Enantio- and Diastereoselective Synthesis of Chromeno[4,3-b]pyrrole Derivatives Bearing Tetrasubstituted Chirality Centers through Carbene Catalyzed Cascade Reactions

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ABSTRACT: An NHC-catalyzed cascade cycloaddition reaction is developed for quick access to structurally sophisticated tetrahydrochromeno[4,3-b]pyrrole derivatives. A sterically congested tetrasubstituted chirality carbon center is formed during the cyclization process. All the α-, β-, and carbonyl carbons of the enal substrates are functionalized in chemo- and stereoselective fashion. The multicyclic chromeno[4,3-b]pyrrole products are generally afforded in good yields with excellent enantio- and diastereoselectivities. Heavily substituted pyrrole derivatives can be afforded from the chiral products through simple protocols.

Tetrahydrochromeno[4,3-b] derivatives bearing multiple chirality centers are widely used in the development of human drugs with proven biological activities. For example, the chiral molecule named MLS002174161 is a fully constrained rigid TRPV1 agonist and has potential applications in the treatment of localized chronic pain (Figure 1a). A variety of functional molecules containing tetrahydrochromeno[4,3-b]pyrrole cores possess partial agonist properties on TRPV1 and have been used in the mechanistic studies of analgesic agents (e.g., Figure 1a, A, B, and C). The HCl salt of azamedicarpin exhibits reliable inhibition activities against various microorganisms including bacteria and fungi. Therefore, the development of a facile and stereoselective method for the construction of tetrahydrochromeno[4,3-b]pyrrole frameworks is interesting.

N-Heterocyclic carbene (abbreviated as NHC or carbene) organocatalysis has experienced tremendous development in the past two decades. A number of simple and readily available functional molecules can be activated by NHC catalysts to participate in various transformations in chemoselective fashion. α,β-Unsaturated acylazolium is one of the most important reactive intermediates generated from NHC catalysts and α,β-unsaturated carbonyl compounds. The β carbons of the α,β-unsaturated acylazolium intermediates are readily attacked by various nucleophiles through (hetero-) Michael addition reactions, with various cyclization products afforded in both enantioselective and nonasymmetric fashion. Specifically, cascade cycloaddition reactions involving the functionalizations of all the α-, β-, and carbonyl carbons of the α,β-unsaturated acylazolium intermediates have been disclosed in recent years (Figure 1b). In 2013, Lupton and co-workers reported a facile synthesis of β-lactone derivatives through an NHC-catalyzed Ireland–Coates Claisen rearrangement, with all the α-, β-, and carbonyl carbon atoms of the α,β-un saturated acylazolium intermediates functionalized in chemo- and diastereoselective fashion (Figure 1b, eq 1). Hui, Xu, Biju and co-workers reported a cascade cyclization process for the preparation of tricyclic δ-lactone molecules (Figure 1b, eq 2). Chiral pyrrolo[3,2-c]quinolinine derivatives can be efficiently produced from rationally designed starting materials through a carbene-catalyzed Michael addition/Mannich reaction/lactam formation sequence (Figure 1b, eq 3). Similarly, cyclopenta[c]pyrano derivatives can be afforded in both chemo- and stereoselective fashion through various cascade addition reactions promoted by NHC organic catalysts (Figure 1b, eqs 4 and 5). In 2018, Biju and co-workers synthesized chiral pyrroloquinolinine derivatives bearing up to four fused cyclic structures with good to excellent yields and enantioselectivities as single diastereomers (Figure 1b, eq 4). However, enantioselective synthesis of multicyclic molecules containing chromeno[4,3-b]pyrrole frameworks has not been reported. It is also worth noting that the formation of a tetrasubstituted chirality center is challenging during the construction of the multicyclic fused structures.

Herein, we report a chiral NHC-catalyzed cascade cycloaddition reaction for enanti- and diastereoselective synthesis...
of tetrahydrochromeno[4,3-b]pyrrole derivatives (Figure 1c). The benzylic carbon of the 4-nitrobenyl group in the rationally designed reaction substrate (2a) is activated as a nucleophilic carbon to react with the NHC-bound α,β-unsaturated acylazolium intermediates 8 through Michael addition and gives intermediate I. A sterically congested tetrasubstituted chirality carbon center is formed in excellent stereoselective fashion during the intramolecular Mannich reaction of the intermediate I and gives intermediate II bearing a chiral substituted pyrrolidine structure. After a proton transfer process, the final product 3 is readily formed through lactone formation from intermediate III, with the NHC catalyst released for additional catalytic cycles.

α-Bromocinnamaldehyde 1a was chosen as the α,β-unsaturated acylazolium precursor5c to react with the multi-functional substrate 2a under the catalysis of various NHC organic catalysts (Table 1). To our great delight, the target multicyclic product 3a could be afforded in promising yield with excellent enantio- and diastereoselectivities with the NHC A used as the reaction catalyst (Table 1, entry 1). Aminoindanol derived NHC catalyst B bearing an N-Ph group could only give the desired product 3a in low yield, although with acceptable er and dr values (entry 2). Electron-deficient NHC catalysts were not effective for this transformation (e.g., entry 3). Electron-rich NHC catalysts derived from other chiral scaffolds could give the products (3a) in moderate yields and stereoselectivities (e.g., entries 4 and 5). The reactions went well with organic or inorganic bases with weak basicities, with the desired products (3a) afforded in moderate yields with good to excellent enantio- and diastereoselectivities (e.g, entries 6 and 7). Strong bases could not be used for this cascade cycloaddition reaction (e.g., entries 8 and 9). The product yields could be dramatically improved when switching THF to organic solvents with lower polarities, with retention of the reaction stereoselectivities (e.g., entries 10 to 12). Highly polar organic solvents were not suitable for this catalytic reaction (e.g., entry 13). Finally, our desired cyclopenta[c]pyranone product 3a could be afforded in 82% yield with 98:2 er and 19:1 dr values with a reduced amount of NHC A (5 mol %) used as the reaction catalyst, DABCO as the base, and a mixture of EtOAc/toluene = 1/2 as the reaction solvent (entry 14).

