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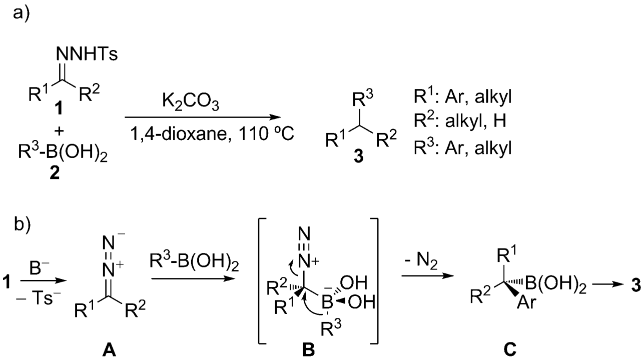
Synthetic Methods

Olefination of Carbonyl Compounds through Reductive Coupling of Alkenylboronic Acids and Tosylhydrazones**

*M. Carmen Pérez-Aguilar and Carlos Valdés**

The formation of C–C bonds is a fundamental transformation of organic synthesis. Among the enormous variety of C–C bond-forming reactions currently available, metal-catalyzed cross-couplings stand as some of the more versatile and reliable methodologies.[1] In spite of this, the need of a transition-metal catalyst is a drawback because of the high cost and toxicity of the most popular metals. For these reasons, C–C bond-forming reactions that might work with the same levels of efficiency and selectivity as transition metal catalyzed reactions, but that do not need the addition of a transition metal, so called metal-free cross-couplings, are highly desirable, and indeed, have attracted increasing attention in the recent years.[2]

In the context of our interest on sulfonylhydrazones as versatile intermediates in organic synthesis,[3] we have recently described a new C–C bond-forming reaction between tosylhydrazones **1** and boronic acids **2**, which gives rise to the reductive coupling products **3** (Scheme 1 a).[4–6] This process takes place without the need for a metal catalyst[7–8] under extremely simple reaction conditions (just in the presence of K_2CO_3), and exhibits a remarkably wide scope.[9] The mechanism proposed for this reaction comprises the following steps (Scheme 1 b): 1) decomposition of the hydrazone in the presence of the base to form the diazo compound **A**, 2) formation of the boronate intermediate **B** by interaction of the boronic acid with the diazo compound, 3) C–C bond formation by migration of the R group with loss of nitrogen to give the intermediate boronic acid **C**, and 4) protodeboronation to give the final product.

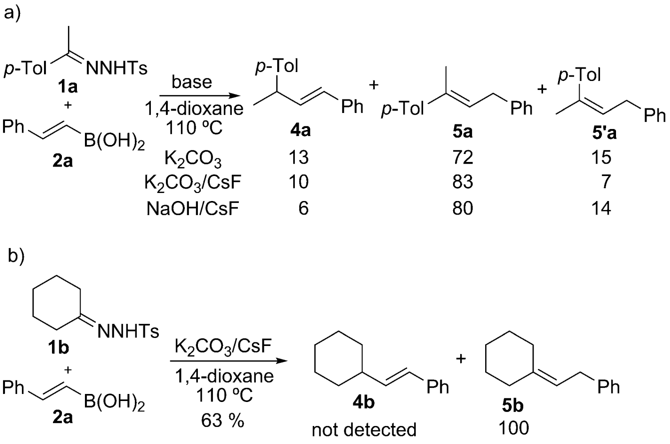


Scheme 1. Reductive coupling of tosylhydrazones with aryl and alkylboronic acids and mechanism proposed. Ts = 4-toluenesulfonyl.

These reactions proceed very efficiently with aryl and alkylboronic acids. However, preliminary investigation of the reactions with alkenylboronic acids gave a less satisfactory result because of the formation of a mixture of isomers arising from the position of the double bond. This result could be rationalized considering that the initially formed allylboronic acid could suffer a direct γ-protodeboronation or a 1,3-borotropic rearrangement/α-protodeboronation sequence.[10]

Taking into consideration the interest of these metal-free reductive couplings, we initiated a study to investigate in more detail the reactions with alkenylboronic acids, with the aim to develop reaction conditions or combinations of reagents which might lead to a single isomer of the reductive coupling alkene, and therefore, convert these transformations into more relevant synthetic processes.

