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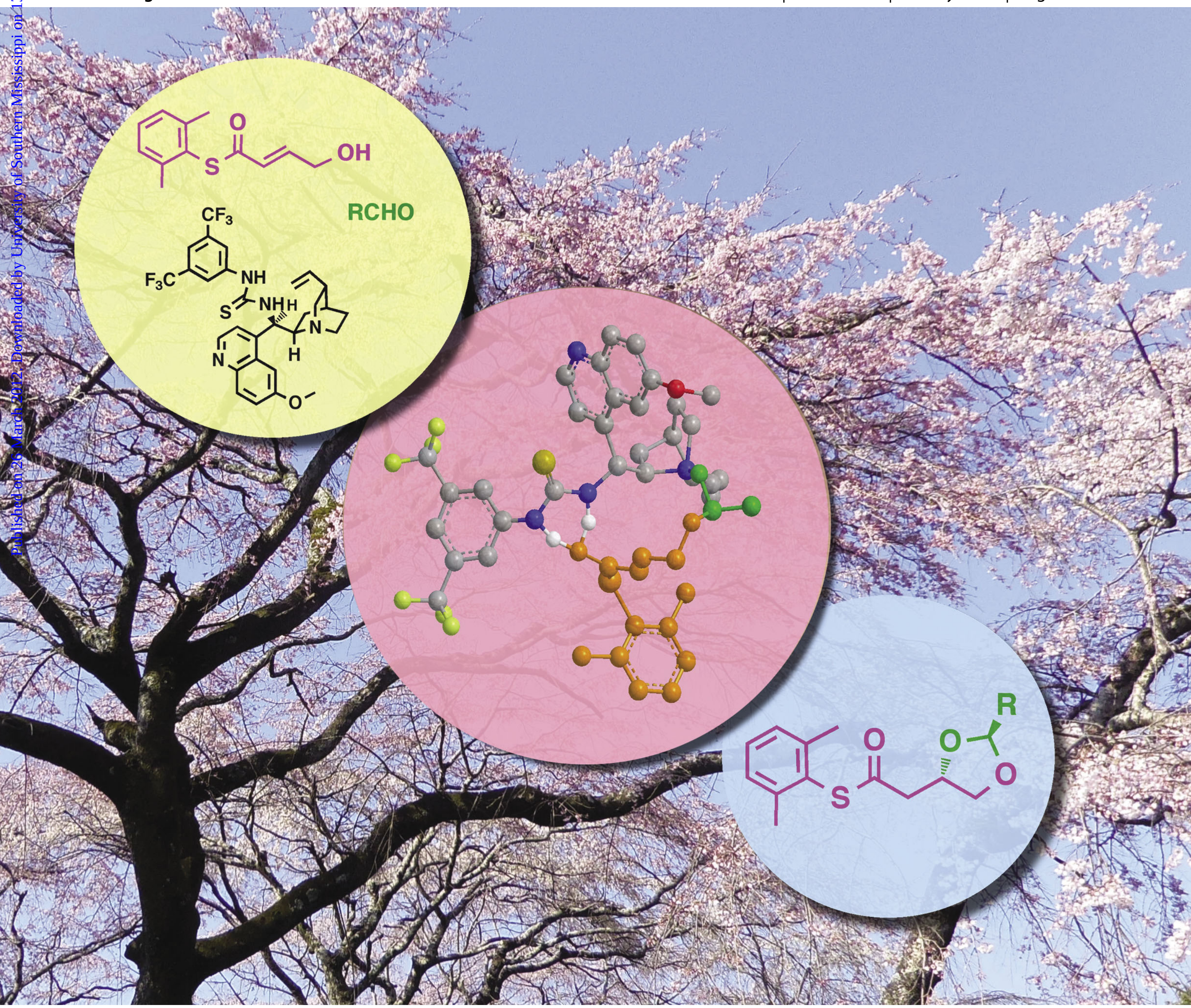

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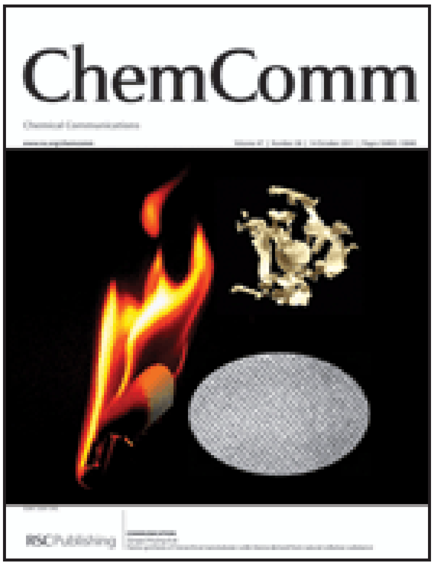

