Stereoselective Domino Carbocyclizations of γ- and δ-Cyano-*N*-tosylhydrazones with Alkenylboronic Acids with Formation of Two Different C(sp^3)-C(sp^2) Bonds on a Quaternary Stereocenter

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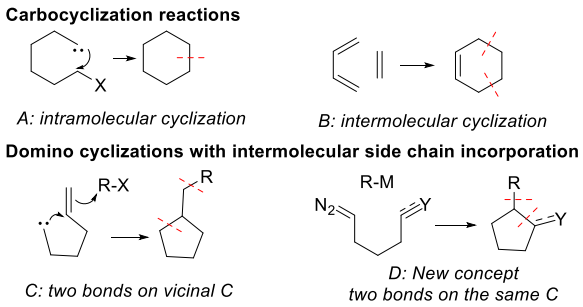
Supporting Information Placeholder

A novel strategy for the synthesis of functionalized carbocycles is defined, through the cascade carbocyclization of alkenylboronic acids with δ- or γ-cyano-*N*-tosylhydrazones. In the reaction, 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. The processes are conducted under very simple experimental conditions, only in the presence of K_2CO_3, 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 amongst the most important transformations in organic synthesis.[1] 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 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.[2] In this regard, cyclizations that take place with concomitant incorporation of a carbon side chain are noteworthy (Scheme 1, C). 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.[3]

Much more unusual are the carbocyclizations that occur with formation of two bonds on the same carbon atom.[4] 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 1, D). These 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.[5]

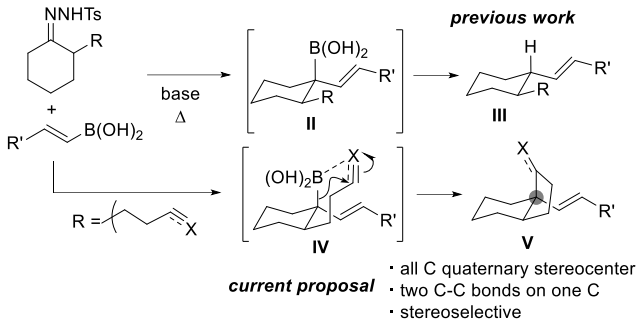
Scheme 1. Schematic representation of the different modes of carbocyclization and our proposal.



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.[6] Specifically, the transition-metal-free reactions between sulfonylhydrazones and boronic acids represent a powerful method for the reductive arylation[7] or alkenylation[8] 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^3)-C(sp^2) bond and a C(sp^3)-H bond are formed on the same carbon atom (Scheme 2).[9] The mechanism proposed for this transformation involves the generation of an intermediate allylboronic acid II, that undergoes a stereoretentive protodeboronation[10] 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,[11] 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.[12] We 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,[13] leading to the formation of a new carbocycle V. The overall transformation would consist on the conceptually new cyclization pattern discussed in scheme 1, D. 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.

Scheme 2. Transition-Metal-free reductive alkenylation (previous work) and stereoselective domino carbocyclization (current proposal).

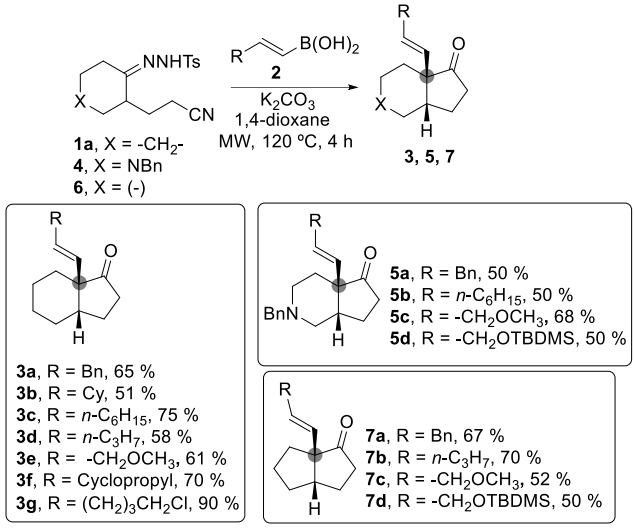


Our preliminary experiments were conducted with *N*-tosylhydrazone 1a, which features a cyano group at an optimal position to undergo the intramolecular nucleophilic attack (scheme 3). The reaction was carried out mixing hydrazone 1a with (*E*)-(3-phenylprop-1-en-1-yl)boronic acid 2a under the standard conditions described for the reductive alkenylation reaction: K_2CO_3 (2 equiv), CsF (2 equiv), in 1,4-dioxane at 120°C under microwave irradiation. Delightfully, the bicyclic ketone 3a was isolated as reaction product and as a single diastereoisomer in 65 % yield. Thus, the alkenylation/intramolecular 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_2CO_3. 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_2CO_3 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 parters (scheme 3). First, the reaction was examined with a variety of alkenylboronic acids 2,[14] 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 hexahydropentanlen-2-ones 7, and importantly, again as single diastereoisomers.

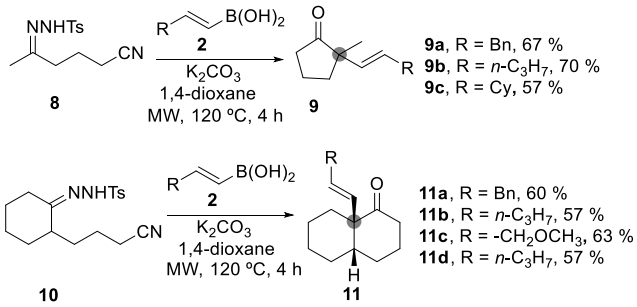
Scheme 3. Diastereoselective synthesis of bicyclic cyclopentanones 3, 5 and 7.[a,b]



[a] Tosylhydrazone (0.3 mMol), boronic acid (0.6 mMol), K_2CO_3 (0.6 mMol), 1,4-dioxane (2.4 mL), MW (120°C). [b] Isolated yields.

