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Quinine-Catalyzed Highly Enantioselective Cycloannulation of o-Quinone Methides with Malononitrile

Alafate Adili, Zhonglin Tao, Dianfeng Chen and Zhiyong Han*

2-Amino-3-cyano-4H-chromenes hold great potential as novel anticancer agents. Here we report a quinine-catalyzed highly enantioselective formal 4+2 cycloaddition of ortho-quinone methides and malononitrile, providing a unique approach to 4-arylvinyl, 4-aryl and 4-vinyl 2-amino-3-cyano-4H-chromenes with excellent yields and enantioselectivities. Moreover, this reaction can be performed in up to 6 mmol scale without noticeable loss of yield and stereoselectivity.

2-Amino-3-cyano-4H-chromenes (Fig. 1) were found to exhibit strong cytotoxicity against human cancer cells.

o-QMs are significant intermediates in various transformations handled by nature. Many biologically molecules, such as anthracycline antibiotics, are able to bring us therapeutic benefits through their o-QMs variant, which can be targeted by enzymes in vivo. Moreover, the o-QMs are usually highly active and hold unique synthetic potential in the construction of complex molecules (Figure 1), thus interesting chemists around the world.

Mechanically, the inherent reactivity of o-QMs depends on their rapid rearomatization propensity, mainly by two reaction pathways (Scheme 1): a) Michael addition of nucleophiles; b) cycloannulation reaction with 2π partners or dipoles. On account of the products’ complexity and diversity, the cycloannulation reaction of o-QMs is now a hot topic that various reaction partners with o-QMs or other precursors have been discovered. However, as far as we know, there are only a few examples describing enantioselective cycloannulation processes (Scheme 1). In 2013, Ye’s group and Scheidt’s group independently reported similar chiral N-Heterocyclic carbine (NHC)-catalyzed highly enantioselective [4+3] annulations of enals with o-QMs (Scheme 1). Lectka and Ye chronologically demonstrated similar formal [4+2] cycloaddition reactions of prepared o-QMs with ketenes by using a chiral cinchona alkaloid-derived ammonium fluoride or an NHC catalyst (Scheme 1). Very recently, Schneider and co-workers developed an enantioselective [4+2] annulations of in situ generated o-QMs.
with β-diketones, providing an direct access to optically pure efficient synthesis of 4-aryl-4\(H\)-chromenes (Scheme 1).\(^{28}\) Inspired by these achievements of trapping active \(\alpha\)-QMs intermediate in enantioselective manners, we envisioned that optically active 2-amino-3-cyano-4\(H\)-chromenes might be accessed through a formal [4+2] cycloaddition of \(\alpha\)-QMs with malononitrile in the presence of a proper bifunctional catalyst.\(^{29}\) \(^{33}\)

**Scheme 1** Enantioselective Cycloannulation of \(\alpha\)-QMs

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Considering that the acidic \(\alpha\)-H of malononitrile can be activated by Lewis base, and on the other hand, \(\alpha\)-QMs might be activated by acidic H-bond donors, initially we chose quinine or cinchonine based chiral bifunctional-urea as the catalyst\(^{13-15}\) (Table 1). Our investigation began with the reaction of 1a and 2a catalyzed by 10 mol% of chiral bifunctional-urea (in toluene, 0 °C Table 1, entries 1 - 4). To our delight, the chiral bifunctional-ureas exhibited high reactivity and efficiency. Catalyst 3a could render the reaction with 98% yield and 86% ee. In the case of catalyst 3b - 4d, the desired product could also be obtained in good yields and slightly lower enantioselectivities. Encouraged by these results we kept to our investigations to find more effective catalysts. Bearing both a tertiary amine and a hydroxyl group in one chiral scaffold, quinine is also an effective chiral bifunctional organocatalyst. We tried quinine and its derivatives as the catalyst (Table 1, entries 5 - 8). Despite that 3f and 3g showed poor enantioselectivity, 3e (quinine) was able to bring about 98% yield and 88% ee (Table 1, entries 5 - 7). As expected, hydroxyl group protected quinine 3h led to very poor enantioselectivity (Table 1, entry 8), implying that the hydroxyl group based hydrogen bond played a crucial role in controlling the stereoselectivity of the reaction. Chiral amine/ urea or thiourea bifunctional catalyst failed to improve the results (Table 1, entries 9 - 10). By reducing the reaction temperature to -40 °C

