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Stereoselective Csp^3–Csp^2 Bond-Forming Reactions by Transition-Metal-Free Reductive Coupling of Cyclic Tosylhydrazones with Boronic Acids

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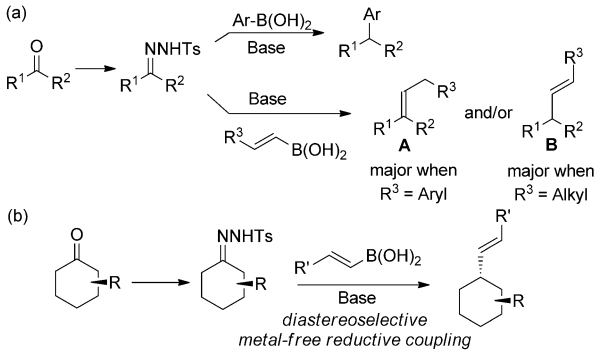
Abstract: The reactions between alkenylboronic acids and tosylhydrazones derived from substituted cyclohexanones lead to the construction of disubstituted cyclohexanes with total regio- and stereoselectivity. In these transition-metal-free processes, a Csp^3–Csp^2 and Csp^3–H bond are formed on the same carbon atom. The stereoselective reaction is general for 2-, 3-, and 4-substituted cyclohexanone tosylhydrazones, as well as for 2-substituted cyclopentanones. However, no stereoselectivity is observed for acyclic derivatives. DFT computational modeling suggests that the stereoselectivity of the reaction is determined by the approach of the boronic acid to the diazocyclohexane on its most stable chair conformation through an equatorial trajectory.



Scheme 1. a) Metal-free Csp^3–Csp^2 bond-forming reactions from tosylhydrazones and boronic acids. b) This work.

Sulfonylhydrazones are highly versatile intermediates for the modification of carbonyl compounds. Noteworthy is the discovery over the last fifteen years of a variety of new transition-metal-catalyzed and also noncatalytic processes based on these substrates, which has fostered a growing interest in these intermediates.[1–4] In particular, the reductive cross-coupling between boronic acids and sulfonylhydrazones represents a very versatile method for the modification of carbonyl compounds through a transition-metal-free reductive Csp^2–Csp^3 bond-forming reaction.[5,6] Since our initial report in 2009, this transformation has shown considerable usefulness in medicinal chemistry and diversity-oriented synthesis.[7–9]

In this context, the reaction between tosylhydrazones and alkenylboronic acids is particularly appealing. In a previous communication,[10] we showed that two different double bond regioisomers—the olefination product **A** or the reductive alkenylation derivative **B**, respectively, can be obtained depending on the nature of both coupling partners, and in a totally predictable manner (Scheme 1 a). Interestingly, in a single particular example when a 4-substituted cyclohexanone was employed, the coupling reaction proceeded with total diastereoselectivity leading to the reductive alkenylation product as a single diasteroisomer. It is noteworthy that an important limitation of the reactions based on sulfonylhydrazones or diazo compounds that proceed without the need of a metal catalyst is their lack of stereocontrol;[11] therefore, this particular reaction was indeed a rare example of a diastereoselective reaction based on diazo compounds in the absence of a metal catalyst.[12]

Taking into consideration the ample synthetic possibilities that these reductive couplings offer, we decided to investigate in more detail the stereoselectivity of these metal-free Csp^3–Csp^2 bond-forming reactions. We envisioned that if a general stereoselective reaction could be developed, it might represent a very direct way to achieve a challenging transformation from carbonyl compounds via their tosylhydrazones: the formation of a Csp^3–Csp^2 bond and a Csp^3–H bond on the same carbon atom; therefore, a reductive coupling reaction, in a diastereoselective manner, and in one single synthetic operation (Scheme 1 b).

We started our investigation with the tosylhydrazone **1a** derived from the corresponding 2-aminomethylcyclohexanone (Scheme 2). At the outset of this work we believed that this might be a quite demanding reaction, as this particular molecule consisted in a 2-substituted cyclohexanone featuring a potentially reactive NH group. Our initial efforts were carried out under the experimental conditions previously developed for the tosylhydrazone of 4-phenylcyclohexanone, which had resulted in a very high regio- and stereoselective reaction. Indeed, with these new substrate, the reaction afforded the reductive coupling product **3a** as a single diastereoisomer, but

