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Highly Enantioselective Michael Addition of Malonate Derivatives to Enones Catalyzed by an *N*,*N*′-Dioxide–Scandium(III) Complex

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The catalytic asymmetric conjugate addition reaction is one of the most powerful methods for the carbon–carbon bond formation because various chiral functionalized adducts can be obtained from numerous Michael acceptors and donors.[1] Among them, the asymmetric Michael addition of 1,3-dicarbonyl compounds to enones provides a simple way for the preparation of synthetically useful 1,5-dicarbonyl compounds and attracts more and more chemists' interests.[2–6] There have been several catalysts developed for this reaction, such as chiral metal complexes,[3] chiral ammonium salts,[4] chiral amine catalysts[5] and thiourea catalysts,[6] but only few reports appeared successfully when chalcone derivatives were used as Michael acceptors.[3k,4e,6b] Despite excellent enantioselectivity have been achieved by Maruoka,[4e] Wang[6b] and Kobayashi et al.,[3k] developing new and efficient chiral catalyst systems is still in great need. Recently, *N*,*N*′-dioxide–metal complexes have been successfully applied to promote many kinds of asymmetric transformations,[7] herein we wish to report a highly enantioselective Michael addition of malonate derivatives to chalcone derivatives catalyzed by L-Ramipril acid derived *N*,*N*′-dioxide–scandium(III) complex. A wide range of substrates can be tolerated, affording the desired products with up to 99% yield and 99% *ee*.

Inspired by our previous studies,[7i] we initiated the experiment by using L-Ramipril acid derived *N*,*N*′-dioxide **L1**–nickel(II) complex to catalyze the asymmetric Michael addition of diethyl malonate **1a** to chalcone **2a** in EtOH at 35 °C. However, only racemic product **3a** was obtained. Then serveral other Lewis acids, such as Cu^{II}, Zn^{II}, La^{III}, Y^{III}, Sc^{III} salts were investigated, which were known to be chelated well with dicarbonyl compounds.[8] As summarized in Table 1, scandium triflate was found to be superior to all the other metals tested, producing **3a** in good yield with 91% *ee* (Table 1, entries 1–6). Encouraged by the results, scandium triflate was selected as the central metal for further research. Then a series of *N*,*N*′-dioxides was synthesized and combined with scandium triflate to promote the conjugate addition reaction (Figure 1). We found that the amide moiety in the *N*,*N*′-dioxide ligands had significant effect on the enantioselectivity (Table 1, entries 6–9). Unexpectly, when introducing bulky substitute at the *ortho* position of the aromatic ring, the enantioselectivity as well as the yield decreased remarkably (Table 1, entry 7). When R was replaced by aliphatic *tert*-butyl group, product **3a** was obtained in lower yield with slightly decreased enantioselectivity (Table 1, entries 8 vs 6). Excitingly, when R was benzyl group, the enantioselectivity rapidly increased up to 99% *ee* with moderate yield (Table 1, entry 9). Next, the chiral backbone of the *N*,*N*′-dioxides was also examined, but no better results were obtained (Table 1, entries 10–11 vs 9). It should be noted that when 4 Å molecular sieves was added as additives, the reactivity was largely improved and **3a** could be obtained in 95% yield without loss of enantioselectivity (Table 1, entry 12). The catalyst loading could be reduced to 5 mol% while the yield and enantioselectivity were almost maintained (Table 1, entry 13).

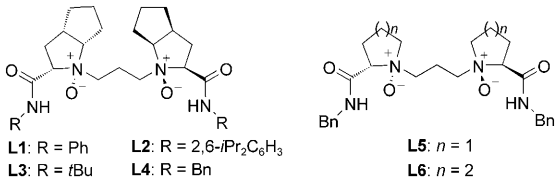

Figure 1. Chiral *N*,*N*′-dioxide catalysts used in the study.

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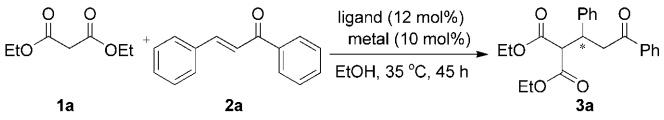
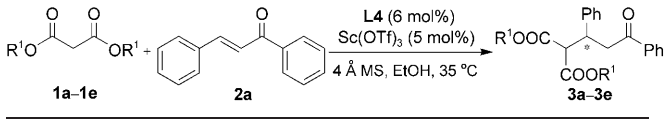
Table 1. Screen of catalysts in the asymmetric Michael addition of diethyl malonate to chalcone.[a]



