DOI: 10.1002/adsc.200800070

Base–Base Bifunctional Catalysis: A Practical Strategy for Asymmetric Michael Addition of Malonates to α,β-Unsaturated Aldehydes

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Received: January 30, 2008; Revised: March 20, 2008; Published online: May 16, 2008

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Lewis base–Brønsted base bifunctional catalysis is a novel and practical strategy for the asymmetric Michael addition. The addition of malonates to a series of α,β-unsaturated aldehydes can take place under base–base bifunctional catalytic conditions using 0.5–5 mol% of (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine as catalyst and 5–30 mol% of lithium 4-fluorobenzoate as additive base with up to 99% *ee*.

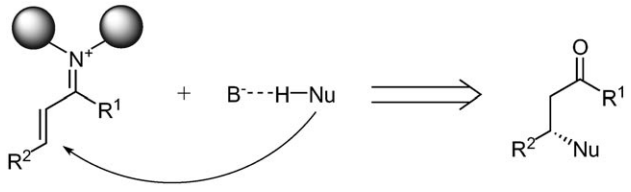
Keywords: aldehydes; asymmetric catalysis; bifunctional catalysis; malonates; Michael addition

Introduction

The catalytic asymmetric synthesis of chiral compounds is one of the most important, exciting and challenging areas in modern synthetic organic chemistry. In the last decade, many new concepts have been introduced into the field of asymmetric catalysis and have had a significant impact on chemical synthesis. One of these concepts, bifunctional or multifunctional asymmetric catalysis,[1] has been a very efficient strategy and tool to access a range of chiral compounds with atomic economy. Shibasaki et al. have developed Lewis acid–Brønsted base,[2] Lewis acid–Lewis base[3] and Lewis acid–Lewis acid[4] bifunctional catalysis for a wide variety of enantioselective transformations. List,[5] Deng[6] and Takemoto et al.[7] have developed Brønsted acid–Lewis base bifunctional organocatalysis for a range of asymmetric 1,2- and 1,4-addition reactions. These chiral bifunctional catalysts activate and arrange electrophilic and nucleophilic substrates with both LUMO-lowering and HOMO-raising mechanisms, and deliver unique enantioselectivities.

In 2000, MacMillan et al. elegantly discovered a new and very general strategy of organocatalysis with a LUMO-lowering catalyst,[8] and asymmetric organocatalysis with the iminium mechanism[9] has developed into an important tool for asymmetric Michael additions in the last few years.[10] But there are still disadvantages in these catalytic systems such as high catalyst loading and low turnover number.[11] We wondered if there was a possibility to improve catalytic reactivity and turnover in these Michael additions, and envisioned that a new concept, namely Lewis base–Brønsted base bifunctional catalysis combining both HOMO-raising and LUMO-lowering mechanisms could be a new tool for asymmetric Michael additions (Scheme 1).

In this bifunctional catalysis, a Lewis base such as chiral amine catalyst was used to activate the α,β-unsaturated carbonyl compound and induce the chirality of the reaction by the iminium mechanism and a Brønsted base such as basic lithium salt was used to activate the nucleophilic reagent by deprotonation or hydrogen-bond interaction. Thus, it was expected that this kind of bifunctional catalysis could enhance the



Scheme 1. Base–base bifunctional catalytic Michael addition.

efficiency and practicability, especially for the addition of relatively weak nucleophilic reagents.

Results and Discussion

To verify the feasibility of Lewis base–Brønsted base bifunctional catalysis, the asymmetric Michael addition of malonates to α,β-unsaturated aldehydes[12] was selected to test this concept. In an initial screening, diethyl malonate (**2a**) was added to cinnamaldehyde (**1a**) under base–base bifunctional catalytic conditions using 10 mol% of 2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (**C1–1**) as an amine catalyst[11] and 30 mol% of lithium acetate as an additive base. The result showed that the reaction proceeded to full conversion within 12 h with 95% *ee*. This encouraging result indicated that base–base bifunctional catalysis might be an efficient tool for this Michael addition. Thus, the effects of various reaction conditions on this reaction were investigated.