**Table 1** Evaluation of catalysts and optimization of reaction Conditions\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield [%](^{[b]})</th>
<th>ee [%](^{[c]})</th>
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<tr>
<td>1</td>
<td>3a</td>
<td>toluene</td>
<td>98</td>
<td>86</td>
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<tr>
<td>2</td>
<td>3b</td>
<td>toluene</td>
<td>95</td>
<td>80</td>
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<tr>
<td>3</td>
<td>3c</td>
<td>toluene</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
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<td>3d</td>
<td>toluene</td>
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<td>79</td>
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<td>3e</td>
<td>toluene</td>
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<td>90</td>
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</table>

\(^{[a]}\) Unless indicated otherwise, the reaction of 1a (0.1 mmol) and 2a (0.12 mmol) was carried out in 2 mL solvent at 0 °C in the presence of catalyst 3 (10 mol%) for 6-10 hours. \(^{[b]}\) Isolated yield. \(^{[c]}\) The ee value was determined by HPLC. \(^{[d]}\) Reaction lasted for 48 hours. \(^{[e]}\) Reaction performed at -40 °C for 18 - 24 hours. \(^{[f]}\) Catalytic amount reduced to 5%; reaction performed at -40 °C for 18 - 24 hours. \(^{[g]}\) Catalytic amount reduced to 2%; reaction performed at -40 °C for 18 - 24 hours.
and extending the reaction time, a higher enantioselectivity could be achieved (92% ee) without any loss of the yield. Further, we examined the solvent effect of the reaction (Table 1, entries 12-14). Polar solvents such as diethyl ether gave poor enantioselectivity. DCM and Chloroform led to moderate yields and enantioselectivities. Toluene was found to be the ideal solvent for this reaction. Reducing catalyst loading to 5 mol% and 2 mol% led to only a slight loss of the enantioselectivity (Table 1, entries 15-16).

With the optimized reaction condition in hand, we then examined the scope of the substrates (Table 2). Generally, for various substituted o-QMs tested, the reaction run smoothly and gave the desired product in very high yields. In terms of enantioselectivity, the electronic feature of substrates did not play an obvious part. Corresponding ortho-Quinone methides showed high reactivity and led to the product (3a - 3g) in high enantioselectivity ranging from 90 to 94% ee. o-QMs bearing an electron-withdrawing group exhibited much higher reactivity (3e, 3g). Thiophenyl and naphenyl substituted o-QMs also tolerated the reaction pretty well, giving the corresponding product with excellent yield and enantioselectivity (4h, 4i). Importantly, 4H-4-aryl-chromene, which holds great potential as an antitumor agent, could also be synthesized with excellent yield and enantioselectivity (4j). 4H-4-Vinyl chromene 4k was obtained as well with 98% yield and 91% ee. The absolute configuration of 4b was determined by X-ray analysis of its single crystal.

Due to the enantioenriched 2-amino-3-cyano-4H-chromenes synthesized via our methodology hold potential as antitumor agents, we tried to scale up the reaction (Scheme 2). To our delight, under 2 mol% catalytic amount, 6mmol 1a (1.512g) and 9 mmol malononitrile (2a, 0.621g) was able to generate 4a in 95% yield and 90% ee.

In conclusion, we have developed a chiral bifunctional-organocatalyzed formal 4+2 reaction of ortho-quinone methides and malononitrile, providing 2-amino-3-cyano-4H-chromenes, a class of potential anti-cancer agents, in excellent yields and enantioselectivities. Employed as catalyst, quinine is the best choice for our reaction, which represents excellent generality for a diversity of ortho-quinone methides, and leads to high yields and enantioselectivity. Significantly, we also managed to scale up the reaction with excellent results. Further studies will be continued on constructing complex molecules from ortho-quinone methides.

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Notes and references