We initially focused on the reaction between the hydrazone **1a**, and 2-phenylvinylboronic acid (**2a**; Scheme 2 a). An extensive study of bases and reaction conditions was carried out,[11] and although a moderate influence of the base employed was found, the process could not be driven to give a single compound. The best results in terms of yield and selectivity were obtained by employing K_2CO_3 or NaOH as



Scheme 2. Preliminary experiments of reductive couplings of tosylhydrazones with alkenylboronic acid **2a**. Influence of the base and the structure of the hydrazone on the ratio of isomers.

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[*] M. C. Pérez-Aguilar, Dr. C. Valdés
Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo
c/Julián Clavería 8, 33006 Oviedo (Spain)
E-mail: acvg@uniovi.es

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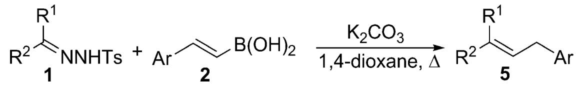
the base, and incorporating 2 equivalents of CsF into the reaction mixture (Scheme 2 a). In all cases, the stereoisomeric compounds **5a** and **5a′**, wherein the double bond has migrated, are obtained as the major product. Notably, by employing an equimolar amount of NaOH and CsF, the formation of the isomer **4a**, which retains the double bond in the original position, is reduced to only 6 %.

Interestingly, when the same reaction was conducted by employing the hydrazone **1b**, derived from cyclohexanone, the isomer **5b** was the only product detected in the reaction mixture (Scheme 2 b). After some optimization,[11] the best reaction conditions found employed of a combination of K_2CO_3 (2 equiv) and CsF (2 equiv) in 1,4-dioxane at 110 °C. These reaction conditions were then applied to a set of structurally diverse hydrazones to evaluate the scope of the process. In the course of the study, we found that the use of microwave heating under similar reaction conditions (K_2CO_3, CsF, 1,4-dioxane; Method B) or in the absence of CsF but employing a 1:1 mixture of 1,4-dioxane/MeOH as the solvent (Method C), not only reduces dramatically the reaction times (12 h to 30 min), but also increases the yields in many of the examples. Moreover, some reactions that failed under thermal conditions gave rise to the desired olefination product with satisfactory yields under microwave irradiation. The most relevant results of this study are presented in Table 1.[11]

First of all, it must be pointed that in all the reactions with hydrazones derived from dialkyl ketones, the trisubstitued alkene **5** was the only product detected in the crude reaction mixture (Table 1, entries 1–27). The reaction is very general with regard to the structure of the dialkyl ketone, and can be applied to a wide variety of systems, including hydrazones derived from carbocyclic, heterocyclic (entries 7–10, 21), and acyclic ketones (entries 25–27). Interestingly, the reactions with nonsymmetrically substituted hydrazones provide, depending on the size of the substituents, a single isomer (entries 20, 24, and 27) or a mixture of *Z*/*E* steroisomers (entries 18, 19, and 21) in which the major isomer has the benzyl group on the side opposite to the bulkier substituent.

The reaction was extended also to other styrylboronic acids, featuring either electron-withdrawing or electron-donating substituents, and proceeded with similar yields (Table 1, entries 2–5, 8, 9, 14–17, and 26). The regioselective reaction is not restricted to dialkyl hydrazones, as diaryl-substituted hydrazones also exclusively provided the olefination isomer **5** (entries 28 and 29). Another challenging example is the olefination of the hydrazone derived from carvone (entry 30) as a representative of a α,β-unsaturated carbonyl compound. Again the reaction gives rise to a single positional isomer, and moreover, to a single stereoisomer, because of the presence of the methyl substituent, which determines the configuration of the new double bond. However, the reaction with the hydrazone derived from methyl pyruvate led to a 1:1 mixture of the two double bond regioisomers (entry 31), and as in the example presented in Scheme 2, reactions of hydrazones derived from alkyl aryl ketones participate in a reaction leading to *Z*/*E* mixtures of the two possible olefination products **5** and **5′**, and in some cases small amounts of the regioisomer **4**.[11,12]