The substrate scope of the α-bromo enals 1 was then examined to react with substrate 2a under the optimized reaction conditions as stated in Table 1, entry 14. Both electron-withdrawing and -donating substituents could be
installed on the α-position of the β-phenyl group of the enal 1a, with the corresponding products afforded in good yields with excellent er values as single diastereomers (3b to 3e; Scheme 1). Substituents were also well tolerated on the m-position of the β-phenyl group, with the corresponding products afforded in good yields with excellent er values as single diastereomers (3f to 3g). Electron-withdrawing substituents on the p-position of the phenyl rings gave the cyclopenta[c]pyranone products in moderate to good yields with excellent enantio- and diastereoselectivities (3h to 3j), while electron-donating groups on these positions could give the optically pure products in good yields as single diastereomers (3k to 3m). The β-phenyl group on the enal 3a could be switched to various heteroaromatic groups with retention of the product optical purities, although the reaction yields and diastereoselectivities were slightly decreased (3n and 3o).

Gratifyingly, an aliphatic enal substrate could also be used in this NHC-catalyzed cascade cycloaddition process and give the tricyclic product 3p with excellent er and good dr values, although the yield was poor under the current reaction conditions.

Scheme 1. Scope of α-Bromo Enals 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>dr</th>
<th>er</th>
</tr>
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<tbody>
<tr>
<td>3b</td>
<td>76%</td>
<td>20:1 dr</td>
<td>99:1 er</td>
</tr>
<tr>
<td>3c</td>
<td>78%</td>
<td>20:1 dr</td>
<td>99:1 er</td>
</tr>
<tr>
<td>3d</td>
<td>91%</td>
<td>20:1 dr</td>
<td>99:1 er</td>
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Scheme 2. Scope of Substrates 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>dr</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>55%</td>
<td>18:1 dr</td>
<td>99:1 er</td>
</tr>
<tr>
<td>4b</td>
<td>70%</td>
<td>18:1 dr</td>
<td>99:1 er</td>
</tr>
<tr>
<td>4c</td>
<td>76%</td>
<td>7:1 dr</td>
<td>99:1 er</td>
</tr>
</tbody>
</table>

“Reaction conditions as stated in Table 1, entry 14. Yields are isolated yields after purification via SiO2 column chromatography. Er values were determined via HPLC on chiral stationary phase. Dr values were determined by 1H NMR on the crude reaction mixture.”

As a technical note, this catalytic reaction could also be carried out at gram scale without erosion on the enantioselectivity, although the product yield and diastereoselectivity were slightly decreased (Scheme 1, 3a).

Electronic properties, with the corresponding products afforded in moderate to excellent yields with excellent enantio- and diastereoselectivities (4a to 4i). Substitution on the 3-position of the phenol ring led to a decrease in the product yield, although the stereoselectivities of the reaction remained excellent (4j). It is worth noting that the methyl group on the imine moiety of 2a could be replaced with an ethyl group or even an aromatic phenyl group, with the corresponding target products afforded in good yields with excellent enantioselectivities as single diastereomers (4k and 4l). The 4-nitrobenzyl group on the imine substrate is crucial to this cascade cycloaddition reaction. Replacing the 4-nitrophenyl group with other electron-withdrawing groups resulted in no formation of the desired products (Scheme 2, 2aa to 2ae). This might be due to either the decreased acidities of the benzyl C(sp3)−H bonds (e.g., 2ab, 2ac, 2ad, 2ae) or the increased steric hindrance of the nucleophilic carbon centers (e.g., 2aa, 2ae).

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The lactone ring of the chiral chromeno[4,3-b]pyrrole product 3a was broken from our methodology could be broken through a trans-esterification process and gave the heavily substituted pyrrole S in moderate yield with retention of the excellent optical purity and diastereomeric ratio (Figure 2).

Chiral pyrroline derivatives have been widely used as efficient organic catalysts in asymmetric secondary amine-catalyzed reactions. The nitro group of 3a could be effectively reduced by Raney Ni under a H₂ atmosphere in almost quantitative yield without erosion of the product stereoselectivities. These data can be obtained free of charge.*

In summary, we have developed an NHC-catalyzed cascade cycloaddition reaction for facile synthesis of optically pure tetrahydrochromeno[4,3-b]pyrrole derivatives. The multicyclic products have been afforded in generally good yields with excellent enantio- and diastereoselectivities. A sterically congested tetrasubstituted chirality carbon center was formed during the cascade cyclization process. All the α, β-, and carbonyl carbons of the enal substrates were functionalized in chemo- and stereo-selective fashion. The chiral tetrahydrochromeno[4,3-b]pyrrole products afforded from our methodology could be transformed to heavily substituted pyrroline derivatives with excellent optical purity. All of the chiral products afforded from our protocols contain free secondary amino groups and have potential applications in asymmetric organic synthesis.

**REFERENCES**


(4) For pioneering work on the generation of α,β-unsaturated acylazoliums in NHC organocatalysis, see: Zeitler, K. Org. Lett. 2006, 8, 637.


(11) For a detailed study on the relative acidities of the nucleophilic C(sp3)–H bonds of the substrates, see Supporting Information.
