

# Stereoselective Domino Carbocyclizations of $\gamma$ - and $\delta$ -Cyano-*N*-tosylhydrazones with Alkenylboronic Acids with Formation of Two Different C(sp<sup>3</sup>)-C(sp<sup>2</sup>) Bonds on a Quaternary Stereocenter

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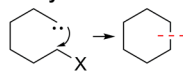
**S** Supporting Information

**ABSTRACT:** A novel strategy for the synthesis of functionalized carbocycles is defined, through the cascade carbocyclization of alkenylboronic acids with  $\delta$ - or  $\gamma$ -cyano-*N*-tosylhydrazones. In the reaction, two C(sp<sup>3</sup>)-C(sp<sup>2</sup>) bonds are formed on the former hydrazone carbon generating an all-carbon quaternary stereocenter, and leading to cyclic ketones featuring an alkenyl side chain with complete diastereoselectivity. The processes are conducted under very simple experimental conditions, only in the presence of K<sub>2</sub>CO<sub>3</sub>, in 1,4-dioxane as solvent and under microwave irradiation, and have been applied for the synthesis of a wide structural variety of fused cyclopentanones and cyclohexanones. Moreover, the versatility of this methodology has been demonstrated in the structural modification of androsterone.

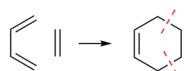
The construction of carbocyclic scaffolds is among the most important transformations in organic synthesis.<sup>1</sup> In a carbocyclization reaction, at least one new C-C bond must be formed, and attending to the cyclization mode two main approaches can be considered (Scheme 1): (A) intramolecular

**Scheme 1. Schematic Representation of the Different Modes of Carbocyclization and Our Proposal**

**Carbocyclization reactions**

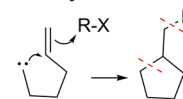


A: intramolecular cyclization

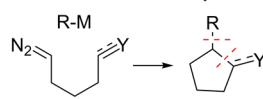


B: intermolecular cyclization

**Domino cyclizations with intermolecular side chain incorporation**



C: two bonds on vicinal C



D: New concept  
two bonds on the same C

reactions where the carbocycle is formed by connecting two carbon atoms of a single linear molecule; and (B) intermolecular reactions, in which the formation of the carbocycle is achieved by joining together two molecules, with formation of two C-C bonds. Another appealing family of strategies are domino reactions, where various bonds are formed in a sequential

manner, leading to a complex cyclic molecule from simpler linear precursors.<sup>2</sup> In this regard, cyclizations that take place with concomitant incorporation of a carbon side chain are noteworthy (Scheme 1C). These processes are usually triggered by the activation of a multiple bond through radical, polar, or transition metal catalyzed reactions and result in the formation of two C-C bonds at both carbon atoms of the unsaturation.<sup>3</sup>

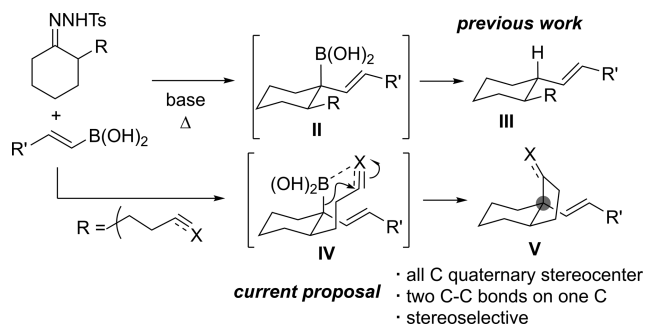
Much more unusual are the carbocyclizations that occur with formation of two bonds on the same carbon atom.<sup>4</sup> In particular, cascade cyclizations in which formation of two bonds, the bond that forms the cycle and a side-chain-linking bond, occur at the same center are very rare (Scheme 1D). This new class of cyclizations would be synthetically very attractive and will enable novel disconnections in retrosynthetic analysis, the application in diversity oriented synthesis through previously unexplored synthetic routes, and the access to previously unavailable molecular structures, and, thus, the exploration of new areas of the chemical space.<sup>5</sup>

