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Asymmetric synthesis of chromene skeletons *via* organocatalytic domino reactions of *in situ* generated *ortho*-quinone methide with malononitrile and β-functionalized ketone†

Lili Zhang,‡[a] Xiao Zhou,‡[a] Pengfei Li,[b] Zhantao Liu,[a] Yang Liu,[a] Yong Sun[a] and Wenjun Li *[a]

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Enantioselective organocatalytic domino reactions of *in situ* generated *ortho*-quinone methides with malononitrile and β-functionalized ketones have been developed. This strategy could generate various chiral chromenes in high yields (up to 99%) and stereoselectivities (up to >99 : 1 e.r.) in the presence of 5 mol% of a bifunctional organocatalyst. Gram-scale and useful synthetic transformations of this process are also presented.

As an important structure in biologically active compounds, the chromene skeleton is a pervasive structural moiety in a plethora of pharmaceuticals.[1] In particular, 2-amino-4*H*-chromenes are widely found in many biologically active molecules and exhibit various biological activities.[2] Compared with racemic 2-amino-4*H*-chromenes, studies on the synthesis of chiral 2-amino-4*H*-chromenes are still rare.[3,4] Wang *et al.* reported a chiral thiourea-catalyzed Mannich/cyclization sequence and conjugate additions of nitroalkanes to 2-iminochromenes.[4a,b] The Feng group developed metal complex catalyzed cascade reactions.[4d] Despite significant progress in this area, a few issues, such as unsatisfactory yields, poor stereoselectivities and limited substrate scope, have not yet been resolved. Hence, the development of an efficient protocol to access purely chiral chromenes remains in high demand.

ortho-Quinone methides (*o*-QMs) are highly reactive intermediates and are easily obtained from various precursors.[5] Due to their distinctive electrophilic properties, *o*-QMs have been widely explored in organic chemistry. In recent years, much attention has been made in their use in catalytic asymmetric reactions.[6] For instances, Sigman and co-workers reported a palladium-catalyzed asymmetric dialkoxylation of 2-propenyl phenols through a palladium *ortho*-quinone methide intermediate.[6a] Lectka *et al.* developed an organocatalyzed [4 + 2] cycloaddition reaction of *o*-QMs with silylketene acetals to afford coumarin derivatives in good enantioselectivities.[6b] More recently, *o*-QMs have been utilized for the synthesis of chiral chromenes.[7] Schneider and Rueping independently developed Brønsted acid catalyzed conjugate addition/cyclodehydration reactions of β-diketones with *in situ* generated *o*-QMs for the synthesis of 4*H*-chromenes.[7a,b] Moreover, the Han group reported quinine-catalyzed annulations of *o*-QMs with malononitrile to furnish chiral 2-amino-4*H*-chromenes in high stereoselectivities (Scheme 1a).[7c] Later, Zhou *et al.* developed a novel method for the asymmetric synthesis of 2-amino-4*H*-chromenes from *in situ* generated *o*-QMs and active methylene compounds (Scheme 1b).[7d] Bernardi's group reported a bifunctional squaramide-catalyzed reaction of *o*-QMs generated *in situ* from 2-(1-arylsulfonyl-alkyl)phenols with active methylene compounds (Scheme 1c).[4e]

Although some progress have been made in the synthesis of chiral chromenes, the substrate scope is still limited. Very recently, Enders's group have developed organocatalytic domino oxa-Michael/1,6-addition reactions to synthesize functionalized chromenes (Scheme 1d).[8] Inspired by this work, we envisioned that an organocatalytic 1,6-conjugate addition and subsequent cycloaddition reactions of *in situ* generated *o*-QMs with malononitrile and β-functionalized ketones might provide a novel approach for the construction of various types of chiral chromenes (Scheme 1e).

We started our preliminary investigation with the reaction between quinone methide **1a** and malononitrile **2** in the presence of catalyst **4a**. To our delight, 84% yield and 85 : 15 e.r. were obtained (Table 1, entry 1). With the initial experimental results in hand, we then switched our attention to other organocatalysts. The assessment of catalysts indicated that bifunctional catalyst **4e**, which was pioneered by Rawal and co-workers,[9] was the most efficient catalyst to furnish the desired

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[a] Department of Medicinal Chemistry, School of Pharmacy, Qingdao University, Qingdao, 266021, China. E-mail: liwj@qdu.edu.cn

[b] Department of Chemistry, South University of Science and Technology of China, Shenzhen, 518055, China

