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Enantioselective Synthesis of Coumarin Derivatives Catalyzed by Primary Amines

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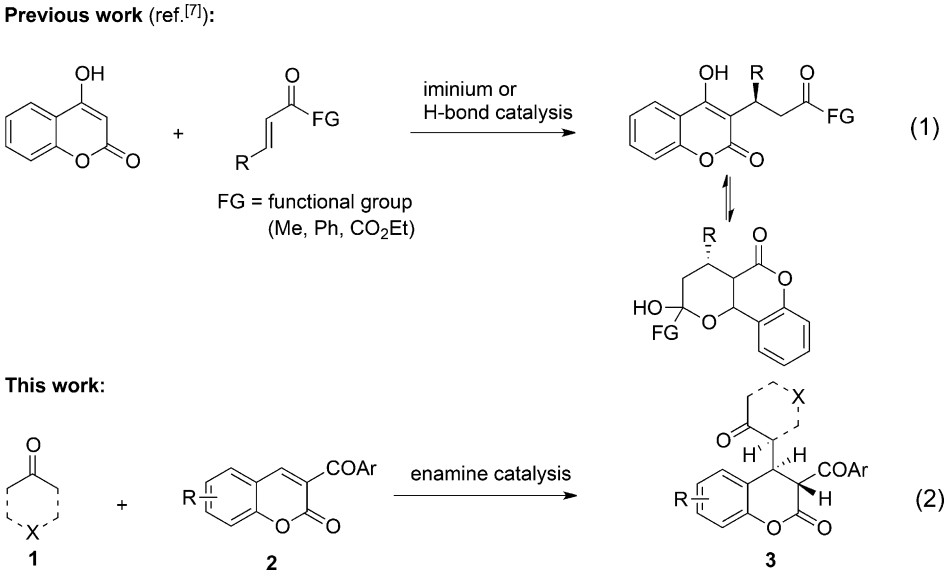
Abstract: *Cinchona* alkaloid-derived primary amines were used as organocatalysts for the preparation of enantioenriched coumarin derivatives. A series of optically active coumarin derivatives was obtained in good yields with excellent enantioselectivities (up to 98% *ee*).

Keywords: asymmetric catalysis; coumarin derivatives; Michael addition; organocatalysis; primary amines

Coumarin is a well-known oxygen heterocycle that can be found as a structural motif in numerous natural products.[1] Modification of this class of compounds has been of great importance due to their broad spectrum of pharmacological properties, including antioxidant, anti-inflammatory, antibacterial and antiviral activities.[2] Coumarin derivatives have also found applications in fluorescent sensors for fluoride anions as well as for chromogenic and fluorescent turn-on type signaling.[2g,h] Thus, there has been a continuous effort towards the synthesis of coumarin and its derivatives.[3] Over the last decade, organocatalysis has emerged as one of the promising and rapidly expanding fields in organic synthesis and has become a parallel method to the conventional approaches utilized in asymmetric catalysis.[4] In particular, aminocatalytic approaches[5] have gained much attention in this regard. The iminium or H-bond catalyzed[6] Michael reaction of 4-hydroxycoumarin to α,β-unsaturated carbonyls has been widely investigated because the obtained products are direct precursors to various biologically active compounds such as warfarin, acenocoumarol [Scheme 1, Eq. (1)].[7] However, the alternative approach to prepare coumarin derivatives *via* a Michael addition of ketones (**1**) to 3-aroylcoumarins (**2**) has not been reported. This led us to evaluate the



Scheme 1. Organocatalyst-mediated preparation of coumarin derivatives.