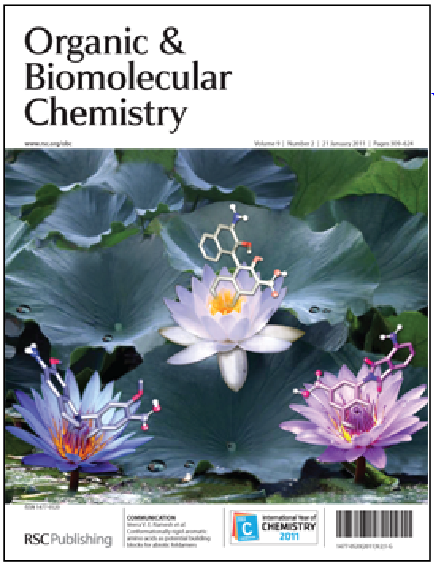

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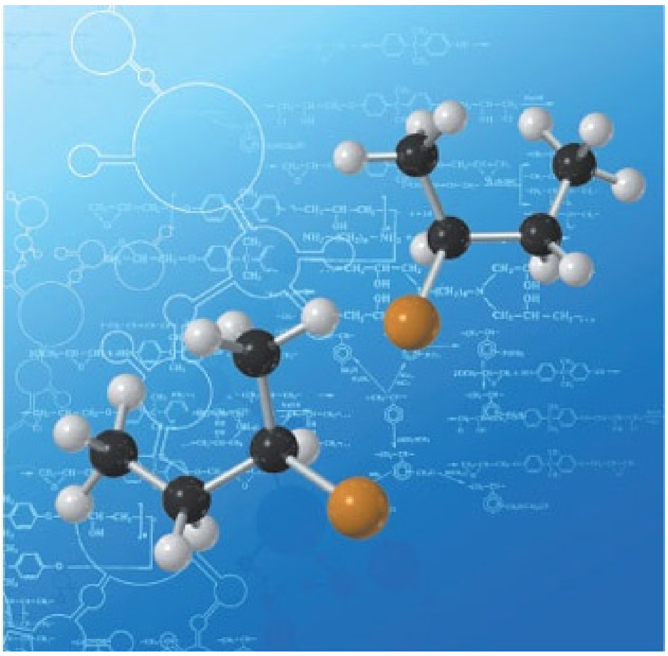

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Organocatalytic asymmetric oxy-Michael addition to a γ-hydroxy-α,β-unsaturated thioester *via* hemiacetal intermediates†‡

Takaaki Okamura, Keisuke Asano* and Seijiro Matsubara*

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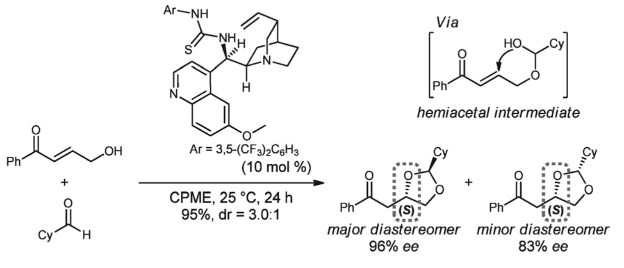
We report an asymmetric oxy-Michael addition to a γ-hydroxy-α,β-unsaturated thioester *via* hemiacetal intermediates in the presence of *Cinchona*-alkaloid-thiourea-based bifunctional organocatalysts. This method provides a novel enantioselective route to β-hydroxy carboxyl compounds, which in turn can be used to synthesize valuable chiral building blocks.