Sulfonylhydrazones are very useful reagents for the modification of carbonyl compounds. Their ability to generate diazo compounds upon base-promoted decomposition has enabled the development of a variety of transition-metal-free C-C bond forming reactions.<sup>6</sup> Specifically, the transition-metal-free reactions between sulfonylhydrazones and boronic acids represent a powerful method for the reductive arylation<sup>7</sup> or alkenylation<sup>8</sup> of carbonyl compounds. We have recently reported that the reaction of *N*-tosylhydrazones of substituted cyclic ketones with alkenylboronic acids leads to the reductive alkenylation products with total diastereoselectivity, in a process in which a C(sp<sup>3</sup>)-C(sp<sup>2</sup>) bond and a C(sp<sup>3</sup>)-H bond are formed on the same carbon atom (Scheme 2).<sup>9</sup> The mechanism proposed for this transformation involves the generation of an intermediate allylboronic acid **II** that undergoes a stereoretentive protodeboronation<sup>10</sup> to give the final product **III**. If the protodeboronation pathway could be avoided, the intermediate allylboronic acid might participate in a further C-C bond-forming reaction,<sup>11</sup> rendering higher synthetic potential to the transformation. In fact, during the development of this work, Ley's group reported the intermolecular interception of transient allylboronic acids formed by reaction of boronic acids with diazo compounds generated under mild flow conditions.<sup>12</sup> We

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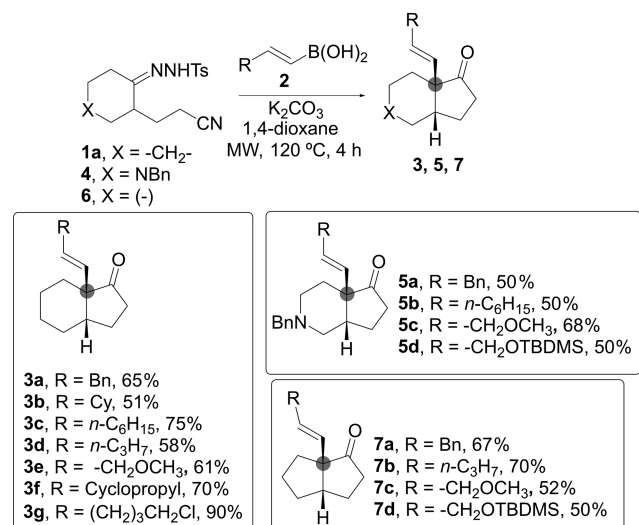
### Scheme 2. Transition-Metal-Free Reductive Alkenylation (Previous Work) and Stereoselective Domino Carbocyclization (Current Proposal)



envisioned that the presence of a proper electrophilic functionality tethered at the side chain of the cyclic *N*-tosylhydrazone might enable the intramolecular nucleophilic attack of the intermediate allylboronic acid IV,<sup>13</sup> leading to the formation of a new carbocycle V. The overall transformation would consist of the conceptually new cyclization pattern discussed in Scheme 1D. Additionally, creation of a quaternary stereocenter in a diastereoselective fashion would be also expected. We report herein our progress in the development of this concept, which has resulted in the discovery of a new type of transition-metal-free carbocyclization reaction, with great synthetic potential and experimental simplicity.

Our preliminary experiments were conducted with *N*-tosylhydrazone 1a, which features a cyano group at an optimal position to undergo the intramolecular nucleophilic attack (Scheme 3). The reaction was carried out mixing hydrazone 1a

### Scheme 3. Diastereoselective Synthesis of Bicyclic Cyclopentanones 3, 5, and 7<sup>a,b</sup>



<sup>a</sup>Tosylhydrazone (0.3 mmol), boronic acid (0.6 mmol), K<sub>2</sub>CO<sub>3</sub> (0.6 mmol), 1,4-dioxane (2.4 mL), MW (120 °C). <sup>b</sup>Isolated yields.

with (*E*)-(3-phenylprop-1-en-1-yl)boronic acid 2a under the standard conditions described for the reductive alkenylation reaction: K<sub>2</sub>CO<sub>3</sub> (2 equiv) and CsF (2 equiv), in 1,4-dioxane at 120 °C under microwave irradiation. Delightfully, the bicyclic ketone 3a was isolated as the reaction product and as a single diastereoisomer in 65% yield. Thus, the alkenylation/intra-