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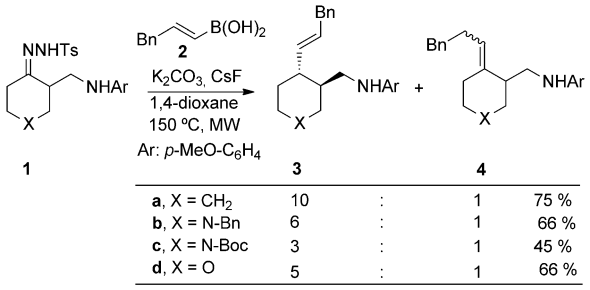


a, X = CH_2	10	:	1	75 %
b, X = N-Bn	6	:	1	66 %
c, X = N-Boc	3	:	1	45 %
d, X = O	5	:	1	66 %

Scheme 2. Preliminary experiments on the reaction between tosylhydrazones **1** and boronic acid **2**.

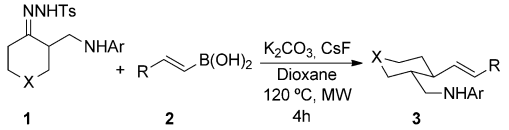
was accompanied with a minor amount of the two *Z/E* isomers of the olefination product **4**; a 10:1 ratio was determined by GCMS and ^{1}H NMR spectroscopic analysis of the reaction crude. However, the regioselectivity of the reaction was not reproduced when the reductive coupling was attempted with the tosylhydrazones **1b**, **1c**, and **1d** derived from the N-protected 4-piperidones and 4-pyranone, respectively. In these cases, the coupling took place with excellent conversion, but a substantial amount of the regioisomers **4** were obtained in the reaction crude (Scheme 2).

In an attempt to improve the regioselectivity of the reactions and drive the coupling to the exclusive obtention of the regioisomer **3**, a large set of experiments was conducted for tosylhydrazones **1a** and **1b**, with variations in the nature of the base (Na_2CO_3, K_2CO_3, Cs_2CO_3, CsF, Li*O*t*Bu*), the solvent (THF, 1,4-dioxane, MeOH, CH_3CN), the temperature, and the heating source. It was found that the regioselectivity could be improved by reducing the temperature of the reaction. The best results, without compromising the conversion of the coupling reactions, were obtained by running the reactions at 120 °C under microwave heating, employing a combination of K_2CO_3 (2 equiv) and CsF (2 equiv), in 1,4-dioxane for 120 min. It must be noted that the microwave heating turned out to be essential for the outcome of the reaction, as the results could not be efficiently reproduced under conventional heating after testing an array of temperatures and reaction times. Nevertheless, under the optimized reaction conditions, the reductive coupling products **3** could be obtained as single diastereoisomers, and with less than 5% of the olefination regioisomer **4** being detected in the reaction crude.

As depicted in Table 1, the reaction could be performed with very similar results for tosylhydrazones derived from cyclohexanone, pyranone, and N-protected piperidone derivatives with no variation on the regio- and stereoselectivity. Analysis of the stereochemistry through ^{1}H NMR, homonuclear decoupling, and bidimensional NMR spectroscopy experiments revealed that compounds **3** feature both substituents in a *trans* equatorial arrangement in the six-membered ring.

Next, we moved to evaluate the employment of other cyclohexanone derivatives, featuring different classes of substituents at the 2-position, including alkyl, aryl, allyl, and even a trifluoromethyl substitution. The main results are highlighted in Table 2. In all cases, the disubstituted cyclohexanes **5** derived from the reductive coupling were obtained in moderate yield, and as single regio- and diastereoisomers. Importantly, the reaction could be applied to both cyclohexanone and 4-piperidone tosylhydrazones with similar results.

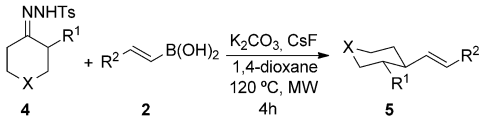
Table 1. Stereoselective synthesis of *trans*-1-aminomethyl-2-(1-alkenyl)cyclohexanes **3**.



Compd.	R	X	Ar	Yield [%][a]
3a	Bn	CH_2	PMP	62
3b	Bn	NBn	PMP	68
3c	Bn	NBoc	PMP	56
3d	Bn	O	PMP	60
3e	Bn	CH_2	4-Tol	65
3f	*n*-C_6H_{13}	CH_2	4-Tol	66
3g	*n*-C_4H_9	CH_2	4-Tol	52

[a] Isolated yield after column chromatography. Boc = *tert*-butoxycarbonyl; PMP = *p*-methoxyphenyl.