β-Hydroxy carbonyl compounds are important synthetic intermediates, and they exist as structural motifs in a variety of natural products; hence, considerable efforts have been devoted to their stereoselective synthesis.[1] One of the most notable methods for the enantioselective synthesis of β-hydroxy carbonyls, besides the aldol reaction[2] and the hydrogenation of β-ketoesters,[3] is the conjugate addition of oxygen-centred nucleophiles to α,β-unsaturated substrates.[4] Direct hydration of α,β-unsaturated substrates by the conjugate addition of water is challenging because of the low nucleophilicity of water, high reaction reversibility, and the difficulty involved in efficient stereochemical control.[5] Nevertheless, several protocols for stereoselective formal hydration using *O*-nucleophiles bearing a removable group have been developed.[6–11] Catalytic enantioselective reactions involving the conjugate addition of benzyl alcohol[8] or allyl alcohol[9] suffer from drawbacks similar to those observed when using water as the nucleophile. However, the use of an oxime[10a–c] or hydrogen peroxide[10d] as a water surrogate is advantageous because of its high nucleophilicity; the labile *N–O* or *O–O* bond facilitates the subsequent reductive cleavage, leading to free β-hydroxy products. Another efficient route is intramolecularization[12] using boronic acid hemiesters generated *in situ* from γ-hydroxy-α,β-unsaturated ketones and boronic acids; the hemiester undergoes intramolecular oxy-Michael addition to form a dioxaborolane, which then affords the corresponding optically active β,γ-dihydroxy ketone upon oxidative hydration.[11] However, in most of the reported examples, α,β-unsaturated ketones or aldehydes have been used as substrates, and there are very few demonstrations of asymmetric oxy-Michael addition to a higher-oxidation-state substrate such as an α,β-unsaturated carboxylic acid derivative,[10a,13] which can be an alternative to the acetate aldol reaction.[14]

We recently reported intramolecular oxy-Michael addition reactions mediated by *Cinchona*-alkaloid-thiourea-based bifunctional organocatalysts.[15] By our protocol, enantioselective oxy-Michael addition to γ-hydroxy-α,β-unsaturated ketones *via* hemiacetal intermediates was realized, and 1,3-dioxolanes bearing an easily removable acetal functionality were obtained (Scheme 1).[15a] Although the diastereoselectivity of this reaction was only moderate, the absolute configurations at the β-positions of the carbonyl group were consistent in both diastereomers; further, this reaction proceeded with high enantioselectivity. Therefore, we sought to apply the abovementioned method to reactions in which carboxylic acid derivatives were used as substrates. Herein, we present a novel asymmetric oxy-Michael addition to a γ-hydroxy-α,β-unsaturated carboxylic acid derivative *via* a hemiacetal intermediate in the presence of bifunctional organocatalysts derived from *Cinchona* alkaloids.[6,16]

Initially, we employed the optimized conditions reported in our previous work of the reaction with γ-hydroxy-α,β-unsaturated ketones as substrates (Table 1).[15a] The reaction of γ-hydroxy-α,β-unsaturated ester **1a** with cyclohexanecarboxaldehyde (**2a**) in the presence of quinidine-based bifunctional catalyst **4a** (Fig. 1) did not proceed at all, presumably because of the poor electrophilicity of the substrate (Table 1, entry 1). Phenyl ester **1b** afforded the desired products, albeit in very low yield (Table 1, entry 2). In order to increase the electrophilicity of the substrate, we used some thioesters as substrates (Table 1, entries 3–6).[17] Thioester **1c** afforded the corresponding product



Scheme 1 Oxy-Michael addition *via* hemiacetal intermediates to γ-hydroxy-α,β-unsaturated ketones *via* hemiacetal intermediates.

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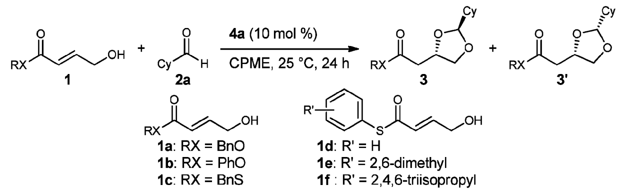
‡ Electronic supplementary information (ESI) available: Experimental procedures, analytical and spectroscopic data for synthetic compounds, copies of NMR and HPLC spectra. See DOI: 10.1039/c2cc31602a

Table 1 Optimization of substrates[a,b]



Entry	1	Yield[c,d] (%)	ee (%) (**3**, **3′**)	dr (**3**/**3′**)
1	**1a**	0 (97)	—	—
2	**1b**	13 (87)	96, 84	3.0
3	**1c**	18 (69)	94, 61	3.6
4	**1d**	7 (<1)	97, 87	3.7
5	**1e**	62 (38)	97, 84	4.3
6	**1f**	28 (60)	93, 85	4.0

[a] Reactions were run using **1** (0.25 mmol), **2a** (0.25 mmol), and **4a** (0.025 mmol) in CPME (0.5 mL). [b] CPME = cyclopentyl methyl ether. [c] Isolated yields. [d] Values in parentheses show the starting material recovery.

