Highly enantioselective Michael addition of malonates to β,γ-unsaturated α-ketoesters catalyzed by chiral *N*,*N*′-dioxide-Yttrium(III) complexes with convenient procedure†

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Highly enantioselective Michael addition of malonates to β,γ-unsaturated α-ketoesters has been promoted by chiral *N*,*N*′-dioxide-Yttrium(III) complexes, providing the corresponding products in excellent yields with 94–99% *ee* values.

The catalytic asymmetric Michael addition, affording synthetically useful building blocks in organic synthesis, is one of the most powerful methods for construction of stereocenters.[1,2] Comparing with numerous Michael addition of α,β-unsaturated ketones,[3–5] the reactions which used β,γ-unsaturated α-ketoesters as Michael acceptors were very limited.[6] To the best of our knowledge, the asymmetric Michael addition of malonates to β,γ-unsaturated α-ketoesters has not been achieved. So, it is highly desirable to develop an enantioselective version due to the fact that the adducts have the potential for functionalizing to the corresponding amino acid esters[7] or α-hydroxy acid esters.

Inspired by our previous studies,[8] we studied the asymmetric Michael addition of malonates to β,γ-unsaturated α-ketoesters catalyzed by a metal complex, it was found that *N*,*N*′-dioxide-$Y(OTf)_3$ complex could highly catalyze the reaction with a convenient procedure, affording the desired products with up to 99% yield and 99% *ee*. This catalytic reaction is remarkable as no exclusion of air and humidity is required, the liquid substrates can be used as solvent, and there are very convenient operation and mild reaction conditions.

In our preliminary investigation, the chiral *N*,*N*′-dioxide ligand **L1** (Fig. 1) derived from (*S*)-pipecolic acid was coordinated with Lewis acid $Sc(OTf)_3$ to catalyze the asymmetric Michael addition of dimethyl malonate **1a** to β,γ-unsaturated α-ketoester **2a** in CH_2Cl_2 at 0 °C, however, only a trace of product was obtained. Several other Lewis acids, such as $La(OTf)_3$, $Sm(OTf)_3$, $Yb(OTf)_3$ and $Y(OTf)_3$ were then investigated. It was found that $Y(OTf)_3$ was superior to all the other metals, producing **3a** in 79% yield with 66% *ee* (Table 1, entries 2–5). To further improve the enantioselectivity, the steric and electronic effects of the ligand were examined (Table 1, entries 6–10). As shown in Table 1, ligands with a bulkier group at the *ortho* position of aniline, such as isopropyl in **L6**, could obtain the Michael adduct with higher enantioselectivity (up to 99% *ee*; Table 1, entry 10 *vs.* entries 6–9). As for the chiral backbone moiety, the *N*,*N*′-dioxide derived from (*S*)-pipecolic acid exhibited its superiority in enantioselectivity toward this reaction compared with the ones derived from L-proline and (*S*)-ramipril (Table 1, entry 10 *vs.* entries 11 and 12).

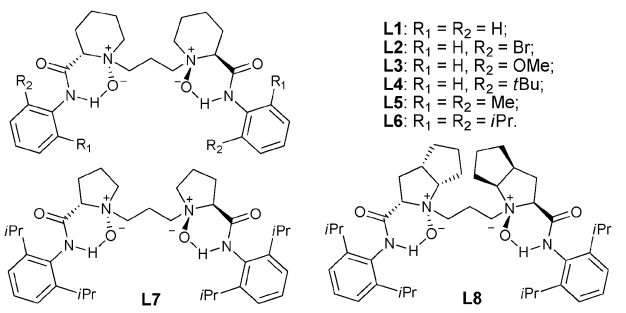
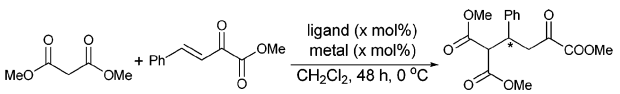


Fig. 1 Chiral ligands used in the study.