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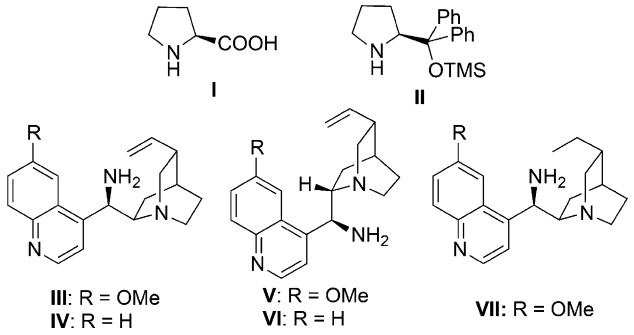

Figure 1. Identification of catalysts for the organocatalytic Michael addition.

enantioselective Michael addition of ketones to diversely substituted 3-aroylcoumarins (**2**) [Scheme 1, Eq. (2)].

Herein we present a new approach for the synthesis of optically active coumarin derivatives by using readily available *Cinchona* alkaloid-derived primary amines.[8] The research group of Connon has demonstrated that *Cinchona* alkaloid-derived primary amines are efficient catalysts for the enamine activation of ketones.[9] We have also recently demonstrated enantioselective synthesis of substituted pyrans *via* a *Cinchona* alkaloid-derived primary amine-catalyzed Michael addition and subsequent enolization/cyclization of cyclohexanone and *trans*-2-aroyl-3-arylacrylonitriles.[10]

On the basis of these considerations, we envisioned that the *Cinchona* alkaloid-derived primary amines (Figure 1) may catalyze a direct enantioselective Michael addition of ketones to 3-aroylcoumarin derivatives.

We began our investigation by using cyclohexanone (**1a**) and 3-benzoyl-6-bromocoumarin (**2a**) as model substrates. Initial catalyst screening confirmed our expectation that the secondary amines are ineffective catalysts for this process probably because of their lower reactivity with **1a**. Thus, use of 20 mol% of (*S*)-proline (**I**) or diphenylprolinol silyl ether (**II**) resulted in only trace amounts of product (Table 1, entries 1 and 2). In contrast, the quinidine-derived primary amine catalyst **III** (20 mol%) promoted the reaction with an improved yield (61%), and complete conversion of **2a** was observed in ethyl acetate at room temperature within 24 h (entry 3). However, the product **3a** was obtained with moderate enantioselectivity (63% *ee*) and a 4:1 diastereomeric ratio. Encouraged by this result, we decided to further optimize the reaction conditions. Primary amine catalysts **IV–VII** were also investigated. Although all the catalysts (**IV–VII**) promoted the reaction, the enantioselectivity remained low to moderate (entries 4–7). A screen of solvents indicated that several solvents were suitable for this reaction. However, no improvement of enantioselectivity was observed by using either polar or non-polar solvents (entries 8–11). Employment of neat conditions was also disappointing (52% *ee*, entry 12). An improvement of chemical yield was noticed on lowering the reaction concentration or on increasing the concentration of cyclohexanone (**1a**, 2 mmol), but the enantioselectivity remained moderate (53% *ee*, entries 13 and 14). A significant improvement of enantioselectivity (73% *ee*) was obtained by carrying out the reaction at 0 °C (entry 15). Further lowering of the reaction temperature (−25 °C) turned to be beneficial, as the enantioselectivity was further improved to 95% *ee* (entry 16). It is worth mentioning that both the diastereoselectivity and enantioselectivity of **3a** dropped upon lowering the catalyst loading (10 mol%) under these reaction conditions (entry 17). The presence of an acidic co-catalyst to ensure an effective process (primary amine is engaged in efficient enamine formation) is well documented.[8] However, a very poor result was obtained by using benzoic acid as co-catalyst (see the Supporting Information). Interestingly, use of 20 mol% phenol furnished the product in improved diastereoselectivity (>20:1 *dr*, 92% *ee*, see the Supporting Information). We have recently observed that the presence of precise quantities of water (as co-solvent) were critical for such a reaction to proceed.[11] Eventually, when the reaction was carried out in anhydrous ethyl acetate, both the yield and enantioselectivity were dropped to a considerable extent (76% yield and 90% *ee*, entry 16 *vs.* 18).

