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Domino Synthesis of Benzo-Fused β,γ-Unsaturated Ketones from Alkenylboronic Acids and *N*-Tosylhydrazone-Tethered Benzonitriles

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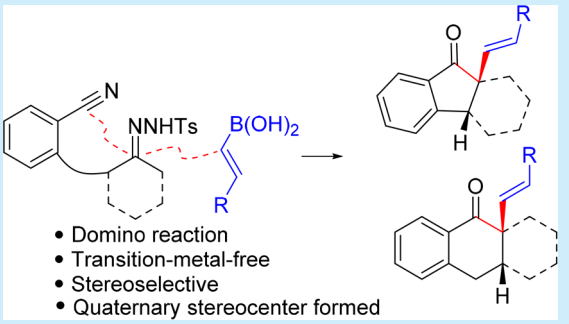
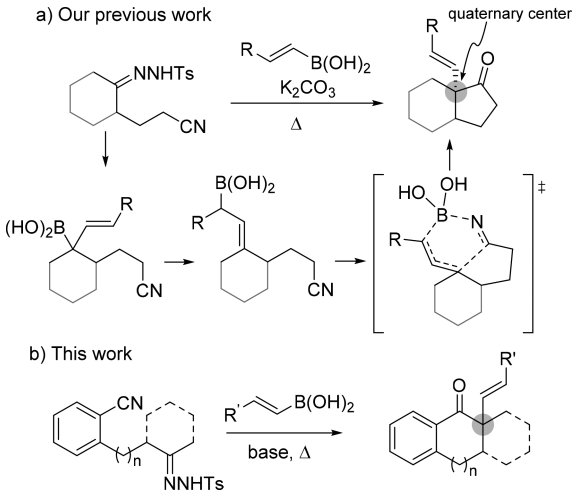
Supporting Information

ABSTRACT: The transition-metal-free domino reaction between alkenylboronic acids and *N*-tosylhydrazones from *o*-(2-oxoalkyl)- and *o*-(3-oxoalkyl)benzonitriles leads to β,γ-unsaturated indanones and tetralones featuring an α-"all-carbon" quaternary center. The employment of derivatives of α-substituted cyclopentanones and cyclohexanones led to the stereoselective preparation of β,γ-unsaturated tetrahydrocyclopenta[*a*]inden-8(1*H*)-ones, hexahydrofluorenones, and hexahydroanthracenones as *cis*-fused single stereoisomers. A domino sequence involving diazo compound formation/reductive alkenylation/1,3-borotropic rearrangement/intramolecular bora-aza-ene reaction is proposed to justify the formation of the products as well as the stereoselectivity.



Cyclic scaffolds featuring "all-carbon" quaternary stereocenters are structural motifs found in many biologically active natural and unnatural molecules.[1] Among the synthetic methods to achieve the construction of these challenging structures, carbocyclization processes that take place with formation of two C_{sp^3}−C bonds on the same carbon atom are very efficient yet unconventional solutions, which, in most of the cases, take place through transition-metal-catalyzed cascade reactions.[2,3] In particular, processes that generate a bridgehead "all-carbon" quaternary center[4] during the cyclization are particularly appealing. These transformations enable the synthesis of molecular scaffolds with well-defined three-dimensional arrangements in a straightforward manner. In recent years, we have concentrated on these synthetic strategies through both Pd-catalyzed[5] and transition-metal-free reactions,[6] employing *N*-tosylhydrazones as the divalent C1-synthon that can participate in the formation of the two bonds through cascade reactions.[7] In particular, we have recently uncovered a cascade carbocyclization between γ- and δ-cyano-*N*-tosylhydrazones and alkenyl boronic acids, which provides substituted cyclopentanones and cyclohexanones featuring an "all-carbon" quaternary center.[6a] In these processes, carbocyclization and incorporation of a side chain occur during the domino reaction. We have also shown that this strategy can be applied for the construction of a variety of complex polycyclic carbo- and heterocycles as well as spirocycles featuring a bridgehead quaternary center.[6b] According to our computational studies, the cascade reaction may involve formation of an allylboronic acid by carboboration of the *N*-tosylhydrazone, followed by intramolecular allylborylation of the nitrile through an intramolecular bora-aza-ene reaction (Scheme 1a).

