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Highly Enantioselective Synthesis of α-Stereogenic Esters through Catalytic Asymmetric Michael Addition of 4-Oxo-4-arylbutenoates

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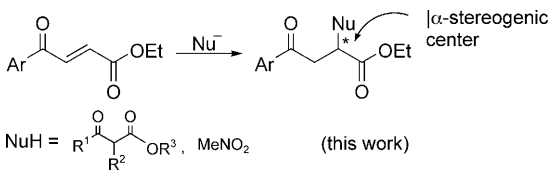
Abstract: Highly enantioselective Michael addition of 1,3-dicarbonyl compounds and nitromethane to 4-oxo-4-arylbutenoates catalyzed by *N,N′*-dioxide–$Sc(OTf)_3$ complexes has been developed. Using 0.5–2 mol% catalyst loading, various α-stereogenic esters were obtained regioselectively with excellent yields (up to 97%) and enantioselectivities (up to >99% *ee*). Moreover, the reaction performed well under nearly solvent-free conditions. The products with functional groups are ready for further transformation, which showed the potential value of the catalytic approach. According to the experimental results and previous reports, a plausible working model has been proposed to explain the origin of the activation and the asymmetric induction.

Keywords: asymmetric catalysis · chirality · enantioselectivity · Michael addition · scandium

Introduction

The Michael addition of carbon nucleophiles to electron-deficient olefins represents one of the most powerful strategies for the formation of carbon–carbon bonds in organic synthesis.[1] Recently, 1,4-dicarbonyl but-2-enes have been developed as Michael acceptors to generate an α-stereogenic center with respect to one of carbonyl groups, which are useful building blocks for the synthesis of natural compounds. Tedrow et al. reported that rhodium complexes catalyzed Michael addition of arylboronic acids to 1,4-dicarbonyl but-2-enes, such as (*E*)-4-oxo-4-arylbutenamides and dialkyl fumarates, with high enantioselectivities.[2a] Tan and co-workers found that chiral bicyclic guanidines catalyzed highly enantioselective Michael addition of 1,3-alkylthiomalonates with 1,4-dicarbonyl but-2-enes to generate α-stereogenic esters, amides, and ketones.[3] Pedro et al. reported that chiral Hf^{IV} and Zr^{IV} complexes promoted Friedel–Crafts reaction of indoles to electrophiles including 1,4-diaryl-2-butene-1,4-diones and 4-oxo-4-arylbutenoates with high enantioselectivities.[4] Xiao and co-workers reported that chiral urea derivatives worked well for conjugate addition of nitroalkanes to 4-oxo-enoates.[5a] Despite these impressive contributions, simple dialkylmalonates and α-substituted malonates have not been developed as nucleophiles in conjugate additions with 4-oxo-4-arylbutenoates. Therefore, the development of new and more efficient approaches for the enantioselective Michael addition of 4-oxo-4-arylbutenoates is still challenging and in high demand (Scheme 1).[6,7]



Scheme 1. Conjugate addition of carbon nucleophiles to 4-oxo-4-arylbutenoates.

$Sc(OTf)_3$, which features such advantages as stability, recovery, and reusability, has shown highly catalytic activity in many transformations.[8] As excellent chiral scaffolds, *N,N′*-dioxides[9] were able to coordinate with $Sc(OTf)_3$ and exhibited great potential in various reactions such as allylation,[10a] aza-Diels–Alder reactions,[10b] Michael reactions,[10c] Friedel–

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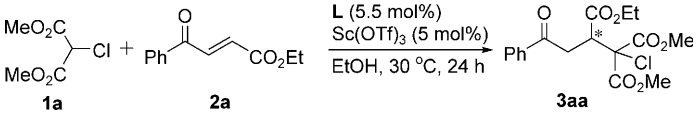
Crafts reactions,[10d–f] and amination.[10k] Herein we expanded the scope of this approach in an asymmetric Michael reaction using 1,3-dicarbonyl compounds and nitromethane as the nucleophiles and (*E*)-4-oxo-4-arylbutenoates as the Michael acceptors. A chiral *N*,*N*′-dioxide–scandium(III) complex system also allowed expedient access to functionalized α-stereogenic esters in high yields with excellent regioselectivities and enantioselectivities (*ee* values up to >99%) with a low catalyst loading (as low as 0.5 mol%).

