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Enantioselective synthesis of functionalized 2-amino-4*H*-chromenes via the *o*-quinone methides generated from 2-(1-tosylalkyl)phenols

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ABSTRACT

An efficient bifunctional squaramide-catalyzed Michael addition/cyclization reaction of *o*-quinone methides generated in situ from 2-(1-tosylalkyl)phenols with active methylene compounds bearing a cyano group has been realized to synthesize chiral 2-amino-4*H*-chromenes with excellent enantioselectivities and broad substrate scope.

Chromenes occupy a prominent position in modern hetero-cyclic chemistry attributing to their extraordinary significance in biologically active molecules, natural products, and synthetic drugs.[1] Among the diverse types of chromenes, 2-amino-4*H*-chromenes are recognized to be particularly important as they belong to 'privileged medicinal scaffolds'.[2] For instance, the tumor antagonist HA14-1 and related substituted alkyl (4*H*-chromen-4-yl)cyanoacetates are a new class of small molecules that exhibit a binding activity for the surface pocket of cancer implicated Bcl-2 protein and induce apoptosis or programmed cell death in tumor cells.[2f] Crolibulin (EPC2407) is a microtubulin inhibitor currently in phase I/II clinical trials as anticancer agent and apoptosis inducer for the treatment of anaplastic thyroid cancer.[2j] IRSP inhibitor acts as an insulin-regulated aminopeptidase inhibitor which is useful in therapeutic application including enhancing memory and learning functions[2k] (Fig. 1). Due to the remarkable importance of 2-amino-4*H*-chromene frameworks, their syntheses are of contemporary interest. Despite various methods for the construction of racemic 2-amino-4*H*-chromenes been reported,[3] asymmetric syntheses of these structures are still limited. In 2008, Zhao group disclosed the first asymmetric synthesis of 2-amino-4*H*-chromenes by bifunctional thiourea catalyzed tandem addition/cyclization reactions of 2-naphthols and α,α-dicyanoolefins with moderate enantioselectivities.[4a] Subsequently, several organocatalytic syntheses of chiral 2-amino-4*H*-chromenes have been developed, including tandem Michael addition/cyclization,[4] Mannich cyclization/tautomerization cascade sequences,[5] three-component cascade reaction,[6] and conjugate addition of nitroalkanes to 2-iminochro-menes.[7] In these organocatalytic strategies, cinchona derivatives, bifunctional thiourea and squaramide were found to be efficient catalysts. In contrast, only two examples of metal complex catalyzed asymmetric synthesis have emerged in recent years. In 2011, Feng group reported enantioselective construction of 2-amino-4*H*-chromenes using salen–cobalt(II) complex or *N*,*N*′-dioxide-Zn(II) complex.[8] In spite of these considerable advances, there are still some drawbacks involving low catalytic efficacy, poor stereoselectivity, and unsatisfactory substrate scope. Hence, developing a facile method for the synthesis of chiral 2-amino-4*H*-chromenes with high enantioselectivities and broad substrate scope is still highly desirable.

o-Quinone methides (*o*-QMs) are a crucial class of intermediates in various biological processes[9] and have been regarded as highly reactive chemical motifs.[10] Despite the wide application of *o*-QMs, only few organocatalytic enantioselective settings of *o*-QMs have been reported owing to their high reactivity and instability.[11] Organocatalytic formal [4+2] cycloaddition of *o*-QMs with active methylene compounds bearing the cyano group is also a streamlined method for the synthesis of optically active 2-amino-4*H*-chromenes. Recently, Han group reported quinine-catalyzed annulation of the electron-rich and stable *o*-QMs with malononitrile to provide 4-arylvinyl, 4-aryl, and 4-vinyl 2-amino-3-cyano-4*H*-chromenes with excellent yields and enantioselectivities. However, the substrate scope was limited.[11u] As our continuing efforts to the employment of *o*-QMs,[11r,12] we focused on bifunctional organocatalytic reactions of *in situ* generated *o*-QMs. In our

