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C−H Oxidation/Michael Addition/Cyclization Cascade for Enantioselective Synthesis of Functionalized 2-Amino-4*H*-chromenes

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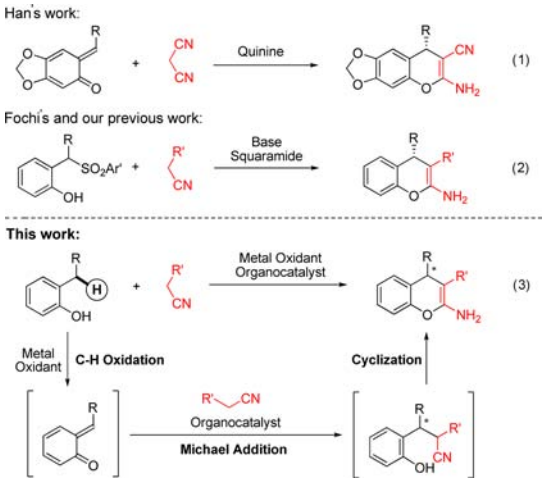
Supporting Information

ABSTRACT: A streamlined method for the enantioselective synthesis of 2-amino-4*H*-chromenes from readily available 2-alkyl-substituted phenols and active methylene compounds bearing a cyano group with up to 97% ee is presented. This reaction is a cascade procedure including manganese dioxide mediated C−H oxidation for the generation of *o*-quinone methides and bifunctional squaramide-catalyzed Michael addition/cyclization.

The development of efficient and novel chemical reactions that allow the rapid and direct construction of complex and diversified molecules from available and inexpensive starting materials stands at the forefront of synthetic chemistry, and it also has impressive significance in industrial processes.[1] One of the most powerful methods to realize these goals is the application of cascade reactions which carry out multiple transformations in a single step, accompanied by undeniable benefits including atom economy, economy of labor, and sustainability of resources.[2] In particular, these cascade strategies are useful and effective in the total synthesis of natural products and bioactive molecules.[2c−e,3] The significant importance of the 2-amino-4*H*-chromene scaffold in biologically active molecules, natural products, and synthetic drugs[4] has motivated chemists to develop various methods for the asymmetric synthesis of 2-amino-4*H*-chromenes, involving organocatalytic tandem Michael addition/cyclization,[5] Mannich cyclization/tautomerization cascade sequences,[6] three-component cascade reaction,[7] conjugate addition of nitroalkanes to 2-iminochromenes,[8] and metal complex catalyzed cascade reactions.[9] Although considerable progress has been made in the formation of chiral 2-amino-4*H*-chromenes, there are several disadvantages including low catalytic efficacy, poor stereoselectivity, and unsatisfactory substrate scope. Hence, the development of facile and enantioselective approaches to such scaffolds with a broad substrate scope is still highly desirable.

o-Quinone methides (*o*-QMs) are a prominent class of intermediates in a large number of biological processes[10] and are recognized as a highly reactive chemical species.[11] In this decade, a series of organocatalytic enantioselective reactions of *o*-QMs[12,13] have been reported due to their inherent reactivity. Organocatalytic formal [4 + 2] cycloaddition of *o*-QMs with active methylene compounds bearing a cyano group is also a concise method for the synthesis of chiral 2-amino-4*H*-chromenes. Recently, the Han group reported quinine-catalyzed annulation of the electron-rich and stable *o*-QMs with malononitrile, giving 2-amino-3-cyano-4*H*-chromenes with excellent enantioselectivity (eq 1, Scheme 1).[12m]

Scheme 1. Synthesis of Chiral 2-Amino-4*H*-chromenes via *o*-Quinone Methides



However, the substrate scope was limited. Fochi's group and our groups independently described a similar bifunctional squaramide-catalyzed reaction of *o*-QMs generated *in situ* from 2-(1-arylsulfonyl-alkyl)phenols with active methylene compounds bearing a cyano group under basic conditions for the preparation of chiral 2-amino-4*H*-chromenes (eq 2, Scheme 1).[12n,o]

2-Alkyl-substituted phenol derivatives are easily available and can be oxidized to generate *o*-QM intermediates.[14] Additionally, we have also disclosed that *o*-QM intermediates could be