Results and Discussion

Initially, we examined the asymmetric Michael addition of α-chloromalonate (**1a**) and ethyl (*E*)-4-oxo-4-phenylbutenoate (**2a**) promoted by $Sc(OTf)_3$–*N*,*N*′-dioxide complexes (Table 1). The amide moiety in the *N*,*N*′-dioxide ligands had

Table 1. Screening of ligands for the Michael addition of **1a** and **2a**.[a]

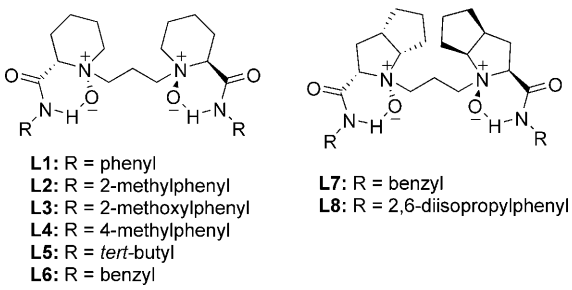


1a **2a** **3aa**

Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	**L1**	75	98
2	**L2**	63	99
3	**L3**	52	98
4	**L4**	72	99
5	**L5**	82	89
6	**L6**	83	92
7	**L7**	85	99
8[d]	**L7**	93	99

[a] Unless otherwise noted, reactions were carried out with **2a** (0.1 mmol) and **1a** (0.3 mmol) with 5 mol% **L**/$Sc(OTf)_3$ (1.1:1) in EtOH (0.2 mL) under nitrogen at 30°C for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] In the presence of 4 Å molecular sieves (10 mg), reaction time: 12 h.

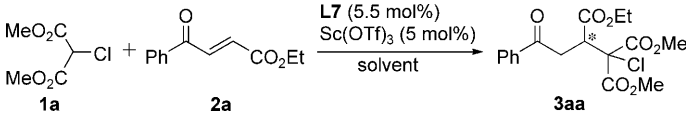
a significant effect on the enantioselectivity and reactivity (Table 1, entries 1–6; for screened ligands, see Scheme 2). *N*,*N*′-Dioxides **L1**–**L4** derived from aromatic amines exhibited excellent enantioselectivities and moderate yields (Table 1, entries 1–4), and ligands with an electron-donating substituent at the *ortho* position of the aromatic ring decreased the yields (entries 2 and 3 vs. entry 1). However, ligands derived from aliphatic amines, such as *tert*-butylamine and benzylamine, could achieve higher yields but slight lower enantioselectivities (up to 83% yields; entries 5 and 6 vs. entry 1). As for the chiral backbone moiety, when (*S*)-ramipril-derived *N*,*N*′-dioxide **L7** was used instead of those derived from (*S*)-pipecolic acid, good yield and excellent enantioselectivity were both achieved (85% yield, 99% *ee*; Table 1, entry 7). It was found that the addition of 4 Å molecular sieves (MS) could further improve the yield without the loss of enantioselectivity (93% yield, 99% *ee*; Table 1, entry 8).



Scheme 2. Ligands screened in this study.

Encouraged by the initial results, various solvents were tested in the presence of **L7**–$Sc(OTf)_3$ (Table 2). As shown in Table 2, the solvent played an important role in governing

Table 2. Solvent and concentration effects on the Michael addition of **1a** and **2a**.[a]



1a **2a** **3aa**

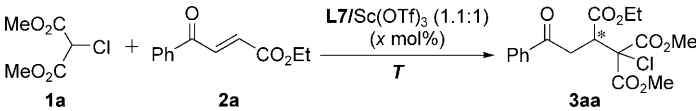
Entry	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	THF	24	73	96
2	CH_3CN	24	65	90
3	DMF	24	43	96
4	EtOH	12	93	99
5	CH_2Cl_2	24	88	85
6	toluene	48	trace	–
7[d]	EtOH	6	95	99
8[e]	EtOH	2	96	99

[a] Unless otherwise noted, reactions were carried out with **2a** (0.1 mmol) and **1a** (0.3 mmol) with 5 mol% **L7**/$Sc(OTf)_3$ (1.1:1) and 4 Å molecular sieves (10 mg) in solvents (0.2 mL) under nitrogen at 30°C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 0.1 mL EtOH was used. [e] The reaction was carried out on a 0.3 mmol scale with 4 Å molecular sieves (30 mg) in the presence of EtOH (10 μL).

the rate and enantioselectivity of the reaction. Highly polar solvents such as THF, EtOH, CH_3CN, and DMF achieved good enantioselectivities (Table 2, entries 1–4). Using CH_2Cl_2 gave moderate results (Table 2, entry 5). However, no reaction took place in toluene (Table 2, entry 6). The concentration of substrate and catalyst were also key factors. When EtOH (0.1 mL) was used, the product was obtained in high yield and the enantioselectivity was maintained (95% yield, 99% *ee*; Table 2, entry 7 vs. entry 4). Excitingly, further decreasing the volume of EtOH to 10 μL still led to an excellent result, and the reaction time was shortened to 2 h (Table 2, entry 8 vs. entry 7).