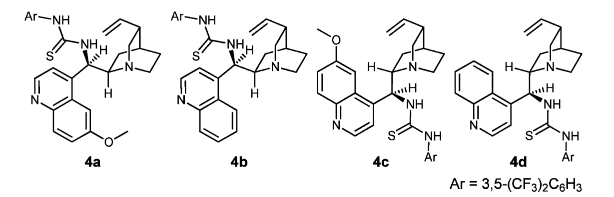
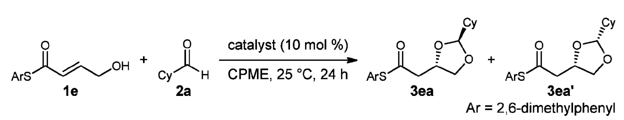


Fig. 1 Bifunctional organocatalysts derived from *Cinchona* alkaloids.

in higher yield than did the abovementioned esters (Table 1, entry 3). Benzenethiol ester **1d** also gave the desired products in low yield, but when thioesters bearing bulkier aryl groups were employed, side reactions were suppressed to a great extent. 2,6-Dimethylbenzenethiol ester **1e** was identified as the best substrate in terms of the product yield (Table 1, entries 4–6).

We next optimized the reaction conditions using **1e** as the substrate (Table 2). After screening a number of solvents, we found that cyclopentyl methyl ether (CPME) was the optimum solvent in terms of both yield and stereoselectivity (Table 2, entries 1–5). Further modification of other conditions such as

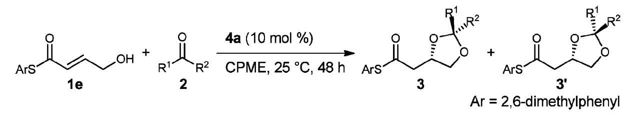
Table 2 Optimization of reaction conditions[a,b]



Entry	Catalyst	Solvent	Yield[c,d] (%)	ee (%) (**3ea**, **3ea′**)	dr (**3ea**/**3ea′**)
1	**4a**	CPME	62 (38)	97, 84	4.3
2	**4a**	THF	20 (78)	96, 76	4.3
3	**4a**	Et_2O	65 (12)	97, 87	3.9
4	**4a**	Benzene	60 (<1)	94, 84	3.4
5	**4a**	CH_2Cl_2	43 (1)	95, 73	4.1
6[e]	**4a**	CPME	90 (8)	96, 81	4.4
7[e]	**4b**	CPME	89 (1)	95, 74	3.5
8[e]	**4c**	CPME	90 (6)	–94, –59	4.2
9[e]	**4d**	CPME	90 (6)	–91, –47	4.1

[a] Reactions were run using **1e** (0.25 mmol), **2a** (0.25 mmol), and the catalyst (0.025 mmol) in the solvent (0.5 mL). [b] CPME = cyclopentyl methyl ether. [c] Isolated yields. [d] Values in parentheses show the starting material recovery. [e] Reactions were run using 0.50 mmol of **2a** in 0.25 mL of CPME for 48 h.

Table 3 Optimization of aldehydes and ketones **2**[a,b]



Entry	R^1	R^2	**2**	Yield[c] (%)	ee (%) (**3**,**3′**)	dr (**3**/**3′**)
1	Cy	H	**2a**	90	96, 81	4.4
2	Et	H	**2b**	99	95, 88	3.4
3	*i*-Pr	H	**2c**	99	96, 87	3.8
4	*t*-Bu	H	**2d**	73	**99**, **97**	3.5
5	CF_3	Ph	**2e**	99	69, 72	1.1
6	CH_3	CH_3	**2f**	<5	N. D.	—
7	$-(CH_2)_5-$		**2g**	31	99	—
8[d]	H	H	**2h**	86	72	—

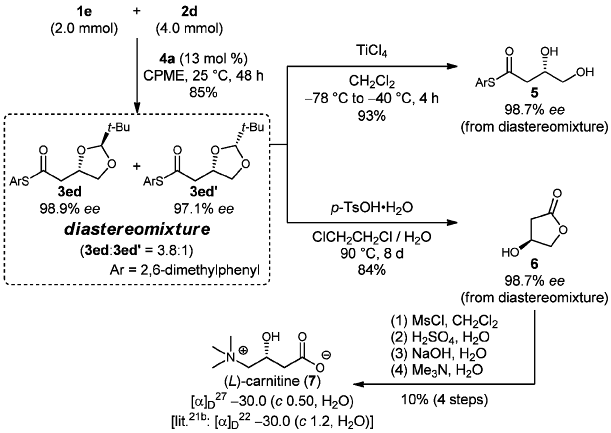
[a] Reactions were run using **1e** (0.25 mmol), **2** (0.5 mmol), and **4a** (0.025 mmol) in CPME (0.5 mL). [b] CPME = cyclopentyl methyl ether. [c] Isolated yields. [d] Reaction was run using aqueous formaldehyde (37% solution, 0.5 mmol).

