Domino Synthesis of Benzo-fused $\beta,\gamma$-Unsaturated Ketones from Alkenylboronic acids and N-Tosylhydrazone-tethered Benzonitriles

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ABSTRACT: The transition metal-free domino reaction between alkenylboronic acids and N-tosylhydrazones from $\alpha$-(2-oxoalkyl) and $\alpha$-(3-oxoalkyl) benzonitriles leads to $\beta,\gamma$-unsaturated indanones and tetralones featuring an $\alpha$-“all-carbon” quaternary center. The employment of derivatives of $\alpha$-substituted cyclopentanones and cyclohexanones led to the stereoselective preparation of $\beta,\gamma$-unsaturated tetrahydrocyclopenta[a]inden-8(1H)-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. Among the synthetic methods to achieve the construction of these challenging structures, carbocyclization processes that take place with formation of two $\text{C}_2$-$\text{C}$ bonds on the same carbon atom are very efficient yet unconventional solutions, that in most of the cases, take place through transition metal catalyzed cascade reactions. In particular, processes that generate a bridgehead “all-carbon” quaternary center 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 the recent years, we have concentrated in these synthetic strategies both through Pd-catalyzed and transition-metal-free reactions, employing N-tosylhydrazones as the divalent C1-synt Thats can participate in the formation of the two bonds through cascade reactions. In particular, we have recently uncovered a cascade carbocyclization between $\gamma$- and $\delta$-cyano-N-tosylhydrazones and alkenyl boronic acids, which provides substituted cyclopentanones and cyclohexanones featuring an “all-carbon” quaternary center. 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. According to our computational studies, the cascade reaction may involve formation of an allylboronic acid by carboborylation of the N-tosylhydrazone, followed by intramolecular allylborylation of the nitrile through an intramolecular bora-aza-ene reaction (Scheme 1, a). 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 benzfused $\beta,\gamma$-unsaturated ketones such as vinylindenones and tetralones, featuring an “all-carbon” quaternary center (Scheme 1, b). These classes of carbocyclic scaffolds might be very relevant for their usefulness as synthetic precursors, and also due to their interest in drug discovery.

We started our investigation considering the N-tosylhydrazone 1a derived from 2-(2-oxopropyl) benzonitrile and 3-phenyl(prop-1-en-1-yl)boronic acid 2a, that 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.
Thus, by treating the N-tosylhydrazone 1a with alkenylboronic acid 2a, in the presence of K_{2}CO_{3} as base, in 1,4-dioxane as solvent, under microwave irradiation at 120 °C for 4h, the 2,2-disubstituted indanone 3a was obtained with good yield through the desired domino alkenylation/carcyclization (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 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-2,4-allylindanones 3i-k (Scheme 2).

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

Noteworthy, this is indeed an original procedure for the construction of the indanone and tetrалone 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 indanes and tetrалones are carried out by introducing a substituent to the existing cyclic ketone, or by cyclization of an acyclic system that already incorporates all the substitutions. In contrast, our methodology integrates both steps in the domino process, allowing for an 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).
Scheme 3. Stereoselective synthesis of tetrahydrocyclopenta[a]inden-8(1H)-ones 8 and hexahydrofluorenones 9.\textsuperscript{a,b}

\begin{equation}
\begin{array}{c}
\text{Scheme 4. Stereoselective synthesis of hexahydroanthracene derivatives 11 and 12.}\text{a,b}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{Scheme 5. Stereoselective reduction of ketimine 11b.}
\end{array}
\end{equation}

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 both the cis-fused and the 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 favoured for both the 5-6 and the 6-6 systems. Inspection of the molecular models reveal 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 are closer to the ideal geometry of the transition state of the bora-aza-ene reaction (Figure 1). A detailed computational study for both systems is provided in the SI.

In summary, we have developed a new method for the synthesis of \(\beta,\gamma\)-unsaturated indanones and tetralones featuring an \(\alpha\)-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.
REFERENCES


(14) The stereochemical assignments were carried out by 2D-NMR and selective nOe experiments (see SI for a detailed discussion).


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