo a 1,3-borotropic rearrangement to give **54'**, or alternatively might suffer α- or γ-protodeboronation. Similarly, the reaction with an α,β-unsaturated *N*-tosylhydrazone **56** with an aryl boronic acid also led to the obtention of a mixture of two regioisomers **58** and **58'** that can be explained again by the particular behaviour of the intermediate allyl boronic acid **57** (Scheme 16, eq b).



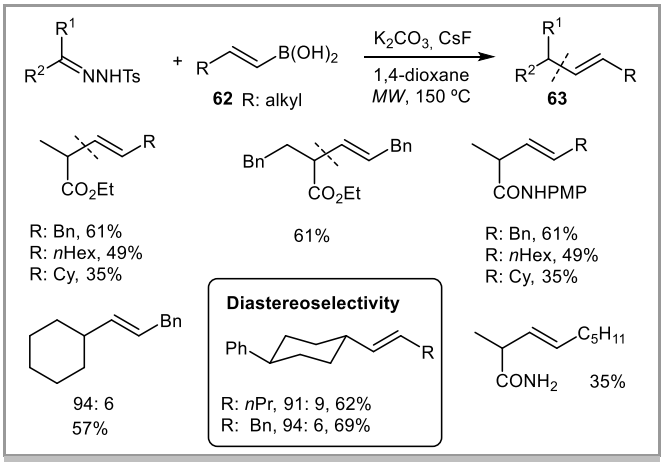
Scheme 16 Reactions involving allylboronic acid intermediates that lead to a mixture of regioisomers.



Scheme 17 Olefination of carbonyl compounds through *N*-tosylhydrazones. Selected examples are highlighted.

Many reaction parameters were changed in an attempt to drive the reaction into one single regioisomer. However, employing the model reactions of scheme 16, the mixture regioisomers was always obtained. Interestingly, modifications on the structure of the coupling partners led to highly regioselective reactions. Thus, the reactions employing dialkyl ketone *N*-tosylhydrazones **59** and aryl-substitued alkenylboronic acids **60** led to the compound in which the double bond migration had taken place **61** as a unique regioisomer. Interestingly, from a synthetic point of view, these reactions could be seen as a new type of olefination of carbonyl compounds through their tosylhydrazones. Additionally, the reaction is very general regarding the structure of the ketone, carbocyclic and heterocyclic ketones of different sizes could be employed as well as acyclic ketones. Moreover, when non-symmetric ketones are employed, moderate to high stereoselectivity is achieved, leading to the lesss hindered *E*-stereoisomer (Scheme 17).[19]

Quite surprisingly, the reactions with alkyl-substituted alkenylboronic acids **62** provided in most cases the opposite isomer **63**, the one in which the double bond does not migrate (scheme 18). Moreover, it was observed that when a 4-substituted cyclohexanone was employed the reaction proceeded with total diastereoselectivity.[19]



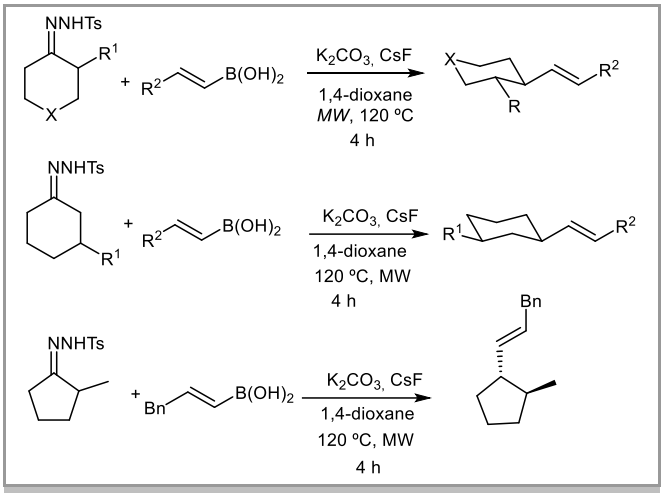
Scheme 18 Reductive alkenylation of *N*-tosylhydrazones with alkyl-substitued alkenylboronic acids **62**.

Therefore, the reactions of *N*-tosylhydrazones and alkenylboronic acids can provide either the olefination or the reductive alkenylation product **61** or **63** respectively with high regioselectivity. Moreover, it is noteworthy that the outcome of the reactions can be predicted based on the nature of the substituents on both coupling partners (Table 1) and this predictability is fundamental from a synthetic point of view.

Table 1 Predicted distribution of isomers based on the substituents of the coupling partners. Highly regioselective combinations are highlighted in bold.

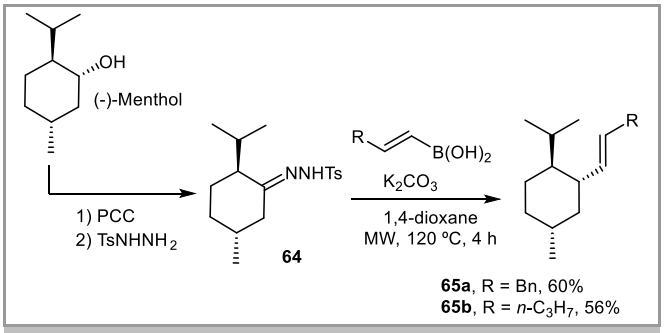
NNHTs R^1	R^2	R^3–B(OH)$_2$	R^1–R^2	R^1–R^2
alkyl	**aryl**	**aryl**	**95-90**	**5-10**
alkyl	**alkyl**	**aryl**	**100**	**0**
aryl	**aryl**	**aryl**	**100**	**0**
alkyl	COX	aryl	50	50
alkyl	aryl	alkyl	50	50
alkyl	**alkyl**	**alkyl**	**5-10**	**95-90**
alkyl	**COX**	**alkyl**	**0**	**100**

The stereoselectivity in the reductive alkenylation of a 4-substituted cyclohexanone prompted us to examine this process in more detail. It must be noted that in this reaction a Csp^3-Csp^2 bond and a Csp^3-H bond are created on the same carbon atom with total stereocontrol. After a comprehensive study it was found that under proper reaction conditions, and employing alkyl-substituted alkenylboronic acids, the reductive alkenylations are totally regio- and stereoselective for *N*-tosylhydrazones derived from cyclohexanones substituted at position 2, 3 or 4. In all cases, the isomers that feature both substituents in equatorial positions were obtained. The same stereoselectivity was also observed for a substituted cyclopentanone (scheme 19).[20]