Effect of Additive Base

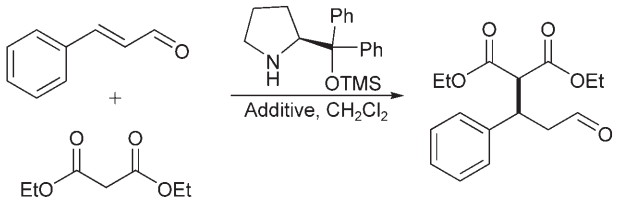
The effects of the additive base including organic bases and basic salts were first investigated and representative results are shown in Table 1.

The addition of diethyl malonate (**2a**) to cinnamaldehyde (**1a**) proceeded with different results using different kinds of additive. The primary investigation showed that lithium acetate as additive base could give better conversion and enantioselectivity than other alkali metal acetates such as sodium or potassium salts (entries 1–3). More experiments showed that a suitable basicity was necessary to obtain satisfactory conversion and enantioselectivity. For example, low enantioselectivity was observed when using strongly basic lithium hydroxide, while slightly weak basic lithium trifluoroacetate also induced low conversion and enantioselectivity (entries 4 and 5). Lithium benzoates, such as benzoate, fluorobenzoate, methoxybenzoate, nitrobenzoate, were suitable bases and 4-fluorobenzoate gave results equivalent to that of acetate (entries 6–11). The results in Table 1 also indicated that an organic base or its salt such as triethylamine or triethylaminium acetate could not efficiently improve the reaction (entries 12 and 13).

Effect of Amine Catalyst

It is known that α,α-disubstituted-2-pyrrolidinemethanols (**C**) are efficient organocatalysts for many kinds of asymmetric reaction with the iminium mechanism. Thus, the effect of these catalysts on the conversion and enantioselectivity of the reaction were then investigated. The results are shown in Table 2.

Table 1. Effect of additive base.



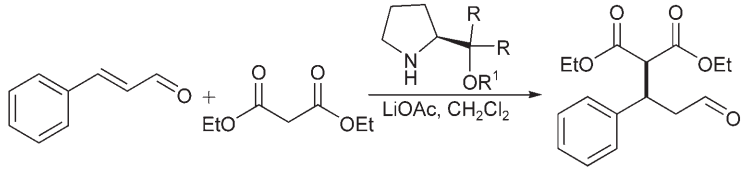
Entry	Additive Base[a]	Conversion [%][b]	*ee* [%][c]
1	LiOAc	95	95
2	NaOAc	85	89
3	KOAc	92	91
4	CF_3CO_2Li	67	76
5	LiOH	92	13
6	$PhCO_2Li$	96	91
7	4-$FC_6H_4CO_2Li$	95	96
8	4-$MeOC_6H_4CO_2Li$	88	95
9	2-$NO_2C_6H_4CO_2Li$	96	93
10	3-$NO_2C_6H_4CO_2Li$	95	92
11	4-$NO_2C_6H_4CO_2Li$	96	93
12	Et_3N	40	93
13	Et_3N-AcOH	63	93

[a] In each case, the reaction was run with cinnamaldehyde (1.0 mmol), diethyl malonate (3.0 mmol), **C1–1** (0.1 mmol) and additive base (0.3 mmol) in CH_2Cl_2 (2.0 mL) at room temperature for 12 h.
[b] The conversion was determined by GC.
[c] The enantiomeric excess was determined by GC after conversion to the corresponding lactone.

The results in Table 2 indicated that addition of diethyl malonate (**2a**) to cinnamaldehyde (**1a**) was influenced by both the α-substituted group (R) and the *O*-substituted group (R^1) of the amine catalyst **C**. An aromatic group in the α-position gave better results than an aliphatic group both in conversion and enantioselectivity. For example, the reaction proceeded to >90% conversion and *ee* within 12 h when using catalysts **C1–1**, **C2** and **C3** [R = Ph, 2-naphthyl and 3,5-$(CF_3)_2C_6H_3$, respectively]; however, when using catalysts **C4** and **C5** (R = Me and *n*-Bu, respectively), only 24–32% conversion and 69–71% *ee* were achieved (entries 1–5).