Table 1 Optimization of the reaction conditions



1a 2a 3a

Entry[a]	Ligand	Metal	*x* (mol%)	Yield[b] (%)	*Ee*[c] (%)
1	**L1**	$Sc(OTf)_3$	5	Trace	—
2	**L1**	$La(OTf)_3$	5	56	24
3	**L1**	$Sm(OTf)_3$	5	50	34
4	**L1**	$Yb(OTf)_3$	5	58	60
5	**L1**	$Y(OTf)_3$	5	79	66
6	**L2**	$Y(OTf)_3$	5	79	66
7	**L3**	$Y(OTf)_3$	5	71	58
8	**L4**	$Y(OTf)_3$	5	74	94
9	**L5**	$Y(OTf)_3$	5	73	90
10	**L6**	$Y(OTf)_3$	5	76	99
11	**L7**	$Y(OTf)_3$	5	76	96
12	**L8**	$Y(OTf)_3$	5	74	96
13[d]	**L6**	$Y(OTf)_3$	5	80	98
14[de]	**L6**	$Y(OTf)_3$	5	83	98
15[f,g]	**L6**	$Y(OTf)_3$	5	91	96
16[f,g]	**L6**	—	5	Trace	—
17[f,g]	—	$Y(OTf)_3$	5	Trace	—
18[f,g]	**L6**	$Y(OTf)_3$	2	91	98

[a] Unless otherwise noted, the reactions were performed with **2a** (0.10 mmol), *N*,*N*′-dioxide (*x* mol%), metal (*x* mol%) in CH_2Cl_2 (0.2 mL) at 25 °C for 0.5 h, then malonates (0.12 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for 48 h. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralcel AD-H). [d] The solvent was 0.1 mL. [e] Reaction was performed for 96 h. [f] Liquid substrates as solvent. [g] Reaction was performed for 4 h.

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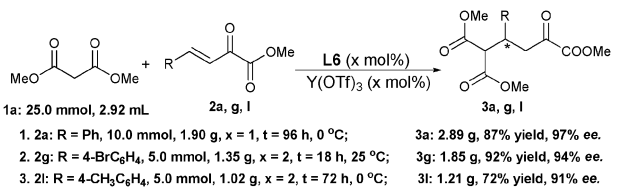
To improve the yield, increasing the reaction concentration and prolonging the reaction time were tried. However, the results were not satisfactory (Table 1, entries 13–14). Interestingly, the yield was improved to 91% and the *ee* was basically maintained when the reaction was carried out with excessive dimethyl malonate as solvent (96% *ee*; Table 1, entry 15), and also the reaction time was reduced to 4 h rather than 96 h in CH_2Cl_2. Moreover, the experimental procedure became very simple since neither ligand nor metal could promote the reaction (Table 1, entries 16–17). Preparing the catalyst beforehand and exclusion of air and humidity were unnecessary. The specific operation was as follow: the solid substrate, ligand and metal were weighed in a dry reaction tube followed by addition of dimethyl malonate at 0 °C, then the reaction mixture was stirred at 0 °C for 4 h. To our delight, reducing the catalyst loading to 2 mol% also gave the desired product with up to 91% yield and 98% *ee* (Table 1, entry 18).

Under the optimized conditions (Table 1, entry 18) with the convenient procedure, the substrate scope for this asymmetric Michael addition of dimethyl malonate to β,γ-unsaturated α-ketoesters was tested and the results were summarized in Table 2. No matter whether R_2 was methyl or ethyl, the substrates **2a–b** gave excellent yields (91%, 97%) and *ee* values (98%, 97%; Table 2 entries 1–2). The substrates with electron-withdrawing or donating groups at any position of the aromatic ring were well tolerated in terms of yields and enantioselectivities, and up to 99% yield and 99% *ee* were obtained (Table 2, entries 3–16). A fused ring β,γ-unsaturated α-ketoester **3q** was also a suitable substrate for the reaction, giving the corresponding product with up to 98% *ee* (Table 2, entry 17). The substrate with cinnamyl group also gave an excellent yield and *ee* value (Table 2, entry 18). Moreover, a heteroaromatic substrate delivered the Michael adduct in excellent yield and enantioselectivity (Table 2, entry 19).

Though dimethyl malonate was used in great excess in these milligram scale reactions (Table 2), the ratio of dimethyl malonate to β,γ-unsaturated α-ketoesters could be reduced to 2.5 : 1 or 5 : 1 when the reactions were amplified to gram scales. As shown in Scheme 1, the reactions proceeded smoothly in high yields with excellent *ee* values on gram scales in the presence of only 1–2 mol% **L6**-$Y(OTf)_3$ complex, which showed the synthetic utility of the catalytic system.