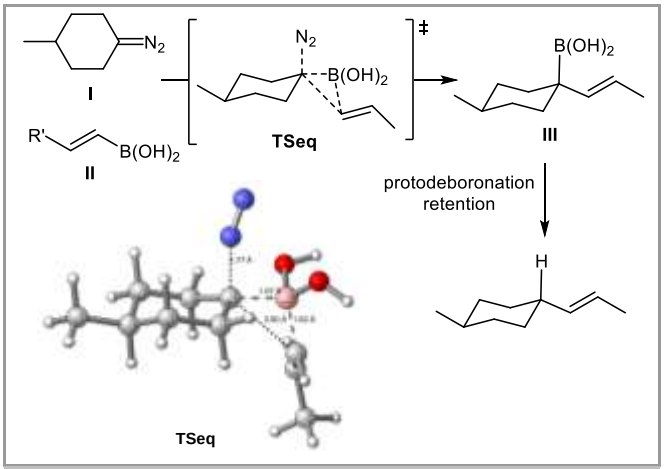
Scheme 19 Stereoselective reductive alkenylations of substituted cyclic *N*-tosylhydrazones

Importantly, the reaction with the *N*-tosylhydrazone of menthone **64** led also to one single diastereoisomer **65**, proving that the process takes place without epimerization of a stereogenic center at the α position, enabling the modification of chiral ketones through this method (Scheme 20).



Scheme 20 Derivatization of (-)-menthol with preservation of stereochemical integrity.

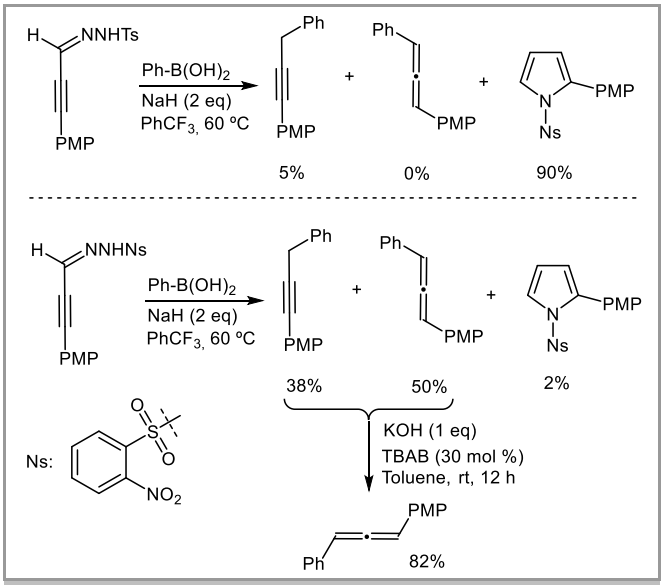
It must be noted that these stereoselective reductive alkenylations are rare examples of diastereoselective reactions based on diazo compounds in the absence of a metal catalyst. To understand the origin of this diastereoselectivity, DFT computational studies were conducted on a model system (Scheme 21). It was found that the reaction between the diazo compound **I** and the alkenyl boronic acid **II** proceeds through a concerted and highly asynchronous transition state **TSeq**, to give the allylboronic intermediate **III**. Considering that the protodeboronation is expected to proceed with retention of configuration, the former step is the one that determines the stereochemistry. It was found that the approximation of the boronic acid through an equatorial trajectory was clearly favoured, justifying the observed stereochemistry (Scheme 21).



Scheme 21 Justification of the stereochemistry observed based on DFT computations.

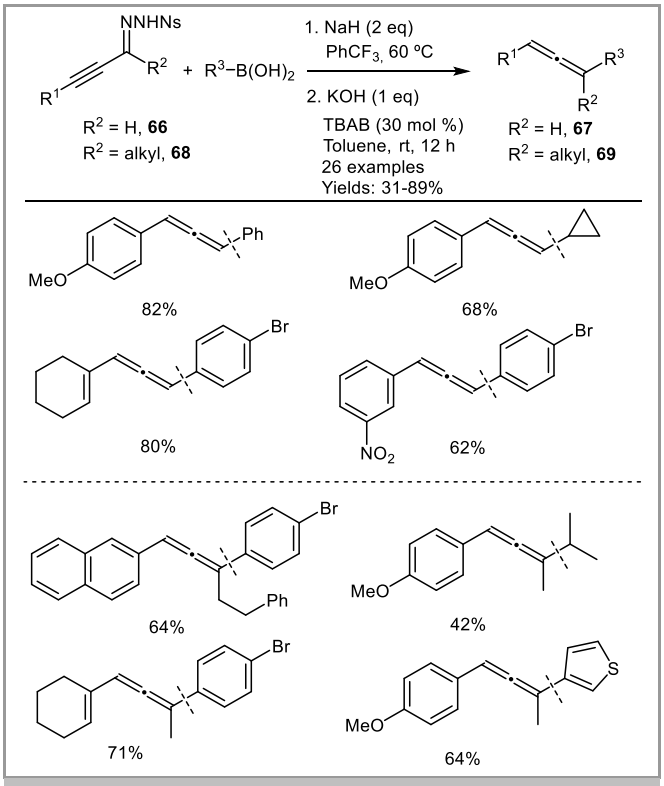
5. Synthesis of allenes by reactions with alkynyl *N*-nosylhydrazones

Alkynyl *N*-tosylhydrazones are known to undergo intramolecular cyclization to give pyrazoles. For this reason the synthetic usefulness of this class of hydrazones has been very limited. In 2017, Bi and coworkers established *N*-nosylhydrazones as a mild source of unstable diazo compounds.[21] In this context, Bi, Zanoni et al. reported the reaction of alkynyl *N*-nosylhydrazones with boronic acids, that led to the formation of allenes.[22] The reaction takes advantage of the ability of *N*-nosylhydrazones to undergo decomposition at lower temperatures than *N*-tosylhydrazones, preventing the intramolecular cyclization and allowing the intermolecular reaction with the boronic acid (Scheme 22).



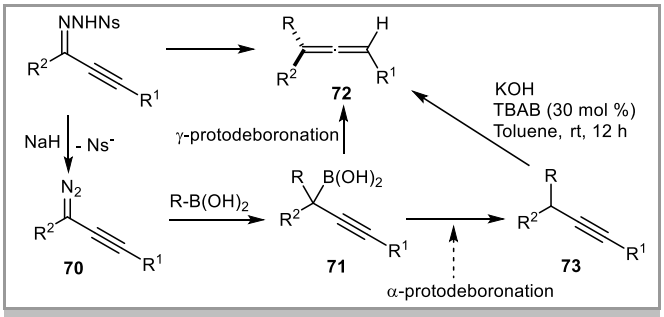
Scheme 22 Different behaviour of *N*-tosyl and *N*-nosylhydrazones in reactions with arylboronic acids.

