Synthetic Methods

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A Powerful Hydrogen-Bond-Donating Organocatalyst for the Enantioselective Intramolecular Oxa-Michael Reaction of α,β-Unsaturated Amides and Esters**

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The rapid and efficient synthesis of a target molecule still represents a major challenge in the field of synthetic organic chemistry. Chiral oxygen-containing heterocycles, such as isoxazolines, isoxazolidines,[1] chromans,[2] and dihydrobenzofurans,[3] can be found in numerous natural products and biologically active compounds, and significant efforts have been directed towards the development of synthetic methods that are capable of providing facile access to these materials. In particular, O-heterocycles bearing an amide moiety,[4] such as roxifiban[1c] and erythrococcamide,[2c,e] exhibit pharmaceutically important activities (Figure 1). Related carboxylic

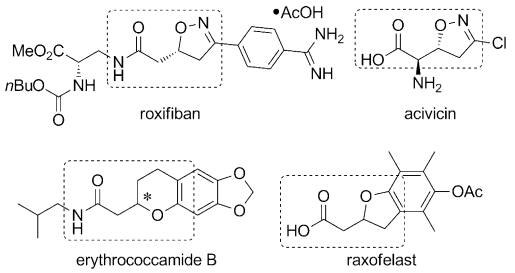
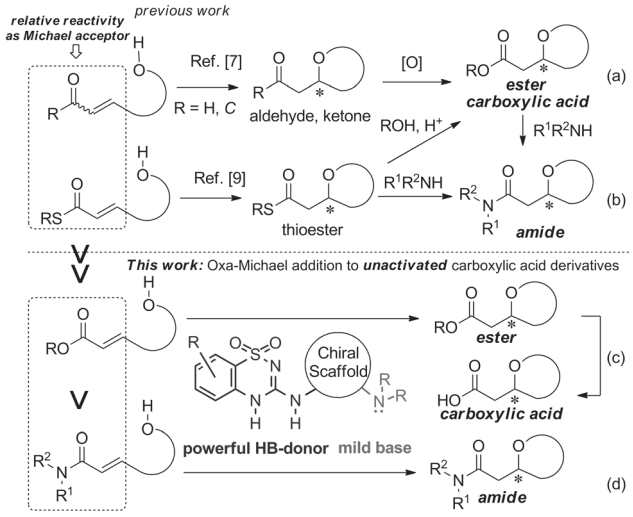


Figure 1. Examples of biologically active carboxylic acids and amides containing different O-heterocyclic scaffolds.

acids, such as acivicin[1d] and raxofelast,[3b,c] have been used as biological tools for drug discovery and as key synthetic intermediates for the construction of more complex derivatives.

One of the most promising approaches to access these chiral carboxylic acid derivatives involves the asymmetric intramolecular oxa-Michael[5,6] reaction (AIOM) of α,β-unsaturated aldehydes or ketones,[7] followed by an oxidation reaction[7g] [Scheme 1 a]. From the perspective of redox economy,[8] a more efficient method has recently been



Scheme 1. A comparison of intramolecular oxa-Michael addition reactions.

reported, using α,β-unsaturated thioesters[9] and imides[10] as activated carboxylic acid equivalents [Scheme 1 b]. However, these approaches are limited, because they require an additional amidation step to obtain the corresponding amide derivatives.[2e,3b,d,10] Furthermore, the products of these reactions can also undergo retro-Michael/Michael racemization in the presence of base;[1c,5] mild conditions and careful manipulation are therefore required for their conversion into the corresponding esters and amides. In contrast to the work outlined above, the direct AIOM reaction of unactivated α,β-unsaturated esters[11] [Scheme 1 c] has received much less attention, likely because of the poor reactivity of the Michael acceptor[12] and the poorer reactivity of oxygen as a nucleophile[5] compared with nitrogen or carbon nucleophiles.[13,14] Therefore, this reaction may still be substantially improved, especially in terms of enantioselectivity, the variation in the O-heterocycles obtained, and their subsequent derivatization.[11] Furthermore, to the best of our knowledge, there have been no reports in the literature concerning the AIOM reaction of much less activated α,β-unsaturated amides [Scheme 1 d], despite the number of different potential uses of the amide functional group.[4] The development of a direct and efficient AIOM reaction for unactivated esters and amides would enable the straightforward synthesis of chiral O-heterocycles bearing carboxylic acid equivalents, without the need for multi-step processes [Scheme 1 c and d]. In