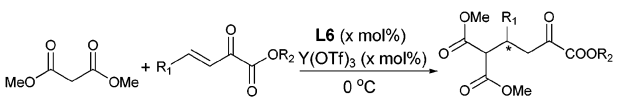
On account of the synthetic potential of this Michael addition, the product **3a** was simply converted into an usefully functionalised α-hydroxy acid ester (Scheme 2) using $NaBH_4$ as the reductive, 99% yield, 97% *ee* (major), 99% *ee* (minor) and 78 : 22 *dr* were obtained.

In conclusion, we have demonstrated that the asymmetric Michael addition of malonates to β,γ-unsaturated α-ketoesters could be carried out without extra solvent. The reaction was promoted by a highly efficient *N*,*N*′-dioxide **L6**-Yttrium(III) complex with low catalyst loadings (2–5 mol%), affording the corresponding 4-oxo-2-arylbutane-1,1,4-tricarboxylate



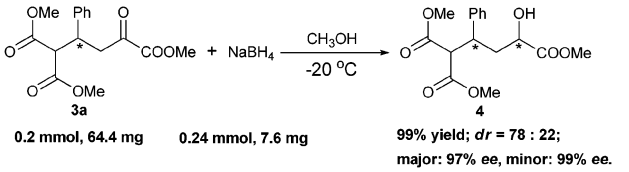
Scheme 1 Asymmetric conjugate addition of dimethyl malonate to β,γ-unsaturated α-ketoesters on a gram scale.

Table 2 Substrate scope for asymmetric Michael addition



Entry[a]	R_1	Product	**1a**[b]/mL	*x* (mol%)	*t*/h	Yield[c] (%)	*Ee*[d] (%)
1	Ph	**3a**	0.1	2	4	91	98
2	Ph	**3b**	0.2	5	12	97	97
3	4-FC_6H_4	**3c**	0.2	5	5	99	98
4	4-ClC_6H_4	**3d**	0.3	5	5	97	98
5	2-ClC_6H_4	**3e**	0.2	5	8	80	95
6	2,4-$Cl_2C_6H_3$	**3f**	0.2	2	4	99	98
7	4-BrC_6H_4	**3g**	0.2	2	20	95	99
8	3-BrC_6H_4	**3h**	0.3	5	5	85	97
9	4-NO_2 C_6H_4	**3i**	1.0	5	24	82	97
10	3-NO_2 C_6H_4	**3j**	0.5	5	24	94	95
11	4-CNC_6H_4	**3k**	0.5	2	24	83	99
12	4-$CH_3C_6H_4$	**3l**	0.2	2	24	99	96
13[e]	3-$CH_3C_6H_4$	**3m**	0.2	5	8	87	96
14	4-PhC_6H_4	**3n**	0.5	5	60	99	95
15	4-$CH_3OC_6H_4$	**3o**	0.3	5	72	89	94
16		**3p**	0.5	5	72	92	94
17	2-Naphthyl	**3q**	0.2	2	24	95	98
18	–CH=CHPh	**3r**	0.5	5	24	86	98
19	2-Thienyl	**3s**	0.2	5	24	95	97

[a] Unless otherwise noted, the reactions were performed with **2** (0.10 mmol), *N*,*N*′-dioxide (*x* mol%), metal (*x* mol%) in a dry reaction tube, then dimethyl malonate **1a** was added at 0 °C. The reaction mixture was stirred at 0 °C for the indicated time. [b] The amount of **1a**. [c] Isolated yield. [d] Determined by HPLC analysis (Chiralcel AD-H). [e] Reaction was performed at 25 °C.



Scheme 2 The conversion of product **3a** into an usefully functionalised α-hydroxy acid ester.

compounds in excellent yields and *ee* values. Atmospheric oxygen and water did not affect the outcome and the procedure was very simple. The reaction could be amplified to gram scales with good yields and *ee* values in the presence of only 1–2 mol% catalyst loading and the adducts could be converted into the corresponding useful α-hydroxy acid esters, which showed the potential value of the catalytic system for practical synthesis. Further applications of the current catalyst system to other reactions are underway.

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