Scheme 1. (a) Domino Reaction between γ-Cyano-*N*-tosylhydrazones and Alkenylboronic Acids for the Synthesis of β−γ-Unsaturated Ketones; (2) This Work



To expand the usefulness of this transformation, we decided to investigate if the domino reaction could be applied also to benzonitrile tethered *N*-tosylhydrazones. This reaction might enable the preparation of benzofused β,γ-unsaturated ketones,[8] such as vinylindanones and tetralones, featuring an "all-carbon" quaternary center (Scheme 1b). These classes of carbocyclic scaffolds might be very relevant for their usefulness as synthetic precursors,[9] and also due to their potential in drug discovery.[10]

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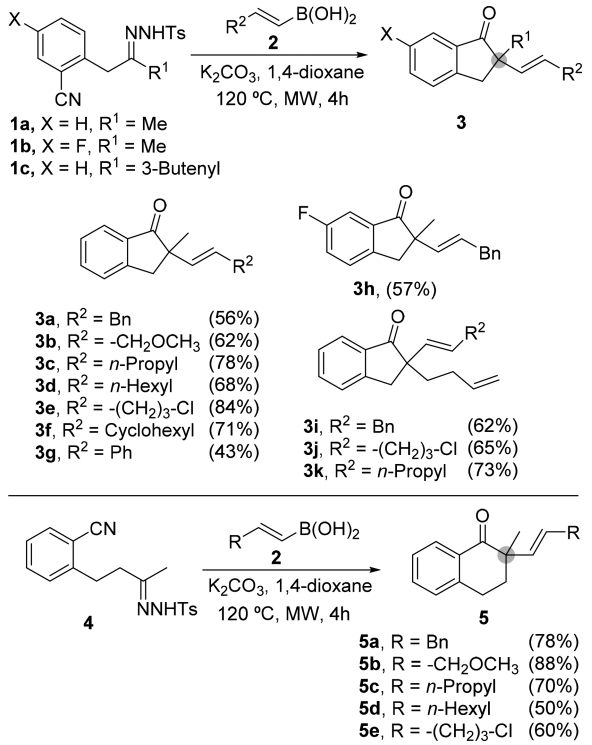
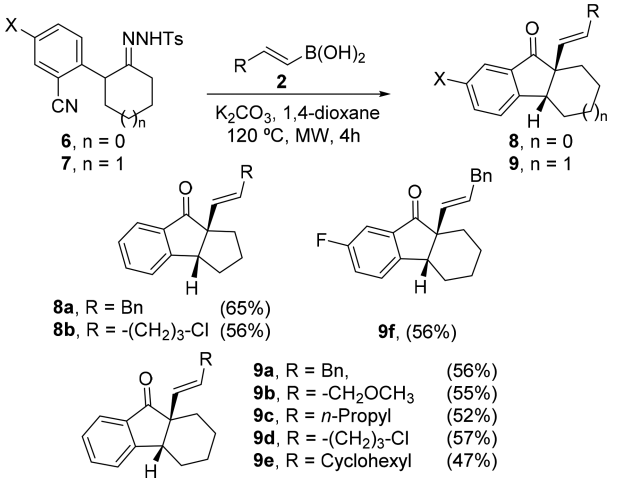
Scheme 2. Synthesis of 2,2-Disubstituted β,γ-Unsaturated Indanones 3 and Tetralones 5 by Reaction of *N*-Tosylhydrazones 1 and 4 with Alkenylboronic Acids 2[a,b]



[a]Reaction conditions: *N*-tosylhydrazone **1** or **4** (0.15 mmol), boronic acid **2** (0.3 mmol), K_2CO_3 (2 equiv), 1,4-dioxane (1.2 mL), microwave irradiation, 120 °C, 4 h. [b]Yields represent isolated yields after column chromatography.

