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COMMUNICATION

Chiral Sc-catalyzed asymmetric Michael reactions of thiols with enones in water†‡

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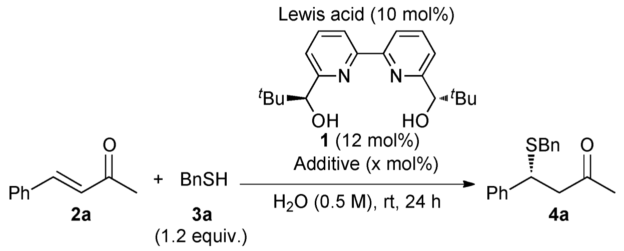
Asymmetric Michael reactions of thiols with enones were catalyzed by a $Sc(OTf)_3$–chiral bipyridine complex at room temperature in water without using any organic solvents, to afford the desired sulfides in high yields with high enantioselectivities.

Organic reactions in water are now of great interest because remarkable reactivity and selectivity that are unobtainable in organic solvents are often observed in water.[1] In addition, from an environmental point of view, it is desirable to use water rather than organic compounds as a solvent. In this context, several types of reactions in aqueous media have been developed; however, organic solvents are required in many cases as cosolvents to dissolve organic materials. Another issue of organic reactions in water is that most reactive species are not stable in the presence of water. This is also the case for chiral catalysts, which are often unstable in the presence of water and thus it is difficult to conduct catalytic asymmetric reactions in the presence of water.[2]

Asymmetric Michael reactions of thiols with enones mediated by chiral catalysts are among the most efficient methods for the preparation of optically active sulfides. Although several chiral catalysts have been developed, most asymmetric reactions have been carried out in organic solvents.[3–5] In addition, Michael acceptors are rather limited to cyclic enones, and few successful examples using acyclic enones have been reported.[4a,4e,4f,4g]

In previous papers, we have disclosed that $Sc(OTf)_3$–chiral bipyridine **1** is an effective catalyst for enantioselective hydroxymethylation of silyl enol ethers with formaldehyde in aqueous media.[6] When $Sc(OSO_3C_{12}H_{25})_3$–chiral bipyridine **1** was used as a chiral Lewis acid catalyst, the same reactions proceeded in water without using any organic solvents.[7] The catalyst has also been applied to enantioselective ring-opening reactions of *meso*-epoxides[8–10] and Nazarov-type reactions[11] in water. In these reactions, the chiral Sc Lewis acids are stable, and efficiently catalyzed the enantioselective reactions in the presence of water.

Table 1 Optimization of reaction conditions in the asymmetric Michael reactions of **1a** with **2a**



Entry	Lewis acid	Additive	Yield (%)	Ee (%)
1	$Sc(OTf)_3$	Pyridine (20)	85	91
2	$Sc(OSO_3C_{12}H_{25})_3$	Pyridine (20)	94	72
3	$Cu(OTf)_2$	Pyridine (20)	19	4
4	$Zn(OTf)_2$	Pyridine (20)	45	0
5	$Bi(OTf)_3$	Pyridine (20)	2	1
6	$Sc(OTf)_3$	Et_3N (20)	75	73
7	$Sc(OTf)_3$	Lutidine (20)	91	89
8	$Sc(OTf)_3$	DBU (20)	86	80
9	$Sc(OTf)_3$	LiOH (20)	93	88
10	$Sc(OTf)_3$	NaOH (20)	91	90
11	$Sc(OTf)_3$	KOH (20)	93	90
12	$Sc(OTf)_3$	CsOH (20)	Quant.	90
13	$Sc(OTf)_3$	NaOH (10)	83	87
14	$Sc(OTf)_3$	NaOH (40)	98	5
15	$Sc(OTf)_3$	—	34	57
16	$Sc(OSO_3C_{12}H_{25})_3$	—	81	72

We then decided to use these chiral Lewis acids for asymmetric Michael reactions of thiols with enones.

First, we set the reaction of benzalacetone (**2a**) with benzylthiol (**3a**) as a model, and several reaction conditions were examined (Table 1). Interestingly, the reaction proceeded in water without using any organic solvents. High yields and high enantioselectivities were obtained even at room temperature. The use of $Sc(OTf)_3$–chiral bipyridine **1** with a base (entry 1) gave better results than that of $Sc(OSO_3C_{12}H_{25})_3$–**1** (entry 2), which is contrary to our previous results.[7] Other metal triflates such as $Cu(OTf)_2$, $Zn(OTf)_2$, and $Bi(OTf)_3$, which worked well in asymmetric ring-opening reactions of *meso*-epoxides, were not effective (entries 3–5).[9,10] For bases, organic bases (pyridine, Et_3N, lutidine, and DBU) as well as inorganic bases (LiOH, NaOH, KOH, and CsOH) worked well to afford the desired adducts in high yields with high enantioselectivities (entries 6–12). In the presence of an excess amount of base (40 mol% (entry 14) *vs.*