A protecting group in the *O*-position was essential for the reaction. Very low conversion was observed when using unprotected catalyst **C1–0** (R^1 = H) within 12 h (entry 6). This result is in accordance with the reported results.[13] An appropriate size of the protecting group was also important for the reaction (entries 1, 7–9). If the size of the R^1 group was too large, the reaction would proceed with low conversion. For example, 70% conversion was obtained when using catalyst **C1–5** (R^1 = *t*-$BuMe_2Si$) within 12 h (entry 10), but if the R^1 group was larger, such as with catalyst

Table 2. Effect of catalyst.



Entry	Catalyst[a]			Conversion [%][b]	*ee* [%][c]
	Code	R	R^1		
1	**C1–1**	Ph	Me_3Si	95	95
2	**C2**	3,5-$(CF_3)_2C_6H_3$	Me_3Si	92	96
3	**C3**	2-Naphthyl	Me_3Si	92	92
4	**C4**	Me	Me_3Si	32	69
5	**C5**	*n*-Bu	Me_3Si	24	71
6	**C1–0**	Ph	H	14	nd
7	**C1–2**	Ph	Et_3Si	92	95
8	**C1–3**	Ph	$PhMe_2Si$	95	94
9	**C1–4**	Ph	*i*-$PrMe_2Si$	97	93
10	**C1–5**	Ph	*t*-$BuMe_2Si$	70	90
11	**C1–6**	Ph	Ph_3Si	4	nd

[a] In each case, the reaction was run with cinnamaldehyde (1.0 mmol), diethyl malonate (3.0 mmol), catalyst (0.1 mmol) and LiOAc (0.3 mmol) in CH_2Cl_2 (2.0 mL) at room temperature for 12 h.
[b] The conversion was determined by GC.
[c] The enantiomeric excess was determined by GC after conversion to the corresponding lactone.

C1–6 ($R^1 = Ph_3Si$), only 4% conversion was obtained in the same time (entry 11).

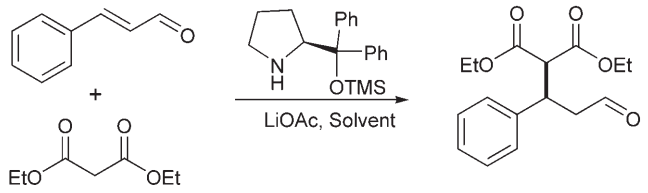
Effect of Solvent

We then investigated the effect of the solvents on the reaction and some representative results are illustrated in Table 3.

It is interesting that the reaction proceeded well in various solvents including chloroalkanes (entries 1 and 2), arenes (entries 3 and 4), alkanes (entries 5 and 6), ethers (entries 7 and 8), ethyl acetate (entry 9), alcohols (entries 10 and 11), acetone (entry 12), acetonitrile (entry 13), dimethylformamide (entry 14) and dimethyl sulfoxide (entry 15). Full conversion was obtained in most of these solvents within 12 h. The enantioselectivity of the reaction was dependent on the properties of the solvent. Generally, reactions in non-polar solvents gave higher *ee*s than in those in polar solvents, although there were some exceptions, such as in ethyl acetate and dimethylformamide.

These encouraging results indicated that base–base bifunctional catalysis might be a general tool for Michael addition in various solvents. The results also indicated that the chemistry for the further conversion of the addition product in a "one-pot" manner was readily accessible because the solvent effect of the Michael addition was unrestrained.

Table 3. Effect of solvent.



