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Enantioselective Michael Addition of a Malonic Ester to a Maleic Ester Catalyzed by Lithium Binaphtholate

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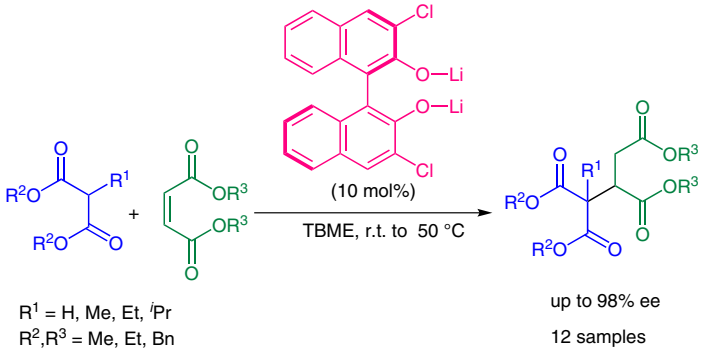

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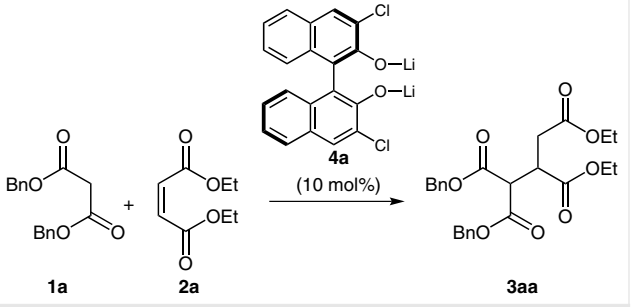
Abstract Lithium 3,3′-chlorobinaphtholate was found to catalyze the enantioselective Michael addition of a malonic ester to a maleic ester. High enantioselectivities (>90% ee) were observed, especially in the reactions of 2-alkylmalonic esters and maleic esters.

Key words asymmetric catalyst, asymmetric synthesis, enantioselectivity, Michael addition, chiral catalyst, lithium binaphtholate



Scheme 1 Enantioselective Michael addition of malonate **1a** to maleate **2a**

The Michael addition is one of the most versatile tools for forming carbon–carbon bonds.[1] A number of catalytic enantioselective Michael additions have been reported for the preparation of biologically active compounds with chiral centers using various Michael donors and acceptors. The Michael addition of a malonic ester to a maleic ester is a typical example of this chemical transformation, which is described even in an early volume of the famous 'Organic Syntheses';[2] however, enantioselective Michael additions to a maleic ester have not been reported to date. We have previously reported that optically active lithium 3,3′-dichlorobinaphtholate is an effective catalyst for the enantioselective Michael addition of α-alkyl-β-keto ester to methyl vinyl ketone.[3–6] Herein, we report the first example of the enantioselective Michael addition of a malonic ester to a maleic ester, affording the corresponding adducts in high enantioselectivities.

First, we investigated the Michael addition using dibenzyl malonate (**1a**) as a donor and diethyl maleate (**2a**) as an acceptor (Scheme 1).

Previously described reaction conditions for the Michael addition of β-keto ester to methyl vinyl ketone[3] were applied here: the donor and acceptor were added dropwise to a diethyl ether solution of lithium 3,3′-chlorobinaphtholate (0.1 mmol/mL) prepared from 3,3′-chlorobinaphthol and *n*-butyllithium[7] at room temperature. The reaction proceeded smoothly to give the corresponding adduct **3aa** in high yield but with moderate enantiomeric excess. Solvent screening (Table 1) revealed that *tert*-butyl methyl ether was the best solvent for optimizing the chemical yield and selectivity. A lower catalyst concentration improved the selectivity, and higher selectivities were not observed at catalyst concentrations below 0.01 mmol/mL. Lowering the temperature did not increase the selectivity.

Among the 3,3′-disubstituted naphthols tested, 3,3′-chlorobinaphthol gave the best enantioselectivity as a catalyst precursor (Table 2). Interestingly, unsubstituted binaphthol (**4e**) significantly reduced the catalytic reactivity and selectivity (Table 2, entry 5).

