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N-Heterocyclic Carbone Catalyzed Quadruple Domino Reactions:
Asymmetric Synthesis of Cyclopenta[c]chromones

Qiang Liu, Xiang-Yu Chen,* Rakesh Puttreddy, Kari Rissanen, and Dieter Enders*

Abstract: A new type of an NHC-catalyzed domino sequence through \(\alpha,\beta\)-unsaturated acyl azolium intermediates has been developed. The strategy provides a convenient asymmetric route to functionalized tricyclic coumarin derivatives and cyclopentanes. DFT studies and control experiments were performed to gain a better insight into the reaction mechanism.

Coumarins and related structures have a wide range of applications in the chemical and pharmaceutical field,[1] a great motivation for chemists to design practical and valuable methods for the synthesis of structurally diverse coumarin derivatives. In this regard, tricylic cyclopenta[c]-fused chromones and the aza-analogous dihydroguinolinones and their derivatives are characteristic structural motifs of various bioactive compounds and have thus received a great deal of attention. Although several elegant strategies already exist for their synthesis,[2] catalytic enantioselective methods to chiral cyclopenta[c]-fused chromones with high asymmetric induction have not been realized so far. In 2013 Biju and co-workers reported a domino reaction of enamines with \textit{ortho}-hydroxy chalcones in their synthesis of racemic chromones through homoenolate intermediates [eq. (1)].[20] To address the challenge of efficient asymmetric syntheses of these compounds, we sought to design a new type of a practical strategy allowing high enantioselectivities and various substitution patterns.

One approach to rapidly assemble such complex chiral compounds is by using organocatalytic domino reactions as defined by Tietze and Beliluss,[3] which have proven to be one of the most efficient strategies. In recent years, N-heterocyclic carbene (NHC) catalyzed processes,[4] for instance via \(\alpha,\beta\)-unsaturated acyl azolium intermediates, have provided new opportunities for organocatalytic domino reactions.[5] The research groups of Zeiter,[6] Scheidt[7] and Studer[8] carried out early studies on \(\alpha,\beta\)-unsaturated acyl azolium intermediates for simple esterifications (Scheme 1, path a). In 2009 Lupton[9] and Bode[10] independently developed an interesting \(\alpha,\beta\)-unsaturated acyl azolium mediated domino reaction with enals, while at the same time Studer and co-workers successfully developed the oxidative NHC-catalyzed domino reaction of enols and diketones with diphenoquinone,[11] which has become a most widely used oxidant in NHC catalysis. Later, the enantioselective version of this domino process has been successfully realized by You and co-workers.[12] Since then a series of NHC-catalyzed domino processes via \(\alpha,\beta\)-unsaturated acyl azoliums intermediates with dinucleophiles have been developed by several groups (Scheme 1, path b).[13] Recently, this strategy has been successfully extended to domino reactions with threefold reactive reagents by Lupton,[14] Studer,[15] Biju,[16] Wang,[17] Chi,[18] Ye[19] and our group[20] (Scheme 1, path c). It is noteworthy that this process becomes much more complex, if another nucleophilic group is introduced to the substrate, and several chemoselectivity issues can arise in the reaction with \(\alpha,\beta\)-unsaturated acyl azolium intermediates. Thus, it will be difficult to selectively control the reactivities of Nu\(^1\), Nu\(^2\), Nu\(^3\) and E of the substrate (Scheme 1, path d). To the best of our knowledge, domino reactions of \(\alpha,\beta\)-unsaturated acyl azoliums with fourfold reactive reagents is still unknown. To investigate these new possibilities of NHC catalysis and given our strong interest in organocatalytic domino reactions, we were...
attracted by the idea of designing reaction partners with four disparate reactive sites to develop new domino processes (Scheme 1, middle). We envisioned that malonates bearing an ortho-hydroxy phenyl group may be employed as fourfold reactive substrates to react with \( \alpha,\beta \)-unsaturated acyl azolium intermediates. However, several challenges need to be overcome, the more difficult ones being suppressing the paths a–c and finding conditions to achieve high enantioselectivities. Herein we report a new Michael-aldol-lactonization-dehydration domino sequence for the catalytic asymmetric synthesis of cyclopenta[c]-fused chromenones (Scheme 1, bottom).