Entry	Solvent[a]	Conversion [%][b]	*ee* [%][c]
1	CH_2Cl_2	95	95
2	$CHCl_3$	85	94
3	Toluene	98	89
4	Benzene	97	91
5	Hexane	98	93
6	Cyclohexane	98	92
7	Et_2O	98	90
8	THF	98	92
9	EtOAc	95	92
10	MeOH	97	86
11	EtOH	98	70
12	Me_2CO	97	71
13	MeCN	97	66
14	DMF	97	91
15	DMSO	93	85

[a] In each case, the reaction was run with cinnamaldehyde (1.0 mmol), diethyl malonate (3.0 mmol), **C1–1** (0.1 mmol) and LiOAc (0.3 mmol) in solvent (2.0 mL) at room temperature for 12 h.
[b] The conversion was determined by GC.
[c] The enantiomeric excess was determined by GC after conversion to the corresponding lactone.

Effect of Catalyst Loading and Effect of Mixed Solvents on the Reduction of Catalyst Loading

The loading of the catalyst is an important aspect of a catalytic reaction. Thus, we were very interested in whether it was possible to reduce the catalyst loading of this bifunctional catalytic reaction. In this section, factors that have an effect on the reduction in the loading of amine catalyst **C1–1** were investigated and some representative results are shown in Table 4.

Unfortunately, preliminary results indicated that the reaction was incomplete in dichloromethane if the loading of **C1–1** was lower than 10 mol% and if the loading was reduced to 1 mol%, very low conversion (22%) was observed even after 72 h (entries 1–3).

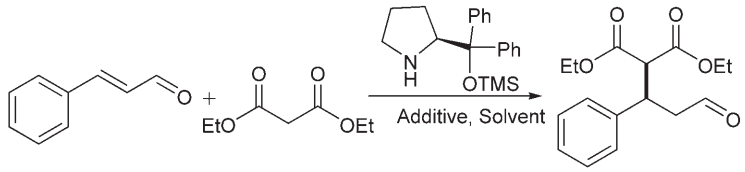
Since the reaction proceeded well in various solvents, it was expected that some solvents would be more "active" than dichloromethane, which could allow the reaction to proceed with lower catalyst loading. It has been reported that a similar reaction could take place in alcohols solely using amine catalyst,[11e] which indicated that alcohols might be more active solvents. But in our case, the use of alcohols would cause low enantioselectivities. Thus, we hoped that introduction of a small amount of alcohol to dichloromethane could increase the reaction efficiency without any decrease in enantioselectivity.

Experiments indicated that this treatment was feasible. For example, full conversion was afforded after 16 h in a mixed solvent of CH_2Cl_2/MeOH or CH_2Cl_2/EtOH (90:10 v:v) using 5 mol% of **C1–1** with, respectively, 89% and 92% *ee* (entries 4 and 5). It is clear that the ratio of dichloromethane to methanol affects both the conversion and the enantioselectivity. An increase in the ratio of methanol could increase the reaction efficiency and decrease the catalyst loading. However, it could also cause a decrease in the enantioselectivity. On the other hand, a decrease in the ratio of methanol could increase the enantioselectivity but decrease the reaction efficiency (entries 5–9). More experiments indicated that the enantioselectivity could be increased even using a mixed solvent of CH_2Cl_2/MeOH (90:10 v:v) if lithium 4-fluorobenzoate was used instead of lithium acetate. Under these conditions, full conversion was afforded using just 1 mol% of **C1–1** with 96% *ee* (entry 10). Further reduction in catalyst loading even to 0.2 mol% of catalyst **C1–1** resulted in 58% conversion after 80 h (entries 11 and 12).

Effect of the Loading of Additive Base

We then investigated the effect of the loading of the additive base, lithium 4-fluorobenzoate, on the reaction. The results are shown in Table 5. The loading of lithium 4-fluorobenzoate could be reduced to 5 mol% without any decrease in reaction efficiency and enantioselectivity (entries 1–5). Further reduction in the loading of lithium 4-fluorobenzoate even to 1 mol% gave 77% conversion after 84 h (entries 6 and 7).