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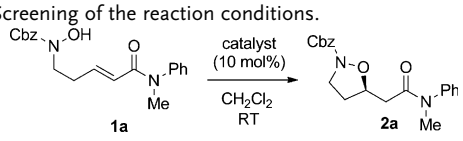
addition, this method has several advantages, in that α,β-unsaturated esters and amides can be prepared using readily available Wittig or Horner–Wadsworth–Emmons (HWE) reagents, and the cyclized products are less likely to racemize because the α-hydrogen atoms of esters and amides are less acidic than those of ketones and thioesters.

Herein, we report the first AIOM reaction of α,β-unsaturated amides using a newly developed powerful hydrogen-bond (HB)-donating organocatalyst. Bifunctional HB-donor organocatalysts have become a particularly promising approach to highly enantioselective reactions,[15] although there is still a strong drive to improve their catalytic activities and expand their scope of application. We envisaged that improving their HB-donating ability could further activate the poorly reactive Michael acceptor, and that this would be more important[10] for an effective cyclization [Scheme 1 d] than increasing the basicity of the catalyst to activate the O-nucleophile,[16] because it is well known that the products of the oxa-Michael reaction often undergo retro-Michael reaction.[5]

The α,β-unsaturated amide **1a**, which bears a hydroxylamine nucleophile (NOH), was selected as a substrate for the screening of catalysts for the AIOM reaction (Table 1). Although readily available organic bases such as triethylamine and cinchonidine did not work at all in this reaction (data not shown), bifunctional thiourea[15a,b] **I** moderately promoted the cyclization of **1a** to afford isoxazoline **2a** in 88% yield and 81% *ee* after five days (Table 1, entry 1). The use of squaramide **III**,[15f] which contains two HB-donating N–H protons, which are conformationally fixed in the active form, led to slight improvements in the reaction time and enantioselectivity, and gave **2a** in an 88% yield (88% *ee*) after four days (Table 1, entry 3). Encouraged by this result, we investigated several other HB-donating catalysts bearing a heterocyclic scaffold, such as benzimidazole[15g,h] **IV**, quinazoline[17a] (TQC) **V**, and the benzothiadiazines[17b] (TBCs) **VI**–**IX** (entries 4–9). The results revealed that TBC **VI** gave the best results, with the reaction reaching completion in 24 h to give **2a** in 92% yield and a high enantioselectivity (95% *ee*, entry 6).[18] These results suggested that the HB-donating ability plays a crucial role in the reaction by tightly binding amide **1a**, and providing excellent levels of catalytic activity. To achieve a more powerful catalytic system, we proceeded to design and evaluate a series of TBC-based organocatalysts bearing an electron-withdrawing group on their aromatic ring, and found that the fluorine-containing TBCs (FTBCs) **VII**–**IX** improved the chemical yields (99%). These results provide further indication of the importance of the HB-donating ability of the catalyst (entries 7–9). Interestingly, 6-FTBC (**VIII**) gave the best enantioselectivity (97% *ee*), presumably because of the catalytic activity derived from the balance between the inductive and mesomeric effects of the fluorine substituent (entry 8).[19]

With the optimized conditions in hand, we proceeded to investigate the effect of the substituents (R^1–R^3) on the amides **1** (Table 2). Catalyst **VI** could be successfully applied to the cyclization of both tertiary (Table 2, entries 1–3) and secondary amides (entries 4 and 5), with the corresponding amides **2b–f** obtained in 70–99% yields with *ee* values in the range of 84–96%. In addition to the biological importance of these compounds,[2] as discussed above, isoxazolidines **2** could also be regarded as δ-amino-β-hydroxy-amino acid equiva-

Table 1: Screening of the reaction conditions.