To further improve the efficiency of the reaction, the reaction temperature and catalyst loading were examined. The results are presented in Table 3. A decrease in the reaction temperature led to low reactivity (Table 3, entry 1 vs. entry 2). When the temperature was increased from 30 to 40°C, the reactivity increased without any loss of enantioselectivity (Table 3, entry 3 vs. entry 2). The catalyst loading was then evaluated. A reduction in the catalyst loading could still result in excellent enantioselectivities; however,

Table 3. Effects of temperature and catalyst loading on the Michael addition of **1a** and **2a**.[a]



1a **2a** **3aa**

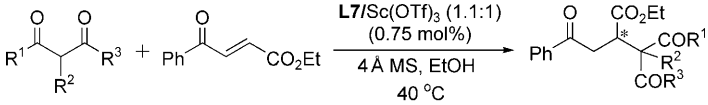
Entry	*T* [°C]	Catalyst loading [mol%]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	0	5	24	83	98
2	30	5	2	96	99
3	40	5	1	95	99
4	40	1	12	96	99
5	40	0.75	20	95	99
6[d]	40	0.5	30	86	99

[a] Unless otherwise noted, reactions were carried out with **2a** (0.3 mmol) and **1a** (0.9 mmol) in the presence of EtOH (10 μL) with **L7**/Sc(OTf)$_3$ (1.1:1) and 4 Å molecular sieves (30 mg) under nitrogen. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out with **2a** (0.4 mmol) and **1a** (1.2 mmol) in the presence of EtOH (10 μL) and 4 Å molecular sieves (40 mg) with **L7**/Sc(OTf)$_3$ (1.1:1) under nitrogen at 40 °C.

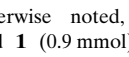
the reactivity decreased slightly (Table 3, entries 4–6). Therefore, the optimal conditions were identified as follows: **L7**–Sc(OTf)$_3$ complex (0.75 mol%; **L7**/Sc(OTf)$_3$ 1.1:1), 4 Å MS (30 mg), (*E*)-4-oxo-4-arylbutenoate (0.3 mmol), malonate (0.9 mmol), and EtOH (10 μL) at 40 °C.

Under the optimized conditions, we next examined the scope of the Michael addition with series of malonates **1a**–**k** (Table 4, entries 1–9). As shown in Table 4, the ester groups apparently had little effect on the enantioselectivity of the reaction, and the large ester groups such as isopropyl and *tert*-butyl esters increased the reactivity of the reaction

Table 4. Enantioselective Michael additions of **2a** with malonates and ketoesters under the optimal conditions.[a]



1a–k **2a** **3aa–3ka**

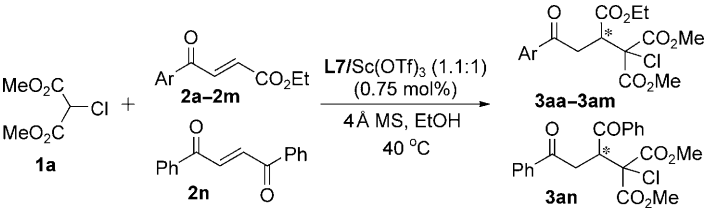
Entry	**1**	R^1, R^3	R^2	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	OMe, OMe	Cl	20	95	99
2[d]	**1b**	OMe, OMe	H	36	72	95
3[d]	**1c**	OEt, OEt	H	36	82	98
4	**1d**	O*i*Pr, O*i*Pr	H	15	93	98
5[d]	**1e**	O*t*Bu, O*t*Bu	H	36	90	97
6	**1f**	OEt, OEt	Me	26	94	98
7	**1g**	OEt, OEt	allyl	48	89	>99
8	**1h**	OEt, OEt	Br	48	trace	–
9[d]	**1i**	OEt, OEt	Ph	48	trace	–
10[e]	**1j**	Me, O*i*Pr	H	30	85	90/90
11[d,f]	**1k**			30	83	95/95