Finally, we choose entry 16 (Table 1) as the optimized reaction conditions and explored the scope and limitations of the asymmetric Michael addition with respect to different electrophiles and nucleophiles. A broad range of 3-aroylcoumarins (**2a–k**) having different substitution patterns were converted to the corresponding coumarin derivatives (**3a–k**) in moderate to high yields and selectivities with cyclohexanone (**1a**) as the nucleophilie (Table 2). 6-Cl-substituted Michael acceptor **2b** afforded the product **3b** in equal ease as in the case of **2a**, and the corresponding coumarin derivative was obtained in 86% yield and 91% enantiomeric excess along with a 19:1 diastereomeric ratio. In the case of electronically neutral Michael acceptor 3-benzoylcoumarin (**2c**), the corresponding product **3c** was furnished with very good chemical yield (93%) and diastereomeric ratio (18:1) albeit with slightly lower enantioselectivity (84% *ee*). The presence of an electron-donating group was also tolerated in the present reaction conditions. 3-Benzoylcoumarin derivatives (**2d–f**) bearing 6-, 7- and 8-methoxy substituents delivered the corresponding products **3d–f** in moderate to good yields (30–87%) and good to excellent enantioselectivity (67–96% *ee*). 6,8-Dichloro-substituted Michael acceptor (**2g**) was also examined in our protocol. Gratifyingly, the coumarin adduct (**3g**) was

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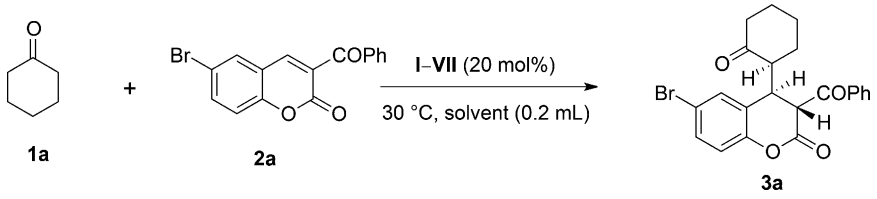
Table 1. Screening of catalysts and condition for the organocatalytic Michael addition of **1a** and **2a**.[a]



1a 2a 3a

Entry	Catalyst	Solvent	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**I**	ethyl acetate	trace	–	–
2	**II**	ethyl acetate	trace	–	–
3	**III**	ethyl acetate	61	4:1	63
4	**IV**	ethyl acetate	80	3:1	20
5[e]	**V**	ethyl acetate	76	2.5:1	47
6	**VI**	ethyl acetate	22	4.5:1	nd
7	**VII**	ethyl acetate	76	3:1	43
8	**III**	THF	48	2:1	60
9	**III**	CH_2Cl_2	39	3:1	58
10	**III**	toluene	58	3:1	59
11	**III**	MeOH	69	4:1	16
12	**III**	neat	68	2:1	52
13[f]	**III**	ethyl acetate	88	4:1	53
14[g]	**III**	ethyl acetate	84	2:1	53
15[h]	**III**	ethyl acetate	91	4:1	73
16[i]	**III**	**ethyl acetate**	**95**	**10:1**	**95**
17[i,j]	**III**	ethyl acetate	51	4:1	88
18[i,k]	**III**	ethyl acetate	76	17:1	90

[a] Unless noted, all reactions were carried out with **1a** (1 mmol), **2a** (0.2 mmol) and catalyst (20 mol%) in the indicated solvent (0.2 mL, laboratory grade solvent) for 24 h.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by HPLC analysis.
[e] *ent*-**3a** was obtained.
[f] 0.4 mL ethyl acetate was used.
[g] 2 mmol of **1a** were used.
[h] The reaction was carried out at 0 °C, $t = 1.5$ days.
[i] The reaction was carried out at −25 °C, $t = 1.5$ days.
[j] 10 mol% of **III** was used.
[k] Anhydrous ethyl acetate was used. nd = not determined.