Entry	Catalyst	Time [h]	Yield[a] [%]	*ee*[b] [%]
1	**I**	120	88	81
2	**II**	24	trace	n.d.
3	**III**	96	88	88
4	**IV**	24	trace	n.d.
5	**V**	336	74	51
6	**VI**	24	92	95
7	**VII**	24	99	93
8	**VIII**	24	99	97
9	**IX**	24	99	79

[a] Yields of isolated products. [b] The *ee* values were determined by HPLC analysis on a chiral stationary phase. n.d. = not determined.

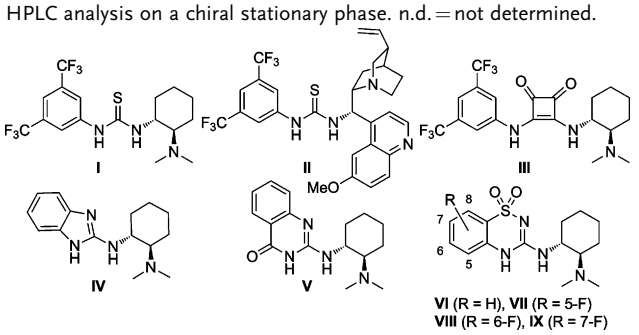
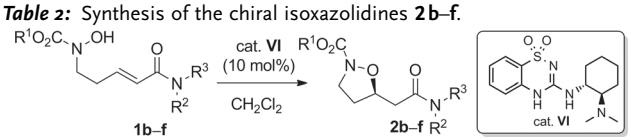
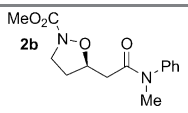
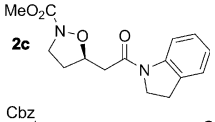
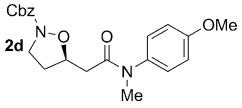
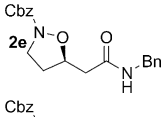
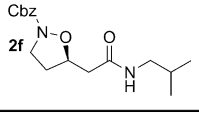
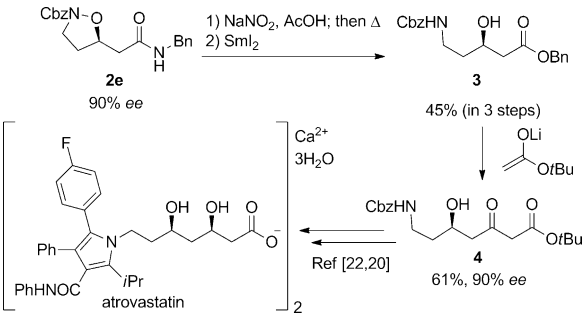


Table 2: Synthesis of the chiral isoxazolidines **2b–f**.



Entry	Product	Conditions	Yield[a] [%]	*ee*[b] [%]
1		RT, 24 h	89	92
2		RT, 24 h	97	84
3		RT, 24 h	99	96
4		40 °C, 24 h	99	90
5		40 °C, 72 h	70	84

[a] Yields of isolated products. [b] The *ee* values were determined by HPLC analysis on a chiral stationary phase.