[a] Unless otherwise noted, reactions were carried out with **2a** (0.3 mmol) and **1** (0.9 mmol) in the presence of 10 μL EtOH with 0.75 mol% **L7**/Sc(OTf)$_3$ (1.1:1) and 4 Å molecular sieves (30 mg) under nitrogen at 40 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out with 1.5 mol% **L7**/Sc(OTf)$_3$ (1.1:1) and 30 mg 4 Å molecular sieves in EtOH (0.1 mL) under nitrogen at 30 °C. [e] Diastereomeric ratio (d.r.): 56:44. [f] d.r. 67:33.

(Table 4, entries 2–5). Other α-substituted malonates were also employed as nucleophiles in the Michael reaction, and various products that bore a quaternary carbon center were obtained (Table 4, entries 6–9). α-Methyl malonate **1f** and α-allyl malonate **1g** reacted smoothly with 4-oxo-4-phenylbutenoate (**2a**) to afford the products with excellent results (Table 4, entries 6 and 7). Unfortunately, the reactions with α-bromomalonate **1h** or α-phenylmalonate **1i** gave only trace products (Table 4, entries 8 and 9). The α-unsubstituted β-ketoester **1j** and α-substituted β-ketoester **1k** were also tolerated in the current system (Table 4, entries 10 and 11).

Subsequently, the scope of the conjugate addition of α-chloromalonate **1a** to a variety of (*E*)-4-oxo-4-arylbutenoates was tested, and the results are summarized in Table 5. It was noteworthy that either the electronic nature

Table 5. Enantioselective Michael additions of (*E*)-4-oxo-4-arylbutenoates **2** with malonate **1a** under the optimal conditions.[a]

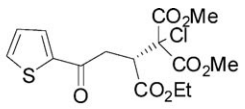


1a **2a–2m** **2n** **3aa–3am** **3an**

Entry	Ar	*t* [h]	Adduct	Yield [%][b]	*ee* [%][c]
1	Ph	20	**3aa**	95	99
2	4-MeC_6H_4	24	**3ab**	96	99
3	2-ClC_6H_4	24	**3ac**	96	95
4[d]	3-ClC_6H_4	28	**3ad**	95	99
5[d]	4-ClC_6H_4	24	**3ae**	95	99
6[d]	3,4-$Cl_2C_6H_3$	24	**3af**	97	98
7[d]	4-BrC_6H_4	24	**3ag**	96	99
8[d]	4-FC_6H_4	28	**3ah**	95	98
9	3-MeOC_6H_4	32	**3ai**	86	90
10	4-MeOC_6H_4	32	**3aj**	90	98
11	2-furyl	30	**3ak**	84	93
12	2-thienyl	26	**3al**	92	99 (*S*)[e]
13	2-naphthyl	24	**3am**	93	98
14	**2n**[f]	48	**3an**	78	98

[a] Unless otherwise noted, reactions were carried out with **2** (0.3 mmol) and **1a** (0.9 mmol) in the presence of EtOH (10 μL) and 4 Å molecular sieves (MS; 30 mg) with **L7**/Sc(OTf)$_3$ (0.75 mol%, 1.1:1) under nitrogen at 40 °C for 24–30 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out with **2** (0.4 mmol) and **1a** (1.2 mmol) in the presence of EtOH (10 μL) and 4 Å molecular sieves (40 mg) with **L7**/Sc(OTf)$_3$ (0.5 mol%, 1.1:1) under nitrogen at 40 °C. [e] The absolute configuration was determined by X-ray analysis. [f] (*E*)-1,4-Diphenyl-2-butene-1,4-dione was used as the Michael acceptor in CH_2Cl_2/EtOH (0.3 mL:0.1 mL) with 2 mol% catalyst at 35 °C for 48 h.

or the position of the substituents at the aromatic ring had little influence on the enantioselectivity (up to 99% *ee*; Table 5, entries 1–10). Substrates that bore a heteroaryl condensed ring also proved to be competent candidates for conjugate addition (Table 5, entries 11–13; Figure 1). In addition, (*E*)-1,4-diphenyl-2-butene-1,4-dione (**2n**) was used as a Michael acceptor to generate an α-stereogenic ketone with excellent enantioselectivity (Table 5, entry 14).