Under the optimized conditions the reaction features a remarkable scope, as both alkyl and arylboronic acids can participate in the coupling process. The employment of *N*-nosylhydrazones from propargyl aldehydes **66** furnishes disubsutituted allenes **67** with excellent yields. Moreover the reaction with *N*-nosylhydrazones form ketones **68** leads to trisubstituted allenes **69** with slightly lower, but still synthetically useful yields (Scheme 23).



Scheme 23 Synthesis of di- and trisubstituted allenes by reaction of alkynyl *N*-nosylhydrazones with boronic acids. Selected examples are shown.

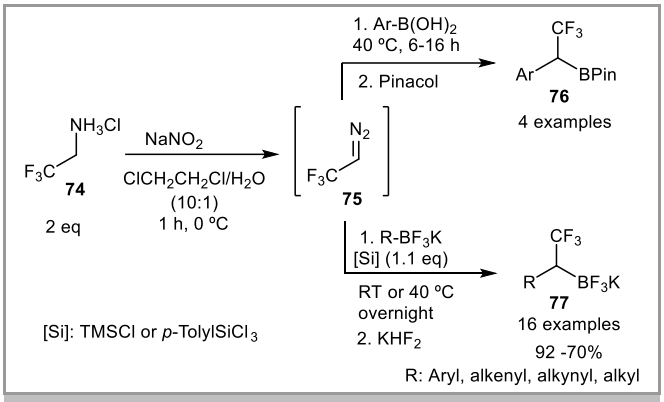
The formation of the allenes can be rationalized considering the typical mechanism of the reactions of sulfonylhydrazones with boronic acids. Upon formation of the propargylboronic acid **71**, α-protodeboronation leads to the alkyne **73**, and γ-protodeboronation to the allene **72**. The final treatment with KOH/TBAB isomerizes the alkyne **73** into the allene **72**. According to the authors, both protodeboronation pathways operate, representing an unprecedented example of γ–protodeboronation of propargylboronic derivatives (Scheme 24).



Scheme 24 Mechanism proposed for the formation of allenes **72**.

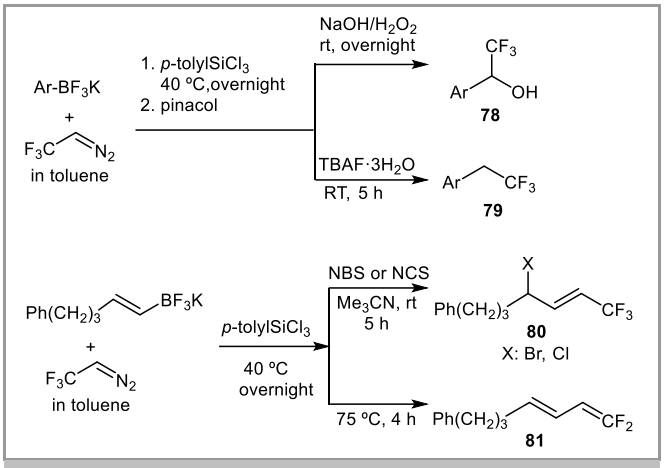
6. Reactions with diazo compounds generated by diazotization of primary amines

An alternative mild and efficient methodology for the in situ generation of diazo compounds is the diazotization of primary amines. In 2013, Molander and co-workers developed a new methodology for the synthesis of α-trifluoromethylated alkylboron compounds.[23] The first step of this transformation involves the in situ generation of 2,2,2-trifluorodiazoethane **75** from 2,2,2-trifluoroethylamine hydrochloride **74**, following the protocol described by Carreira et al.[24] Then, the reaction with arylboronic acids led to an intermediate benzylboronic acid that could be trapped by treatment with pinacol to obtain α-trifluoromethylbenzylpinacolboranes **76** (Scheme 25). Unlike the reactions with *N*-tosylhydrazones, under the mild reaction conditions no protodeboronation occurs. However, the reactions were quite sluggish. To overcome the limitations of the reaction with boronic acids, the transformation was studied with potassium organotrifluoroborates in the presence of a chlorosilane. The role of the chlorosilylated additive is to transform the trifluoroborate into a highly reactive dichloroorganoborane.[25] This reaction led to unprecedented α-trifluoromethylated potassium trifluoroborates **77**, upon quenching with KHF_2. Noteworthy, the reaction features wide scope including the employment of aryl, alkyl, alkenyl and alkynyl trifluoroborates (Scheme 25).



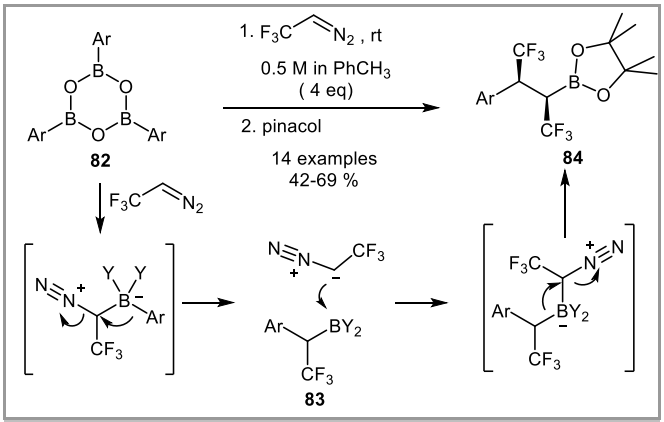
Scheme 25 Reactions of 2,2,2,-trifluorodiazoethane generated in situ with boronic acids and trifluoroborates.

The synthetic value of the α-trifluoromethylated organoborons **77** was demonstrated through several transformations (scheme 26). Thus, quench of the reaction crude with pinacol affords pinacolboranes that can be oxidized to the α-trifluoromethyl alcohols **78**, or protodeboronated to the substituted trifluoroethyl derivatives **79**. Moreover, treatment with NCS or NBS leads to the corresponding chlorides or bromides **80** respectively. Additionally, β-fluoride elimination can be also promoted from the haloboranes to yield difluoroalkenes **81**. It is important to note that in this contribution, the intermediate organoboron is employed in a further transformation other than protodeboronation, increasing the synthetic potential of the reactions of organoborons and diazo compounds.



Scheme 26 Synthetic applications of the reactions of 2,2,2,-trifluorodiazoethane with organic trifluoroborates.