Table 1. Optimization of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMEDA</td>
<td>DCM</td>
<td>48</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>DBU</td>
<td>DCM</td>
<td>60</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>DIPEA</td>
<td>DCM</td>
<td>trace</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>NEt(_3)</td>
<td>DCM</td>
<td>trace</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Cs(_2)CO(_3)</td>
<td>DCM</td>
<td>trace</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>K(_2)CO(_3)</td>
<td>DCM</td>
<td>trace</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>DBU</td>
<td>THF</td>
<td>30</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>DBU</td>
<td>Toluene</td>
<td>75</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>DBU</td>
<td>CH(_2)CN</td>
<td>34</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>DBU</td>
<td>CHCl(_3)</td>
<td>47</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>DBU</td>
<td>DCE</td>
<td>70</td>
<td>98</td>
</tr>
<tr>
<td>12</td>
<td>DBU</td>
<td>Dioxane</td>
<td>33</td>
<td>96</td>
</tr>
<tr>
<td>13</td>
<td>DBU</td>
<td>DME</td>
<td>86</td>
<td>99</td>
</tr>
<tr>
<td>14(\text{[a]})</td>
<td>DBU</td>
<td>DME</td>
<td>73</td>
<td>60</td>
</tr>
</tbody>
</table>

[a] Yield of isolated product 3a after chromatography. [b] The ee was determined by HPLC analysis of the purified product on a chiral stationary phase. [c] No LiCl was added. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TMEDA = tetramethylethylenediamine; DIPEA = N,N-diisopropylethylamine; DME = 1,2-dimethoxyethane; DCM = dichloromethane; THF = tetrahydrofuran; DCE = 1,2-dichloroethane.

To validate the feasibility of the proposed process, the model reaction of the malonate 1a bearing an ortho-hydroxy phenyl group with the enal 2a was investigated under NHC catalysis (Table 1). In the presence of the tetracyclic NHC A derived from aminodindan, TMEDA as the base, diphenoquinone as the oxidant and LiCl as a cooperative Lewis acid, the desired domino product 3a could be obtained in 48% yield, with 95% ee (entry 1). Encouraged by this promising result, a variety of bases were then screened. The yield and the enantioselectivity improved when DBU was employed as the base (entries 2-6). Next we explored the influence of solvents and demonstrated that DME was the best choice as the reaction outcome was improved to 86% yield and 99% ee (entries 7-13). It should be noted that poorer results were obtained without the addition of LiCl (entry 14).

Table 2. Reaction scope.

Yields of isolated products 3a after chromatography. The ee was determined by HPLC analysis of the purified product on a chiral stationary phase.
With the optimized conditions in hand, the scope of the new type of domino reaction was studied (Table 2). A series of enals 2 bearing electron-donating or electron-withdrawing substituents (R1 = 4-MeC6H4, 4-MeOCH3, 4-MeNC6H4, 4-BrC6H4 and 4-
ClC6H4) reacted smoothly and gave the desired domino products 3b–f in good yields and high enantioselectivities. The reaction of an enal bearing a disubstituted aromatic ring also proceeded well without apparent change in the yield and enantioselectivity (3g). The enal bearing a 2-naphthyl group worked as well to give the corresponding domino product 3h in 89% yield with 88% ee. This was also true for a heterocyclic substituent (R1 = furyl) giving rise to product 3i. Notably, the alkynyl enal 2j also worked well in the reaction albeit in somewhat decreased yield. The scope of the reaction with respect to the ortho-hydroxy aryl malonates was also examined. The electronic properties of the substituents (R2 = 5-Me, 5-Br, 5-F and 5-Cl) at the aromatic ring of 1 had a limited effect on the yields and enantioselectivities (3k–n). Substituents at the 4-position (R1 = 4-Cl and 4-Me) were also tolerated as well and gave the desired products 3o–p with very high enantioselectivities. Furthermore, the effect of the ester substituents R3 at the malonate moiety was studied too, and the desired domino products 3q (R2 = Et) and 3r (R2 = Bn) were obtained in high yields with excellent enantioselectivities. The reaction of ethyl acetoacetate derived substrate 1s also worked, thus providing the product 3s in 85% yield with 1:8:1 dr and very good ee. Unfortunately, the ortho-substituent and β-
alcohol substituted enal gave only a trace amount of the products under our reaction conditions (3t and u).