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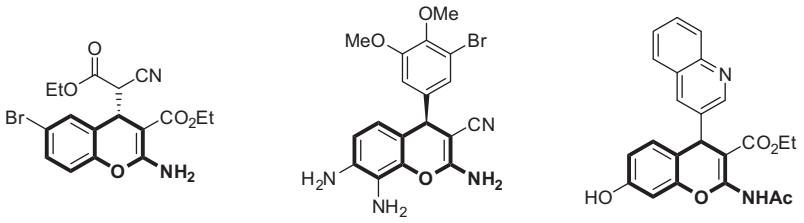
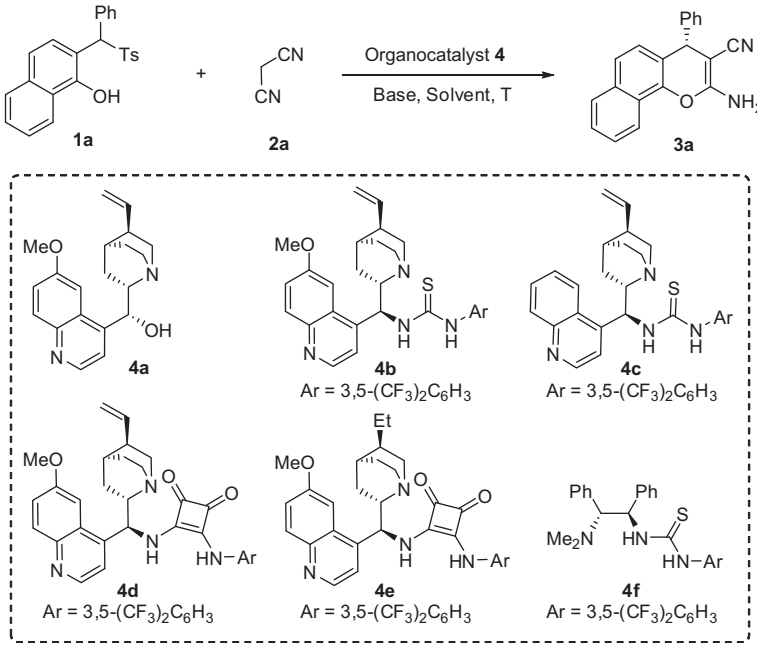


Figure 1. Bioactive 2-amino-4*H*-chromene derivatives.

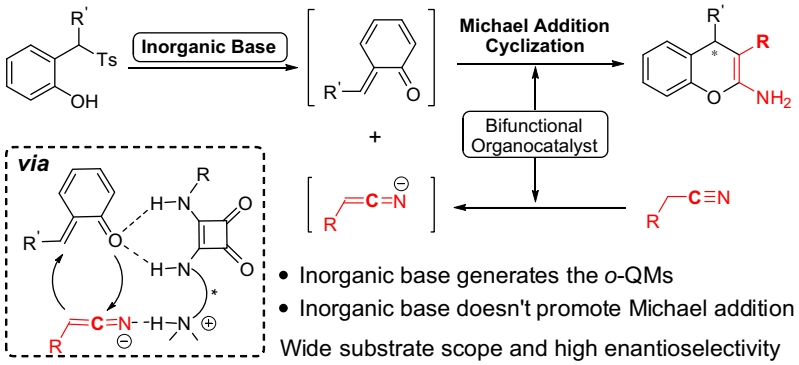
Table 1
Condition Optimization[a]



