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Communication

Organocatalytic cascade 1,6-conjugate addition/annulation/tautomerization of functionalized *para*-quinone methides: Access to chiral 2-amino-4-aryl-4*H*-chromenes

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ABSTRACT

A novel organocatalytic cascade process initiated by 1,6-conjugated addition has been successfully developed. A range of pharmaceutically active 2-amino-4-aryl-4*H*-chromenes were readily obtained in high yields (88%-99%) and excellent enantiopurities (86%-99% *ee*). The functionalized *para*-Quinone methides (*p*-OMs) could be facilely obtained.

2-Amino-4*H*-chromene is a class of privileged structural motif frequently appearing in natural products and pharmaceutically active compounds [1]. In particular, 2-amino-4*H*-chromene possessing a cyano group at the 3-position attracted considerable attention due to its powerful antitumor activity [1a,2]. Among all these compounds, 2-amino-3-cyano-4*H*-chromenes containing an aryl group at the 4-position were identified as potent apoptosis inducers [3]. These compounds were found to be potent inhibitors of tubulin polymerization as well and to effectively inhibit the binding of colchicine to tubulin [3]. MX-58151 (Fig. 1) retained activity in tumor cells resistant towards current antimitotic agents, taxanes (including Taxol and Taxotere) and Vinca alkaloids [2a,3-4]. Therefore, it represented a new class of potential therapeutic agent for the treatment of drug-resistant cancer. In addition, several 4-aryl-4*H*-chromenes were also determined to be effective vascular disrupting agents (VDA) [2b,5]. One of the lead VDA candidates, Crolibulin (Fig. 1), also known as EPC2407, is currently in phase I/II clinical trials [2b]. Notably, the antitumor activity of Crolibulin is closely correlated with its absolute configuration. It is revealed that the *R*-isomer is approximately 50-100 times more active than its *S*-enantiomer [6].

Considering these appealing pharmaceutical activities, elegant approaches have been proposed to prepared these enantioenriched 2-amino-3-cyano-4*H*-chromene [7]. However, to the best of our knowledge, current protocol mainly focuses on the synthesis of 4-alkyl-substituted ones [7a-g]. The catalytic enantioselective synthesis of 4-aryl chromenes was relatively less explored [7h-n]. Meanwhile, the reported strategies for the synthesis of 4-aryl chromenes suffered from several drawbacks such as unsatisfactory enantiopurity [7i,k] and specialized substrate scope [7 h,7j-m]. Therefore, developing a highly enantioselective and general strategy for the construction of chiral 2-amino-3-cyano-4-aryl-4*H*-chromene is still highly desirable.

para-Quinone methides (*p*-QMs) have been increasingly utilized as a class of prevailing Michael acceptor for 1,6-conjugate additions [8]. As a result, a range of diarylmethine compounds were obtained with high degrees of optical purities [9]. In contrast, the functionalized *p*-QMs have been less explored and the related domino reaction has not been well investigated, despite the great potential in the construction of complex diarylmethine-containing natural product and functional molecules [10]. In this context, Enders group presented a subtle domino oxa-Michael/1,6-conjugated addition process in a highly stereoselective manner, employed the functionalized *ortho*-hydroxyl-substituted *p*-QMs [11]. More recently, Jiang and his co-operator utilized this versatile precursor to construct densely functionalized spiro[chromane-2,1′-isochromene] scaffold in an achiral fashion [12]. Regretfully, the tedious prior preparation procedure of this functionalized starting material might limit their wide application. Based on our continuous effort in the asymmetric organocatalytic cascade reactions [7g], herein we would like to present a highly efficient tandem 1,6-conjugate addition/annulation/tautomerization of

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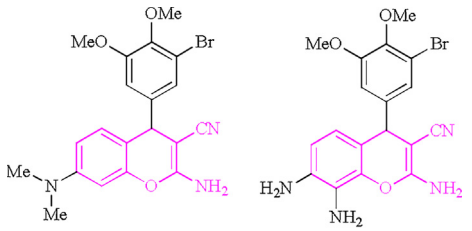


Fig. 1. Structures of the pharmaceutically active moleculars.

functionalized *p*-QMs [13]. A variety of 2-amino-3-cyano-4-aryl-4*H*-chromenes were afforded with high optical purities. Notably, the functionalized *ortho*-hydroxyl-substituted *p*-QMs could be feasibly accessed *via* one-step transformation (see Supporting information), using the simple commercially available precursor.

We commenced our investigation with utilizing *ortho*-hydroxyl *p*-QM **1a** and malononitrile **2a** as the model substrates. Initially, the catalytic effect of various bifunctional thiourea based on cinchona alkaloids [14] was evaluated in chloroform. Gratifyingly, catalysts **C1**-**C4** (Fig. 2) properly promoted the designed 1,6-conjugated addition/annulation/tautomerization domino process, and the desired 4-aryl-substituted chromene **3aa** was generated in acceptable yield and promising optical purity (Table 1, entries 1-4). Further solvent screening revealed that chloroform was the favorable one in terms of reactivity and enantioselectivity (Table 1, entries 5-7 *vs.* entry 1). In order to further improve the enantioselectivity, the quinine-based squaramides **C5** and **C6** were then investigated. Notably, an obvious enhancement of enantiomeric purity was observed in the presence the squaramide **C5** [15] in comparison with the corresponding thiourea **C1** (Table 1, entry 8 *vs.* entry 1). The quinine-based squaramide **C5** proved to be the preferred catalyst in view of reactivity and enantioselectivity (Table 1, entry 8 *vs.* entry 9). The catalyst loading exerted an impact on this cascade process to a certain extent. The model reaction proceeded equally efficiently in the presence of diminished amount of squaramide **C5**, albeit slightly prolonged time was required (Table 1, entries 10 and 11). In contrast, superior enantiomeric excess (90% *ee*) was achieved in the presence of 5 mol% of **C5** (Table 1, entry 11 *vs.* entries 8 and 10).