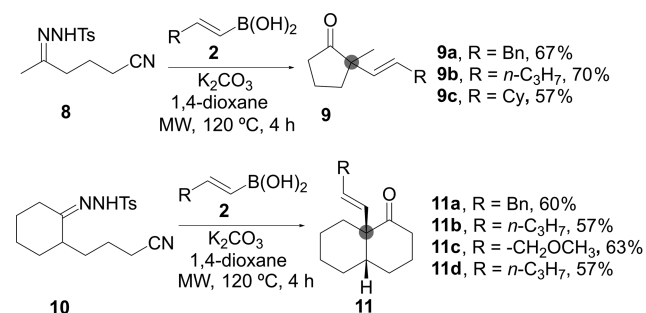
molecular cyclization cascade had taken place, showing that the cyano group was indeed a very appropriate electrophile for the domino process.

After some experimentation, it was found that the presence of the cesium fluoride was not necessary, and therefore the reaction could be carried out simply in the presence of 2 equiv of K<sub>2</sub>CO<sub>3</sub>. Microwave irradiation turned out to be essential, as the same reaction conducted under conventional heating failed to provide the final product in a synthetically relevant yield. Additionally, the 1,4-dioxane/K<sub>2</sub>CO<sub>3</sub> combination proved to be optimal, as variations in the base or the solvent led to a substantial drop in the yield.

The scope of the reaction was explored regarding both coupling partners (Scheme 3). First, the reaction was examined with a variety of alkenylboronic acids 2,<sup>14</sup> including functionalized systems, to provide the expected octahydro-1*H*-inden-1-ones (3a–g). Particularly noteworthy is the synthesis of 3g, in which a primary alkyl chloride remains untouched along the process. Then the reaction was examined with 4-piperidone derived tosylhydrazone 4, leading to the expected heterocycle containing ketones 5, again as single diastereoisomers. The reactions with the analogous cyclopentanone derived tosylhydrazone 6 led to the substituted hexahydropentane-2-ones 7 and, importantly, again as single diastereoisomers.

The reaction is not restricted to cyclic tosylhydrazones, as it could be achieved successfully also with the linear *N*-tosylhydrazone 8, giving rise to the 2,2-disubstituted cyclopentanones 9 (Scheme 4).<sup>15</sup> Thus, these preliminary results offer

### Scheme 4. Synthesis of Cyclopentanones 9 and Decalinones 11<sup>a,b</sup>

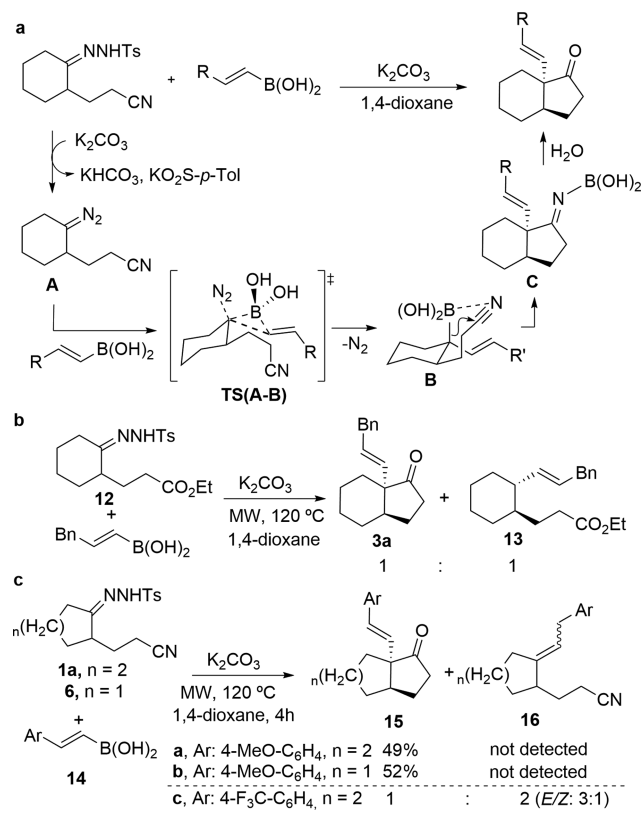


<sup>a</sup>Tosylhydrazone (0.3 mmol), boronic acid (0.6 mmol), K<sub>2</sub>CO<sub>3</sub> (0.6 mmol), 1,4-dioxane (2.4 mL), MW (120 °C). <sup>b</sup>Isolated yields.

