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Asymmetric chroman synthesis *via* an intramolecular oxy-Michael addition by bifunctional organocatalysts†

Ryota Miyaji, Keisuke Asano* and Seijiro Matsubara*

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Cinchona-alkaloid-urea-based bifunctional organocatalysts facilitate the catalytic asymmetric synthesis of chroman derivatives *via* an intramolecular oxy-Michael addition reaction. Phenol derivatives bearing an easily available (*E*)- α,β -unsaturated ketone or a thioester moiety are useful substrates for the title transformation. This method represents a facile synthesis of various optically active 2-substituted chromans in high yield.

Introduction

Chiral 2-substituted chromans are found in an extremely wide range of bioactive compounds, as typified by vitamin E, and their biological activities have attracted much attention (Fig. 1).¹ Thus, the enantioselective synthetic methods toward chroman derivatives are in high demand; indeed, a number of strategies have been reported, addressing this need.^{2–5} Among them, the intramolecular oxy-Michael addition is a promising method for constructing the desired framework from easily available phenol derivatives bearing an α,β -unsaturated carbonyl; the remaining carbonyl group in the product allows for further structural modification, which may lead to the synthesis of various pharmacological compounds. However, only a few examples of such approaches have been reported to date.^{4,5} In addition, most of these strategies display a significant limitation in that the substrate, typically an α,β -unsaturated ester moiety, must be in its (*Z*)-isomer form, and that the (*Z*)-forms of more electron-deficient olefins (α,β -unsaturated ketones and thioesters) are extremely difficult to prepare by means of simple methods such as Wittig reactions using stabilized ylides (Scheme 1). These problems must be solved to expand the scope of synthetically accessible chromans.

We have recently established a useful strategy for the asymmetric synthesis of five- or six-membered oxygen heterocycles *via* an intramolecular oxy-Michael addition starting from (*E*)- α,β -unsaturated carbonyl substrates (Scheme 2).^{6,7} This

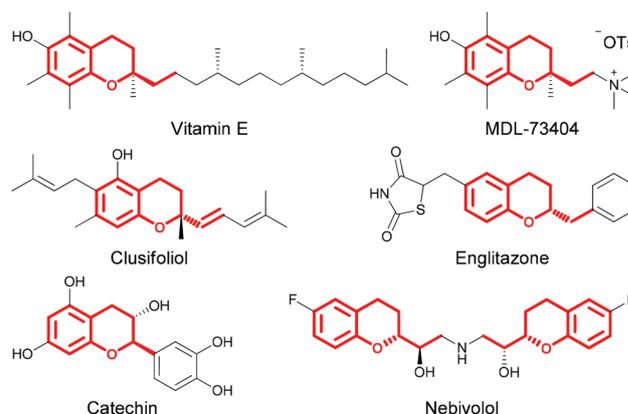
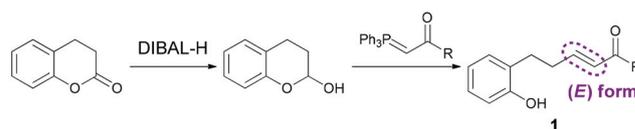
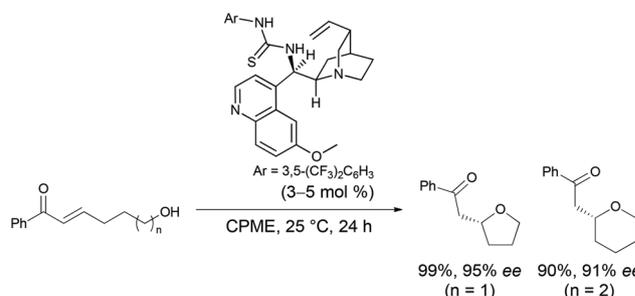


Fig. 1 Representative 2-substituted chromans in bioactive compounds.



Scheme 1 Facile synthetic route to substrates 1.



Scheme 2 Asymmetric synthesis of 2-substituted THF and THP *via* an intramolecular oxy-Michael addition by a bifunctional organocatalyst.

Department of Material Chemistry, Graduate School of Engineering,
Kyoto University, Kyotodaigaku-Katsura, Nishikyo, Kyoto 615-8510, Japan.
E-mail: asano.keisuke.5w@kyoto-u.ac.jp, matsubara.seijiro.2e@kyoto-u.ac.jp;
Fax: +81 75 383 2438; Tel: +81 75 383 7571, +81 75 383 7130

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method utilizes multipoint substrate recognition by bifunctional organocatalysts through hydrogen bonding;^{8,9} the mild characteristics of activation through hydrogen bonding facilitate concerted catalysis efficient for obtaining high enantioselectivity even in rapid intramolecular processes for cycloetherifications.^{6d} The efficiency of this protocol prompted us to explore the use of bifunctional organocatalysts for the intramolecular oxy-Michael addition from phenol derivatives bearing an (*E*)- α,β -unsaturated carbonyl moiety.^{5,10} In this study, we present a novel enantioselective synthesis of 2-substituted chromans *via* an intramolecular oxy-Michael addition using cinchona-alkaloid-urea-based bifunctional organocatalysts.

