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# Enantioselective tandem reaction of chromone-derived Morita–Baylis–Hillman carbonates with benzylamines catalyzed by a trifunctional organocatalyst: the synthesis of chiral 3-aminomethylene-flavanones†

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**An enantioselective tandem reaction of chromones-derived MBH carbonates (1) with benzylamines (2) catalyzed by a trifunctional organocatalyst, cinchonidine–amide–thiourea, has been developed in moderate to good yields (50–87%) and enantioselectivities (up to 89% ee).**

The structural moiety of benzodihydropyranone (chromanone) is a common heterocyclic framework existing in numerous natural compounds and pharmaceutical molecules.[1] Among these compounds, flavanone (2-phenyl-benzodihydropyran-4-one) and its derivatives show excellent biological activities such as being nonsteroidal, aromatase inhibition and exhibiting antimicrobial effects.[2] Several 3-aminomethylene-flavanones with biological activities are shown in Fig. 1. To search a novel compound with biological and pharmaceutical activities, it is desirable and necessary to enhance the diversity of flavanones. In the last decades, synthetic methods to construct the flavanone structural unit have been developed extensively.[3] Correspondingly, the synthesis of the chiral flavanones has also gained great progress.[4]

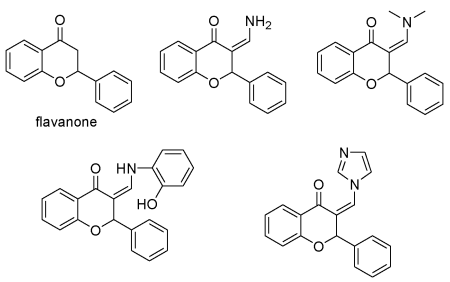
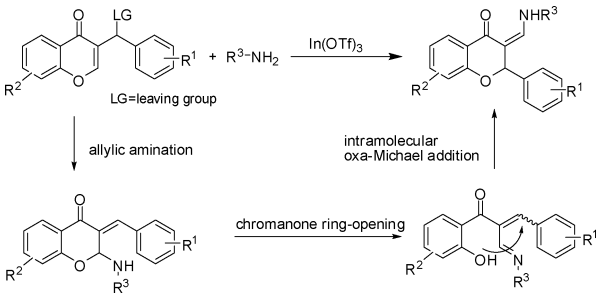



**Fig. 1** 3-Aminomethylene-flavanone.




**Scheme 1** The reaction of chromone-derived MBH adducts with amines.

Very recently, we reported In(III)-catalyzed reactions of chromone-derived Morita–Baylis–Hillman (MBH) adducts with amines *via* tandem allylic amination/ring-opening/oxa-Michael addition reactions in a one pot process, affording the products, 3-aminomethylene-flavanones (Scheme 1).[5] It was noteworthy that only one chiral center at the C2-position was newly formed in the course of the tandem reactions. The configuration of the chiral center depends on the stereochemistry of the intramolecular oxa-Michael addition to α,β-unsaturated imine. In order to access chiral flavanone derivatives by this one-pot synthetic protocol a chiral In(III)-catalyst was employed in the same tandem reaction. When (*R*,*R*)-Ph-BOX/In(OTf)$_3$ was used as a chiral Lewis acid catalyst, the desired product was obtained in a yield of 72%, but as a racemic mixture, unfortunately.

In view of the process of the tandem reaction, a multifunctional catalyst, which could activate the MBH adduct in the allylamination, as well as the generated intermediate bearing phenol unit and α,β-unsaturated imine moieties, and provide excellent stereochemical control in the subsequent asymmetric intramolecular oxa-Michael addition, was required. Probably, the use of the organocatalyst with bifunctions could meet the multiple demands.[6] Moreover, recently, the organocatalytic tandem reaction has emerged as a powerful tool in organic synthesis.[7] For asymmetric oxa-Michael addition, which offered a powerful and efficient tool