Table 2. Stereoselective synthesis of *trans*-1,2-disubstituted cyclohexanes **3**.

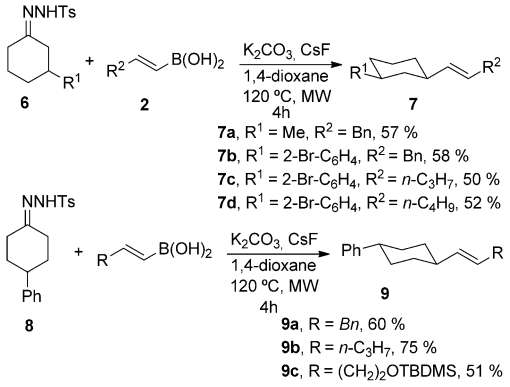


Compd.	R^1	R^2	X	Yield [%][a]
5a	CH_3	Bn	$-CH_2-$	52
5b	CH_3	*n*-Hexyl	$-CH_2-$	56
5c	CH_3	$-(CH_2)_2$OTBDMS	$-CH_2-$	60
5d	Bn	Bn	$-CH_2-$	56
5e	Allyl	Bn	NBoc	58
5f	Allyl	*n*-Propyl	NBoc	50
5g	Allyl	*n*-Hexyl	NBoc	50
5h	Allyl	$-(CH_2)_2$OTBDMS	NBoc	65
5i	Ph	Bn	$-CH_2-$	55
5j	Ph	*n*-Propyl	$-CH_2-$	51
5k	CF_3	Bn	$-CH_2-$	63

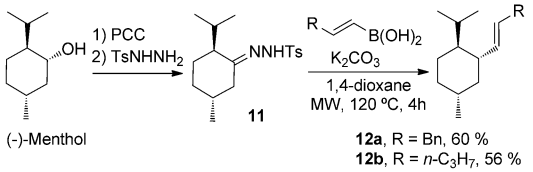
[a] Isolated yield after column chromatography. TBDMS = *tert*-butyldimethylsilyl.

The same reaction was then explored with tosylhydrazones derived from 3-substituted cyclohexanones **6**. Again, the reductive coupling proceeded with complete regio- and stereoselectivity leading to the 1,3-disubstituted cyclohexanes **7**, that featured both substituents at equatorial positions, and, therefore, in a *cis* relationship (Scheme 3). Additionally, under these reaction conditions, the reductive alkylation of the tosylhydrazone derived from 4-phenylcyclohexanone **8** took place also with complete regio- and stereoselectivity, providing the expected *trans*-1,4-disubstituted cyclohexanes **9**.

To test if the diastereoselective reductive cross-coupling of 2-substituted tosylhydrazones **4** could take place with retention of the configuration on the potentially epimerizable α-



Scheme 3. Stereoselective synthesis of *cis*-1,3-disubstituted cyclohexanes **7** and *trans*-1,4-disubstituted cyclohexanes **9**.

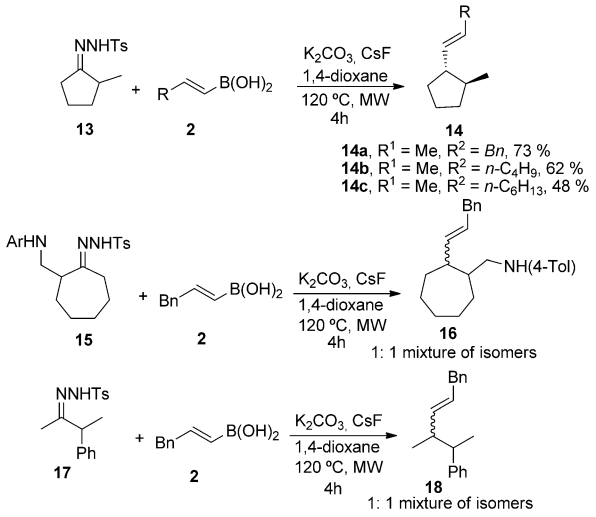


Scheme 4. Synthesis of enantiomerically pure alkenes **12** from (−)-menthol.

carbon atom,[13] we selected the tosylhydrazone **11**, that can be readily obtained as a unique enantiomer from (−)-menthol (Scheme 4). Both menthone and its tosylhydrazone **11** have been reported to undergo easy partial epimerization of the α-carbon atom,[14] but nevertheless **11** has been successfully employed for the synthesis of sterochemically pure menthol derivatives through Shapiro reactions.[15] In our case, when freshly prepared tosylhydrazone **11** was treated with the alkenyl boronic acid under our standard conditions, the reductive coupling product was obtained as a unique enantiomer, showing that the whole process from (−)-menthol, including the reductive coupling reaction had taken place without epimerization (Scheme 4).