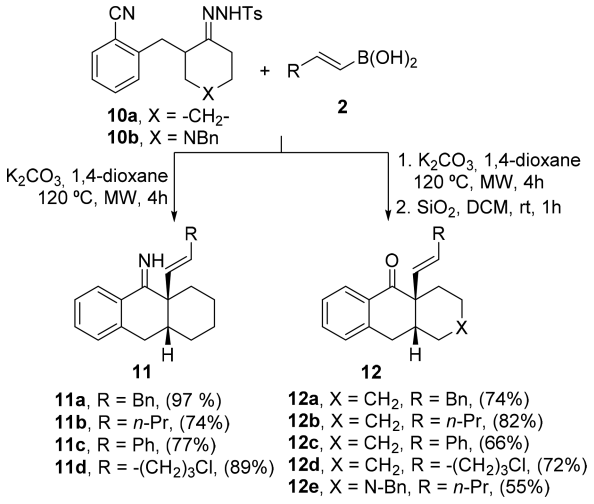
Scheme 3. Stereoselective Synthesis of Tetrahydrocyclopenta[*a*]inden-8(1*H*)-ones 8 and Hexahydrofluorenones 9[a,b]



[a]Reaction conditions as in Scheme 2. [b]Yields represent isolated yields after column chromatography.

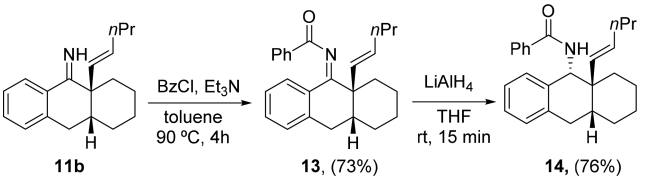
We started our investigation considering the *N*-tosylhydrazone **1a** derived from 2-(2-oxopropyl)benzonitrile and 3-phenylprop-1-en-1-yl)boronic acid **2a**, which might lead to the $\beta-\gamma$-unsaturated indanone **3a** (Scheme 2). After some experimentation, we found that the reaction conditions that we had originally developed for the reactions involving alkyl nitriles were also appropriate for the reaction with the benzonitrile.

Scheme 4. Stereoselective Synthesis of Hexahydroanthracenone Derivatives 11 and 12[a,b]

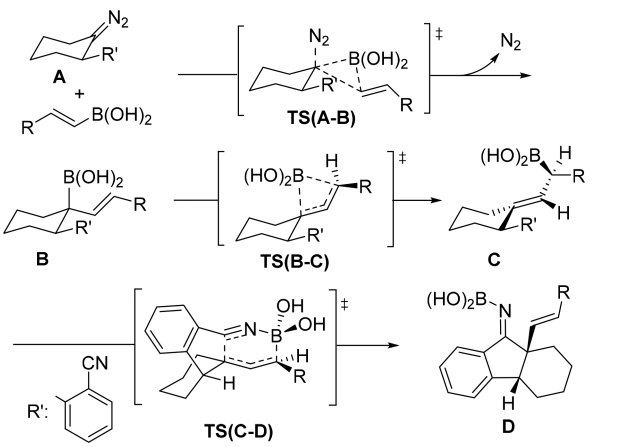


[a]Reaction conditions for the first step as in Scheme 2. [b]Yields represent isolated yields after column chromatography.