3al

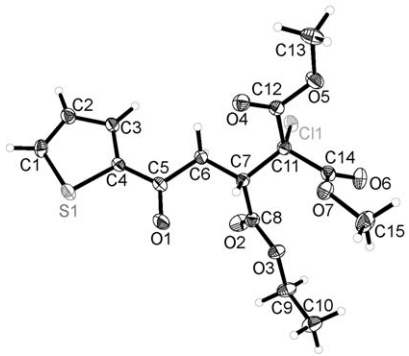
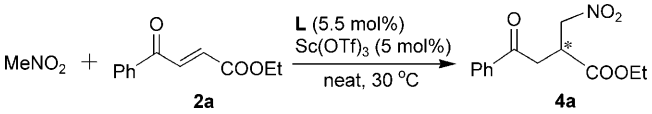


Figure 1. X-ray structure of compound **3al**.

Encouraged by the success of the conjugate addition of malonate to (*E*)-4-oxo-4-arylbutenoates, we also investigated nitromethane as nucleophile. As shown in Table 6, *N*,*N*′-dioxide **L8** derived from aromatic amine exhibited superior results to **L7** based on aliphatic amine with excellent enantioselectivity (Table 6, entry 2 vs. 1). For the improvement of the yield, the addition of *N*,*N*-dimethylpyridin-4-amine (DMAP) was effective to afford the desired Michael adduct **4a** in 85% yield with 98% *ee* (Table 6, entry 3). The role of the organic base DMAP is that it might deprotonate the α proton of nitromethane to generate an ammonium nitronate and accelerate the reaction rate. Excitingly, the catalyst loading could be decreased to 2 mol% without affecting the efficiency of the catalyst (Table 6, entry 4). Under the optimized conditions, the substrate scope was then surveyed. Various (*E*)-4-oxo-4-arylbutenoates with electron-withdrawing or -donating groups on the aromatic ring reacted with nitromethane smoothly using 2 mol% catalyst under mild conditions, thereby giving the corresponding products in good yields and excellent enantioselectivities (95–99% *ee*, Table 7, entries 1–11).

Table 6. Optimization of reaction conditions.[a]

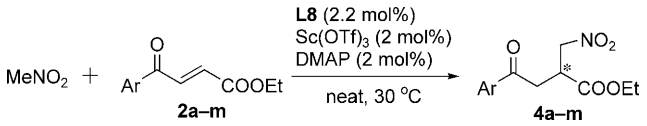


2a **4a**

Entry	Ligand	Additive	Yield [%][b]	*ee* [%][c]
1	**L7**	–	17	30
2	**L8**	–	25	98
3[d]	**L8**	DMAP	85	98
4[e]	**L8**	DMAP	82	98

[a] Unless otherwise noted, reactions were carried out with **2a** (0.3 mmol) and nitroalkane (0.32 mL) with **L**/$Sc(OTf)_3$ (1.1:1) under nitrogen at 30°C for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] In the presence of *N*,*N*-dimethylpyridin-4-amine (DMAP; 5 mol%). [e] The catalyst was **L8**/$Sc(OTf)_3$/DMAP (2 mol%, 1.1:1:1).

Table 7. Enantioselective Michael additions of (*E*)-4-oxo-4-arylbutenoates **2** with nitromethane.[a]