Table 1: Olefination of tosylhydrazones **1** by reaction with alkenylboronic acids **2**.[a]



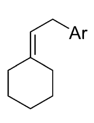
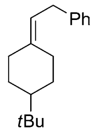
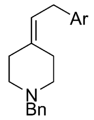
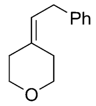
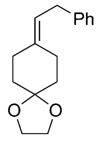
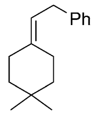
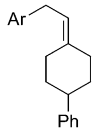
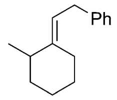
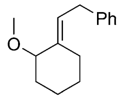
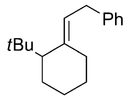
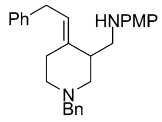
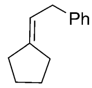
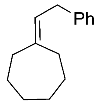
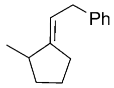
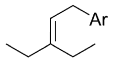
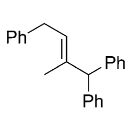
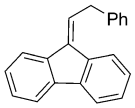
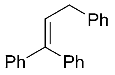
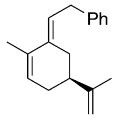
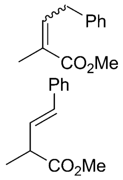
Entry	Product	Ar (**5**)	Method[b]	Yield [%][c]
1		Ph (**5 b**)	B	88 (78)[e]
2		4-MeOC$_6$H$_4$ (**5 bb**)	B	92
3		4-CF$_3$C$_6$H$_4$ (**5 bc**)	B	52 (51)[e]
4		3-FC$_6$H$_4$ (**5 bd**)	B	89
5		4-ClC$_6$H$_4$ (**5 be**)	B	76 (59)[e]
6		Ph (**5 c**)	B	86
7		Ph (**5 da**)	B	82 (57)[e]
8		4-MeOC$_6$H$_4$ (**5 db**)	A	57
9		4-CF$_3$C$_6$H$_4$ (**5 dc**)	B	68
10		Ph (**5 e**)	B	82
11		Ph (**5 f**)	B	77
12		Ph (**5 g**)	C	80
13		Ph (**5 ha**)	C	81
14		4-MeOC$_6$H$_4$ (**5 hb**)	C	70
15		4-CF$_3$C$_6$H$_4$ (**5 hc**)	C	83
16		3-FC$_6$H$_4$ (**5 hd**)	C	93
17		4-ClC$_6$H$_4$ (**5 he**)	C	79
18[d]	 *E*:*Z*, 10:1	Ph (**5 i**)	A	93
19[d]	 *E*:*Z*, 4:1	Ph (**5 j**)	A	50
20[d]		Ph (**5 k**)	A	49
21[d]	 *E*:*Z*, 4:1	Ph (**5 l**)	B	78

Table 1: (Continued)

Entry	Product	Ar (**5**)	Method[b]	Yield [%][c]
22		Ph (**5m**)	C	78
23		Ph (**5n**)	C	89
24[d]		Ph (**5o**)	C	86
25		Ph (**5pa**)	B	88
26		4-MeOC$_6$H$_4$ (**5pb**)	A	87
27[d]		Ph (**5q**)	A	96
28		Ph (**5r**)	B	63
29		Ph (**5s**)	A	55
30		Ph (**5t**)	B	70
31	 1 : 1	Ph (**5u/4u**)	A	73