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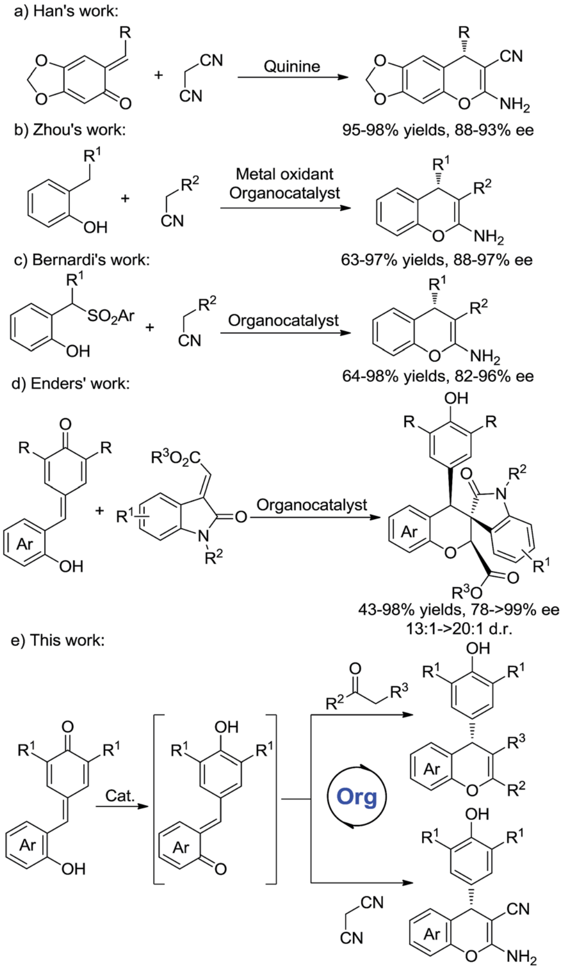
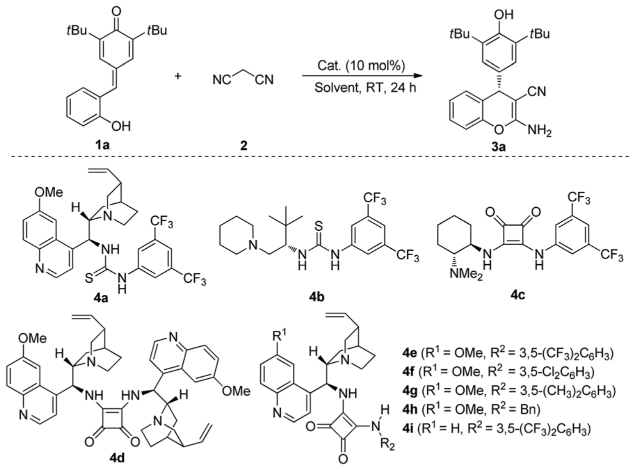
‡ These authors contributed equally.



Scheme 1 Synthesis of chiral chromenes *via* *o*-quinone methides.

Table 1 Optimization of the reaction conditions[a]



Entry	Cat.	Solvent	Yield[b] (%)	e.r.[c]
1	**4a**	CH_2Cl_2	84	85 : 15
2	**4b**	CH_2Cl_2	70	82 : 18
3	**4c**	CH_2Cl_2	98	13 : 87
4	**4d**	CH_2Cl_2	65	74 : 26
5	**4e**	CH_2Cl_2	86	93 : 7
6	**4f**	CH_2Cl_2	87	91 : 9
7	**4g**	CH_2Cl_2	85	87 : 13
8	**4h**	CH_2Cl_2	98	79 : 21
9	**4i**	CH_2Cl_2	87	91 : 9
10	**4e**	Toluene	58	89 : 11
11	**4e**	$PhCF_3$	82	81 : 19
12	**4e**	Anisole	34	90 : 10
13	**4e**	Xylenes	63	87 : 13
14	**4e**	DCE	86	88 : 12
15	**4e**	$CHCl_3$	89	94 : 6
16[d]	**4e**	$CHCl_3$	90	97.5 : 2.5
17[e]	**4e**	$CHCl_3$	94	95 : 5
18[d,f]	**4e**	$CHCl_3$	90	95 : 5
19[d,g]	**4e**	$CHCl_3$	97	97.5 : 2.5