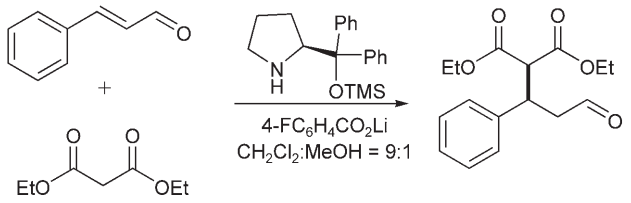
Table 4. Effect of catalyst loading.



Entry	Solvent (v:v)[a]	Catalyst [%]	Additive	Time [h]	Conversion [%][b]	*ee* [%][c]
1	CH_2Cl_2	10	LiOAc	12	95	95
2	CH_2Cl_2	5	LiOAc	72	87	94
3	CH_2Cl_2	1	LiOAc	72	22	nd
4	CH_2Cl_2:EtOH (90:10)	5	LiOAc	16	95	89
5	CH_2Cl_2:MeOH (90:10)	5	LiOAc	16	95	92
6	CH_2Cl_2:MeOH (95:5)	5	LiOAc	16	95	95
7	CH_2Cl_2:MeOH (95:5)	2	LiOAc	72	85	94
8	CH_2Cl_2:MeOH (95:5)	1	LiOAc	72	82	95
9	CH_2Cl_2:MeOH (90:10)	1	LiOAc	36	95	92
10	CH_2Cl_2:MeOH (90:10)	1	4-$FC_6H_4CO_2Li$	40	95	96
11	CH_2Cl_2:MeOH (90:10)	0.5	4-$FC_6H_4CO_2Li$	80	85	96
12	CH_2Cl_2:MeOH (90:10)	0.2	4-$FC_6H_4CO_2Li$	80	58	96

[a] In each case, the reaction was run with cinnamaldehyde (1.0 mmol), diethyl malonate (3.0 mmol), **C1–1** and additive base (0.3 mmol) in solvent (2.0 mL) at room temperature.
[b] The conversion was determined by GC.
[c] The enantiomeric excess was determined by GC after conversion to the corresponding lactone.

Table 5. Effect of the amount of additive base.



Entry	Additive Base [%][a]	Time [h]	Conversion [%][b]	*ee* [%][c]
1	50	40	96	96
2	30	40	95	96
3	20	40	95	96
4	10	40	96	95
5	5	40	96	96
6	2	84	85	96
7	1	84	77	96
8	0	84	11	nd

[a] In each case, the reaction was run with cinnamaldehyde (1.0 mmol), diethyl malonate (3.0 mmol), **C1–1** (0.01 mmol) and 4-F-$C_6H_4CO_2Li$ in CH_2Cl_2:MeOH = 90:10 (v:v, 2.0 mL) at room temperature.
[b] The conversion was determined by GC.
[c] The enantiomeric excess was determined by GC after conversion to the corresponding lactone.

Although it has been reported that this reaction could take place with ordinary iminium catalysis in ethanol using **C2** solely as organocatalyst, the reaction in the base–base bifunctional condition was quite different and had higher efficiency. In fact, the existence of additive base was essential when the reaction was taking place at a low level of catalyst loading. The reaction was almost inactive in the absence of additive base, for example, only 11% conversion was observed after 84 h with 1 mol% of catalyst **C1–1** alone (entry 8). This result indicated that the Brønsted base was actually playing a role in activating the nucleophilic reagent. Thus, Lewis base–Brønsted base bifunctional catalysis might provide a practical and efficient dual-activation method for enantioselective Michael additions.

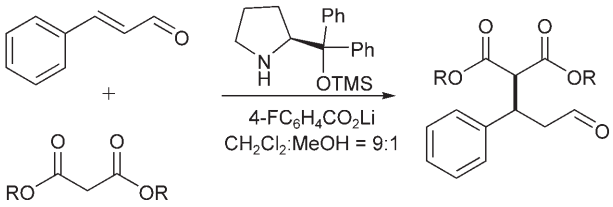
Thus, after investigating the effects of a series of factors, the optimized reaction conditions can now be outlined as follows: reaction using 1.0 mol% of amine catalyst **C1–1**, 5.0 mol% of lithium 4-fluorobenzoate and a mixed solvent of CH_2Cl_2/MeOH (90:10 v:v) at room temperature. Under these conditions, the addition of diethyl malonate to cinnamaldehyde could proceed to full conversion within 40 h with 96% *ee*.