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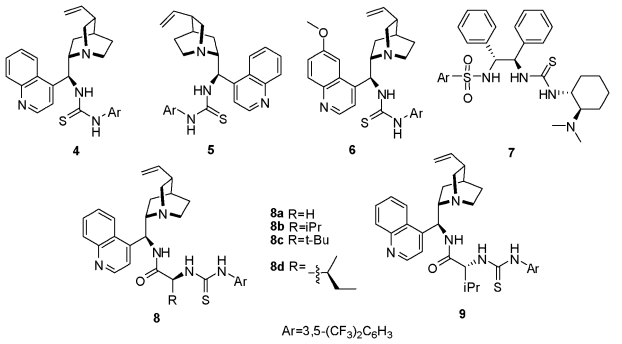


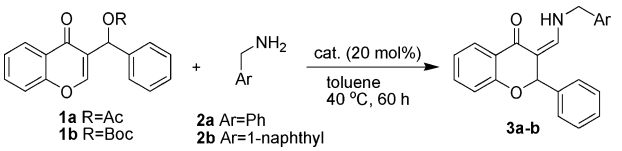

**Fig. 2** Organocatalysts for screening.

for the synthesis of chiral heterocycles and natural products,[8] its organocatalytic version has attracted considerable attention. The Michael acceptor such as α,β-unsaturated carbonyl compounds were activated by organoamine catalysts, diarylprolinolsilyl ether mostly, through iminium ion activation mode.[9] Some oxa-Michael addition reactions, including intramolecular conjugate addition of a phenol to an unsaturated ketone,[10a] the hydroxylation of nitroalkenes[10b] and intramolecular conjugate addition with bononate,[10c] could be catalyzed by cinchona alkaloid-based thiourea through hydrogen bond activation mode,[11] providing good to high enantioselectivities.[10] However, to the best of our knowledge, it has not been reported that α,β-unsaturated imine as a Michael acceptor was activated by the hydrogen bond interaction in the asymmetric oxa-Michael addition reaction.

Herein we describe the enantioselective tandem reaction of chromone-derived MBH carbonates with benzylamines catalyzed by chinconidine–amide–thiourea for the synthesis of chiral 3-aminomethylene-flavanones in moderate to good yields with good enantioselectivities.

Initially, the reaction of chromone-derived MBH acetate **1a** (R = Ac) with benzylamine **2a** in the presence of the cinchonidine-derived thiourea catalyst **4** (20 mol%) was carried out in toluene for 60 h at 40 °C to afford the product **3a** in a yield of 30% with enantioselectivity of 32% ee (Fig. 2 and Table 1, entry 1). When **2a** was changed to **2b** (Ar = 1-naphthyl), the yield of the product **3b** increased to 72%, but the ee value was only 34% (entry 2). For the catalyst **4**, the yield and enantioselectivity of the reaction of **1b** (R = Boc) with **2b** only had a marginal improvement (entry 3). Next, the pseudoenantiomer of **4**, cinchonine-derived thiourea **5**, was employed as a catalyst in the reaction of **1b** with **2b**, giving the product with the opposite ee value of −23% (entry 4). When quinine-derived thiourea catalyst **6** was employed the results obtained with entry 5 are similar to that from the catalyst **4**. Obviously, although simple cinchona alkaloid-based thiourea could catalyze the tandem reaction, it was not applicable to the asymmetric intramolecular oxa-Michael addition of the generated intermediate bearing the α,β-unsaturated imine unit. The stronger hydrogen bond interaction between the catalyst and the intermediate at multi points was desired. On the other hand, for the thiourea-type organocatalyst derived from chiral diamine **7**, poor asymmetric induction (7% ee) was observed (entry 6). As suggested by Zhu and Lu,[12] trifunctional catalysts containing primary amino acid units were more favorable for the asymmetric conjugate addition than the bifunctional thiourea catalyst. The trifunctional catalyst interacted with both electro- and nucleophiles simultaneously through the formation of a multiple hydrogen bond in a cooperative manner. According to the method described in ref. 12, various trifunctional catalysts, cinchonidine–amide–thioureas (**8a–d** and **9**), were prepared and employed in the reaction of **1b** with **2b**. The results in Table 1 (entries 7–13) indicate that the amide unit played an important role in governing the enantioselectivity of the tandem reaction. To our delight, when the trifunctional catalyst **8b** was used, the enantioselectivity of the product **3b** was increased to 77% ee, but the yield was only 42% (entry 7). It was found that the close system was turbid during the reaction time. When the reaction tube was not sealed, exposed to air, the system became very clear and the yield was increased to 71% (entry 8). Upon changing the ratio of **1b**/**2b** to 2 : 1, the ee value increases slightly up to 79% (entry 9). The results on solvent effect (in ESI†) revealed that toluene was the best choice. The best results (75% yield and 82% ee) were obtained by the use of the catalyst **8d** (20 mol%) under the conditions: in an open tube with toluene at 40 °C for 60 h (entry 12).