Scheme 5. Stereoselective Reduction of Ketimine 11b



Scheme 6. Mechanism Proposed Based on DFT Computational Modeling Studies



Thus, by treating the *N*-tosylhydrazone **1a** with alkenylboronic acid **2a**, in the presence of K_2CO_3 as the base, in 1,4-dioxane as the solvent, under microwave irradiation at 120 °C for 4 h, the 2,2,-disubstituted indanone **3a** was obtained in good yield through the desired domino alkenylation/carbocyclization (Scheme 2). The reaction exhibited a wide scope with regard to substitution in the alkenylboronic acids **2**, including the presence of a MOM group (**3b**), and the potentially reactive alkyl chloride functionality in the side chain (**3e**) that may enable further diversification. Interestingly, the

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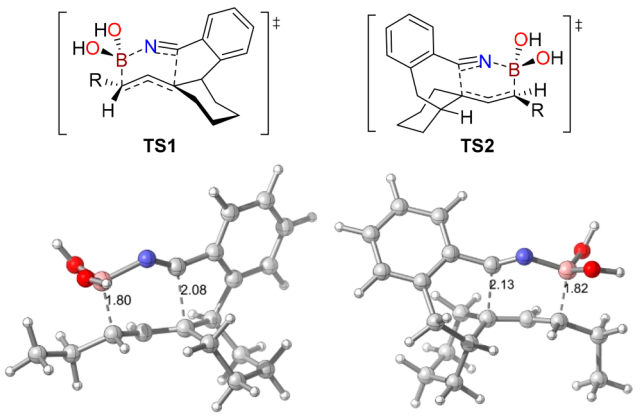

Figure 1. Molecular models for the lowest energy transition states (M06-2*X*/6-311++G**) for the concerted carboborylations that lead to the *cis*-fused indanones **9** (**TS1**) and anthracenones **11** (**TS2**) respectively.

use of phenylvinylboronic acid, which did not perform well in our previous studies, also granted the formation of the indanone **3g**. Finally, the reaction was also applied to the *N*-tosylhydrazone of 4-butenyl phenyl ketone **1c**, leading to 2-vinyl-2-allylindanones **3i**−**k** (Scheme 2).

We next turned our attention to the synthesis of 2,2-disubstituted tetralones through the same methodology. To this purpose the *N*-tosylhydrazone **4** featuring an additional methylene group in the tether between the hydrazone and the cyano functionalities was employed. Pleasantly, under similar reaction conditions, the expected *β*,*γ*-unsaturated tetralones **5** were obtained with fairly good yields and a similar scope regarding the alkenylboronic acid (Scheme 2).

Noteworthy, this is indeed an original procedure for the construction of the indanone and tetralone scaffolds that implies cyclization and incorporation of a side chain in the domino process. It must be noted that typical methods for the synthesis of substituted indanones and tetralones are carried out by introducing a substituent to the existing cyclic ketone,[8,11] or by cyclization of an acyclic system that already incorporates all the substitutions.[12] In contrast, our methodology integrates both steps in the domino process, allowing for easy diversification, and, remarkably, in a very simple process that does not even require the employment of transition metal catalysts.

In order to apply this methodology to more challenging and synthetically attractive substrates, we turned our attention to *N*-tosylhydrazones **6** and **7**, readily available from 2-(*o*-cyanophenyl)cyclopentanone and 2-(*o*-cyanophenyl)cyclohexanone respectively (Scheme 3).

These reactions were particularly interesting for various reasons: (i) the presence of a stereogenic center at the *α*-position of the *N*-tosylhydrazone might allow study of the diastereoselectivity of the reaction; (ii) the expected reaction products feature scaffolds, such as hexahydrofluorenone, that are present in a large number of natural products and biologically active molecules.[13]

Delightfully, under the standard conditions the final products were furnished as pure diastereoisomers to afford substituted tetrahydrocyclopenta[*a*]inden-8(1*H*)-ones **8** and hexahydrofluorenones **9** from *N*-tosylhydrazones **6** and **7** respectively (Scheme 3). As determined by 2D-NMR and selective NOE experiments, the diastereoisomers featuring a *cis* fusion between the rings were always obtained.[14] Notably, this stereoselectivity could be reproduced regardless of the size (five- or six-membered ring) of the preexisting ring.