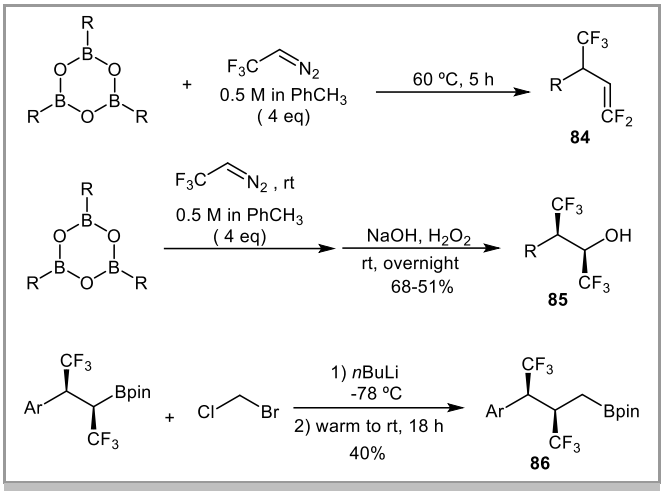
In a subsequent publication by Molander et al., it was described an unprecedented diastereoselective reaction for the synthesis of vicinally bis(trifluoromethylated) alkylboronates **84** (Scheme 27).[26] Interestingly, in the reaction of 2,2,2,-trifluorodiazoethane with boroxines **82**, the organoborane **83** generated after the first diazo insertion (1:1 adduct) was susceptible to experiment a second insertion with another molecule of trifluorodiazoethane (2:1 adduct). After a detailed reoptimization of the reaction, it was found that the employment of arylboroxines **82** as organoboranes, at room temperature, allowed for the efficient formation of the 2:1 adducts. Moreover, the reaction takes place with high diastereoselectivity, giving rise to the *syn* diastereoisomer as major product. DFT calculations were carried out to explain the observed diastereoselectivity.



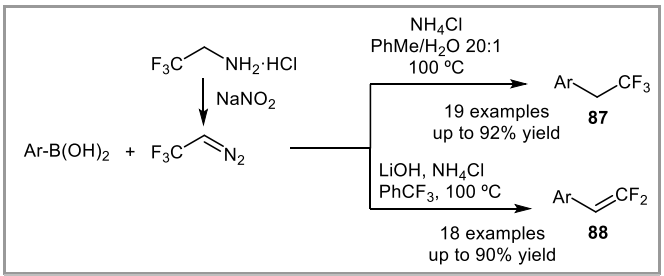
Scheme 27 Stereoselective synthesis of bis(trifluoromethylated) alkylboronates by sequential insertion of two trifluorodiazoethane molecules.

Like in their preceding communication, the boronates can be further modified through β-fluoride elimination to furnish difluoroalkenes **84**, oxidation, to give alcohols **85**, and also through a Matteson homologation for the preparation of a new boronic ester **86** (Scheme 28).

The employment of in situ generated 2,2,2-trifluorodiazoethane was also studied by Wang et al., who published their work in 2014. Depending on the specific conditions, the reactions with arylboronic acids led to the 2,2,2-trifluoroethylation of the boronic acid, to give **87**, or to the *gem*-difluorostyrenes **88** upon β-fluoride elimination (Scheme 29).[27]



Scheme 28 Synthetic applications of the 2: 1 adducts obtaeind by reaction of aryl boroxines with 2,2,2-trifluorodiazoethane.

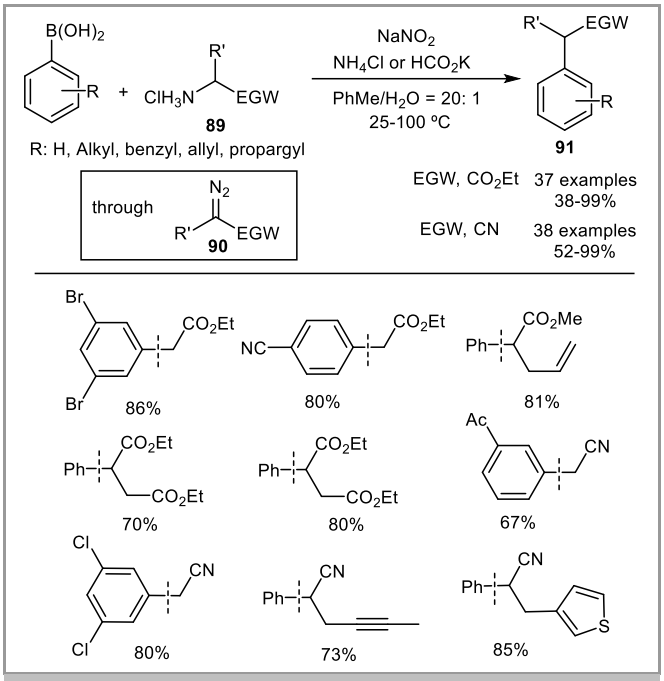


Scheme 29 Reactions of in situ generated 2,2,2-trifluorodiazoethane with arylboronic acids.

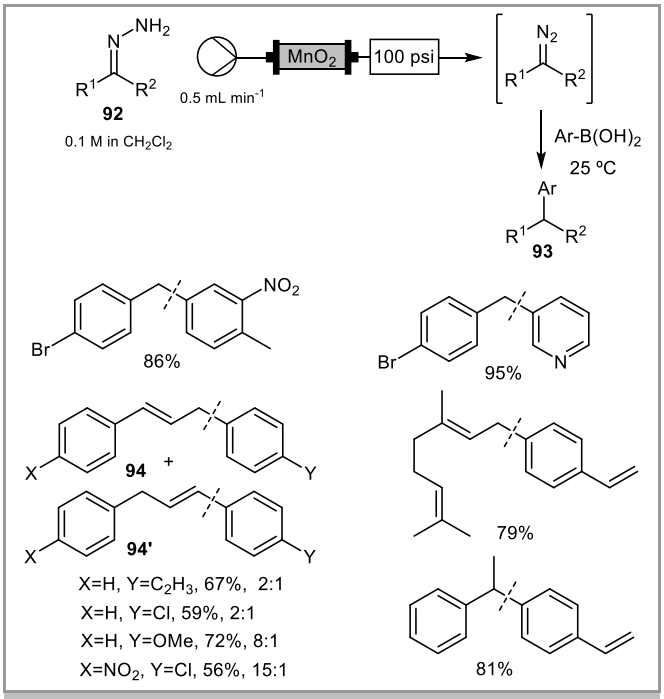
Similarly, in 2014, Wang et al. developed a deaminative coupling of α-aminoesters and α-aminoacetonitriles **89** with arylboronic acids (Scheme 30).[28] The in situ generation of the corresponding diazo compounds **90** is the first step of this transformation, which is achieved, like in the work described above, through diazotization followed by deprotonation of the corresponding α-amino partners. Then, reductive arylation with arylboronic acids provides α-aryl esters and nitriles **91**.