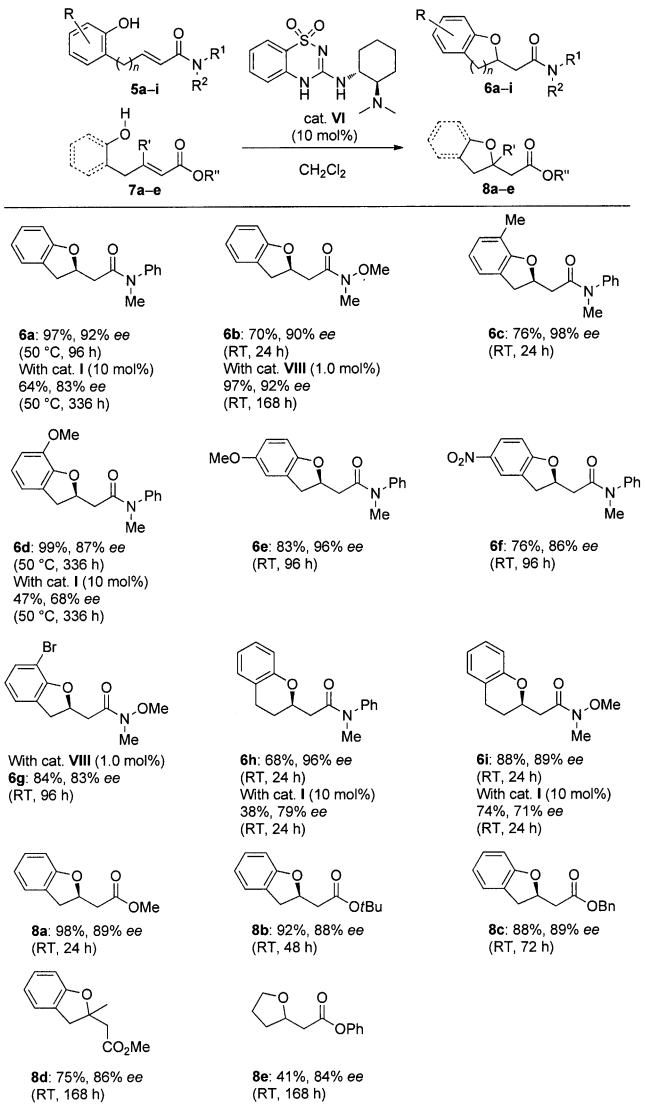


Scheme 2. Application of **2e** to a concise formal total synthesis of atrovastatin. Cbz = carbobenzyloxy.

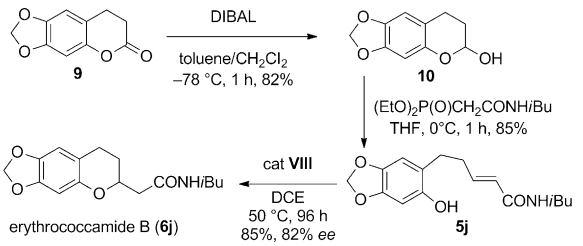
lents, following the cleavage of the N–O bond. With this in mind, and to highlight the overall utility of **2**, we performed a concise formal total synthesis of atorvastatin (Scheme 2).[20] Thus, amide **2e** was readily converted into δ-amino-β-hydroxyester[21] **3** in three steps through N–O bond cleavage[18] followed by a cross-Claisen condensation with *tert*-butyl acetate to give intermediate **4**, which is a known intermediate for atorvastatin.[22,20]

We then focused on the AIOM reaction of α,β-unsaturated amides **5** and esters **7** bearing phenolic OH groups (Scheme 3). Pleasingly, a variety of different dihydrobenzofurans (**6a**–**g**; Scheme 3) were synthesized in good yields (70–99%) and high enantioselectivities (83–96% *ee*), with methyl, methoxy, nitro, and bromo groups being well tolerated under the reaction conditions. In sharp contrast with literature precedent for the oxa-Michael reaction of α,β-unsaturated esters to give six-membered rings,[11] the current method provided much higher enantioselectivities (89–96% *ee*) for the synthesis of chromanes **6h** and **6i**. A gram-scale reaction of **5b** (1.15 g, 5.2 mmol) cleanly furnished the corresponding amide **6b** (1.12 g, 97%, 92% *ee*) with only 1.0 mol% of the catalyst 6-FTBC (**VIII**), albeit with a longer reaction time. The resulting Weinreb amides **6b**, **6g**, and **6i** could, in principle, be transformed into a variety of different ketones following the coupling reaction with organolithium or organomagnesium reagents.[3d] The powerful catalytic activity of the TBC catalyst was demonstrated by comparing its results with those from the thiourea-type catalyst **I** (**6a**, **6d**, **6h**, and **6i**). The chemical yields and enantioselectivities were improved considerably by using the TBC. The absolute configurations of the products were assigned as 2′*R* by synthesizing the known ester **8a** and comparing the optical rotation data with the literature value.[11e] Pleasingly, the construction of a chiral quaternary carbon center was also successful, and the corresponding O-heterocycle **8d** was obtained in 75% yield with 86% *ee*. Much to our surprise, an aliphatic OH group could be used as the nucleophile in this AIOM reaction to furnish the chiral tetrahydrofuran **8e** with good enantioselectivity.