**Table 1** The reaction of MBH carbonates (**1a** and **b**) with amines (**2a** and **b**)[a]



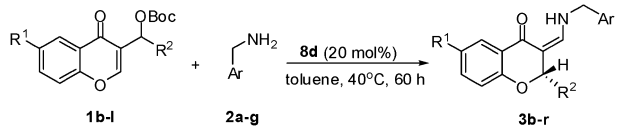

| Entry | MBH carbonate | Amine | Catalyst[b] | Yield[c] (%) | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | 1a | 2a | 4 | 30 | 32 |
| 2 | 1a | 2b | 4 | 72 | 34 |
| 3 | 1b | 2b | 4 | 74 | 36 |
| 4 | 1b | 2b | 5 | 70 | −23 |
| 5 | 1b | 2b | 6 | 72 | 36 |
| 6 | 1b | 2b | 7 | 42 | −7 |
| 7 | 1b | 2b | 8b | 42 | 77 |
| 8[e] | 1b | 2b | 8b | 71 | 77 |
| 9[e,f] | 1b | 2b | 8b | 75 | 79 |
| 10[e,f] | 1b | 2b | 8a | 81 | 43 |
| 11[e,f] | 1b | 2b | 8c | 72 | 79 |
| 12[e,f] | 1b | 2b | 8d | 75 | 82 |
| 13[e,f] | 1b | 2b | 9 | 63 | −58 |

[a] Reaction conditions: **1a**, **1b** (0.1 mmol), **2a**, **2b** (0.2 mmol), solvent (1 mL), 40 °C. [b] Catalyst loading: 20 mol%. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] Open system. [f] **1b** (0.2 mmol), **2b** (0.1 mmol).

Under the optimized reaction conditions, the substrate scope of MBH carbonates and benzylamines was examined (Table 2). The MBH carbonates, the substituent ($R^2$) with either an electron-withdrawing (**1c–f**) or electron-donating group (**1h**) at the *ortho* position of the phenyl ring can react smoothly with **2b** in moderate to excellent yields with good enantioselectivities (entries 2–5 and 7). Notably, the high enantioselectivities (89% and 80% ee) were obtained when $R^2$ was *o*-biphenyl (**1g**) or *p*-biphenyl (**1i**) (entries 6 and 8), which are important structural units present in a number of natural and artificial compounds with bioactivity. Moreover, the MBH carbonates **1j** ($R^1$ = F) and **1k** ($R^1$ = $CH_3$) also gave products **3j** and **3k**, respectively, in good yields and enantioselectivities (entries 10 and 11). If the $R^2$ group was changed from phenyl (**1b**) to 1-naphthyl (**1l**) the yield of the product was increased to 87% and