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).[15] Thus, these preliminary results offer the opportunity for the development of a new general method for the synthesis of substituted and functionalized cyclic ketones.[16] 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.

Scheme 4. Synthesis of cyclopentanones 9 and decalinones 11. [a,b]



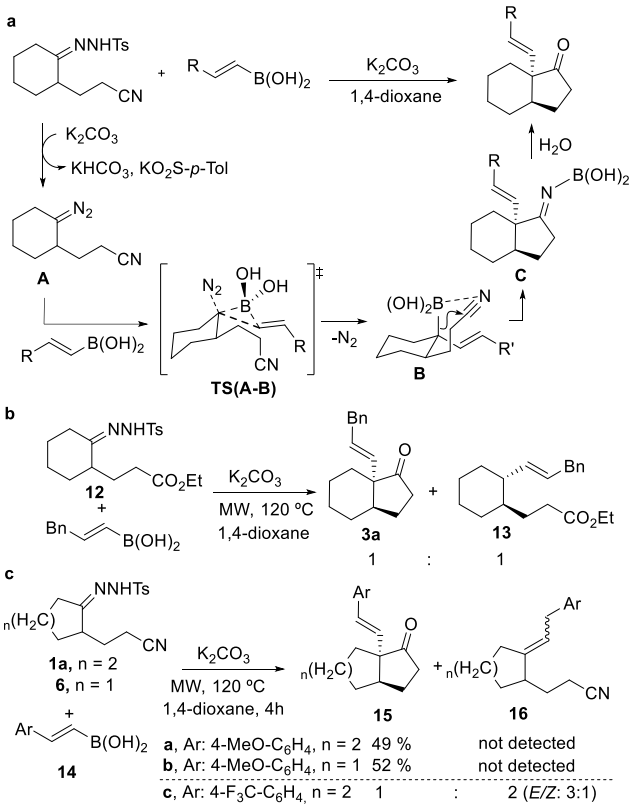
[a] Tosylhydrazone (0.3 mMol), boronic acid (0.6 mMol), K_2CO_3 (0.6 mMol), 1,4-dioxane (2.4 mL), MW (120°C). [b] Isolated yields.

Mechanistic considerations: In agreement with previous experimental evidence,[17] as well as with computational studies on the stereoselective reductive alkenylations of cyclic tosylhydrazones,[9] the mechanism proposed for the cascade reaction may involve the following steps (scheme 5, a): 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 diazo compound through an equatorial trajectory);[9] 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.[18]

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 5, b).

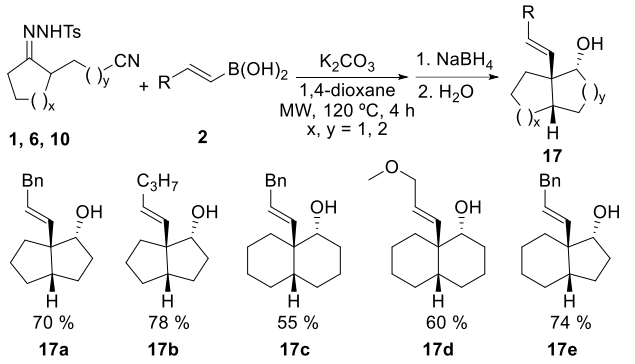
Scheme 5. Mechanistic proposal and additional experiments.



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-arylsubstituted ethenylboronic acids showed a different behaviour.[8] For the alkenylation/cyclization domino process, the reaction of tosylhydrazones 1a and 6 with boronic acid 14a (Ar = 4-MeO-C_6H_4) 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_3C-C_6H_4) with 1a led to a 1: 2 mixture of the expected ketone 15c and (*Z*/*E*) isomeric alkenes 16, derived from a formal γ-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 $NaBH_4$ 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 a complete facial selectivity promoting the stereoselective reduction in all the examples studied (scheme 6). Notably, the global transformation 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.

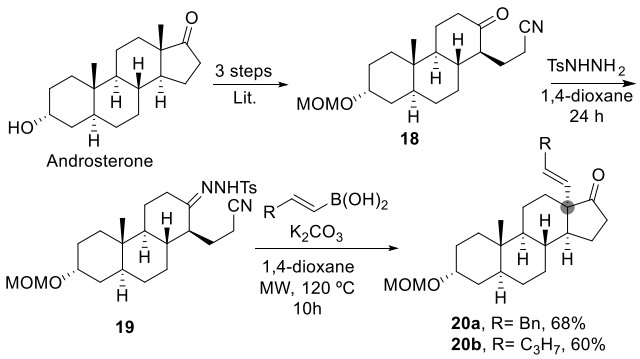
Scheme 6. One pot cyclization/reduction: stereoselective synthesis of homoallylic alcohols 17



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.[19] Formation of the tosylhydrazone 19 proceeded uneventfully from 18. Then, the reaction of 19 with alkenylboronic acids 2a and 2b under the standard 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 α-position to the carbonyl. Finally, focusing in the specific transformation, it is a novel way for the modification of steroids, which in overall consists in the replacement of the angular methyl group by an alkenyl substituent with inversion of configuration.[20] Thus, this method will allow the synthesis of previously unavailable modified steroids with unknown biological activities.

Scheme 7. Application of the domino cyclization to the modification of androsterone



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, ii) the simplicity of the process, which takes place without the need of any metal catalyst, only K_2CO_3 as 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-0oriented synthesis, as well as in the modification of natural products.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all the compounds described. Stereochemical analysis for compounds 3, 11, 17 and 20 (pdf). This material is available free of charge via the Internet at http://pubs.acs.org.

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