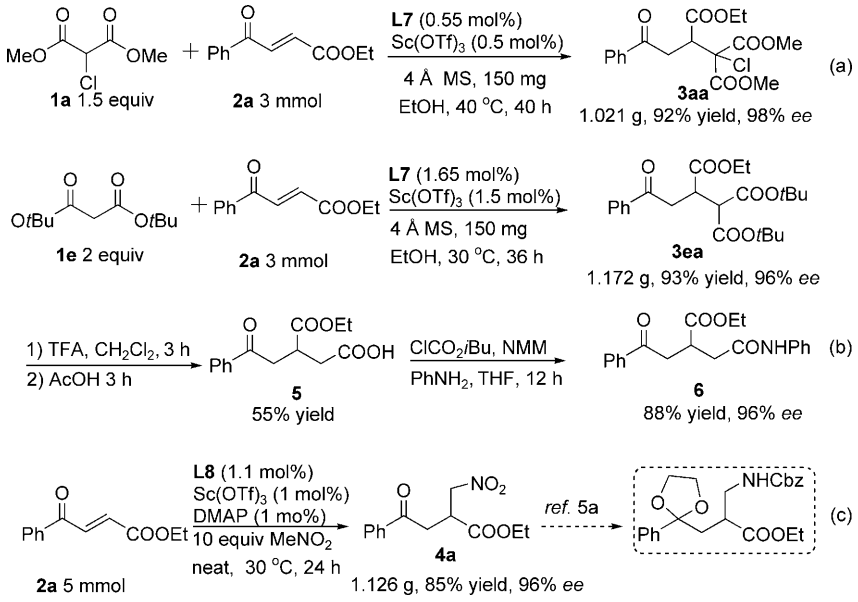
2a–m **4a–m**

Entry	Ar	Adduct	Yield [%][b]	*ee* [%][c]
1	Ph	**4a**	85	98
2	4-MeC_6H_4	**4b**	87	99
3	2-ClC_6H_4	**4c**	93	95
4	3-ClC_6H_4	**4d**	85	96
5	4-ClC_6H_4	**4e**	83	99
6	3,4-$Cl_2C_6H_3$	**4f**	83	>99
7	4-BrC_6H_4	**4g**	78	98 (*R*)[d]
8	4-FC_6H_4	**4h**	83	99
9	4-$MeOC_6H_4$	**4j**	85	99
10	2-thienyl	**4l**	88	99
11	2-naphthyl	**4m**	83	99

[a] The reactions were carried out with **2** (0.3 mmol) and nitromethane (0.32 mL) with **L8**/$Sc(OTf)_3$/DMAP (2 mol%, 1.1:1:1) under nitrogen at 30°C for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined by comparison with literature data.[5a]

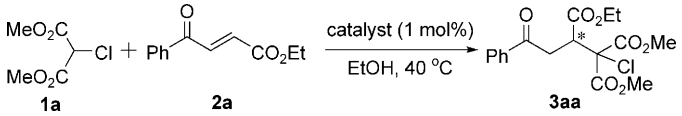
To show the synthetic application of the current system, a gram-scale synthesis of **3aa**/**4a** was tested. As shown in Scheme 3, using only 0.5 mol% of **L7**–$Sc(OTf)_3$, catalytic asymmetric Michael addition of α-chloromalonate (**1a**) with ethyl (*E*)-4-oxo-4-phenylbutenoate (**2a**) was accomplished with excellent results (1.021 g, 92% yield, 98% *ee*). Importantly, the amount of α-chloromalonate **1a** was decreased to 1.5 equiv with respect to ethyl (*E*)-4-oxo-4-phenylbutenoate (**2a**; Scheme 3a). In addition, the product **3ea** can also be easily transformed into optically active compound **6** in two steps (48% yield, 96% *ee*), which is a versatile building block (Scheme 3b). The reaction could be performed with nitromethane in the presence of 1 mol% **L8**–$Sc(OTf)_3$, thus giving the desired product **4a** with excellent enantioselectivity. Also, a β^2-amino acid[11] derivative could be prepared from the product **4a** by following known procedures (Scheme 3c).[5a]

To gain insight into the reaction mechanism,[12] several control experiments were carried out, and the results are summarized in Table 8. As shown in Table 8, the ratio of ligand **L7** to $Sc(OTf)_3$ was crucial. The enantioselectivity decreased remarkably when a 1.5:1 molar ratio of $Sc(OTf)_3$/**L7** was used because of the strong background reaction of $Sc(OTf)_3$ (Table 8, entry 1). In addition, when the molar ratio of ligand **L7** to $Sc(OTf)_3$ was increased from 1:1 to 2:1, the chemical yields and enantioselectivities were clearly decreased (Table 8, entries 2–5). The catalytic composition was also investigated by using ESIMS, and the results indicated that an MS peak at 903.2973 (HR-ESIMS: *m*/*z* calcd for



Scheme 3. Catalytic asymmetric conjugate addition of α-chloromalonate (**1a** and **1e**) and nitromethane to ethyl (*E*)-4-oxo-4-phenylbutenoate (**2a**) on a gram scale, and the transformation of **3ea** to **6**.