	Ligand	Metal	Yield [%][b]	*ee* [%][c]
1	**L1**	$Ni(acac)_2$	24	0
2	**L1**	$Cu(OTf)_2$	NR[d]	–
3	**L1**	$Zn(OTf)_2$	NR[d]	–
4	**L1**	$La(OTf)_3$	34	8 (*S*)
5	**L1**	$Y(OTf)_3$	46	0
6	**L1**	$Sc(OTf)_3$	68	91
7	**L2**	$Sc(OTf)_3$	4	49
8	**L3**	$Sc(OTf)_3$	36	88
9	**L4**	$Sc(OTf)_3$	57	99
10	**L5**	$Sc(OTf)_3$	52	85
11	**L6**	$Sc(OTf)_3$	64	96
12[e]	**L4**	$Sc(OTf)_3$	95	99
13[e,f]	**L4**	$Sc(OTf)_3$	93	99

[a] Unless otherwise noted, the reactions were performed with **2a** (0.1 mmol), *N*,*N*′-dioxide (12 mol%), metal (10 mol%) in EtOH (0.5 mL) under nitrogen at 35°C for 0.5 h, then diethyl malonate (0.12 mmol) was added. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralcel AS-H). Unless specified, the absolute configuration was *R*, which was determined by comparison with the optical rotation values in the literature.[3k] [d] No reaction. [e] 4 Å molecular sieves (10 mg) were added. [f] 6 mol% **L**4 and 5 mol% scandium triflate were used.

Table 2. Scope of malonate derivatives in the asymmetric Michael addition to chalcone.[a]



	R^1	*t* [h]	Product	Yield [%][b]	*ee* [%][c]
1	Et **1a**	45	**3a**	93	99 (*R*)
2	Me **1b**	70	**3b**	50	97 (*R*)
3	*i*Pr **1c**	15	**3c**	98	99
4	*t*Bu **1d**	65	**3d**	90	98
5	Bn **1e**	70	**3e**	40	97
6[d]	*i*Pr **1c**	72	**3c**	66	99
7[e]	*i*Pr **1c**	64	**3c**	72	97

[a] Unless otherwise noted, the reaction was carried out with **2a** (0.1 mmol), 5 mol% **L4**–Sc^{III} complex (1.2:1) and 4 Å MS (10 mg) in EtOH (0.5 mL) under nitrogen at 35°C for 0.5 h, then the respective malonate **1** (0.12 mmol) was added. [b] Isolated yield. [c] Determined by HPLC analysis (see Supporting Information). The absolute configuration was determined by comparison of the optical rotation values in the literature.[3k] [d] 1 mol% **L4**–Sc^{III} complex (**L4**/$Sc(OTf)_3$ 1.2:1) was used. [e] The reaction was performed in water (0.5 mL). No molecular sieves were used.

Having optimized the reaction parameters, an ester group effect of malonate derivates was investigated for the asymmetric Michael addition of chalcone. As shown in Table 2, the ester groups apparently had little or no effect on the enantioselectivity of the reaction (Table 2, entries 1–5). Interestingly, the more sterically hindered malonate derivates **1c** and **1d** seemed more reactive compared to **1b** and **1e**. Diisopropyl malonate turned out to be an outstanding Michael donor that the reaction accomplished in 15 h in 98% yield with 99% *ee* (Table 2, entry 3). Moreover, the catalyst loading could be further reduced to 1 mol% with good yield without loss of enantioselectivity (Table 2, entry 6). It is noteworthy that the reaction proceeded well even in water in 72% yield with a slightly decreased enantioselectivity (Table 2, entry 7).

Under the optimized conditions, the scope of the conjugate addition of diisopropyl malonate to a variety of substrates was tested, and the results were summarized in Table 3. In all cases, the substrates could give the desired products in high yields with excellent enantioselectivities. It is interesting that either the electronic nature or the position of the substituents at the aromatic ring of R^2 or R^3 had little influence on the enantioselectivity (Table 3, entries 1–16, 19–24). Notably, when R^2 was unsaturated cinnamyl group or aliphatic cyclohexyl group, Michael adducts **3u**–**v** could also be obtained in good yield with 97% and 96% *ee*, respectively (Table 3, entries 17–18). Remarkably, substrates bearing heteroaromatic substituentes, either in R^2 or R^3, were also suitable acceptors for the conjugate reaction and afforded the corresponding products **3ac**–**ah** with excellent enantioselectivities (Table 3, entries 25–30).

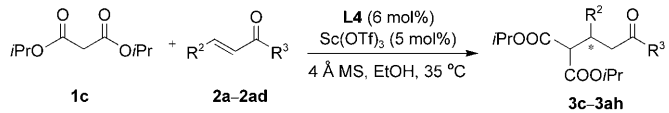
Finally, in order to show the synthetic utility of the catalyst system, Michael addition of diisopropyl malonate to chalcone was expanded to a gram-scale (Scheme 1). As shown in Scheme 1, the reaction proceeded smoothly in 77% yield with 98% *ee* using 1 mol% *N*,*N*′-dioxide **L4**–scandium(III) complex as catalyst.