the opportunity for the development of a new general method for the synthesis of substituted and functionalized cyclic ketones.<sup>16</sup> The reaction can be applied also to the construction of a cyclohexanone ring by introducing a 3-cyanopropyl side chain, as represented by the reactions of *N*-tosylhydrazone 10. As expected, the decalin-2-ones 11, featuring an angular quaternary stereocenter, were obtained again as pure diastereoisomers.

**Mechanistic Considerations.** In agreement with previous experimental evidence,<sup>17</sup> as well as with computational studies on the stereoselective reductive alkenylations of cyclic tosylhydrazones,<sup>9</sup> the mechanism proposed for the cascade reaction may involve the following steps (Scheme 5a): (1) formation of the diazo compound A by decomposition of the tosylhydrazone 1; (2) stereoselective addition of the boronic acid to the diazo compound through the transition state TS(A-B) that forms the allylboronic acid B (DFT calculations on similar systems predict the approximation of the boronic acid to the

## Scheme 5. Mechanistic Proposal and Additional Experiments



diazo compound through an equatorial trajectory);<sup>9</sup> (3) stereoretentive nucleophilic attack of the allylboronic acid to the cyano group which leads to the intermediate imine derivative C; (4) hydrolysis of the imine that provides the final product.

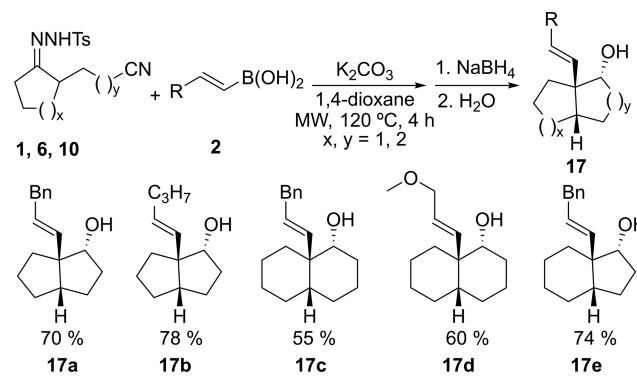
Noteworthy, to the best of our knowledge, there is only one previous example of the intramolecular addition of boronates to nitriles, which is restricted to aryl nitriles, and requires the presence of a silver catalyst.<sup>18</sup> To provide additional evidence for a nucleophilic cyclization, the same reaction was conducted with ester **12**, giving rise to a nearly 1:1 mixture of the bicyclic ketone **3a** and the reductive alkenylation ester **13**. This result points to a polar mechanism for the cyclization reaction and, additionally, opens the door to the incorporation of different electrophiles in the intramolecular cyclization upon proper tuning of the reaction conditions (Scheme 5b).

A key aspect in the success of the alkenylation/cyclization sequence is that the cyclization reaction must be faster than the spontaneous protodeboronation of intermediate B. In our previous work on the reductive alkenylation of tosylhydrazones, we had observed that the protodeboronation step was influenced by the substitution of the alkenylboronic acid, and in fact, 2-aryl-substituted ethenylboronic acids showed a different behavior.<sup>8</sup> For the alkenylation/cyclization domino process, the reaction of tosylhydrazones **1a** and **6** with boronic acid **14a** (Ar = 4-MeO-C<sub>6</sub>H<sub>4</sub>) followed the same pathway observed for alkenylboronic acids **2**, furnishing the bicyclic ketones **15a** and **15b** respectively as single reaction products. However, the reaction of boronic acid **14c** (Ar = 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>) with **1a** led to a 1:2 mixture of the expected ketone **15c** and (*Z/E*) isomeric alkenes **16**, derived from a formal  $\gamma$ -protodeboronation reaction. Clearly, the electronic effects of the aromatic ring play a decisive role in the rate of the protodeboronation. Detailed studies on the scope of

the reaction with 2-arylethenylboronic acids are currently ongoing.