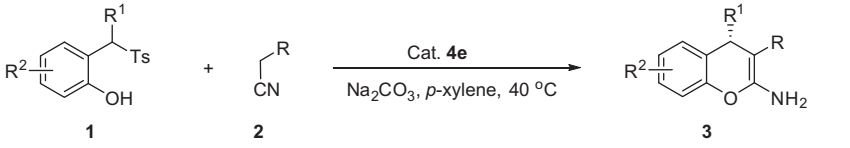
Entry	Cat.	Base	Solvent	*t* (h)	Yield[b] (%)	Ee[c] (%)
1	—	K_2CO_3	PhMe	2	80	—
2	—	Na_2CO_3	PhMe	2	Trace	—
3	**4a**	Na_2CO_3	PhMe	24	83	56
4	**4b**	Na_2CO_3	PhMe	24	80	94
5	**4c**	Na_2CO_3	PhMe	24	87	95
6	**4d**	Na_2CO_3	PhMe	72	80	97
7	**4e**	Na_2CO_3	PhMe	24	83	97
8	**4f**	Na_2CO_3	PhMe	24	83	−95
9	**4e**	K_2CO_3	PhMe	4	83	67
10	**4e**	$NaHCO_3$	PhMe	24	Trace	—
11	**4e**	Na_2CO_3	DCM	24	93	93
12	**4e**	Na_2CO_3	THF	24	90	24
13	**4e**	Na_2CO_3	*p*-Xylene	24	97	96
14[d]	**4e**	Na_2CO_3	*p*-Xylene	6	97	97
15[e]	**4e**	Na_2CO_3	*p*-Xylene	4	97	96
16[f]	**4e**	Na_2CO_3	*p*-Xylene	1	43	96

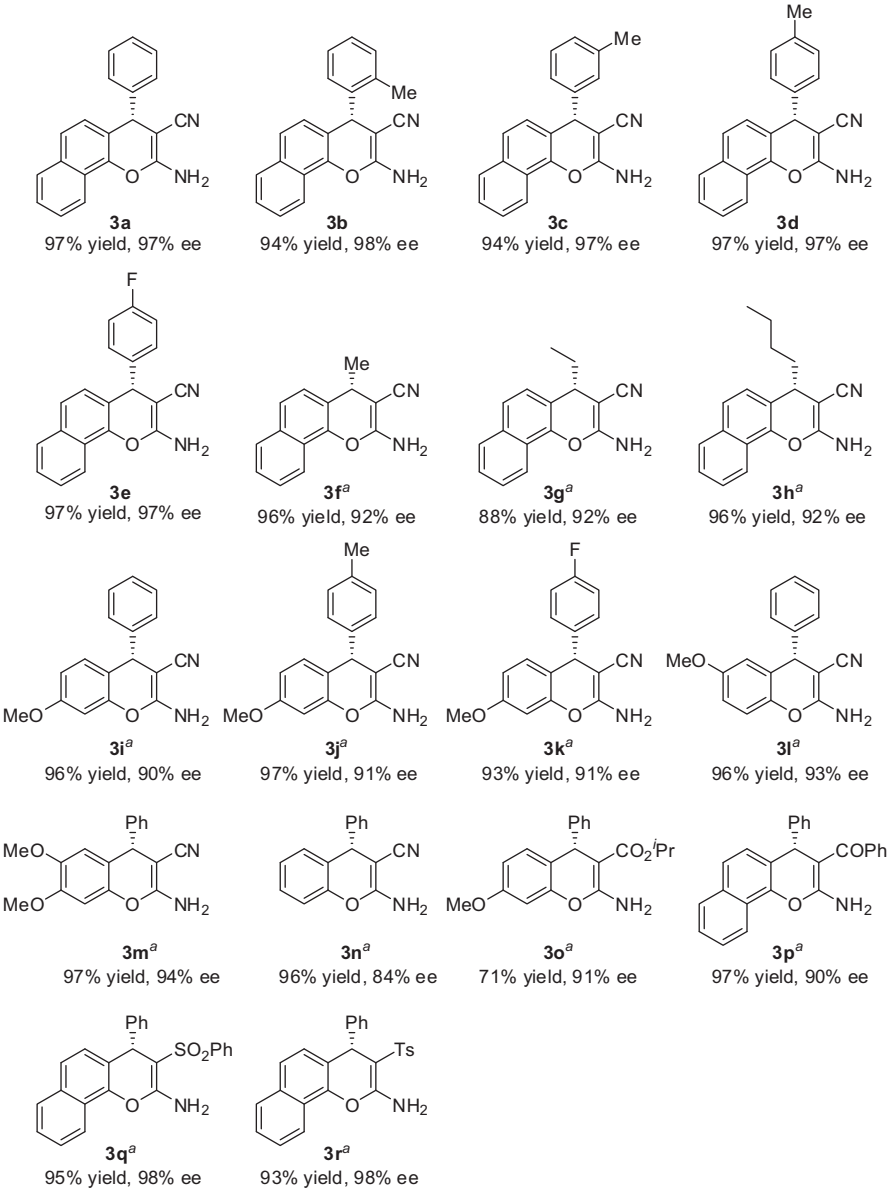
[a] **1a** (0.10 mmol), **2a** (0.12 mmol), cat. (0.01 mmol), base (0.12 mmol), solvent (1.5 mL), 25 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] 40 °C.
[e] 60 °C.
[f] 80 °C.