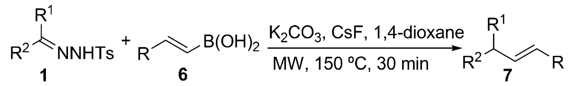
[a] Method A: *N*-tosylhydrazone **1**, (1.0 equiv); boronic acid **2**, (2 equiv); K$_2$CO$_3$, (2 equiv); CsF, (2 equiv), 1,4-dioxane, 110°C, 12–14 h. Method B: *N*-tosylhydrazone **1**, (1.0 equiv); boronic acid **2**, (2 equiv); K$_2$CO$_3$, (2 equiv); CsF, (2 equiv), 1,4-dioxane, MW, 150°C, 30 min. Method C: *N*-tosylhydrazone **1**, (1.0 equiv); boronic acid **2**, (2 equiv); K$_2$CO$_3$, (2 equiv); 1,4-dioxane/methanol (1:1 v/v) MW, 150°C, 30 min. [b] Data for the highest yielding method (see the Supporting Information for a more detailed table). [c] Yields of isolated products after column chromatography. [d] The stereochemistry of the major isomer was established based on two-dimensional and selective nOe experiments. [e] The yield for the one-pot reaction is indicated within parentheses. Reaction conditions: ketone, (1 equiv); tosylhydrazide, (1 equiv), 1,4-dioxane, MW, 46°C, 30 min; then, boronic acid **2** (2 equiv); K$_2$CO$_3$, (2 equiv); CsF, (2 equiv), MW, 150°C, 30 min. Bn = benzyl, MW = microwave, PMP = *para*-methoxyphenyl.

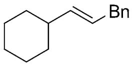
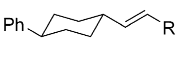
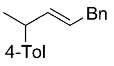
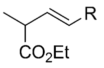
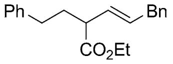
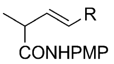
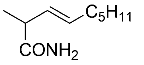
Finally, like in many other processes involving tosylhydrazones, the reductive couplings can be conducted in a one-pot fashion directly from the carbonyl compounds,[4,8e,13] thus providing the olefination products **5** with complete regioselectivity albeit in yields slightly lower than the reactions from the recrystallized tosylhydrazones (Table 1, entries 1, 3, 5, and 7).

The reactions of cyclic tosylhydrazones are noteworthy for various reasons: 1) cyclic tosylhydrazones provide extremely poor yields in the reductive couplings with arylboronic acids, however, perform very well with alkenylboronic acids; 2) the products obtained are the thermodynamically unstable isomers which feature an exocyclic double bond and are not conjugated with the aromatic ring. Moreover, from a synthetic point of view, these transformations can be envisioned as a new type of olefination reaction of carbonyl compounds,[14] a key transformation in organic synthesis, and is achieved in a very simple manner—no metal catalyst, no inert atmosphere or dry solvents are needed—and from readily available starting materials.

We next turned our attention to 2-alkyl-substituted alkenylboronic acids **6** (Table 2). The reactions proceeded with moderate yields, and in general, the microwave-promoted reactions provided better results. Quite surprisingly, the regioselectivity of the reactions was completely reversed from the reactions with styrylboronic acids **2**. Now, in most of the examples studied, the regioisomer **7**, in which the double bond in the original position is preserved, was obtained as the major isomer. Remarkable regioselectivity was obtained for the reactions of dialkyl hydrazones (entries 1–3). Moreover,

Table 2: Reductive alkenylation of tosylhydrazones **1** by reaction with alkenyl boronic acids **6**.[a]



Entry	Product	R (**7**)	Yield [%][b]
1		Bn (**7a**)	57(94:6)[c]
2[e]		*n*C$_3$H$_7$ (**7ba**)	62 (91:9)[c]
3[e]		Bn (**7bb**)	69 (94:6)[c]
4		Bn (**7c**)	68 (50:50)[c]
5		Bn (**7da**)	61
6		*n*C$_6$H$_{13}$ (**7db**)	49
7		Cy (**7dc**)	35
8		Bn (**7e**)	61
9		Bn (**7fa**)	63
10		*n*C$_6$H$_{13}$ (**7fb**)	58
11		Cy (**7fc**)	40
12		*n*C$_6$H$_{13}$ (**7fd**)	35