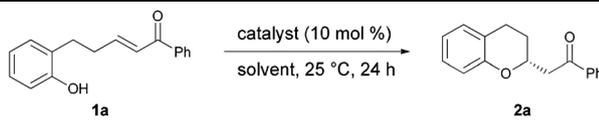
Results and discussion

We initiated our investigation using substrate **1a** with 10 mol% quinidine-derived bifunctional aminourea catalyst **3a** in CH₂Cl₂ at 25 °C over 24 h; chroman product **2a** was obtained with moderate enantioselectivity (Table 1, entry 1). Solvent screening revealed that THF was effective for both enantioselectivity and yield (Table 1, entry 9). A decrease in reaction temperature improved the enantioselectivity (Table 1, entry

10). However, the use of a smaller amount of catalyst (5 mol%) led to lower enantioselectivity, which was likely due to the competing non-catalytic reaction (Table 1, entry 11). A time of 12 h was found to be sufficient for reaction completion, and higher enantioselectivity could be obtained (Table 1, entry 12). In this reaction, the urea catalyst **3a** was revealed to be more efficient than the corresponding thiourea catalyst **3b** (Table 1, entries 12 and 13).^{7a} Further screening of urea catalysts showed that quinine-derived **3d** was an efficient catalyst for obtaining the opposite enantiomer of **2a** with good enantioselectivity (Table 1, entry 15).

With catalyst **3a** and optimized reaction conditions identified, we next investigated the reactions of substrates bearing

Table 1 Optimization of conditions^a



Entry	Catalyst	Solvent	Yield ^b (%)	ee (%)
1	3a	CH ₂ Cl ₂	99	63
2	3a	Benzene	87	60
3	3a	Pyridine	99	58
4	3a	DMSO	88	25
5	3a	Et ₂ O	91	69
6	3a	<i>t</i> -BuOMe	99	55
7	3a	CPME ^c	93	63
8	3a	1,4-Dioxane	96	72
9	3a	THF	99	72
10 ^d	3a	THF	99	81
11 ^{d,e}	3a	THF	99	76
12 ^{d,f}	3a	THF	95	84
13 ^{d,f}	3b	THF	95	75
14 ^{d,f}	3c	THF	86	82
15 ^{d,f}	3d	THF	98	-80
16 ^{d,f}	3e	THF	86	-78

^a Reactions were run using **1a** (0.1 mmol) and the catalyst (0.01 mmol) in the solvent (0.2 mL). ^b Isolated yields. ^c CPME = cyclopentyl methyl ether. ^d Reactions were run at 0 °C. ^e Reaction was run using 5 mol% of **3a** (0.005 mmol). ^f Reactions were run for 12 h.

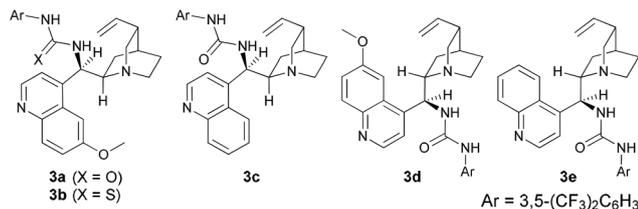
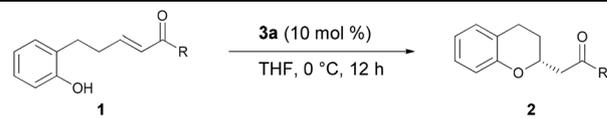
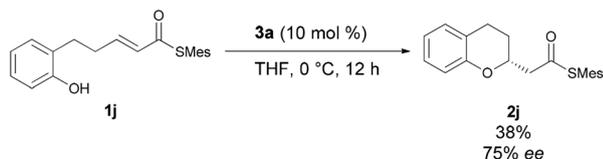


Table 2 Scope of α,β -unsaturated ketones^a



Entry	Product (2)	Yield ^b (%)	ee (%)
1	2a	95	84
2	2b	81	84
3	2c	95	84
4	2d	95	70
5	2e	99	83
6	2f	66	72
7	2g	64	36
8	2h	86	74
9	2i	68	65

^a Reactions were run using **1** (0.1 mmol) and **3a** (0.01 mmol) in THF (0.2 mL). ^b Isolated yields.



Scheme 3 Reaction of α,β -unsaturated thioester.

other (*E*)-Michael-acceptor moieties.¹¹ Electron-rich substrates were also effective, providing the chroman products in high yield and comparable enantioselectivity (Table 2, entries 2 and 3). A starting material bearing an electron-withdrawing group afforded the corresponding product in high yield, although the enantiomeric excess was slightly lower (Table 2, entry 4). A substrate with a *p*-bromophenyl substituent yielded the corresponding product quantitatively in high enantioselectivity (Table 2, entry 5); however, a 2-naphthyl-substituted enone gave the resultant product in lower yield and stereoselectivity (Table 2, entry 6). Unfortunately, a methylketone proved to be an unsuccessful substrate (Table 2, entry 7). Substituents on the phenol moiety were also investigated, and a substrate with a methoxy group gave the corresponding product in good yield with moderate enantioselectivity (Table 2, entry 8), although a phenol derivative with a bromo group resulted in lower yield and stereoselectivity (Table 2, entry 9). To our delight, an α,β -unsaturated thioester participated in the cyclization reaction, yielding a chroman derivative suitable for various subsequent transformations, demonstrating the synthetic utility of our method (Scheme 3). The absolute configuration of 2e was determined as (*R*) using X-ray analysis (see ESI† for details), and the configurations of all other examples were assigned accordingly.

Conclusions

In summary, we have presented a novel asymmetric chroman synthesis *via* an intramolecular oxy-Michael addition employing bifunctional aminourea catalysts. In this method, substrates bearing an easily available (*E*)-Michael acceptor including α,β -unsaturated ketones and thioesters could be used, thereby leading to a facile and versatile approach to optically active chromans. Further studies on the expansion of the substrate scope and the application of this methodology toward other heterocyclic scaffolds are currently underway in our laboratory and will be reported in due course.

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