Addition of Malonates to Cinnamaldehyde

To demonstrate the generality of the base–base bifunctional catalytic Michael addition, a series of α,β-unsaturated aldehydes and malonates were then tested. The addition of various malonates to cinnamaldehyde was investigated first and the results are presented in Table 6.

The addition reaction proceeded well for various malonates such as dimethyl, diethyl, dibenzyl and diisopropyl esters with full conversion and excellent enantioselectivities using only 1 mol% of catalyst **C1–1** and 5 mol% of lithium 4-fluorobenzonate within 40 h (entries 1–3, 5). Low conversion was observed

Table 6. Addition of malonates to cinnamaldehyde.



Entry	R[a]	Malonate:Cinnamaldehyde [mol:mol]	Time [h]	Yield [%][b]	*ee* [%][c]
1	Me	3.0:1.0	40	71	95
2	*i*-Pr	3.0:1.0	40	82	95
3	Bn	3.0:1.0	36	86	95
4	*t*-Bu	3.0:1.0	72	45 (65)	97
5	Et	3.0:1.0	40	81 (95)	96
6	Et	1.5:1.0	60	(85)	96
7	Et	1.0:1.5	60	(75)	96
8	Et	1.0:3.0	40	(95)	96

[a] In each case, the reaction was run with cinnamaldehyde (1.0 mmol), malonate (3.0 mmol), **C1–1** (0.01 mmol) and 4-F-$C_6H_4CO_2Li$ (0.05 mmol) in CH_2Cl_2:MeOH = 90:10 (v:v, 2.0 mL) at room temperature.
[b] Isolated yield, the values in parenthesis indicated the conversion that was determined on GC.
[c] The enantiomeric excess was determined by GC after conversion to the corresponding lactone.

for less active di-*tert*-butyl ester while excellent enantioselectivity was still obtained (entry 4).

More experiments indicated that the ratio of malonate to cinnamaldehyde also affected the conversion of the reaction. An excess of one of the substrates, either malonate or cinnamaldehyde, was necessary for the reaction. For full conversion, at least 3:1 (molecule ratio) of substrate was needed (entries 5–8).

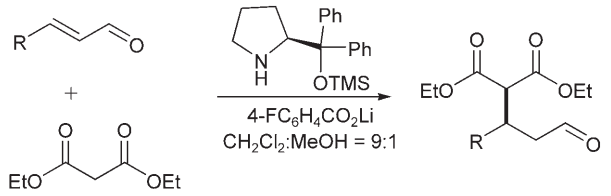
Addition of Diethyl Malonate to α,β-Unsaturated Aldehydes

The addition of diethyl malonate to various α,β-unsaturated aldehydes was also evaluated and some of the representative results are shown in Table 7.

The addition of diethyl malonate to aromatic α,β-unsaturated aldehydes achieved good results. Cinnamaldehyde derivatives with an electron-withdrawing or -donating group in the *o*-, *m*-, or *p*-position of the benzene ring all yielded full conversion and good to excellent enantioselectivity ranging from 87% to 99% using only 1 mol% of catalyst **C1–1** and 5 mol% of lithium 4-fluorobenzonate (entries 1–9). Aromatic heterocyclic α,β-unsaturated aldehydes such as 3-(furan-2-yl)acrylaldehyde also resulted in full conversion and 84% *ee* under the same conditions (entry 10).