afforded in excellent yield (98%) and enantioselectivity (95% *ee*) coupled with a very good diastereomeric ratio (12:1). The presence of a substituent at the 3-benzoyl group of the Michael acceptor was also compatible to our reaction condition. 4-Chlorophenyl- or naphthyl-substituted compounds (**2h–k**) provided the corresponding products **3h–k** in moderate to excellent yields (36–95%) and enantioselectivities (72–98% *ee*). The moderate yield in the case of adduct **3h** was partly because of the low solubility of the corresponding starting material (**2h**). A re-examination of solvents revealed that the yield and diastereomeric ratio (58%, *dr* > 20:1) can be improved by employing tetrahydrofuran as solvent albeit with somewhat diminished enantioselectivity (87%, see the Supporting Information). As a limitation to the present method, the product containing a 3-acetyl substituent was obtained in poor chemical yield (< 10%).

Having demonstrated the suitability of this process for the Michael addition of cyclohexanone (**1a**) to different Michael acceptors (**2a–k**), we then turned our attention toward various cyclic and acyclic ketones (**1b–e**) with **2a** or **2b** as the electrophilic part in our optimized reaction conditions to provide the corresponding coumarin derivatives **3l–o** (Table 3). Moderate diastereoselectivity (4:1) but good enantioselectivity (77% *ee*) and good yield (85%) were obtained when cyclopentanone (**1b**) was used as nucleophile with **2a** (entry 1). Acetone (**1c**) was also a suitable substrate in our protocol. The adduct **3m** was obtained in excellent yield (93%) and high diastereoselectivity (> 20:1) but with a poor enantioselectivity (14% *ee*, entry 2). The scope of using acyclic aliphatic ketones was further extended by employing 2-hexanone (**1d**) as nucleophile. The corresponding adduct **3n** was obtained with good stereoselectivities (> 20:1 *dr*

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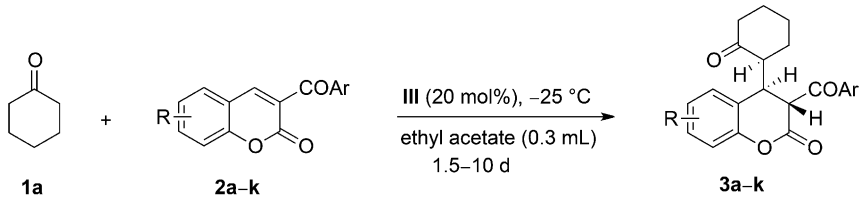
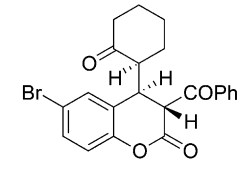
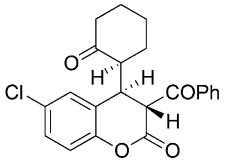
Table 2. Substrate scope for the organocatalytic Michael addition of cyclohexanone (**1a**) and 3-aroylcoumarins **2**.[a–d]



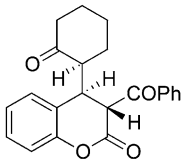
1a **2a–k** **3a–k**



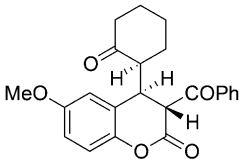
3a,[e] 95%, 1.5 d
10:1 *dr*, 95 (>99)% *ee*