previous work, we reported the thiourea catalyzed enantioselective amination of *o*-QMs with aqueous ammonia in 33% ee.[12d] Low enantioselectivity possibly attributes to the fact that the *o*-QMs generated in situ from 2-(1-tosylalkyl)phenols under basic conditions may furnish racemic products as a result of an obvious background reaction. Considering active methylene compounds bearing the cyano group had been broadly employed as nucleophilic reagents in asymmetric organocatalytic additions,[13]



Scheme 1. New strategy for enantioselective synthesis of functionalized 2-amino-4*H*-chromenes.





Scheme 2. Substrate scope. Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), **4e** (0.01 mmol), Na_2CO_3 (0.12 mmol), *p*-xylene (1.5 mL), 40 °C. [a]60 °C.

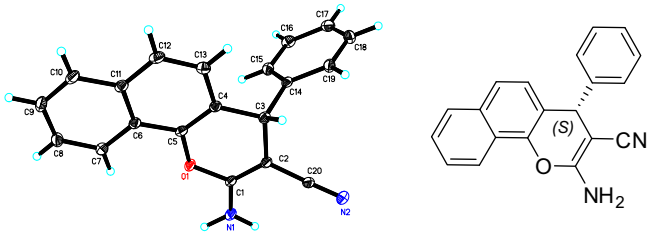


Figure 2. X-ray single crystal structure of 2-amino-4*H*-chromene **3a**.

we envisioned the combination of 2-(1-tosylalkyl)phenols and active methylene compounds bearing the cyano group for synthesis of chiral 2-amino-4*H*-chromenes in the presence of inorganic bases and bifunctional organocatalysts. The key for this tandem reaction is a suitable option of bifunctional organocatalysts and inorganic bases. The bifunctional organocatalysts could be used for deprotonation of active methylene compounds bearing the cyano group to produce the nucleophilic species in the chiral environment. The inorganic bases should not promote the following Michael addition to effectively weaken background reaction and guarantee the control of high enantioselectivities by the organocatalysts. Herein, we reported bifunctional squaramide-catalyzed Michael addition/cyclization of *o*-quinone methides generated in situ from the 2-(1-tosylalkyl)phenols with active methylene compounds bearing the cyano group for the synthesis of 2-amino-4*H*-chromenes with excellent enantioselectivities and broad substrate scope (Scheme 1).