The greatest advantage of using the current AIOM reaction of α,β-unsaturated amides is perhaps best demonstrated by the rapid asymmetric total synthesis of the natural product erythrococcamide B[2c,e] (**6j**) (Scheme 4). The readily available lactone **9** was reduced with diisobutylaluminum hydride (DIBAL) to the corresponding lactol **10**, which was then subjected to a HWE reaction to give the α,β-unsaturated amide **5j**. The first enantioselective synthesis of **6j** was subsequently achieved using the 6-FTBC-catalyzed oxa-Michael reaction.

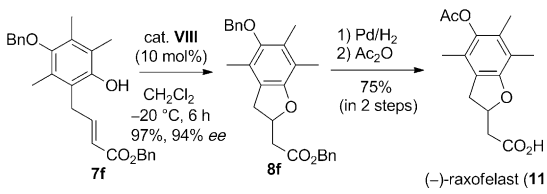


Scheme 3. Scope and limitations. Yields of isolated products. The *ee* values were determined by HPLC analysis on a chiral stationary phase. The stereochemistry of **6** was assigned in analogy to **8**.



Scheme 4. Application of the TBC-catalyzed asymmetric oxa-Michael reaction to the rapid asymmetric total synthesis of erythrococcamide B. DCE = 1,2-dichloroethane.

The high catalytic activity of 6-FTBC was further exemplified by the AIOM reaction of the α,β-unsaturated ester **7 f**, as the cyclization reaction proceeded at an unprecedentedly low temperature,[11] affording the corresponding product **8 f** in 97 % yield with 94 % *ee* (Scheme 5). The first enantioselective



Scheme 5. Further application of the TBC-catalyzed asymmetric oxa-Michael reaction.

synthesis of raxofelast,[3b,c] which is used as an antioxidant to modulate inflammatory response, was accomplished through the double debenzylation of **8 f**, followed by selective acetylation of the phenolic OH group.

In conclusion, we have developed a powerful HB-donating organocatalyst for the AIOM reaction, which effectively activated relatively inert α,β-unsaturated amides and esters as electrophiles, and facilitated the production of a variety of chiral O-heterocycles with useful functional groups for derivatization. The potential of organocatalysts of this particular type could be further increased by refining the design of the molecular structure of catalysts, and identifying applicable reactions. Further studies to expand the scope of this method are currently underway in our laboratory.

Experimental Section

General procedure: The benzothiadiazine catalyst **VI** (3.2 mg, 0.01 mmol, 10 mol %) was added to a solution of **1**, **5**, or **7** (0.1 mmol) in CH_2Cl_2 (1.0 mL, 0.1 M), and the resulting mixture was stirred at ambient temperature for 24 h. The reaction mixture was then evaporated, and the resulting crude residue was purified by column chromatography on silica gel, eluting with *n*-hexane/ethyl acetate to give the analytically pure compound **2**, **6**, or **8**. The enantiomeric ratios of all of the compounds were determined by HPLC analysis on a chiral stationary phase.

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Communications

Synthetic Methods

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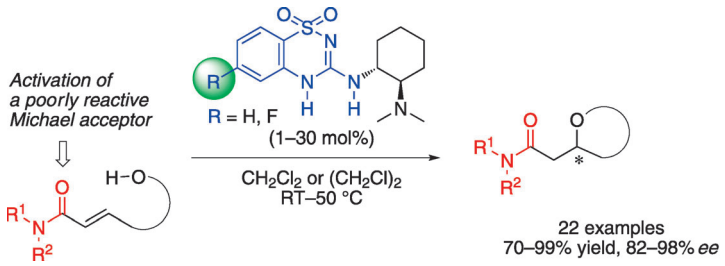
A Powerful Hydrogen-Bond-Donating Organocatalyst for the Enantioselective Intramolecular Oxa-Michael Reaction of α,β-Unsaturated Amides and Esters



Tuning the organocatalyst: An unprecedented enantioselective intramolecular oxa-Michael reaction of unactivated α,β-unsaturated amides and esters catalyzed by a powerful hydrogen-bond-donating organocatalyst has been developed. Furthermore, the products obtained from this reaction have been used for the straightforward asymmetric synthesis of several natural products and biologically important compounds.