7. Reactions with diazo compounds generated by oxidation of hydrazones

Another procedure for the in situ generation of diazo compounds is the oxidation of unsubstituted hydrazones. This method has been throughly explored recently by Ley's group. In 2015, Ley and coworkers reported the reductive coupling between boronic acids and diazo compounds generated by oxidation of hydrazones under flow conditions.[29] They developed a very convenient method for the generation of unstabilized diazo compounds by flowing a solution of a hydrazone **92** through a column packed with activated MnO_2 as the oxidant (Scheme 31). The addition of boronic acids to the diazo compound solution led to the coupling products **93** under mild conditions and with yields ranging from good to excellent. The reaction withstands different functionalities, such as ethers, halogens, nitro groups, and even heterocycles as pyiridine. The employment of vinyl diazo compounds was compatible with this methodology, although a mixture of regioisomers **94** and **94'** was normally obtained depending on the electronic properties of the aryl ring in the boronic acid (Scheme 31).



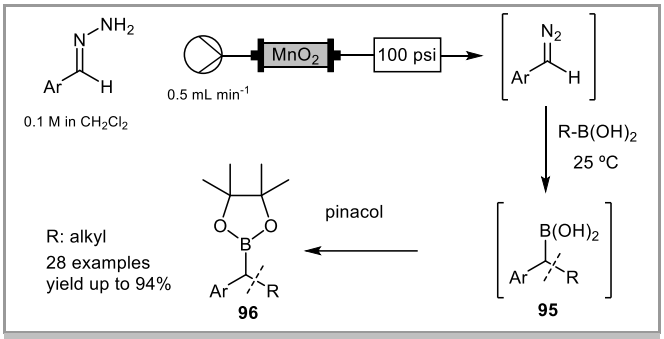
Scheme 30 Deaminative coupling of α-aminoesters and α-aminoacetonitriles with arylboronic acids via diazotization. Selected examples.



Scheme 31 Reductive coupling of hydrazones with boronic acids by means of the continuous flow generation of diazo compounds.

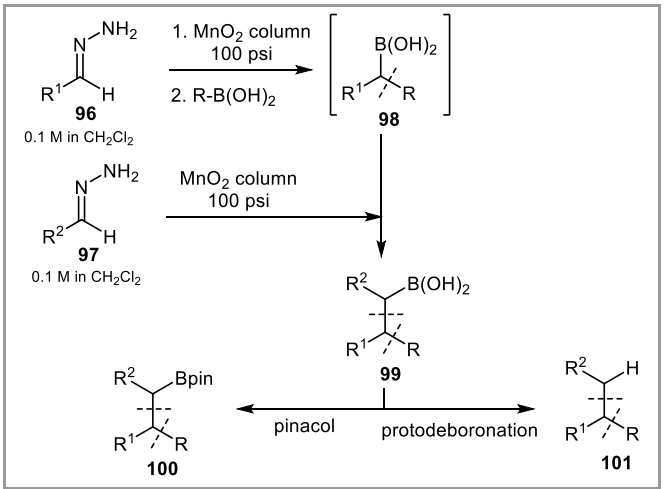
Remarkably, taking advantage of the mild reaction conditions, the boronic intermediate **95** could be intercepted prior to the protodeboronation step. This intermediate could be trapped upon oxidation with H_2O_2 to give the corresponding alcohol.

The interception of the transient secondary boronic acid **95** formed by room temperature reaction of a flow generated diazo compound with a boronic acid led to Ley and coworkers to develop a very elegant method for the sequential formation of C-C bonds.[30] This transformation enables to rapidly increase molecular complexity in a sequential manner starting from very simple starting materials. It was first demonstrated that the intermediate boronic acid **95** could be efficiently trapped by treatment with pinacol to isolate the corresponding boronic esters **96** (Scheme 32). Although some of the intermediates were observed to be unstable, and prone to protodeboronation, in most of the cases it was possible to isolate the boronic ester. Diazocompounds 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.



Scheme 32 Synthesis of pinacol boronates by interception of intermediate secondary boronic acids.

During the development of the work it was observed that the intermediate boronic acid **95** could eventually react with another molecule of diazo compound. This fact prompted the authors to develop a sequential process by the sucessive incorporation of various diazo compounds (Scheme 33). Thus, the solution resulting from the treatment of the diazo compound generated from hydrazone **96** with a boronic acid, that gives secondary boronic acid **98**, is treated with the solution of the diazo compound obtained by the flow oxidation of hydrazone **97**. Reaction between the diazo compound generated from **97** with secondary boronic acid **98** forms a new secondary boronic acid **99.** In the sequential process two C-C bonds and a C-B bond have been created. Boronic acid **99** can be trapped as a pinacol boronate **100** by treatment with pinacol, or isolated upon protodeboronation to give the final boron free compound **101**. This remarkable sequential procedure represents a very efficient way of generation of molecular diversity (Figure 1).



Scheme 33 Iterative strategy for the sequential addition of diazo species to the initial boronic acid

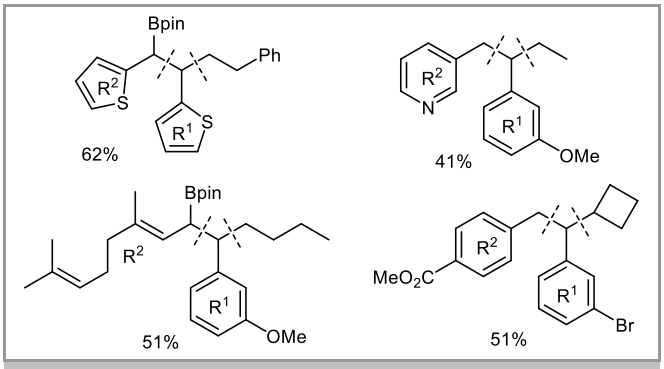
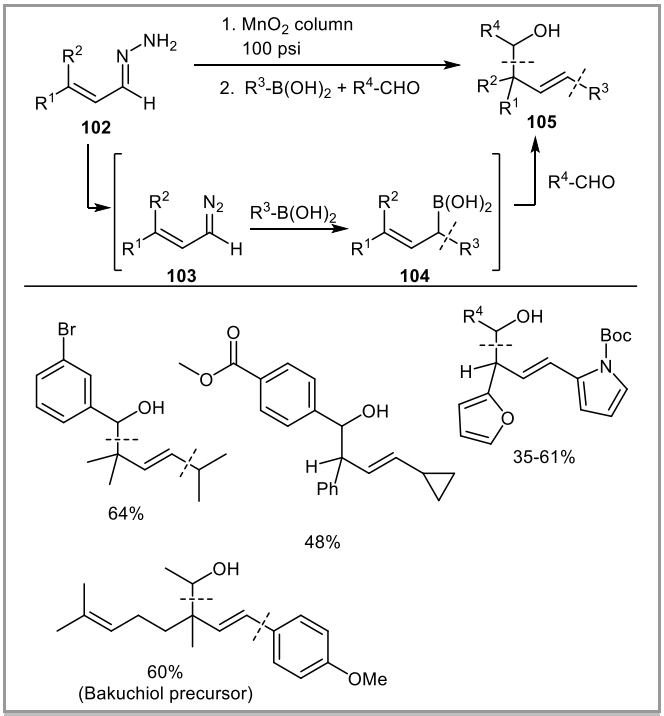


Figure 1 Selected examples of compounds obtained by continuous flow sequential C-C bond forming reaction .