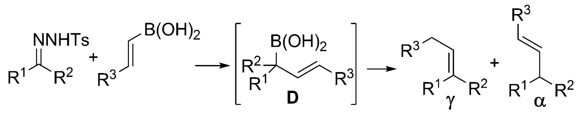
[a] Reaction conditions: *N*-tosylhydrazone **1**, (1.0 equiv); boronic acid **6**, (2 equiv); K$_2$CO$_3$, (2 equiv); CsF, (2 equiv); 1,4-dioxane, MW, 150°C, 30 min. [b] Yields of isolated products after column chromatography. [c] The ratio of double bond regioisomers determined by ^{1}H NMR spectroscopy of the crude reaction mixture is indicated within parentheses. [e] The stereochemistry was established based on the ^{1}H NMR spectra.

in the reactions with hydrazones derived from ethyl pyruvate and pyruvic amides, the disubstitued alkenes are obtained as a unique positional isomer (entries 5–12).[15] Only the reaction with an aryl-substituted hydrazone (entry 4) led to a 1:1 mixture of regioisomers. Furthermore, the *E* stereochemistry of the boronic acid is retained in the final product. The high functional-group tolerance of the reaction must be noted, that is, it can be carried out in the presence of a carboxylic ester and even NH- or NH_2 unprotected amides.

The complete diastereoselectivity observed in the reactions with the hydrazone derived from 4-phenylcyclohexanone (Table 2, entries 2 and 3) is also worth noting. Only one of the two possible diastereoisomers was detected in the reaction, and thus corresponds to the incorporation of the new R group in the equatorial position.[16] These are examples of facial diasteresoselectivity in the reactions between a tosylhydrazone and a boronic acid, a new feature that enhances the synthetic value of this C–C bond-forming reaction.

Considering the results presented in Table 1 and Table 2, the dramatic influence of the substituents of both coupling partners in the outcome of these reactions is apparent. Table 3 summarizes our observations, and allow one to predict the particular isomer that is expected depending on the nature of the reactants. An explanation of these observations will probably depend on the relative rate of α and γ protodeboronations of the allylboronic intermediate **D**, which will be affected by the substitution.[17] As suggested by one of the referees, in the reactions with styrylboronic acids ($R^3 = Ar$) the stabilization of an incipient negative charge at the benzylic position may favor the γ protodeboronation, and therefore the alternation of the double bond. This effect is not present in the reactions with alkyl-substituted boronic acids ($R^3 = Ar$), and consequently α-protodeboronation, with preservation of the stereochemistry of the double bond, might take place. In contrast, and for similar reasons, electron-withdrawing groups in the hydrazone fragment ($R^2 = CO_2Me$, CONHR) may favor the α protodeboronation, thus either decreasing or enhancing the regioselectivity of the reactions with styrylboronic acids and alkyl-substituted boronic acids, respectively. Mechanistic and theoretical studies are underway.

Table 3: Summary of the expected product distribution depending on the substituents of the coupling partners.



R^1	R^2	R^3	γ	α
alkyl	aryl	aryl	95–90	5–10
alkyl	**alkyl**	**aryl**	**100**	0
aryl	**aryl**	**aryl**	**100**	0
alkyl	EWG]	aryl	50	50
alkyl	aryl	alkyl	50	50
alkyl	**akyl**	**alkyl**	**5–10**	**95–90**
alkyl	**EWG**	**alkyl**	0	**100**

EWG = electron-withdrawing group.

In conclusion, we have presented a very general and efficient reductive coupling between tosylhydrazones and alkenylboronic acids, a coupling that can be envisoned as a new type of olefination of carbonyl compounds though tosylhydrazones. This C–C bond-forming reaction takes place under very simple reaction conditions without the need of metal catalysts or inert atmosphere, and tolerates a variety of functional groups. Depending on the nature of the substituents, and in a predictable manner, the reaction gives rise to different isomers that differ in the position of the double bond. For the reasons above, and taking into consideration the generality of the process, and the ready availability of both types of coupling partners, we believe that these reactions may be very useful in organic synthesis.

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Keywords: alkenes · boron · cross-coupling · hydrazones · synthetic methods

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