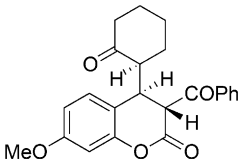
3b, 86%, 3 d
19:1 *dr*, 91% *ee*



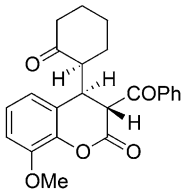
3c, 93%, 1.5 d
18:1 *dr*, 84% *ee*



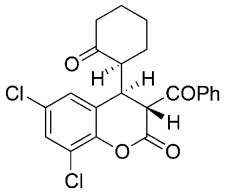
3d, 87%, 1.5 d
>20:1 *dr*, 96% *ee*



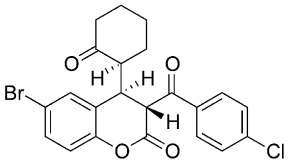
3e, 30%, 10 d
10:1 *dr*, 67% *ee*



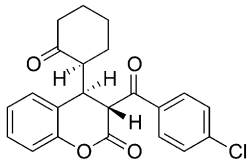
3f, 85%, 10 d
>20:1 *dr*, 80% *ee*



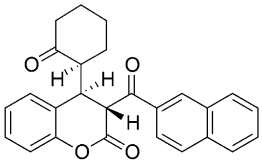
3g,[e] 98%, 1.5 d
12:1 *dr*, 95 (98)% *ee*



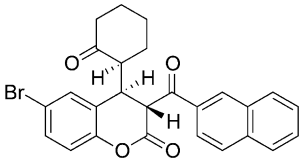
3h, 36%, 10 d
5:1 *dr*, 98% *ee*



3i, 58%, 10 d
7:1 *dr*, 72% *ee*



3j, 95%, 4 d
20:1 dr, 75% ee



3k, 95%, 2 d
12:1 *dr*, 89% *ee*

[a] Unless noted, all reactions were carried out with **1** (1.5 mmol), **2** (0.3 mmol) and catalyst (20 mol%) in ethyl acetate (0.3 mL) for 1.5–10 days.
[b] Isolated yield.
[c] Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Enantiomeric excess was determined by HPLC analysis (major isomer).
[e] Value in parenthesis indicates the *ee* value after a single recrystallization.

and 68% *ee*) but only in 10% chemical yield (entry 3). Tetrahydropyran-4-one (**1e**) turned out to be a very good substrate for the present conditions and the adduct **3o** was obtained with an excellent diastereoselective ratio (>20:1) and enantioselectivity (94% *ee*) albeit with moderate yield (41%, entry 4).

The absolute configurations of **3a**, **3g** and **3l** were determined by single crystal X-ray data analyses and those of the other products were assigned by analogy.[12] We believe that the reaction proceeds *via* enamine formation between cyclohexanone and primary amine (**III**), which performs a Michael addition with **2a–k**, leading to the product **3a–o**. In addition, it is necessary to use an excess amount of cyclohexanone (**1a**, up to 5 equiv.) to have full conversion of **2a** into **3a** because the reverse reaction of **3a** does indeed

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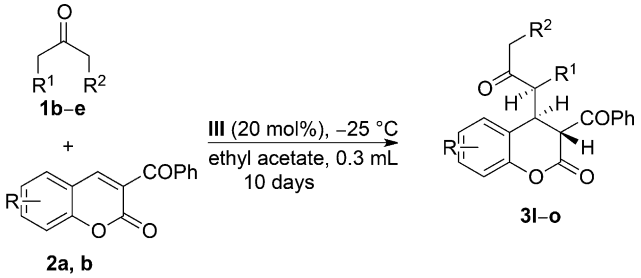
Table 3. Substrate scope for the organocatalytic Michael addition of ketones **1** and 3-aroylcoumarins **2**.[a]



1b: R^1, R^2 = -$(CH_2)_2$-; **1c**: R^1 = H, R^2 = H
1d: R^1 = H, R^2 = C_3H_7 ; **1e**: R^1, R^2 = -(CH_2OCH_2)-
2a: R = 6-Br; **2b**: 6,8-Cl_2