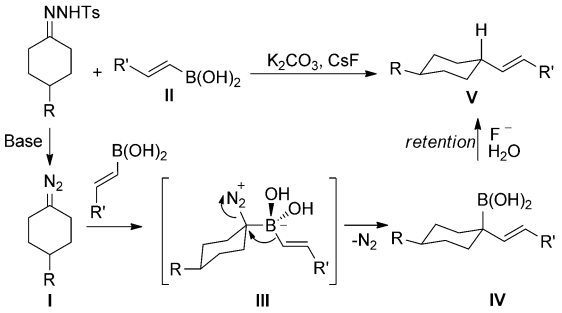
The reductive coupling reaction was also explored by employing tosylhydrazones derived from other cyclic and also acyclic ketones, to establish the scope of the stereoselective transformation. When the couplings were conducted with tosylhydrazone **13**, derived from 2-methylcyclopentanone, the expected 1,2-disubstituted cyclopentanes **14** were obtained again as single regio- and diastereoisomers (Scheme 5). Therefore, according to this result, the stereoselective reductive coupling is also useful for the modification of 2-substituted cyclopentanones. However, when the same transformation was attempted with cycloheptanone derivative **15**, a 1:1 mixture of the two diastereoisomers of cycloheptane **16** was detected in the reaction crude.

Finally, the coupling reaction with tosylhydrazone **17**, as an example of an acyclic system led to the expected alkene, but again as a nearly 1:1 mixture of diastereoisomers **13**. These latter results clearly establish the need of a rigid cyclic system to enable the stereoselective reaction.



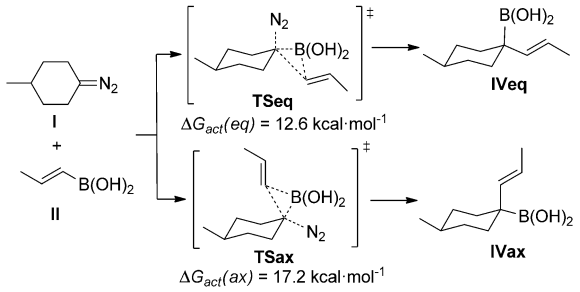
Scheme 5. Scope of the stereoselective reductive coupling.

The mechanism proposed for the reactions between tosylhydrazones and alkenyl boronic acids involves: 1) the decomposition of the hydrazone to give a diazo compound **I**, 2) reaction of the diazo compound **I** with the boronic acid **II** through the boronate species **III**, to give the allylboronic acid **IV**,[16] and 3) protodeboronation of **IV** that provides the final alkene **V** (Scheme 6). It has been previously observed that the protodeboronation of tertiary boronic esters takes place with retention of the configuration under conditions quite similar to those employed herein.[17] If a similar mechanism operates for the protodeboronation of the allylboronic acids, the stereochemical control should come from the formation of the intermediate allylboronic acid **IV**. Thus, to explain the stereoselectivity observed in the reductive alkenylation reactions, a DFT-based computational study of the addition of the boronic acid to the diazo compound was conducted.[18]



Scheme 6. Mechanism proposed for the reductive alkenylation.

As a model reaction, the addition of *E*-1-propenylboronic acid **II** to 1-diazo-4-methylcyclohexane **I** was considered (Scheme 7). In our initial studies, the starting geometries were chosen by considering the methyl group in an equatorial position. Interestingly, it was found that the boronate species typically proposed as an intermediate in these reactions (**III** in



Scheme 7. DFT computational modelling of the reaction between 1-diazo-4-methylcyclohexane **I** and 1-propenylboronic acid **II** at the M06-2X/6-311++G**/PCM(1,4-dioxane) level.