Considering that the formation of the ketones takes place through a transient imine C, we attempted to trap the intermediate upon reduction. Thus, after the typical reaction time, an excess of NaBH<sub>4</sub> was added to the reaction mixture. However, the corresponding amines were not detected in any case, but the alcohols **17** were obtained as single stereoisomers. Clearly, the highly unstable imine intermediates undergo hydrolysis under the reaction conditions prior to the reduction step. The conformation of the ketone induces complete facial selectivity promoting the stereoselective reduction in all the examples studied (Scheme 6). Notably, the global trans-

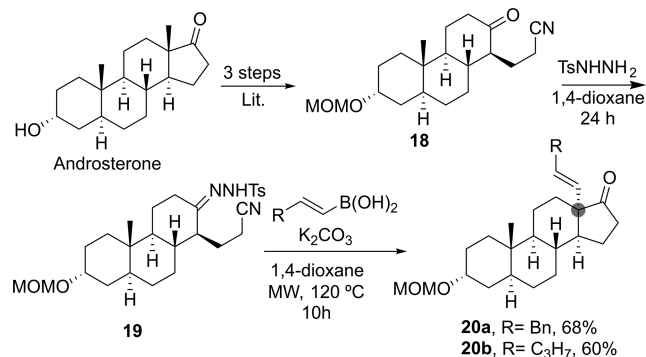
## Scheme 6. One Pot Cyclization/Reduction: Stereoselective Synthesis of Homoallylic Alcohols 17



formation is a *one-pot* transition-metal-free diastereoselective reaction that leads to bicyclic homoallylic alcohols **17** that feature three contiguous stereocenters, where the stereochemistry of the two new stereocenters is controlled by the configuration of the stereogenic carbon present in the initial substrate. As presented in Scheme 6, the stereoselective process took place successfully for the preparation of bicyclic systems featuring 5–5, 6–6, and 6–5 fused rings.

Finally, to investigate the applicability of this transformation in a more demanding environment, we studied the modification of the structure of an enantiopure natural product: the steroid androsterone (Scheme 7). To this purpose, the cyanoketone **18** was synthesized from androsterone through a straightforward previously described methodology.<sup>19</sup> Formation of the tosylhydrazone **19** proceeded uneventfully from **18**. Then, the reaction of **19** with alkenylboronic acids **2a** and **2b** under the standard

## Scheme 7. Application of the Domino Cyclization to the Modification of Androsterone



conditions led to the modified steroids **20**, importantly, as unique stereoisomers. Thus, reconstruction of the five membered ring of the steroid took place through the domino reaction, with the incorporation of the alkenyl side chain.

These results proved the usefulness of the stereoselective cascade transformation in more complex scenarios. Additionally, the reaction occurred with preservation of the existing stereogenic centers, including the potentially epimerizable center in  $\alpha$ -position to the carbonyl. Finally, focusing in the specific transformation, it is a novel way for the modification of steroids, which overall consists of the replacement of the angular methyl group by an alkenyl substituent with inversion of configuration.<sup>20</sup> Thus, this method will allow the synthesis of previously unavailable modified steroids with unknown biological activities.

In summary, we have developed a new type of cascade cyclization by reaction of alkenylboronic acids with 2-cyanoethyl or 3-cyanopropylcyclohexanone *N*-tosylhydrazones. This reaction defines a new carbocyclization mode, with formation of two C–C bonds on the same carbon atom and incorporation of a side chain. Additional features of this reaction are (i) the creation of an all-carbon quaternary stereocenter with total diastereoselectivity and (ii) the simplicity of the process, which takes place without the need for any metal catalyst, with only  $K_2CO_3$  as an additional reagent. These results open the door to the development of other new carbo- and heterocyclization reactions by the incorporation of different electrophiles, and for the employment of this strategy in both diversity- and target-oriented synthesis, as well as in the modification of natural products.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08116.

Detailed experimental procedures and characterization data for all the compounds described. Stereochemical analysis for compounds **3**, **11**, **17**, and **20** (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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