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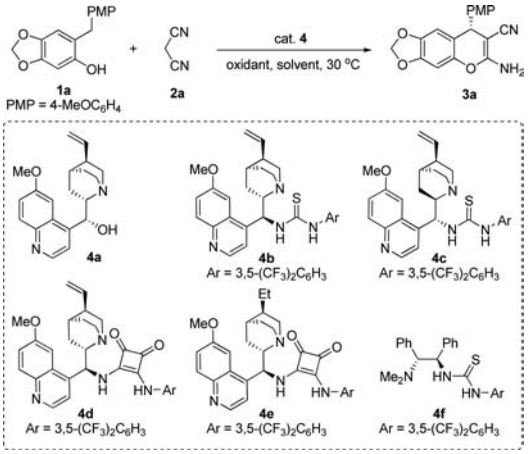
generated *in situ* from 2-alkyl-substituted phenol derivatives by metal oxidant mediated oxidation, which could be rapidly trapped by the sulfur ylides to allow stereoselective synthesis of *trans*-2,3-dihydrobenzofurans.[14g] Therefore, we envisioned a metal oxidant mediating the C−H oxidation of 2-alkyl-substituted phenol derivatives to produce the *o*-QM intermediates that underwent asymmetric Michael addition with active methylene compounds bearing a cyano group via an organocatalytic system followed by cyclization for the construction of optical active 2-amino-4*H*-chromenes. The combination of a metal oxidant and organocatalyst in this cascade reaction could effectively impede background reactions and ensure high enantioselectivity. Generally, a simple combination of metal oxidant and organocatalyst remains challenging in organic chemistry. Organocatalysts experience difficulty in tolerating highly oxidizing conditions.[15] Moreover, a metal oxidant might bind tightly with the organocatalyst, which causes the deactivation of the organocatalyst.[16] Herein, we reported cascade C−H oxidation/Michael addition/cyclization reactions with the combination of a metal oxidant and an organocatalyst for the enantioselective synthesis of 2-amino-4*H*-chromenes (eq 3, Scheme 1).

At the outset, 2-alkyl-substituted phenol **1a** and malononitrile **2a** (1.2 equiv) were chosen as model substrates. The oxidant had a significant influence in the reaction and triggered the generation of *o*-QM intermediates. In this respect, we initially turned our attention to the evaluation of oxidants. To our delight, the anticipated product 2-amino-4*H*-chromene **3a** was obtained in 81% isolated yield and 78% ee in the presence of silver oxide and a catalytic amount of quinine (Table 1, entry 1). However, other metal oxidants, AgOAc and $K_3Fe(CN)_6$, exhibited lower reactivity (Table 1, entries 2 and 3). Organic oxidants such as DDQ and $PhI(OAc)_2$ afforded mixed products. Additionally, the yield could be further improved, and the enantioselectivity was maintained by using MnO_2 as the oxidant (Table 1, entry 4). Subsequently, various solvents were extensively examined, and it was found that solvent effect played a crucial role in the reactivity and enantioselectivity. Among them, $CHCl_3$ proved to be a suitable solvent in view of the excellent yield and good enantioselectivity (Table 1, entries 5−10). Next, a series of organocatalysts were explored. Cinchona alkaloid-based thiourea catalysts **4b** and **4c** provided disappointing results with moderate enantioselectivity (Table 1, entries 11 and 12). Gratifyingly, quinine-based squaramide catalyst **4d** gave the best enantioselectivity (91% ee) (Table 1, entry 13). Satisfactorily, no decrease in enantioselectivity and yield was observed when the catalyst loading was reduced to 5 mol % (Table 1, entry 16).

With the aforementioned optimal reaction conditions, we next explored the substrate scope of the current cascade reaction between 2-alkyl-substituted phenols **1** and active methylene compounds bearing a cyano group **2**. As summarized in Scheme 2, in all cases, the reaction performed very well, delivering the corresponding chiral 2-amino-4*H*-chromenes in good yields and high enantioselectivities. For 2-alkyl substituted sesamols **1a**−**1g**, electronic and steric properties had no obvious influence on the enantioinduction. Notably, vinyl substrates **1h** and **1j** were favorable reaction partners, and the reaction proceeded smoothly with good enantioselectivities and moderate yields. In addition, 2-alkyl-substituted 4,5-dimethoxyphenol substrates **1i**−**k** were employed in the cascade reaction with excellent enantiocontrol. Interestingly, 2-alkyl-substituted 4-methoxynaphthols **1l** and

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	oxidant	solvent	yield[b] (%)	ee[c] (%)
1	**4a**	Ag_2O	CH_2Cl_2	81	78
2	**4a**	AgOAc	CH_2Cl_2	28	10
3	**4a**	$K_3Fe(CN)_6$	CH_2Cl_2	25	72
4	**4a**	MnO_2	CH_2Cl_2	91	78
5	**4a**	MnO_2	$CHCl_3$	97	82
6	**4a**	MnO_2	$ClCH_2CH_2Cl$	91	75
7	**4a**	MnO_2	benzene	75	82
8	**4a**	MnO_2	toluene	72	82
9	**4a**	MnO_2	*p*-xylene	75	81
10	**4a**	MnO_2	THF	63	28
11	**4b**	MnO_2	$CHCl_3$	97	68
12	**4c**	MnO_2	$CHCl_3$	94	47
13	**4d**	MnO_2	$CHCl_3$	97	91
14	**4e**	MnO_2	$CHCl_3$	97	89
15	**4f**	MnO_2	$CHCl_3$	94	81
16[d]	**4d**	MnO_2	$CHCl_3$	97	94