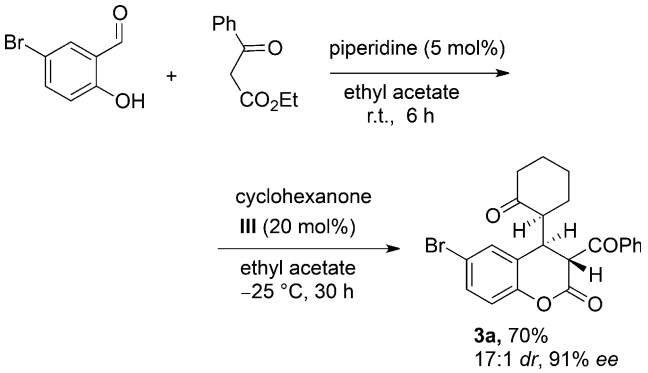
Entry	1	2	3, Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**1b**	**2a**	**3l**, 85	4:1	77
2	**1c**	**2a**	**3m**, 93	>20:1	14
3	**1d**	**2a**	**3n**, 10	>20:1	68
4	**1e**	**2b**	**3o**, 41	>20:1	94

[a] Unless noted, all reactions were carried out with **1** (1.5 mmol), **2** (0.3 mmol) and catalyst (20 mol%) in ethyl acetate (0.3 mL) for 10 days.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by HPLC analysis (major isomer).

take place to provide **2a** and **1a** in the presence of catalyst **III**.[13]

Because the biological activities of the enantiomers are quite different in some cases, development of efficient methods for the preparation of these enantiomeric coumarin units is strongly desired. Indeed, *ent*-**3a** can be prepared by using the same optimized reaction conditions employing quinine-derived primary amine catalyst **V**. The product was obtained with high enantioselectivity (88% *ee*; Scheme 2).

Furthermore, the enantioselective one-pot approach to the synthesis of coumarin derivative **3a** was investigated (Scheme 3). Typical reaction conditions



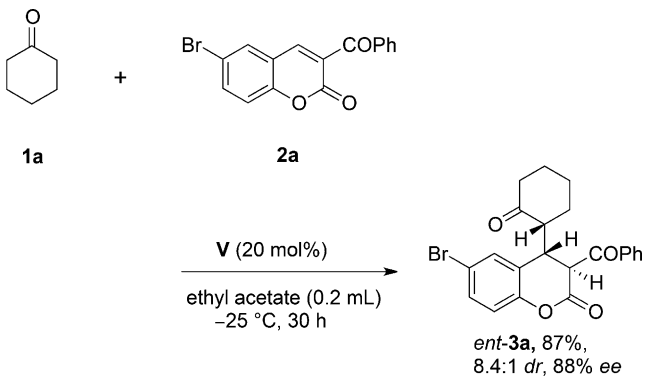
Scheme 3. Organocatalytic one-pot approach to **3a**.

for the Knoevenagel condensation of the representative 5-bromosalicylaldehyde and ethyl benzoylacetate were found to be compatible with the enantioselective route developed herein (see the Supporting Information). The coumarin derivative **3a** was obtained in good yield and notably the level of enantioselectivity mentioned in Table 2 was maintained.

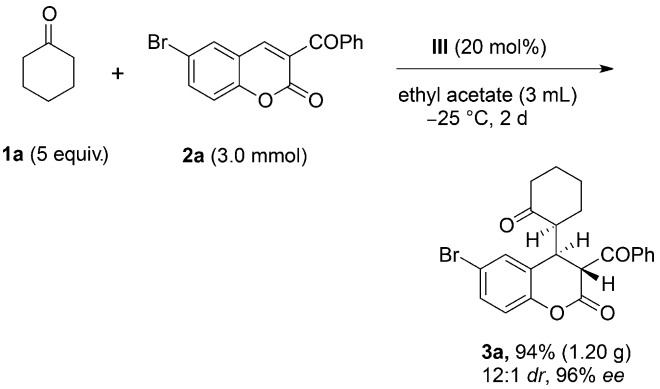
To illustrate the synthetic potential of the catalytic protocol, a gram-scale synthesis of coumarin derivative **3a** was performed. Accordingly, by treatment of 3.0 mmol of **2a** using the optimized conditions, the corresponding product **3a** was obtained in 94% yield (1.20 g) with 96% *ee*. (Scheme 4).