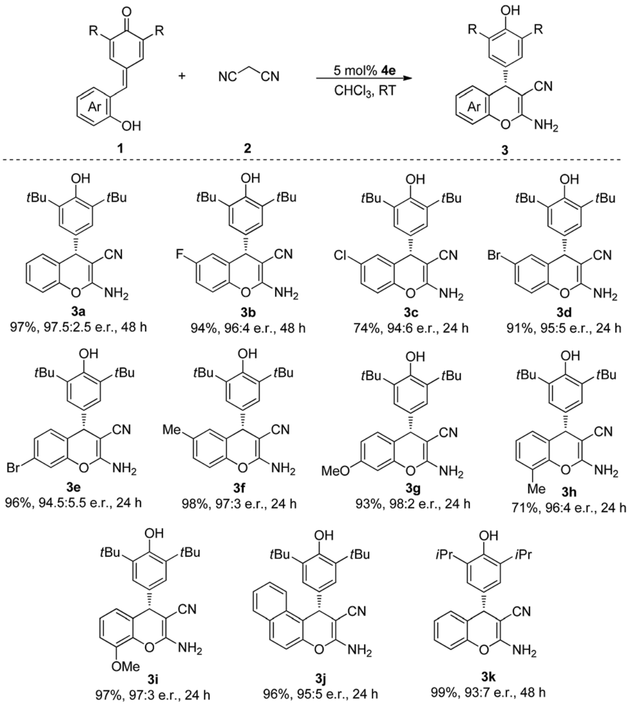
[a] Reaction conditions: a mixture of **1a** (0.05 mmol), **2** (0.06 mmol) and catalyst (10 mol%) in the solvent (0.3 mL) was stirred at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 1.0 mL of $CHCl_3$ was used. [e] 1.5 mL of $CHCl_3$ was used. [f] The reaction was conducted at 0 °C for 48 h. [g] 5 mol% of **4e** was used for 48 h.

product **3a** in 86% yield and 93 : 7 e.r. (Table 1, entry 5). After identifying catalyst **4e** as the best catalyst, we investigated the role of solvent in this process. Further investigations revealed that solvents also played a key role in this transformation. For instances, moderate e.r. were obtained when toluene, $PhCF_3$, anisole, xylenes and dichloroethane were utilized (Table 1, entries 10–14). Switching the solvent to chloroform afforded the product **3a** in 89% yield and 94 : 6 e.r. (Table 1, entry 15). To further optimize the reaction conditions, we changed the concentration and reaction temperature. The results showed that e.r. would improve to 97.5 : 2.5 with 90% yield when 1.0 mL of $CHCl_3$ was used (Table 1, entry 16). Further increasing the volume of $CHCl_3$ would not improve e.r. (Table 1, entry 17). 90% yield and 95 : 5 e.r. were observed when we reduced the reaction temperature to 0 °C for 48 h with 1.0 mL of $CHCl_3$ (Table 1, entry 18). Gratifyingly, if we decreased the catalyst loading to 5 mol%, the desired product **3a** could be still obtained in 97% yield with 97.5 : 2.5 e.r. (Table 1, entry 19).

With the optimized conditions in hand, we then tested the substrate scope of this cascade process. As indicated in Table 2, QMs **1**, which contained various functional groups were surveyed. The substrates bearing both electron-withdrawing groups (F, Cl, Br) and electron-donating groups (Me, OMe) in *para*, *meta* and *ortho* positions of the phenyl ring were all tolerated in this reaction to afford the corresponding products in excellent yields and e.r. (**3a–i**). Furthermore, the substrate **1j**, which contained naphthyl moiety, also participated in this process and gave the desired product **3j** in 96% yield and 95 : 5 e.r. after 24 h at room temperature. When we replaced the *tert*-butyl group of the QMs by isopropyl group, the desired product **3k** was obtained in 99% yield and 93 : 7 e.r.