The interception of the intermediate boronic acid could be extended to a cascade reaction in which transiently generated allylboronic acids reacted with aldehydes (Scheme 34). In this reaction design, the intermediate allylboronic acids **104** are formed by reaction of a boronic acid with unsaturated diazo compound **103**, which is obtained by oxidaton of α,β-unsaturated hydrazones **102**. In this manner, a variety of homoallylic alcohols **105** could be obtained with excellent yields. As further proof of the usefulness of this methodology, the authors extended their work to the synthesis of a Bakuchiol precursor using this iterative coupling method.[30]

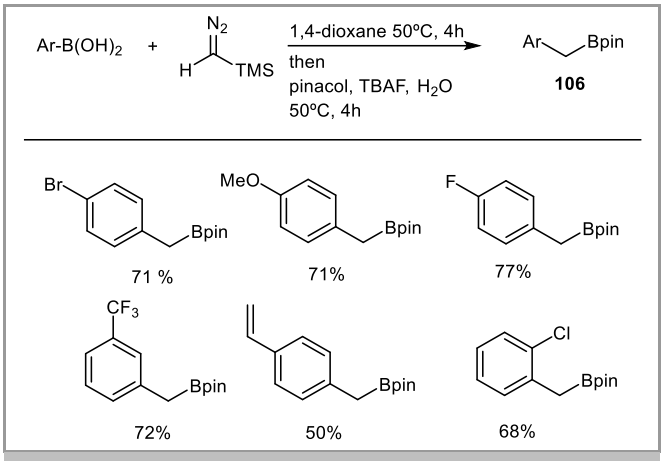


Scheme 34 Cascade interception of allylboronic acids with aldehydes and selected examples.

8. Reactions with trimethylsilyldiazomethane

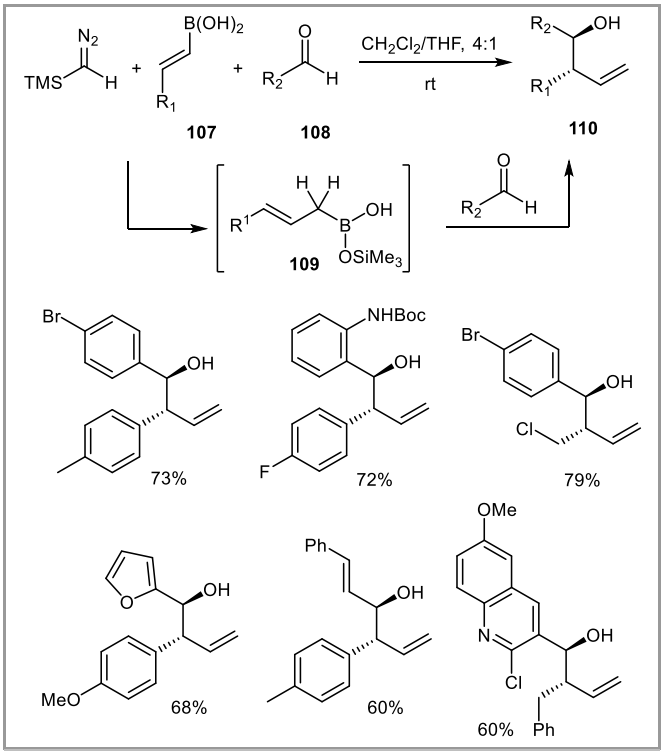
The ability to intercept the intermediate organoboron derivative generated under mild conditions was independently exploited in 2016 by Wang's and Ley´s group employing commercially available trimethylsilyldiazomethane.

Wang et al. developed a one pot procedure to build up benzyl boronates **106** by reaction of arylboronic acids with $TMSCHN_2$ followed by treatment with pinacol.[31] The reaction works well with a variety of aryl boronic acids yielding the corresponding benzyl pinacol boronates with yields varying from moderate to good. Selected examples and the reaction conditions are represented in Scheme 35.



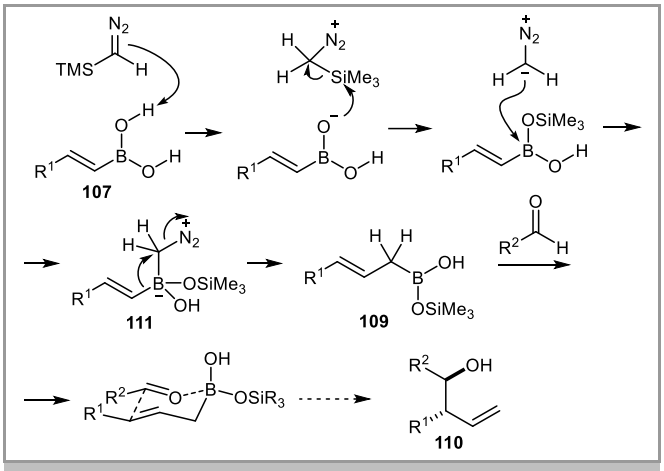
Scheme 35. One pot synthesis of benzyl boronates from trimethylsilyldiazomethane and arylboronic acids.

Continuing with their work on sequencial coupling reactions, Ley's group employed flow chemistry techniques to develop a multicomponent metal-free synthesis of homoallylic alcohols.[32] This transformation consists in the reaction of *E*-alkenylboronic acids **107** with $TMSCHN_2$, forming in situ the homologated allylboronic acid intermediates **109**. This species are eventually intercepted with aldehydes **108** to furnish the corresponding homoallyl alcohols **110**. The procedure was extended to batch conditions to broaden the scope and generality of this multicomponent transformation (Scheme 36).



Scheme 36 Synthesis of homoallylic alcohols by sequential C-C bond forming reactions. Selected examples are shown.

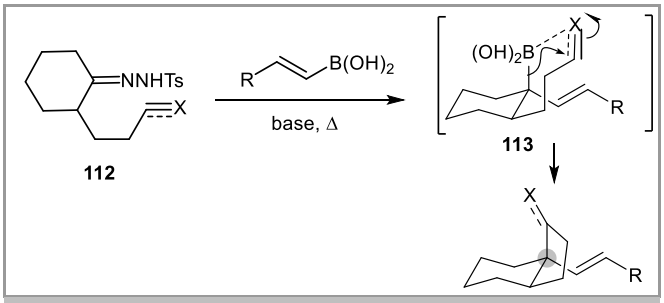
Based on some mechanistic studies, the authors propose the following mechanistic rationale for this transformation (Scheme 37). The reaction starts by the protonation of the $TMSCHN_2$ by the boronic acid **107**, that generates the highly reactive diazomethane. Reaction of diazomethane with the intermediate boronic species leads to the boronate **111**, which upon 1,2 migration and nitrogen loss produces the allylboronic derivative **109**. The reaction of **109** with the aldehyde present in the reaction media, leads to the final homoallylic alcohol **110**. Based on this reaction, and considering that the homoallylic alcohol can be easily transformed into an aldehyde, an iterative procedure was developed to generate polyols by repeating the coupling-allylation/ozonolysis/alcohol protection sequence.