To begin our study, 2-(1-tosylalkyl)naphthol **1a** and malononitrile **2a** were chosen as model substrates. The background reaction was firstly investigated. In the absence of organocatalysts, the reaction occurred smoothly to provide racemic product within 2 h in 80% yield using K_2CO_3 as inorganic base, whereas trace product was obtained with the utility of Na_2CO_3 indicating that using Na_2CO_3 as inorganic base could weaken background reaction (Table 1, entries 1–2). Subsequently, organocatalysts were extensively examined. In the case of quinine catalyst **4a**, the desired product was delivered in good yield and moderate 56% of enantioselectivity (entry 3). Bifunctional thiourea or squaramide catalysts gave higher enantioselectivity and dihydroquinine-based squaramide catalyst **4e** was the best catalyst in terms of 97% ee (entries 4–8). In accordance with our prediction, inorganic bases played a vital role on reactivity and enantioselectivity. Using stronger base K_2CO_3 led to lower enantioselectivity albeit with higher reactivity due to inevitable background reaction (entry 9). Moreover, a weaker base like $NaHCO_3$ shut down the reaction (entry 10). Among all the tested solvents, *p*-xylene was proved to be the most favorable solvent with respect to excellent yield and enantioselectivity (entries 11–13). Finally, the temperature was also evaluated. Increasing the reaction temperature, the rate of the reaction was accelerated and the enantioselectivity could be maintained. However, when the reaction temperature was increased to 80 °C, only moderate yield was obtained. Therefore, the optimal reaction conditions were established: using **4e** as catalyst, Na_2CO_3 as base, and *p*-xylene as solvent to perform the reaction at 40 °C.

With the aforementioned conditions, we next sought to examine the substrate generality for the synthesis of various optically active 2-amino-4*H*-chromenes (Scheme 2). In general, the transformations could be conducted smoothly, providing the desired products in good yields and excellent enantioselectivities. For 2-(1-tosylalkyl)naphthols **1a**–**1e**, electronic and steric property had a slight influence on the enantioselectivities and yields. Notably, alkyl substituted substrates **1f**–**1h** were also suitable reaction partners and the reaction performed well with 92% ee by increasing the temperature to 60 °C. Additionally, the methoxyl substituent was tolerated and the corresponding adducts were achieved in almost quantitative yields from 90% to 94% ee. The reaction of 2-(phenyl(-tosyl)methyl)phenol with malononitrile could also deliver product **3n** with 84% ee. Furthermore, a series of active methylene compounds bearing the cyano group transformed successfully, good yields and excellent enantioselectivities were observed. The absolute configuration of the product, 2-amino-4-phenyl-4*H*-benzo[*h*]-chromene-3-carbonitrile (**3a**; which can be increased to 99% ee by a simple recrystallization with dichloromethane), was unambiguously determined to be *S* by X-ray crystallographic analysis (Fig. 2).[14]

In summary, we have developed a highly efficient asymmetric bifunctional squaramide-catalyzed Michael addition/cyclization reaction of *o*-quinone methides generated in situ from 2-(1-tosylalkyl)phenols with active methylene compounds bearing the cyano group under basic conditions for the preparation of structurally important chiral 2-amino-4*H*-chromene compounds with broad substrate scope.[15] Further explorations on the extension of this strategy to synthesize other compounds are ongoing in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.076.

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14. CCDC 1056260 contains the supplementary crystallographic data for this paper. These can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request /cif.
15. During the preparation of this manuscript, a similar enantioselective synthesis of 2-amino-4*H*-chromenes by using our previous reported strategy appeared: Caruana, L.; Mondatori, M.; Corti, V.; Morales, S.; Mazzanti, A.; Fochi, M.; Bernardi, L. *Chem.-Eur. J.* **2015**, *21*, 6037. Both Fochi's group and we reported bifunctional squaramide-catalyzed reaction of *o*-quinone methides with active methylene compounds bearing cyano group for synthesis of chiral 2-amino-4*H*-chromenes. Fochi's group used the water–oil biphase system to weaken background reaction and ensure high enantioselectivity. Four aryl substituted substrates could react with malononitrile and moderate yield with up to 94% ee were obtained. We chosen suitable inorganic base to weaken background reaction and guarantee excellent enantioselectivity. Good yield and up to 98% ee were achieved by using our strategy. Additionally, alkyl substituted substrates were also suitable reaction partners and a series of active methylene compounds bearing cyano group including malononitrile, benzoylacetonitrile, phenylsulfonylacetonitrile conducted the reaction smoothly with excellent enantioselectivity.