the amount of **2a**, concentration, and reaction time helped improve the yield to a practical level with only a slight decrease in the enantioselectivity (Table 2, entry 5). Catalyst screening showed that **4c** (Fig. 1) efficiently catalyzes the reaction to afford opposite enantiomers of the products in good yield and with high enantioselectivity (Table 2, entry 8).

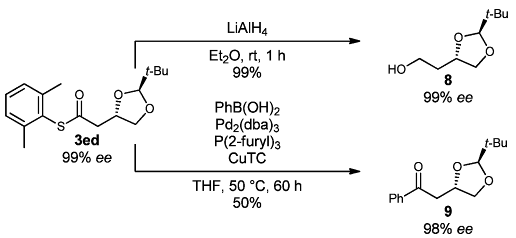
Using the optimized reaction conditions and **4a** as a catalyst, we subsequently investigated the reactions of some other aldehydes and ketones **2** (Table 3).[18] Although aryl aldehydes were much less reactive,[19] some aliphatic aldehydes **2b–2d** gave the corresponding products in high yields and with good enantioselectivities (Table 3, entries 2–4). Pivalaldehyde (**2d**) proved to be a good counterpart and gave excellent enantioselectivity for both diastereomers (Table 3, entry 4). An electron-deficient ketone such as **2e** could also be employed in the reaction; however, the enantioselectivity was only moderate in this case (Table 3, entry 5). Although the use of a symmetric ketone or aldehyde would circumvent the generation of diastereomers, the reaction using acetone (**2f**) was sluggish (Table 3, entry 6), and the yield obtained from cyclohexanone (**2g**) was low despite the excellent enantioselectivity (Table 3, entry 7). On the other hand, aqueous formaldehyde (**2h**) afforded the product in acceptable yield, but the enantioselectivity was unsatisfactory, probably because of the presence of water (Table 3, entry 8).

To demonstrate the utility of the proposed method, we extended the optimized reaction to the asymmetric syntheses of some β-hydroxy carboxyl compounds (Scheme 2). Oxy-Michael addition to **1e** using **2d** as the source of an oxygen-centred nucleophile in the presence of 13 mol % **4a** on the 2 mmol scale afforded the products **3ed** and **3ed′** in 3.8 : 1 diastereomeric ratio, with excellent enantioselectivity. Subsequent treatment of the diastereomixture of **3ed** and **3ed′** with titanium tetrachloride led to the generation of a free β,γ-dihydroxy product **5** with high optical purity while keeping the thioester group intact. Alternatively, treatment of the diastereomixture with *p*-toluenesulfonic acid in aqueous medium gave β-hydroxy-γ-butyrolactone **6**, a versatile chiral synthetic intermediate[20] that could be transformed into (L)-carnitine (**7**), an important bioactive agent, *via* a reported procedure.[21]

Taking advantage of the thioester functionality, we carried out functional group transformations of **3ed**, and found that



Scheme 2 Application of the proposed protocol to asymmetric syntheses of β-hydroxy carboxyl compounds.



Scheme 3 Transformations of the thioester group of **3ed**.

the chiral acetal moiety was unaffected after the transformations (Scheme 3).[15a,22] Reduction of **3ed** with lithium aluminium hydride afforded the corresponding primary alcohol **8** quantitatively without loss of optical purity. Besides, Liebeskind–Srogl cross coupling enabled the replacement of the arylthio group of **3ed** to give ketone **9**, indicating that these thioester products can be easily transformed into various chiral ketones.[23]

In conclusion, we have developed a novel asymmetric oxy-Michael addition reaction to the α,β-unsaturated carboxylic acid derivative. The use of a suitable γ-hydroxy-α,β-unsaturated thioester allowed for enantioselective oxygen induction *via* hemiacetal formation, and subsequent deacetalization afforded valuable optically active β-hydroxy carboxyl compounds. Further studies on the application of this methodology to the asymmetric syntheses of various chiral materials, including natural products, are currently underway in our laboratory.

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