Finally, the cascade reaction was also studied with *N*-tosylhydrazones **10** that would hopefully provide *β*,*γ*-unsaturated hexahydroanthracenones upon cyclization with formation of a six-membered ring (Scheme 4). Much to our surprise, upon reaction with alkenyl boronic acids **2** under the standard conditions, instead of the expected hexahydroanthracenones **12**, the corresponding NH-ketimines **11** were obtained with excellent yields. Thus, in these cases, the hydrolysis of the imine under the reaction conditions was prevented, probably due to the steric congestion around the benzylic position.

This is indeed an interesting result, since it is the first time that the NH-ketimine is isolated in these intramolecular carboborylation reactions. Nevertheless, the imine could be efficiently hydrolyzed upon stirring in a silica gel suspension in methylene chloride to give hexahydroanthracenones **12**. As an exception, the reaction with *N*-tosylhydrazone **10b**, derived from *N*-benzyl-4-piperidone, led directly to the ketone **12e**, and the imine could not be isolated. Importantly, compounds **11** and **12** were isolated as unique diastereoisomers, and again with a *cis*-fusion between the saturated rings.[14]

The ketimines **11** might be susceptible to further simple functional group manipulations leading to the corresponding benzylamine derivatives. For instance, benzoylation of **11b** led to *N*-benzoylimine **13** and subsequent treatment with $LiAlH_4$ furnished benzamide **14**. Noteworthy, the reduction takes place in a stereoselective manner leading to the amide **14** featuring three contiguous stereogenic centers as a unique diastereoisomer (Scheme 5).[14]

Mechanistic Considerations. As in our preceding contributions, the reactions with arylboronic acids did not provide the analogous cyclization products, but instead the typical reductive arylation of the *N*-tosylhydrazone took place. This observation points again to the necessity of an intermediate allylboronic acid to promote the intramolecular carboborylation of the nitrile. As presented in Scheme 6, a plausible mechanism, in agreement with our DFT computational studies, would involve the following: (1) decomposition of the *N*-tosylhydrazone to give the diazo compound **A**;[15] (2) carboborylation of the diazo compound to give allyl boronic acid **B**;[16] (3) borotropic rearrangement to provide allylboronic acid **C**;[17] (4) concerted carboborylation of the nitrile through a bora-aza-ene reaction to give *N*-boroimine **D**, which upon hydrolysis would furnish the final ketones.

Interestingly, this reaction model can also explain the stereoselectivity observed in the reactions with *N*-tosylhydrazones **6**, **7**, and **10** which lead to the *cis*-fused condensed ketones **8**, **9**, and **12** respectively. Although, the concerted carboborylation reaction could occur to give both the *cis*- and *trans*-fused bicyclic ketones, DFT-based molecular modeling computations clearly show that the bora-aza-ene concerted transition states that give rise to the *cis*-fused systems are considerably favored for both the 5−6 and 6−6 systems. Inspection of the molecular models reveals that the transition states that would give rise to the *trans*-fused systems are substantially distorted from the ideal geometry of the six-centered transition state, while for the *cis*-fused systems they are closer to the ideal geometry of the transition state of the bora-aza-ene reaction (Figure 1). A detailed computational

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study for both systems is provided in the Supporting Information (SI).

In summary, we have developed a new method for the synthesis of β,γ-unsaturated indanones and tetralones featuring an α-quaternary center by reaction of alkenylboronic acids with *N*-tosylhydrazones tethered to a benzonitrile. In the domino reaction the incorporation of the alkenyl group and the cyclization reaction occur in a single step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03705.

Experimental procedures, compound characterization data, and NMR spectra for the compounds described; computational molecular modeling studies (PDF)

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Notes

The authors declare no competing financial interest.

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