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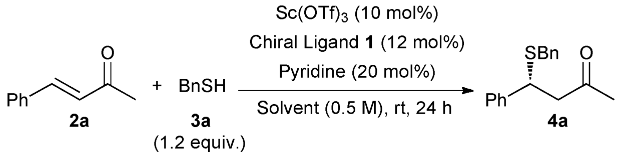
‡ Electronic supplementary information (ESI) available: Experimental details and physical data of the products. See DOI: 10.1039/c1ob05424d

Table 2 Effect of solvents



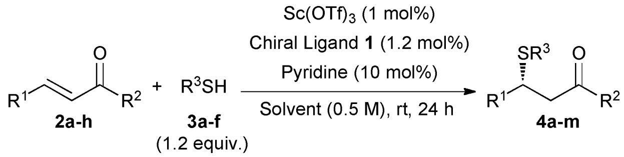
Entry	Solvent	Yield (%)	Ee (%)
1	H_2O	84	91
2	H_2O/THF = 1/9	54	64
3	H_2O/EtOH = 1/9	90	59
4	CH_2Cl_2	93	28
5	THF	91	31
6	Toluene	82	75
7	EtOH	88	63

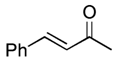
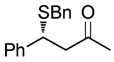
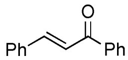
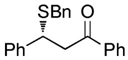
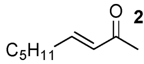
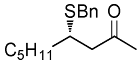
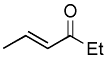
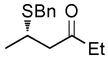
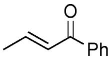
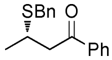
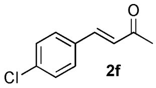
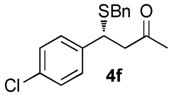
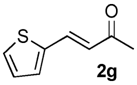
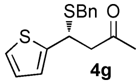
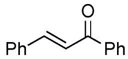
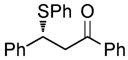
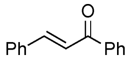
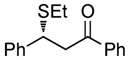
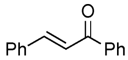
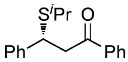
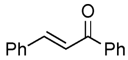
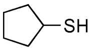
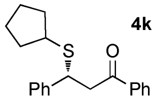
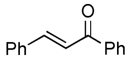
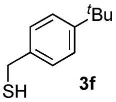
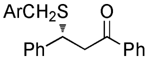
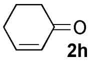
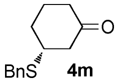
10 mol% (entry 13) catalyst), the reaction proceeded smoothly, but low enantioselectivity was observed, probably because a base-catalyzed racemic reaction was predominant over the chiral Sc-catalyzed enantioselective reaction. The reaction also proceeded without base; however, lower yields and selectivities were obtained (entries 15 and 16). We then investigated the effect of solvents in this catalytic asymmetric reaction (Table 2). Although the reaction proceeded smoothly to afford the desired product in high yield with high enantioselectivity in water (entry 1), selectivities decreased in aqueous organic solvents (entries 2 and 3). In other organic solvents (without water), the adduct was obtained in high yields, but a significant decrease in the enantioselectivity was observed (entries 4–7).

Several examples of asymmetric Michael reactions of thiols with enones are shown in Table 3. In most cases, the reactions proceeded smoothly at room temperature in the presence of 1 mol% of $Sc(OTf)_3$, 1.2 mol% of chiral ligand **1**, and pyridine (10 mol%) in water to afford the desired sulfides in high yields with high levels of enantioselectivities. It is noted that water on its own without using any organic solvents worked well as a solvent in these reactions. Various acyclic enones were successfully employed under the conditions to attain high yields and high enantioselectivities (entries 1–12), although the enantioselectivity was significantly decreased using a cyclic enone (entry 13). For sulfides, while alkyl sulfides gave high yields and high enantioselectivities in most cases, benzenethiol showed lower enantioselectivity (entry 8). It is noteworthy that even 0.5 mol% of the catalyst worked well to afford the desired sulfide **4a** in 92% yield with 91% ee (entry 1).