[a]Conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), cat. (0.01 mmol), oxidant (2.0 equiv), while MnO_2 was used in 4.0 equiv, solvent (1.5 mL), 30 °C. [b]Isolated yields. [c]Determined by chiral HPLC. [d]Catalyst loading was reduced to 5 mol %.

1m could also be oxidized to generate *o*-QMs and reacted with malononitrile to afford the corresponding adducts in high yield and enantioselectivity. Furthermore, a train of active methylene compounds bearing a cyano group proceeded successfully, achieving moderate to good yields and excellent enantioselectivities. It is worth noting that when the substituents R were alkyl groups, mixed products were obtained. The absolute configuration of compounds **3a** and **3k** was determined to be *S* by comparison of the specific rotations with the reported literature data (see the Supporting Information).[12m,o]

Considering that both amino and cyano groups are versatile functional groups, further derivatizations were conducted for the production of biologically active molecules. The reaction of (*S*)-6-amino-8-(4-methoxyphenyl)-8*H*-[1,3]dioxolo[4,5-*g*]-chromene-7-carbonitrile **3a** with cyclohexanone afforded polycyclic compound **5** in 63% yield with 89% ee in the presence of aluminum chloride according to the known literature method (Scheme 3),[17] which is a tacrine analogue and acts as a potential drug for the treatment of Alzheimer's disease.[17b]

In conclusion, we have developed a streamlined method for the asymmetric synthesis of chiral 2-amino-4*H*-chromenes from readily available 2-alkyl-substituted phenols and active methylene compounds bearing a cyano group with excellent

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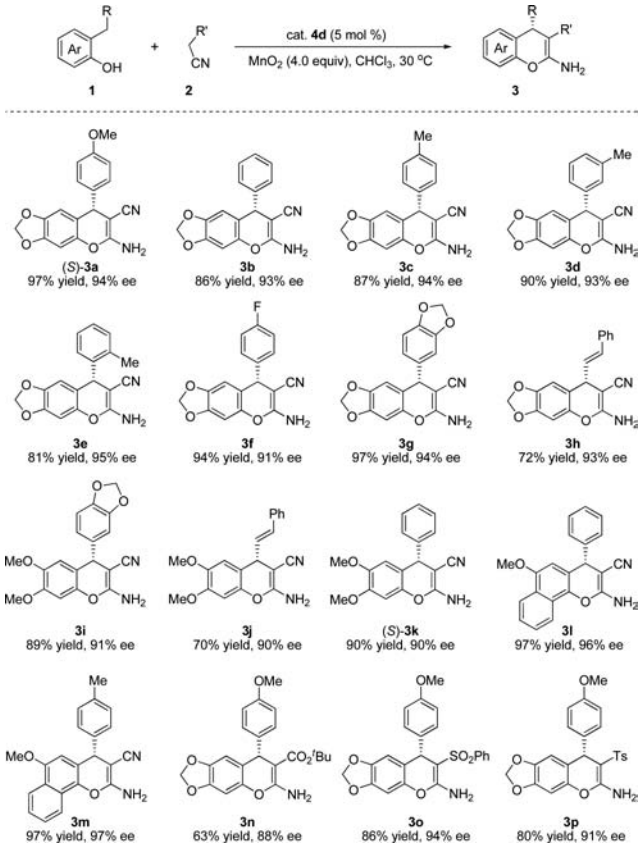
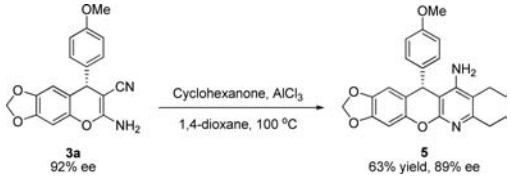
Scheme 2. Substrate Scope for the Synthesis of 2-Amino-4*H*-chromenes



Scheme 3. Synthesis of Bioactive Compound 5



enantioselectivity in the presence of a metal oxidant and an organocatalyst. This reaction is recognized as a cascade procedure including manganese dioxide mediated C−H oxidation for the generation of *o*-quinone methides and a bifunctional squaramide-catalyzed Michael addition/cyclization process. This protocol not only provides new access to chiral 2-amino-4*H*-chromenes but also suggests a useful strategy for the combination of metal oxidants and organocatalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03148.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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