**Table 2** Asymmetric organocatalytic reaction of **1b–l** with **2a–g** [a]




1b-l 2a-g 3b-r

| Entry | MBH carbonate ($R^1$, $R^2$) | Amine (Ar) | Product | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | **1b** (H, Ph) | **2b**, (1-naphthyl) | **3b** | 75 | 82 |
| 2[d] | **1c** (H, 2-BrPh) | **2b** | **3c** | 64 | 86 |
| 3[d] | **1d** (H, 2-ClPh) | **2b** | **3d** | 65 | 84 |
| 4 | **1e** (H, 2-FPh) | **2b** | **3e** | 64 | 79 |
| 5 | **1f** (H, 2-$CF_3$Ph) | **2b** | **3f** | 80 | 85 |
| 6 | **1g** (H, 2-PhPh) | **2b** | **3g** | 84 | 89 |
| 7 | **1h** (H, 2-$CH_3$Ph) | **2b** | **3h** | 72 | 89 |
| 8 | **1i** (H, 4-PhPh) | **2b** | **3i** | 78 | 80 |
| 9 | **1j** (F, Ph) | **2b** | **3j** | 61 | 82 |
| 10 | **1k** ($CH_3$, Ph) | **2b** | **3k** | 60 | 77 |
| 11 | **1l** (H, 1-naphthyl) | **2b** | **3l** | 87 | 85 |
| 12 | **1h** | **2a** (Ph) | **3m** | 60 | 76 |
| 13 | **1h** | **2c** (2-naphthyl) | **3n** | 50 | 84 |
| 14 | **1h** | **2d** (2-ClPh) | **3o** | 70 | 80 |
| 15 | **1h** | **2e** (2-$CH_3$Ph) | **3p** | 75 | 65 |
| 16 | **1h** | **2f** (4-ClPh) | **3q** | 66 | 80 |
| 17 | **1h** | **2g** (4-$CH_3$Ph) | **3r** | 80 | 71 |

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), toluene (1 mL), **8d** (20 mol%), 40 °C, open system, 60 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] At 50 °C.

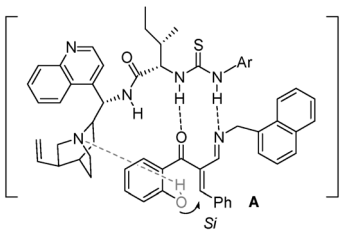



**Fig. 3** Proposed intermediate and transition state.

enantioselectivity to 85% ee (entry 1 *vs.* 11). The tandem reactions of various benzylamines (**2a** and **2c–g**) with **1h** also in the presence of the catalyst **8d** proceeded smoothly, providing good yields (50–80%) with 65–84% ee (entries 12–17).

The molecular structure of the tandem reaction product **3c** was further confirmed by X-ray crystallographic analysis,[13] by which the absolute configuration of newly created chiral centers at the C2 position was deduced as *R* and the configuration of the double bond at the C3 position as *Z*. On the basis of these observations, the intermediate and transition states of the tandem reaction were proposed. In the first step, amines ($ArCH_2NH_2$) attack the MBH carbonate activated by the thiourea-type catalyst (**8d**) through the formation of hydrogen bonds to generate the intermediate **A** (Fig. 3). Then followed by an oxa-Michael addition in which the multiple hydrogen bonds were formed between the trifunctional catalyst and the intermediate **A** to realize rate-enhancement and the optimal stereochemical control, the phenol group attacks the double bond of the α,β-unsaturated imine moiety in the intermediate **A** from the *Si* face of the double bond.

In conclusion, an organocatalytic enantioselective tandem reaction of the chromone-derived Morita–Baylis–Hillman carbonates with benzylamines, *via* allylic amination/ring-opening/oxa-Michael addition, was developed. The protocol provided an efficient and convenient method for the synthesis of chiral 3-aminomethylene-flavonones. The use of a trifunctional catalyst, cinchona alkaloid–amide–thiourea, enforced the interactions between the catalyst and the Michael acceptor through multiple hydrogen bonds, leading to a high enantioselectivity of the intramolecular oxa-Michael addition with α,β-unsaturated imine.

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