Scheme 37 Mechanistic proposal for the synthesis of homoallylic alcohols from trimethylsilyldiazomethane

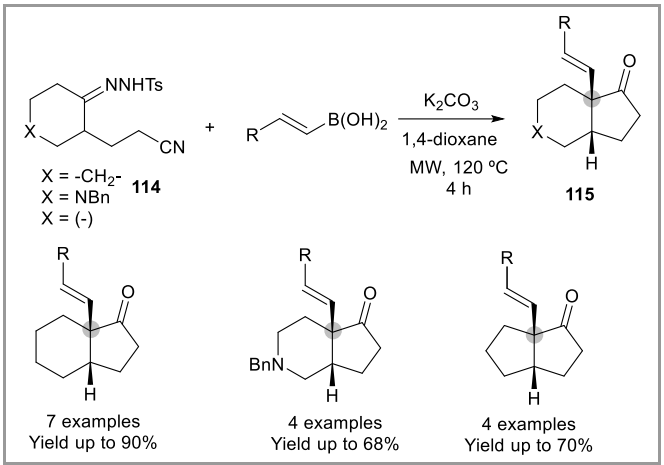
9. Cascade cyclization reactions with γ– and δ-cyano-*N*-Tosylhydrazones

The ability to intercept the transient boronic intermediate discussed in sections 6-8 provides very powerful synthetic strategies for the sequential formation of C-C bonds. These methodologies require mild reaction conditions to avoid the protodeboronation step. For this reason, the application of a similar strategy to *N*-tosylhydrazones, which would allow a much wider scope, and also operational simplicity to this chemistry, has remained elusive. We have recently approached this problem in an intramolecular fashion, in the context of our interest in the reactions of alkenylboronic acids. We considered that the presence of an electrophilic functionality tethered at a side chain of a *N*-tosylhydrazone might enable the intramolecular attack of transient allylboronic acid in **113**, promoting a cascade cyclization process (Scheme 38).



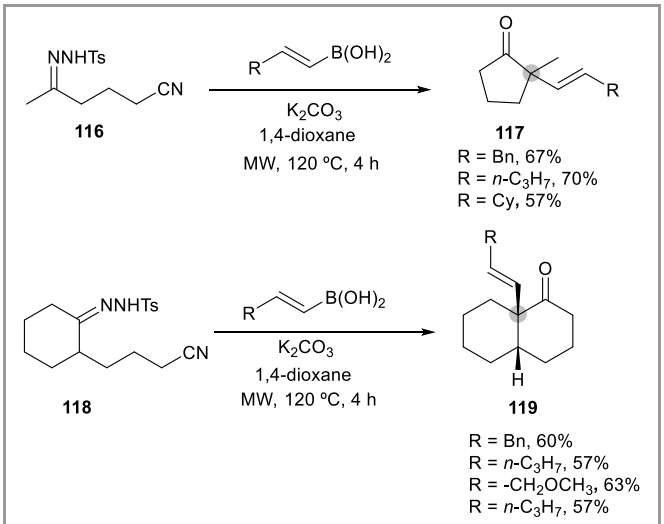
Scheme 38 General strategy for the intramolecular interception of an allyl boronic intermediate with functionalized *N*-tosylhydrazones.

This strategy was initially explored employing cyclic *N*-tosylhydrazones featuring a 3-cyanopropyl substituent at the α-position **114** and alkenylboronic acids.[33] Under the optimized reaction conditions, fused cyclopentanones **115** featuring an alkenyl side chain attached at a quaternary stereocenter were obtained. Importantly, two $C(sp^3)$-$C(sp^2)$ bonds are formed on the former hydrazonic carbon generating an all-carbon quaternary stereocenter, and leading to cyclic ketones featuring an alkenyl side chain with complete diastereoselectivity. This reaction represents a new mode of building carbocycles by formation of two bonds on the same carbon atom (Scheme 39).



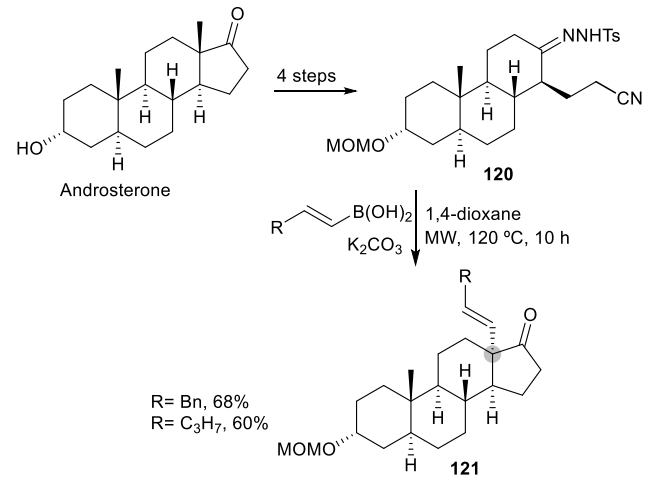
Scheme 39 Stereoselective synthesis of fused cyclopentanones by metal-free cascade cyclization of alkenylboronic acids with cyclic γ-cyano-*N*-tosylhydrazones.

The reaction is not restricted to cyclic tosylhydrazones, as it could be achieved successfully also with the linear *N*-tosylhydrazone **116**, giving rise to the 2,2-disubstituted cyclopentanones **117** (Scheme 40). Moreover, this new cyclization reaction was also appropriate for the construction of a cyclohexanone ring by introducing a 3-cyanopropyl side chain in the initial *N*-tosylhydrazone **118**. In this case, the decalin-2-ones **119**, featuring an angular quaternary stereocenter were obtained again as pure diastereoisomers (Scheme 40).



Scheme 40 Metal-free cyclizations of γ- and δ-cyano-*N*-tosylhydrazones

The usefulness and flexibility of this novel cascade carbocyclization was further illustrated by the modification of androsterone (Scheme 41). After transformation of androsterone into cyanoketone *N*-tosylhydrazone **120** through a known ring-opening procedure, the cascade cyclization led to the reconstruction of the cyclopentanone ring with incorporation of an alkenyl side chain, to produce the unnatural steroid structures **121** and importantly, as single diastereoisomers.[33]



Scheme 41 Application of the cascade carbocyclization to the modification of androsterone.