The addition of diethyl malonate to aliphatic α,β-unsaturated aldehydes also exhibited promising results. The addition of crotonaldehyde yielded full conversion with 80% *ee* using 1 mol% of catalyst **C1–1** and 5 mol% of lithium 4-fluorobenzonate (entry 11). While other kinds of alkyl α,β-unsaturated aldehydes, such as pentenal and hexenal, yielded full conversion, although 5 mol% of catalyst **C1–1** and 30 mol% of lithium 4-fluorobenzonate were needed with, respectively, 85% and 88% *ee* (Entries 12, 13). However, 3-methylpentenal was inactive under these conditions, and only 5% conversion was obtained after 120 h (entry 14). These results implied that base–base bifunctional catalysis might be an efficient method for the enantioselective Michael addition of aliphatic α,β-unsaturated aldehydes and malonates.

Table 7. Addition of diethyl malonate and α,β-unsaturated aldehydes.



Entry	R[a]	Time [h]	Yield [%][b]	*ee* [%][c]
1	Ph	40	81	96
2	4-ClC_6H_4	36	73	95
3	2-$NO_2C_6H_4$	36	85	>99
4	4-$NO_2C_6H_4$	36	81	95
5	2-$MeOC_6H_4$	60	65	94
6	3-MeC_6H_4	36	76	90
7	4-MeC_6H_4	36	75	91
8	4-FC_6H_4	40	72	94
9	3-ClC_6H_4	48	76	92
10	2-Furanyl	40	76	84
11	Me	40	71	80
12	Et	120[d]	61	85
13	*n*-Pr	60[d]	67	88
14	*i*-Pr	120[d]	(5)	nd

[a] In each case, the reaction was run with α,β-unsaturated aldehyde (1.0 mmol), diethyl malonate (3.0 mmol), **C1–1** (0.01 mmol) and 4-F-$C_6H_4CO_2Li$ (0.05 mmol) in CH_2Cl_2:MeOH = 90:10 (v:v, 2.0 mL) at room temperature.

[b] Isolated yield, the values in parenthesis indicated the conversion that was detected on GC.

[c] The enantiomeric excess was determined by GC or HPLC after derivatization.

[d] The reaction was run with 5 mol% of **C1–1** and 30 mol% of 4-F-$C_6H_4CO_2Li$.

Conclusions

In summary, we have developed a new Lewis base–Brønsted base bifunctional catalytic method. The method reported here provides a dual-activation procedure for the asymmetric catalytic Michael addition of malonates to α,β-unsaturated aldehydes with high efficiency and enantioselectivity even using 0.5–1.0 mol% catalyst. The results indicate that this methodology might have practical and general utility for enantioselective catalysis. Further investigations on the scope of this methodology are currently ongoing and the results of these studies will be presented in due course.

Experimental Section

General Information and Starting Materials

The ^1H NMR and ^{13}C NMR were recorded on a Bruker DRX 400 (400 MHz) instrument. Chromatography was carried out with silica gel (350–400 mesh) using mixtures of petroleum ether and ethyl acetate as eluents. NMR data of known compounds are in agreement with literature values. All solvent and inorganic reagents were of *p.a.* quality and used without purification. Malonates and α,β-unsaturated aldehydes were obtained from commercial sources. Cinnamaldehyde and crotonaldehyde were purified by distillation before use; other materials were used without purification. All acetate salts were obtained from commercial sources. Lithium benzoates and trifluoroacetate were prepared by the reaction of lithium hydroxide with corresponding acid. Catalyst **C** was prepared as described in the literature.[14]

General Procedure for the Base–Base Bifunctional Michael Addition of Malonates to α,β-Unsaturated Aldehydes

To a mixed solvent system of CH_2Cl_2:MeOH = 90:10 (v:v, 2.0 mL) was added α,β-unsaturated aldehyde **1** (1.0 mmol), malonate **2** (3.0 mmol), **C1**–**1** (3.3 mg, 0.01 mmol) and lithium 4-fluorobenzonate (7.3 mg, 0.05 mmol). The reaction mixture was stirred at room temperature for the time indicated in Table 6 and Table 7 and then water (5.0 mL) was added. The organic materials were extracted with CH_2Cl_2 three times. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by column chromatography on silica gel (350–400 mesh) to yield the desired addition product.

Acknowledgements

We acknowledge the start-up fund from East China University of Science and Technology.

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