The absolute configuration of the cyclohexene 3h was determined by the X-ray structure analysis[21] and the configurations of all other products were assigned accordingly.

To demonstrate the synthetic utility of this new domino strategy, a convenient protocol for the synthesis of the highly functionalized cyclopentane 4a was developed starting from the resulting domino product 3a[22]. Thus, this reductive lactone ester conversion under ring opening opens an efficient stereoselective entry to highly all-trans substituted cyclopentanes (Scheme 2).

A plausible catalytic cycle is depicted in Figure 1. The addition of the NHC catalyst to the enal 2 leads to the formation of the Breslow intermediate I, which is oxidized by the bisquinone to afford the α,β-unsaturated acyl azolium intermediate II. The reductive enolate III is readily generated from the malonate 1a in the presence of DBU and LiCl. The Michael addition of the enolate III to the α,β-unsaturated acyl azolium II forms the C–C bond and generates the azolone enolate IV. Subsequent intramolecular aldol reaction followed by proton shift and β-lactonization via V and VI leads to VII regenerating the NHC catalyst and final dehydration of VII affords the desired product 3 (path 1). Alternatively, as shown in path 2, the intermediate VII could be formed by the transetherification of the β-lactone VII′, which is generated by β-lactonization of V. However, this possibility was ruled out by control experiments in which the
corresponding cinnamyl esters were observed as the major products, and no products 3' or 5 were formed under the reaction conditions in the presence of an external alcohol to open the β-lactone (Scheme 3). A similar mechanism was also proposed by Biju for the reaction of enals with ortho-hydroxy chalcones through homoenolate intermediates (Scheme 3, bottom).[20]

To further evaluate which mechanism is possible, we carried out DFT calculations for the key intermediates involved in the pathways as well. As shown in Figure 2, the free energies of VI and VII, being -6.7 and -14.2 kcal mol⁻¹, respectively, indicate that the δ-lactonization mechanism is thermodynamically downhill and reasonable, while the high free energy (34.7 kcal mol⁻¹) of VII unambiguously rules out the β-lactonization pathway.

Figure 2. Relative free energies (in kcal mol⁻¹) of the key intermediates. The optimized structures of the intermediates and computational details are given in supporting information.

In conclusion, we have developed a new NHC-catalyzed domino Michael-aldol-lactonization-dehydration reaction of enals with fourfold reactive malonates. This protocol enables the direct organocatalytic assembly of cyclopentane[c]-fused chromenones in good yields with high enantioselectivities. By a subsequent reductive lactone ester conversions under ring opening highly functionalized cyclopentanes can be easily prepared. Finally, DFT calculations and control experiments provided a deeper insight into the reaction mechanism.

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Keywords: N-heterocyclic carbene • domino reaction • chromenone • organocatalysis • DFT calculation

Domino via Acyl Azoliums: An NHC-catalyzed quadruple domino sequence through \( \alpha,\beta \)-unsaturated acyl azolium intermediates has been developed. The strategy provides a convenient direct route to functionalized tricyclic chromenone derivatives and cyclopentanes. DFT studies and control experiments provided a deeper insight into the reaction mechanism.

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