10. Summary and outlook

The reactions between diazo compounds and organoboranes are known for half a century. However, the advances in this field during the last years have taken this fundamental transformation into new grounds. The incorporation of *N*-sulfonylhydrazones as versatile diazo compound sources, and boronic acids as the organoboron component have led to the development of C-C bond forming reactions with wide applicability and usefulness in different areas of synthetic organic chemistry. Moreover, the implementation of alternative mild protocols for the generation of diazo compounds - diazotization and oxidation under flow conditions – have allowed the discovery of domino and sequential reactions by intermolecular trapping of the intermediate boronic species. An intramolecular version of this strategy has led to the development of a completely new domino carbocyclization with great potential in organic synthesis. We believe that these new methodologies will find wide applicability in organic synthesis. Moreover, these novel and original transformations show that the field is still open for the discovery of new processes based on the reactions between diazo compounds and organoboranes.

Funding Information

Financial support of this work by Ministerio de Economía y Competitividad (MINECO) of Spain: Grants CTQ2013-41336-P and CTQ2016-76794-P (AEI/FEDER, UE). FPI predoctoral fellowship (MINECO, Spain) to M. Paraja and a FPU predoctoral fellowship (MECD, Spain) to M. Plaza are gratefully acknowledged.

Acknowledgment

We wish to thank the outstanding contribution of the former members of our research group that developed some of the work discussed in this account: Dr. M. Tomás-Gamasa and Dr. M. C. Pérez Aguilar. Moreover, the encouragement and inspiration of the recently deceased Prof. José Barluenga is greatly acknowledged.

References

(1) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219.
(2) Li, H.; Zhang, Y.; Wang, J. *Synthesis* **2013**, *45*, 3090.
(3) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936.
(4) (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.
(5) (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.
(6) (a) Kabalka, G. W.; Maddox, J. T.; Bogas, E. *J. Org. Chem.* **1994**, *59*, 5530. (b) Kabalka, G. W.; Maddox, J. T.; Bogas, E.; Tejedor, D.; Ross, E. J. *Synth. Commun.* **1996**, *26*, 999. (c) Kabalka, G. W.; Maddox, J. T.; Bogas, E.; Kelley, S. W. *J. Org. Chem.* **1997**, *62*, 3688.
(7) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735.
(8) Peng, C.; Zhang, W.; Yan, G.; Wang, J. *Org. Lett.* **2009**, *11*, 1667.
(9) (a) Aggarwal, V. K.; de Vicente, J.; Pelotier, B.; Holmes, I. P.; Bonnert, R. V. *Tetrahedron Lett.* **2000**, *41*, 10327. (b) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926. (c) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479.
(10) (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.
(11) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494.
(12) Nakagawa, S.; Bainbridge, K. A.; Butcher, K.; Ellis, D.; Klute, W.; Ryckmans, T. *ChemMedChem* **2012**, *7*, 233.
(13) Li, X.; Feng, Y.; Lin, L.; Zou, G. *J. Org. Chem.* **2012**, *77*, 10991.
(14) Kupracz, L.; Kirschning, A. *J. Flow. Chem.* **2012**, *3*, 11.
(15) Allwood, D. M.; Blakemore, D. C.; Brown, A. D.; Ley, S. V. *J. Org. Chem.* **2013**, *79*, 328.
(16) Shen, X.; Gu, N.; Liu, P.; Ma, X.; Xie, J.; Liu, Y.; He, L.; Dai, B. *RSC Adv.* **2015**, *5*, 63726.
(17) Shen, X.; Gu, N.; Liu, P.; Ma, X.; Xie, J.; Liu, Y.; Dai, B. *Chinese J. Chem.* **2016**, *34*, 1033.
(18) Wu, G.; Deng, Y.; Luo, H.; Zhou, J.; Li, T.; Zhang, Y.; Wang, J. *Chem. Commun.* **2016**, *52*, 5266.
(19) Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 5953.
(20) Plaza, M.; Pérez-Aguilar, M. C.; Valdés, C. *Chem. Eur. J.* **2016**, *22*, 6253.
(21) (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.
(22) Yang, Y.; Liu, Z.; Porta, A.; Zanoni, G.; Bi, X. *Chem. Eur. J.*, D.O.I: 10.1002/chem.201701462
(23) Argintaru, O. A.; Ryu, D.; Aron, I.; Molander, G. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 13656.
(24) Morandi, B.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 938.
(25) (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.
(26) Molander, G. A.; Ryu, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 14181.
(27) Wu, G.; Deng, Y.; Wu, C.; Wang, X.; Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2014**, *2014*, 4477.
(28) Wu, G.; Deng, Y.; Wu, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 10510.
(29) Tran, D. N.; Battilocchio, C.; Lou, S.-B.; Hawkins, J. M.; Ley S. V. *Chem. Sci.*, **2015**, *6*, 1120.
(30) 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.
(31) Wu, C.; Wu, G.; Zhang, Y.; Wang. J. *Org. Chem. Front.* **2016**, *3*, 817.
(32) Poh, J.-S.; Lau, S.-H.; Dykes, I. G. ; Tran, D. N.; Battilocchio C.; Ley, S. V. *Chem. Sci.* **2016**, *7*, 6803.
(33) Plaza, M.; Valdés, C. *J. Am. Chem. Soc.* **2016**, *138*, 12061.

Biosketches

	**Miguel Paraja** graduated in Chemistry at the University of Oviedo obtaining his Master degree at the same University in 2014. He then joined Carlos Valdés' group with a FPI predoctoral fellowship (MINECO). His PhD research is dedicated to transition-metal catalyzed cascade reactions based on *N*-sulfonylhydrazones.
	**Manuel Plaza** obtained Bs. and Master degrees in Chemistry at the University of Oviedo. He is currently carrying out PhD studies at the same university devoted to the development of C-C bond forming reactions and cascade processes based on *N*-sulfonylhydrazones. He is currently a FPU fellow (MECD, Spain).
	**Carlos Valdés** received his PhD in 1992, from the University of Oviedo working under the guidance of Profs. Barluenga and Aznar. He then carried out a postdoctoral stay at the group of Prof. Rebek at MIT working on the self-assembly of molecular *tennis balls*. He has occupied various academic positions at the University of Oviedo, and has recently been promoted to full professor. His current research interests are focused on the development of new efficient synthetic methodologies for metal catalyzed and metal-free C-C bond formation, and on the design of cascade reactions oriented to the synthesis of carbo- and heterocycles.

This is the accepted version of the following article: *Synlett.* **2017**, *28*, 2373, which has been published in final form at https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0036-1590868.