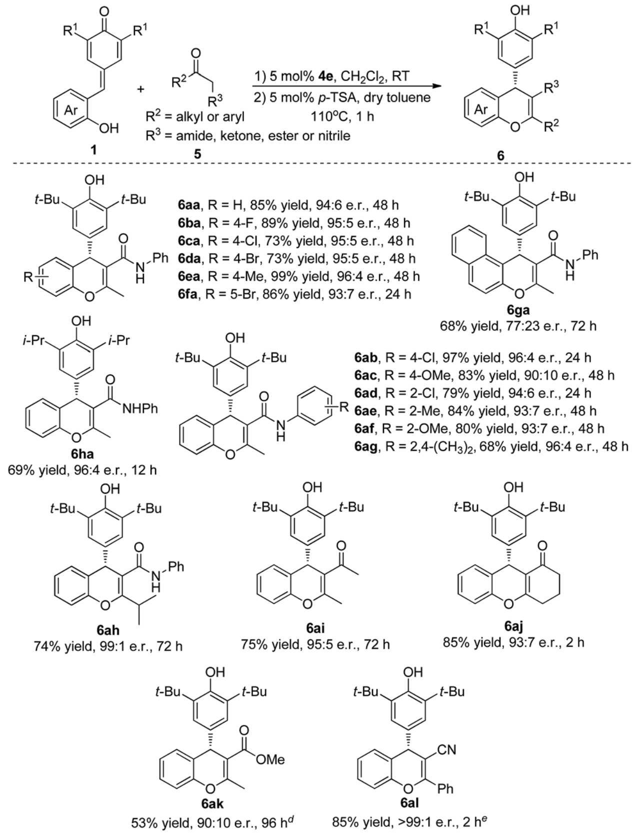
Inspired by the success, we shifted our focus to β-functionalized ketones to access chiral chromenes with more functional groups. As shown in Table 3, we started our investigation with reaction between quinone methide **1a** and β-keto amide **5a**. To our delight, the desired product **6aa** was obtained in 85% yield

Table 2 Substrate scope[a,b,c]



[a] Reaction conditions: a mixture of **1a–k** (0.05 mmol), **2** (0.06 mmol) and cat. **4e** (5 mol%) in $CHCl_3$ (1.0 mL) was stirred at room temperature for 24–48 h. [b] Isolated yield. [c] Determined by HPLC analysis.

Table 3 Substrate scope[a,b,c]

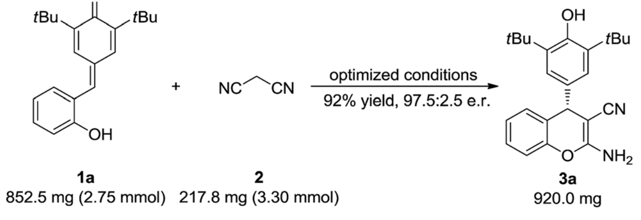


[a] Reaction conditions: a mixture of **1a–h** (0.05 mmol), **5a–l** (0.06 mmol) and cat. **4e** (5 mol%) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 2–96 h. After column chromatography, the intermediate product was treated with 5 mol% of *p*-TSA in dry toluene (0.5 mL) at 110 °C for 1 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 20 mol% catalyst was used and the reaction was conducted at 110 °C for 3 h. [e] The reaction was conducted at 110 °C for 24 h.

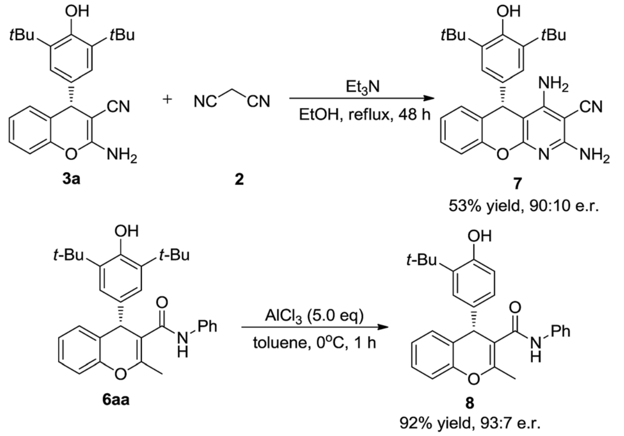
and 94 : 6 e.r. through a cascade reaction in the presence of bifunctional catalyst **4e** and a subsequent dehydration catalyzed by *p*-toluenesulfonic acid (for optimal conditions, see ESI†). The substrates QMs **1**, which bearing electron-withdrawing or electron-donating groups in the different position of phenyl ring, underwent this transformation to give the desired products **6aa–fa** in excellent yields (73–99%) and e.r. (93 : 7–96 : 4). A naphthyl- and hydroxy-substituted QM also took part in this process and gave the desired product **6ga** in 68% yield and 77 : 23 e.r. Replacing the *tert*-butyl group of the QMs by isopropyl group also furnished the desired product **6ha** in 69% yield and 96 : 4 e.r. Encouraged by the above results, the generality of β-functionalized ketones **5** was also evaluated. A wide range of β-keto amides (**5b–h**) was tolerated under the reaction conditions to provide the corresponding products **6ab–ah** in 68–97% yields and 90 : 10–99 : 1 e.r. Gratifyingly, 1,3-diketones **5i** and **5j**, α-ester ketone **5k** and β-ketonitrile **5l** also participated in this transformation successfully to give the desired products **6ai–al** in 53–85% yields and 90 : 10 to >99 : 1 e.r.