Table 8. Control experiments for mechanistic studies.[a]



Entry	**L7** [mol%]	$Sc(OTf)_3$ [mol%]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	1	1.5	15	95	34
2	1	1	15	94	99
3	1.2	1	15	94	98
4	1.5	1	24	89	97
5	2	1	24	85	93

[a] Unless otherwise noted, reactions were carried out with **2a** (0.3 mmol) and **1a** (0.9 mmol) in the presence of EtOH (10 μL) and 4 Å molecular sieves (30 mg) under nitrogen at 40 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

$[C_{35}H_{44}F_6N_4O_{10}S_2Sc]^+$: 903.1962) could be assigned to mono-ligated complex $[\mathbf{L7}–Sc(OTf)_2]^+$ (Figure 2).[13]

Because ligands **L1** and **L7** showed similar catalytic activity and enantioselectivity (Table 1, entries 1 and 7), we next investigated the relationship between the *ee* value of ligand **L1** and the product **3aa** to look for possible nonlinear effects. As shown in Figure 3, a poor positive nonlinear effect[14] was observed, thus suggesting that minor oligomeric aggregates of **L7**–$Sc(OTf)_3$ might exist in the reaction system and the major monomeric species was the active catalytic intermediate. In light of the X-ray structure of the *N,N′*-dioxide–Sc^{III} complex recently reported by us[10d] and the above experimental results, a proposed transition state[15] that rationalizes the observed sense of asymmetric induction is provided in Scheme 4. In this transition state, the N-oxides and amide oxygen atoms of **L7** coordinated to Sc^{3+} in a tetradentate manner to form two six-membered chelate rings. Meanwhile, 4-oxo-4-arylbutenoate was attached to Sc^{3+} at the favorable equatorial position.[16] The incoming α-chloromalonate (**1a**) preferred to attack the *Si* face rather than *Re* face since the latter was strongly shielded by the nearby benzyl ring, thereby giving the *S*-configured product (Scheme 4).

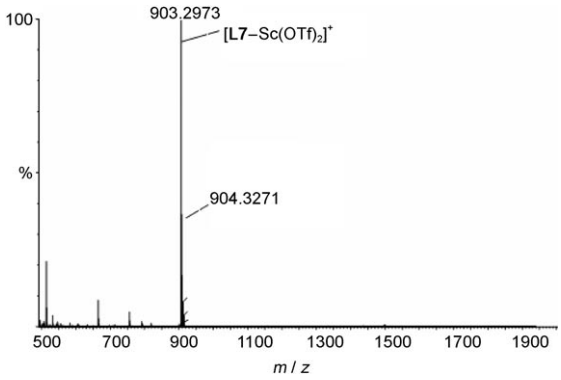


Figure 2. ESIMS spectra of a solution of **L7**–Sc^{3+}.

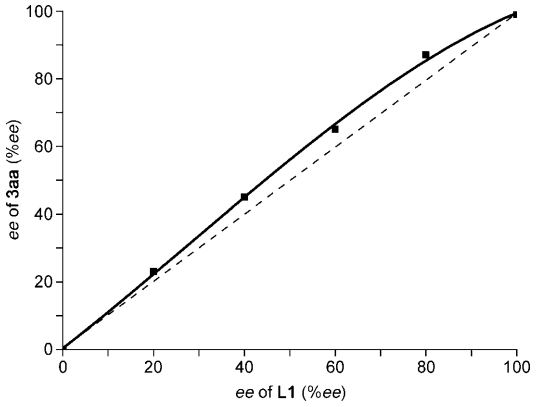
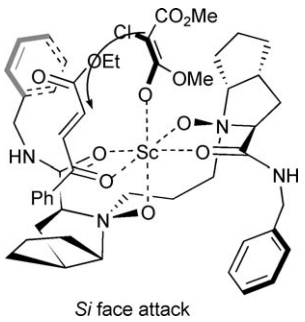


Figure 3. Nonlinear effects observed in the **L1**–$Sc(OTf)_3$-catalyzed reaction of **1a** and **2a**.

Conclusion

We have developed a catalytic asymmetric Michael addition of 1,3-dicarbonyl compounds and nitromethane with a wide range of (*E*)-4-oxo-4-arylbutenoates promoted by *N,N′*-dioxide–Sc-$(OTf)_3$ complexes. This simple experimental protocol affords various α-stereogenic esters in high yields (up to 97%) as well



Scheme 4. Proposed transition-state model.

as excellent regioselectivities and enantioselectivities (*ee* values up to >99%). Given the low catalyst loading (0.5–2 mol%), mild reaction conditions, operational simplicity, and the fact that the diverse functional groups in these adducts are ready for further conversion, this strategy may find wide application in organic synthesis. Meanwhile, a proposed transition-state model was put forward to explain the origin of the asymmetric induction.