Next we turned our attention towards inclusion of aliphatic aldehydes to further extend the substrate scope. In our preliminary study, the reaction of propanal (**4a**) and **2a** in the presence of catalyst **II** and benzoic acid in tetrahydrofuran followed by PCC oxidation provided a rearranged product mixture of **5a** and **5a′** in 53% isolated yield (2.2:1 *dr*; **5a**: 4% *ee*; **5a′**: 43% *ee*) (Scheme 5).[14]

In conclusion, we have successfully demonstrated an unprecedented chiral amine-catalyzed Michael addition reaction of cyclic and acyclic ketones with substituted coumarin derivatives. A series of substituted coumarin compounds was obtained in 98% isolated



Scheme 2. Organocatalytic approach to *ent*-**3a.**



Scheme 4. Gram-scale synthesis of **3a**.

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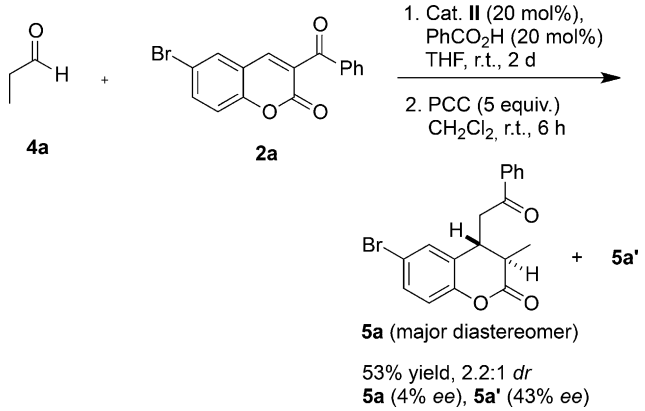

Scheme 5. Organocatalytic Michael addition of **4a** to **2a**.

yield with up to 98% *ee* and >20:1 diastereomeric ratio. Cyclic ketones showed excellent tolerance in the process, which explored a new strategy for the synthesis of optically active coumarin derivatives. Further investigations on asymmetric organocatalytic reactions of 3-aroylcoumarins with other interesting nucleophiles are currently ongoing in our laboratory.

Experimental Section

General Procedure

In a capped glass vial equipped with a magnetic stirring bar was added 3-benzoyl-6-bromocoumarin (**2a**, 98.8 mg, 0.3 mmol) and catalyst **III** (20.3 mg, 20 mol%). Ethyl acetate (0.3 mL) was added and the vial was cooled to −25 °C. Cyclohexanone (**1a**, 147.8 mg, 1.5 mmol) was added and the reaction mixture was stirred for 1.5 days under the same conditions. The reaction was monitored by using TLC and or ^{1}H NMR data analysis. The reaction mixture was diluted with ethyl acetate and then washed with 2 N HCl. The organic layer was concentrated on a rotary evaporater and the residue thus obtained was purified by flash column chromatography on silica gel (hexanes:ethyl acetate = 6:1) to afford the adduct **3a**; yield: 121.8 mg (95%).

Acknowledgements

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[12] CCDC 885634 (**3a**), CCDC 922843 (**3g**), CCDC 922854 (**3l**), and CCDC 885365 (**5a′**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[13] We found that the formation of **2a** was observed when **3a** was treated with 20 mol% of catalyst **III**. For the controlled experiment and the plausible reaction mechanism, please see the Supporting Information.

[14] In our preliminary results, only the relative configurations of **5a** and **5a′** can be determined. When a branched aldehyde, such as isobutyraldehyde was employed to react with **2a** in the presence of pyrrolidine, the similar rearranged adduct **5b** was afforded in low chemical yield. Please also see the Supporting Information for details. Further investigations on the reaction mechanism and for improvement of both chemical yields and stereoselectivities are currently underway.

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