To test the synthetic utility of our method, **3a** was prepared on a gram scale. As shown in Scheme 2, the desired product **3a** was obtained in 92% yield with 97.5 : 2.5 e.r. under optimal reaction conditions. As indicated in Scheme 3, some useful synthetic transformations of this process were also presented. Treatment of **3a** with another equivalent of malononitrile in the presence of triethylamine in EtOH at reflux afforded benzopyranopyridine **7** in 53% yield and 90 : 10 e.r. Furthermore, the $AlCl_3$-mediated de-*tert*-butylation of **5aa** was also attempted and the desired product **8** was obtained in 92% yield and 93 : 7 e.r. (Scheme 3).

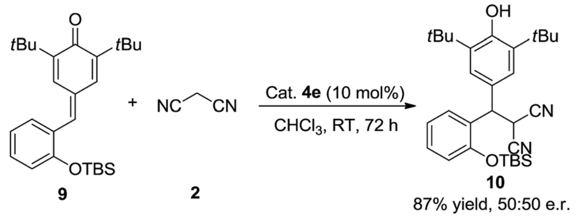
To verify the mechanism of this process, a control experiment using TBS-protected substrate **9** was performed in the presence of catalyst **4e**. The experiment showed that product **10** could be obtained in 87% yield after 72 h at room temperature (Scheme 4). Meanwhile, 50 : 50 e.r. was observed, which indicated that the hydroxy group is important in the enantioselectivity-determining step and this process proceeded



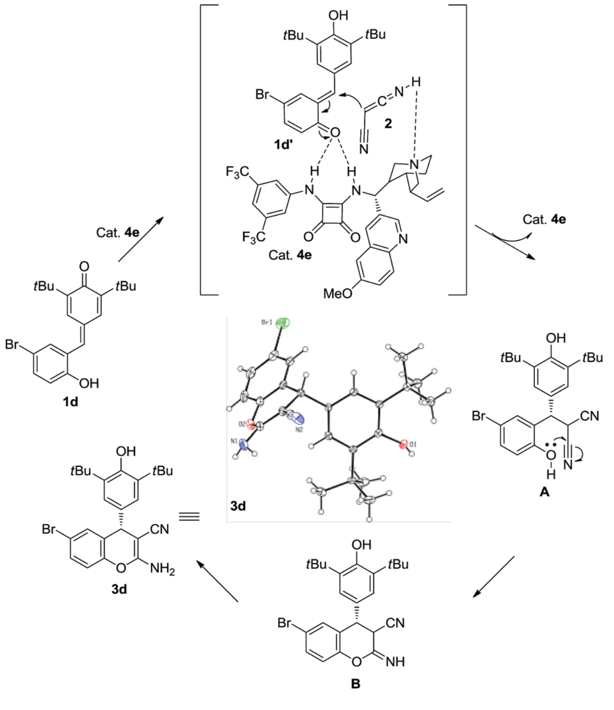
Scheme 2 Gram-scale synthesis of **3a**.



Scheme 3 Synthetic transformations.



Scheme 4 The mechanistic study.



Scheme 5 Plausible mechanism.

through *o*-QM intermediate. As shown in Scheme 5, a plausible mechanism is proposed to explain the reaction process. First of all, substrate **1d** would be transformed into *o*-QM **1d′** in the presence of bifunctional catalyst **4e** and the 1,6-conjugated addition of *o*-QM **1d′** with malononitrile **2** formed the intermediated **A** in the presence of catalyst **4e**. Subsequently, the intramolecular oxa-nucleophilic addition took place to afford the intermediated **B**, which would be transformed into the final product **3d** through tautomerization process. The absolute configuration of the adduct **3d** and **6da** were unambiguously determined by X-ray crystallography.[10]

In summary, we have developed an asymmetric organocatalytic domino reactions of *in situ* generated *ortho*-quinone methides with malononitrile and β-functionalized ketones for the synthesis of chiral chromenes in high yields and enantioselectivities. This strategy provides an efficient and convenient pathway to synthesize chiral chromene skeletons. Further investigation regarding the utilization of this organocatalytic procedure in the preparation of natural products is underway.

Acknowledgements

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10 CCDC 1526191 (**3d**) and 1545246 (**6da**) contain the supplementary crystallographic data for this paper.†