Having established the optimal reaction conditions, we successively surveyed the generality and scope of this tandem 1,6-conjugate addition/annulation/tautomerization process of various *p*-OMs with a range of cyano-containing compounds (Table 2). For electron-rich *p*-OMs **1b**-**e**, the titled cascade process occurred smoothly and afforded the desired chromenes **3ab**-**ae** in excellent yields and satisfactory enantiopurities (Table 2, entries 2-5). The sterical hindrance of substituent on the aromatic ring had a slight influence on the enantioselectivity of this asymmetric

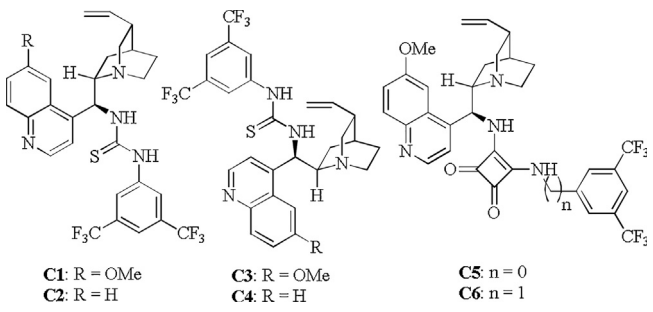
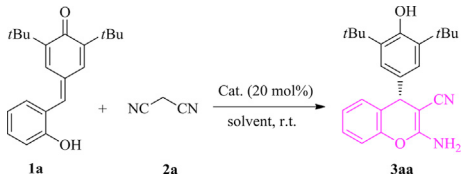


Fig. 2. The structures of bifunctional organocatalysts.

Table 1
Optimization of reaction conditions.[a].

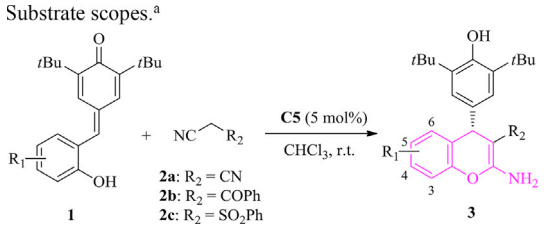


Entry	Cat.	Solvent	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	**C1**	$CHCl_3$	24	92	74
2	**C2**	$CHCl_3$	48	84	70
3	**C3**	$CHCl_3$	24	92	-70
4	**C4**	$CHCl_3$	48	80	-69
5	**C1**	Toluene	120	62	69
6	**C1**	EtOAc	24	60	34
7	**C1**	Ether	168	50	74
8	**C5**	$CHCl_3$	15	95	83
9	**C6**	$CHCl_3$	24	92	51
10[d]	**C5**	$CHCl_3$	30	99	89
11[e]	**C5**	$CHCl_3$	30	99	90

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **1a**, 0.1 mmol of malononitrile and 20 mol% of catalyst in 1 mL of solvent at room temperature (r.t.).
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] Performed with 10 mmol% of **C5**.
[e] Performed with 5 mmol% of **C5**.

process. The sterically more bulky 3-ethoxyl-substituted **1b** offered **3ab** with relatively poorer enantioselectivity (86% *ee*) (Table 2, enty 2). This domino reaction was independent of the

Table 2
Substrate scopes [a].



Entry	R_1	R_2	Time (h)	**3**	Yield (%)[b]	*ee* (%)[c]
1	H (**1a**)	CN	30 (36)[d]	**3aa**	99 (92)[d]	90(90)[d]
2	3-EtO (**1b**)	CN	48	**3ab**	98	86
3	4-MeO (**1c**)	CN	48	**3ac**	92	96
4	4-Et_2N (**1d**)	CN	48	**3ad**	98	90
5	5-MeO (**1e**)	CN	48	**3ae**	93	96
6	4-Cl (**1f**)	CN	48	**3af**	99	90
7	5-Br (**1g**)	CN	48	**3ag**	88	86
8	H (**1a**)	PhCO	24	**3ba**	92	99
9	3-EtO (**1b**)	PhCO	48	**3bb**	97	97
10	4-MeO (**1c**)	PhCO	48	**3bc**	95	98
11	5-Me (**1h**)	PhCO	48	**3bh**	98	98
12	4-Cl (**1f**)	PhCO	48	**3bf**	92	98
13	5-Br (**1g**)	PhCO	48	**3bg**	90	98
14	H (**1a**)	$PhSO_2$	48	**3ca**	90	99
15	4-MeO (**1c**)	$PhSO_2$	120	**3cc**	95	99
16	4-Cl (**1f**)	$PhSO_2$	120	**3cf**	92	99

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **1**, 0.1 mmol of malononitrile and 5 mol% of **C5** in 1 mL of $CHCl_3$ at r.t. for due time.
[b] Isolated yields.
[c] Enantiomeric excesses were determined by chiral HPLC analysis.
[d] Performed with 1.1 g of **1a** (3.3 mmol) under the optimal conditions.

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