In conclusion, we have devoloped a L-Ramipril acid derived *N*,*N*′-dioxide–scandium triflate complex for the asymmetric conjugate addition of malonate to chalcone derivatives. A variety of optical pure ketoesters could be obtained with high yields and excellent enantioselectivities. The reaction performed well in EtOH, making the process environmentally friendly. The reaction could be amplified to gram scales in 77% yield with 98% *ee* under 1 mol% *N*,*N*′-dioxide **L4**–scandium(III) complex as catalyst, which showed the potential value of the catalyst system. Further studies of the mechanism and application of the catalyst system to other reactions are underway.

Experimental Section

Typical experimental procedure: *N*,*N*′-Dioxide **L4** (6.7 mg, 0.012 mmol), scandium triflate (4.9 mg, 0.01 mmol), chalcone (41.7 mg, 0.20 mmol) and 4 Å molecular sieves (20 mg) were stirred in a dry reaction tube in EtOH (1.0 mL) under nitrogen at 35°C for 0.5 h, then diethyl malonate (37 μL, 0.24 mmol) was added. The process was monitored by TLC. After chalcone disappeared, the reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate 12:1) on silica gel to afford the desired product.

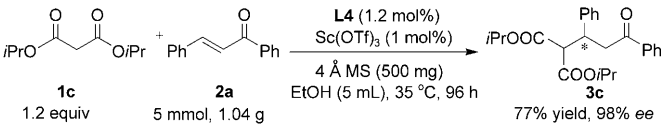
Table 3. Substrate scope of enones with diisopropyl malonate.[a]



1c 2a–2ad 3c–3ah

	R^2	R^3	*t* [h]	Product	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	15	**3c**	98	99
2	2-ClC_6H_4	Ph	40	**3f**	96	99
3	3-ClC_6H_4	Ph	30	**3g**	93	99
4	4-ClC_6H_4	Ph	90	**3h**	80	99
5	2-$MeOC_6H_4$	Ph	40	**3i**	92	97
6	3-$MeOC_6H_4$	Ph	45	**3j**	93	99
7	4-$MeOC_6H_4$	Ph	90	**3k**	87	98
8	3-$NO_2C_6H_4$	Ph	36	**3l**	92	99
9	4-$NO_2C_6H_4$	Ph	36	**3m**	97	98
10	3-MeC_6H_4	Ph	36	**3n**	82	98
11	4-MeC_6H_4	Ph	36	**3o**	90	97
12	4-FC_6H_4	Ph	35	**3p**	95	99
13	4-CNC_6H_4	Ph	40	**3q**	96	99
14	2,4-$Cl_2C_6H_3$	Ph	35	**3r**	92	99
15	3,4-methylenedioxy-C_6H_3	Ph	40	**3s**	60	98
16	2-naphthyl	Ph	35	**3t**	62	99
17	−CH=CHPh	Ph	45	**3u**	66	97
18	cyclohexyl	Ph	90	**3v**	96	96
19	Ph	4-ClC_6H_4	35	**3w**	99	98
20	Ph	4-$NO_2C_6H_4$	45	**3x**	70	96
21	Ph	2-$MeOC_6H_4$	20	**3y**	81	98
22	Ph	3-$MeOC_6H_4$	35	**3z**	72	99
23	Ph	4-$MeOC_6H_4$	20	**3aa**	94	99
24	Ph	2-naphthyl	40	**3ab**	94	98
25	2-furyl	Ph	35	**3ac**	73	98
26	2-thienyl	Ph	40	**3ad**	74	96
27	2-pridinyl	Ph	40	**3ae**	92	99
28	Ph	2-furyl	40	**3af**	92	99
29	Ph	2-thienyl	40	**3ag**	94	99
30	2-furyl	2-furyl	45	**3ah**	81	96

[a] Unless specified, the reactions were performed with **2** (0.1 mmol), 5 mol% **L4**–Sc^{III} complex (1.2:1) and 4 Å MS (10 mg) in EtOH (0.5 mL) under nitrogen at 35 °C for 0.5 h, then diisopropyl malonate (0.12 mmol) was added. [b] Isolated yield. [c] Determined by HPLC analysis (see Supporting Information).



Scheme 1. Asymmetric conjugate addition of diisopropyl malonate to chalcone on a gram scale.

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Keywords: asymmetric synthesis · C–C bond formation · chalcone · Michael addition · scandium

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