As a preliminary kinetic study, we have shown the profile of the reaction of **2a** with **3a** in the presence of $Sc(OTf)_3$ (1 mol%), **1** (1.2 mol%), and pyridine (10 mol%) in water at room temperature (Fig. 1). For the Sc^{3+}–chiral bipyridine **1** complex, we have already obtained solid-state information (X-ray crystallography).[6a] We next conducted experiments on the nonlinear effect to obtain information on the structure in water. As shown in Fig. 2, a positive nonlinear effect between the enantiomeric excess of the product and the enantiomeric excess of **1** was observed, which suggested formation of a dimer (or a similar aggregation form) of the Sc^{3+}–chiral bipyridine **1** complex in water. This result is in contrast to a similar catalyst that was used in asymmetric ring-opening reactions of *meso*-epoxides in water.[12] We also observed a remarkable ligand acceleration by **1** (The reaction of **2a** with **3a** gave **4a** in 17% yield in the presence of $Sc(OTf)_3$ (10 mol%) and pyridine (20 mol%) at room temperature in water). It is noted that the reaction also proceeded sluggishly by using $Sc(OTf)_3$ (10 mol%), ligand **5** (12 mol%), and pyridine (20 mol%) at room temperature in water (2% yield, 19% ee). Further investigations on

Table 3 Chiral Sc-catalyzed catalytic asymmetric Michael reactions of thiols with enones



Entry	Substrate **2**	Thiol **3**	Product **4**	Yield (%)	Ee (%)
1	 **2a**	BnSH **3a**	 **4a**	92 (92)[a]	93 (91)[a]
2	 **2b**	BnSH **3a**	 **4b**	83	94
3	 **2c**	BnSH **3a**	 **4c**	65	85
4	 **2d**	BnSH **3a**	 **4d**	84	84
5	 **2e**	BnSH **3a**	 **4e**	88	90
6	 **2f**	BnSH **3a**	 **4f**	82	92
7	 **2g**	BnSH **3a**	 **4g**	76	85
8	 **2b**	PhSH **3b**	 **4h**	92	44
9[b,c]	 **2b**	EtSH **3c**	 **4i**	80	97
10[b,d]	 **2b**	^{i}PrSH **3d**	 **4j**	81	86
11[b,d]	 **2b**	 **3e**	 **4k**	91	93
12	 **2b**	 **3f**	 Ar = (4-^{t}Bu)C_6H_4 **4l**	87	90
13	 **2h**	BnSH **3a**	 **4m**	78	8

[a] 0.5 mol% $Sc(OTf)_3$, 0.6 mol% ligand **1**, and 10 mol% pyridine were used for the values in parentheses. [b] 5 mol% $Sc(OTf)_3$, 6 mol% ligand **1**, 10 mol% pyridine were used. [c] 1.5 equiv. of thiol **3c** was used. [d] 48 h.

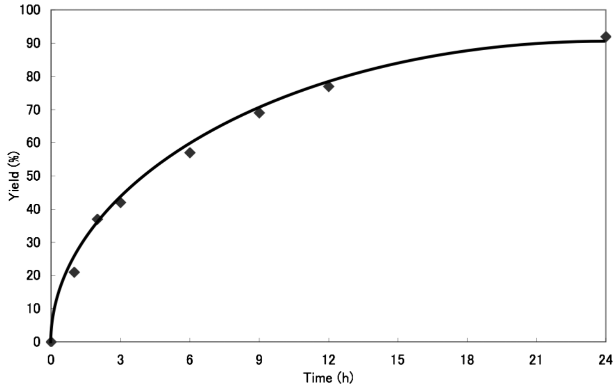


Fig. 1 Profile of the reaction of **2a** with **3a**.

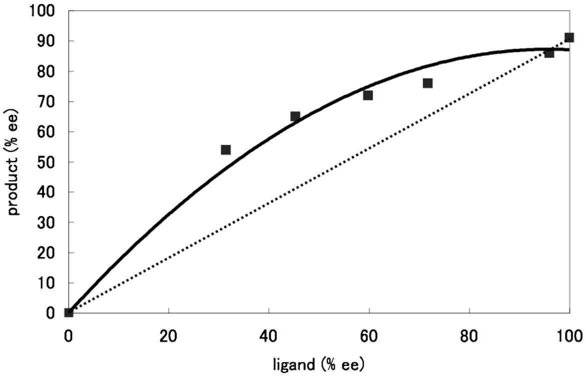
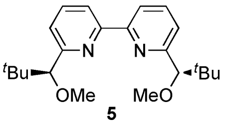


Fig. 2 Nonlinear effect experiments between the ee of the product and ee of **1**.

detailed kinetic studies, structure of catalysts, effects of ligands, *etc.* are now in progress.



5

In conclusion, we have developed chiral Sc-catalyzed asymmetric Michael reactions of thiols with enones in water. $Sc(OTf)_3$–chiral bipyridine **1** was found to be an excellent catalyst. The reactions proceeded smoothly with a small amount of base at room temperature in water without using any organic solvents, and high yields and high enantioselectivities were obtained.

Notes and references

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9 Zn^{2+}- and Cu^{2+}-catalyzed reactions: M. Kokubo, T. Naito and S. Kobayashi, *Tetrahedron*, 2010, **66**, 1111.

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12 A nonlinear effect was not observed in water, but a positive effect was observed in DCM: see also ref. 11.