Experimental Section

General: ^{1}H NMR spectra were recorded at 400 or 600 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet, br=broad), coupling constants [Hz], integration. ^{13}C NMR spectroscopic data were collected at 100 or 150 MHz with complete proton decoupling. Enantiomeric excesses (*ee* values) were determined by chiral HPLC analysis on Daicel Chiralcel AD-H, AS-H, and OD-H columns in comparison with the authentic racemates. Optical rotations were reported as follows: $[\alpha]_D^T$ (*c* is given in g/100 mL, in solvent). HR-ESIMS spectra were recorded using a commercial apparatus and methanol or acetonitrile was used to dissolve the sample. All reactions were performed in sealed oven-dried glass tubes under an atmosphere of nitrogen unless otherwise noted. THF and toluene were distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled over CaH_2. Unless noted, commercial reagents were used without further purification. The *N,N′*-dioxide ligands were prepared according to the literature.[10]

Typical experimental procedure for malonate: *N,N′*-Dioxide **L7** (1.4 mg, 0.0025 mmol), scandium triflate (1.1 mg, 0.00225 mmol), (*E*)-4-oxo-4-phenylbutenoate (**2a**; 71.2 mg, 0.30 mmol), EtOH (10 μL), and 4 Å molecular sieves (30 mg) were stirred in a dry reaction tube under nitrogen at 40°C for 10 min, then α-chloromalonate (**1a**; 110 μL, 0.9 mmol) was added. The sealed tube was stirred for the time indicated in the tables. After that, the reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate 12:1 to 5:1) on silica gel to afford the desired product **3aa** in 95% yield with 99% *ee*. $[\alpha]_D^{20}=-28.59$ ($c=1.53$ in $CHCl_3$); HPLC (chiral OD-H column; hexane/*i*PrOH 90:10; flow rate 1.0 mL min^{-1}; $\lambda=254$ nm): t_R (major)=9.94 min, t_R (minor)=15.61 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.99$ (d, $J=7.5$ Hz, 2H), 7.58 (t, $J=7.3$ Hz, 1H), 7.48 (t, $J=7.7$ Hz, 2H), 4.42 (dd, $J=9.4$, 2.7 Hz, 1H), 4.14 (q, $J=7.1$ Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.77 (dd, $J=17.7$, 9.4 Hz, 1H), 3.36 (dd, $J=17.7$, 2.8 Hz, 1H), 1.19 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=196.63$, 169.43, 166.26, 165.89, 136.47, 133.31, 128.61, 128.14, 71.28, 61.86, 54.13, 54.06, 47.26, 37.17, 13.80 ppm.

Typical experimental procedure for nitromethane: A mixture of (*E*)-4-oxo-4-phenylbutenoate (**2a**; 71.2 mg, 0.30 mmol), **L8** (4.6 mg, 0.0066 mmol), and scandium triflate (3.0 mg, 0.006 mmol) was stirred in nitromethane (0.2 mL) at 30°C under N_2 for 30 min. Then *N,N*-dimethylpyridin-4-amine (DMAP, 0.006 mmol) in nitromethane (0.12 mL) was added sequentially, and the reaction was stirred at 30°C for 12 h. Product **4a** was isolated by column chromatography on silica gel (ethyl acetate/petroleum ether 1:9 to 1:4) in 85% yield with 98% *ee*. $[\alpha]_D^{20}=-1.16$ ($c=0.68$ in $CHCl_3$); HPLC (chiral OD-H column; hexane/*i*PrOH 80:20; flow rate 1.0 mL min^{-1}; $\lambda=254$ nm), t_R (major)=12.59 min, t_R (minor)=20.46 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.88$ (d, $J=7.6$ Hz, 2H), 7.53 (t, $J=7.4$ Hz, 1H), 7.41 (t, $J=7.7$ Hz, 2H), 4.75 (qd, $J=14.5$, 5.7 Hz, 2H), 4.14 (qd, $J=7.1$, 1.9 Hz, 2H), 3.67 (dd, $J=11.8$, 5.9 Hz, 1H), 3.53 (dd, $J=18.4$, 5.1 Hz, 1H), 3.31 (dd, $J=18.4$, 6.9 Hz, 1H), 1.18 ppm (t, $J=7.1$ Hz, 3H).

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