Scheme 6) is not an intermediate but a transition state in the potential energy surface. According to this result, the formation of the allylboronic acid **IV** takes place through a very asynchronous concerted process, in which the release of N_2, the formation of the Csp^3–B bond, the cleavage of the B–Csp^2 bond and the formation of the Csp^3–Csp^2 bond occurs in one single step (Scheme 7, Figure 1).[12,19]

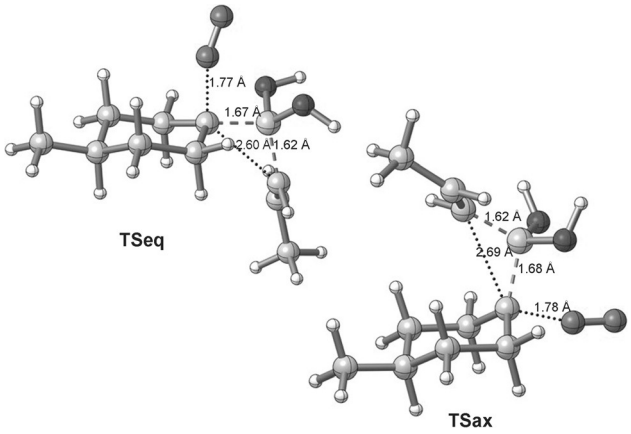


Figure 1. Transition states obtained for the reaction between diazo compound **I** and 1-propenylboronic acid **II** (M06-2X/6-311++G**).

Two different transition states were found (**TSeq** and **TSax**) corresponding to the approximation of the boronic acid to the diazo compound through equatorial or axial trajectories, respectively (Scheme 7 and Figure 1). Both transition states share the common structure typical of a very asynchronous concerted reaction (Figure 1) in which the Csp^3–B bond is almost formed (1.67 Å), and with a very long distance (2.60–2.70 Å) for the incipient Csp^3–Csp^2 bond. Additionally, the alkenyl group and the leaving nitrogen molecule display an antiperiplanar arrangement resembling the transition state of an S_N2 reaction.

The approximation through the equatorial trajectory is clearly favored (ΔG_{act}(equatorial) = 12.6 kcal mol^{-1}; ΔG_{act}(axial) = 17.2 kcal mol^{-1}). The remarkable energy difference found between both transition states ($\Delta\Delta G$ = 4.6 kcal mol^{-1}) may be due to the more distorted structure of **TSax**, which is enforced to avoid the steric interactions with the axial hydrogen atoms of the cyclohexane ring.[20] Moreover, the favored equatorial trajectory leads to allylboronic acid **IVeq**, and after the protodeboronation, to the cyclohexane that features both substituents in equatorial positions, in agreement with the experimental observations.

In summary, we have reported a general stereoselective reductive alkenylation of substituted cyclohexanones and cyclopentanones by their tosylhydrazones by a operationally simple reaction that does not require the participation of any metal catalyst. Noteworthy is that these are rare examples of uncatalyzed stereoselective reactions based on diazo compounds. A rationale for the complete stereoselectivity observed can be found in the asynchronus concerted transition state that leads to the intermediate allyl boronic acid, which is notoriously favored through an equatorial trajectory. From a synthetic point of view, the methodology introduced herein represents a very powerful tool for the diastereoselective modification of substituted cyclic ketones by the simultaneous formation of a Csp^3–Csp^2 and Csp^3–H bond. Importantly, this is a transformation for which no other simple alternative is available. Considering the wide availability of enantiomerically pure substituted cyclohexanones and cyclopentanones from the chiral pool and also through a variety of asymmetric catalytic reactions, we think that this method will be highly useful in organic synthesis.

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Keywords: boronic acids · diazo compounds · reductive coupling · stereoselectivity · tosylhydrazones

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[16] In a very recent contribution by the Ley group, the transient boronic intermediate derived from the reactions of flow-generated diazo compounds with boronic acids could be isolated, giving further support to this mechanistic proposal: C. Battilocchio, F. Feist, A. Hafner, M. Simon, D. N. Tran, D. M. Allwood, D. C. Blackemore, S. V. Ley, *Nat. Chem.* DOI: 10.1038/NCHEM.2439.

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[18] The calculations were carried out with Gaussian 09 (see the Supporting Information for a 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 Supporting Information for a detailed discussion.

[19] Exhaustive attempts to locate a boronate complex as an intermediate for the reaction failed and always led to the dissociation of both reactants. These structures have been characterized as saddle points at several different levels of theory. Moreover, IRC calculations demonstrated that indeed the proposed TS connects the reagents with the allylboronic acid.

[20] Two additional saddle points (**TSeq'** and **TSax**') are expected considering the chair conformation that features the methyl group in an axial position. **TSeq'** features a Gibbs free energy 1.3 kcal mol^{-1} higher than the analogous **TSeq**. This value is very close to the energy difference calculated for the two chair conformers of 4-methyldiazocyclohexane. Although the energy difference between **TSeq** and **TSeq'** is not large in this particular example, this value will depend on the specific substituents for other substituted diazocyclohexanes. Therefore, larger substituents are expected to feature larger energy differences between both transition states (see the Supporting Information).

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