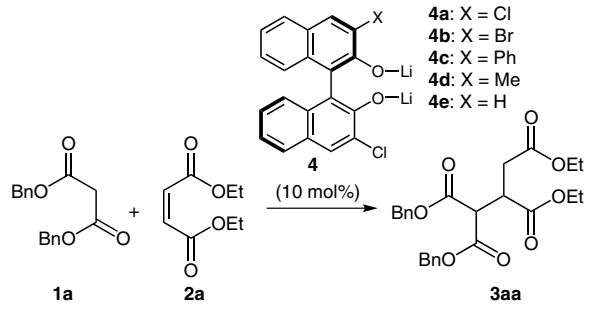
With the optimized conditions in hand, we investigated the Michael addition of malonate to various acceptors.[8] Dimethyl maleate (**2b**) and dibenzyl maleate (**2c**) gave slightly lower selectivities compared with diethyl maleate (Table 3, entries 1 and 2). *N*-Phenylmaleimide[9] (**2e**) and chalcone[10] (**2f**) gave the adducts in good yields but with low enantioselectivities (Table 3, entries 3 and 4). Interestingly, fumarate[11] (**2g**), the geometric isomer of maleate, gave the ad-

Table 1 Michael Addition of **1a** to **2a** with **4a** as a Catalyst

Entry	Solvent	*c* (mol/L)[a]	Conditions	Yield (%)[b]	ee (%)[c]
1	Et_2O	0.1	r.t., 0.5 h	93	45
2	toluene	0.1	r.t., 0.5 h	92	20
3	THF	0.1	r.t., 4 h	85	57
4	TBME	0.1	r.t., 0.5 h	94	58
5	TBME	0.01	r.t., 1 h	94	90
6	TBME	0.003	r.t., 1 h	92	90
7	TBME	0.1	0 °C, 3 h	88	91

[a] Catalyst concentration
[b] Isolated yield.
[c] Determined by chiral HPLC.

Table 2 Michael Addition of **1a** to **2a** with Various Catalysts



Entry	**Cat.** X	Conditions	Yield (%)[a]	ee (%)[b]
1	**4a** Cl	r.t., 1 h	94	90
2	**4b** Br	r.t., 1 h	94	87
3	**4c** Ph	r.t., 3 h	79	18
4	**4d** Me	r.t., 24 h	99	25
5	**4e** H	r.t., 24 h	65	20

[a] Isolated yield.
[b] Determined by chiral HPLC.

Table 3 Michael Addition of Various Donors and Acceptors

Entry	Donor	Acceptor	Conditions	Yield (%)[a]	ee (%)[b]
1	**1a**	**2b**	r.t., 1 h	94	85
2	**1a**	**2c**	r.t., 1 h	75	83
3	**1a**	**2e**	r.t., 2 h	69	18
4	**1a**	**2f**	r.t., 1 h	78	20
5	**1a**	**2g**	r.t., 24 h	83	–8[c]
6	**1a**	**2h**	50 °C, 1 h	79	4
7	**1a**	**2a**	r.t., 1 h	94	90
8	**1b**	**2b**	r.t., 1 h	93	85[d]
9	**1b**	**2a**	r.t., 1 h	92	77
10	**1c**	**2a**	r.t., 1 h	99	55

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] The predominant enantiomer has the opposite absolute configuration to that from **2a**.
[d] The absolute configuration of **3bb** was determined to be *R* by comparison to literature values of the HPLC retention times [CHIRALPAK AD-H, hexane–2-PrOH (9:1), 0.5 mL/min; 23.4 min (*S*), 24.3.2 min (*R*)].[10a]

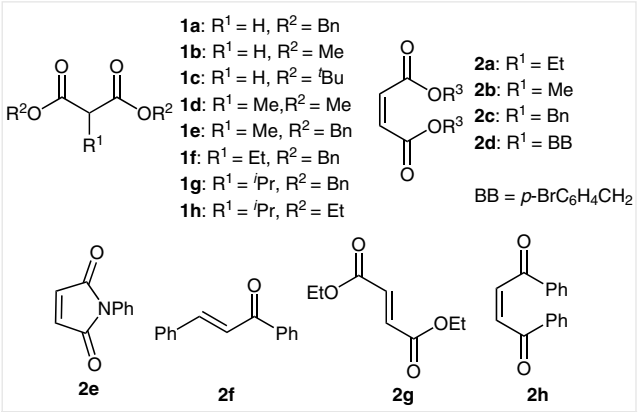


Figure 1 Donors and acceptors for Michael addition

duct in almost racemic form (Table 3, entry 5). These results revealed that a *cis* geometry at the C–C double bond was essential for obtaining a high enantioselectivity, but a ketone with a *cis* geometry (1,4-diphenyl-but-2-ene-1,3-dione, **2h**)[12] gave a very low selectivity (Table 3, entry 6).

Among the Michael donors, no alkyl ester performed better than dibenzyl malonate (Table 2, entries 9 and 10). The absolute configuration of the Michael adduct prepared from **1b** and **2b** (Figure 1) was found to be *R*, assigned by comparison of the HPLC data to literature values;[10a] therefore, other Michael adducts would be expected to have the same absolute configuration.

This Michael addition can be extended to the addition of sterically congested donors (Figure 2).[13] 2-Alkyl malonate donors gave the adducts with a quaternary carbon in high enantioselectivities. Malonate with methyl, ethyl, or even isopropyl groups at the 2-position gave the corresponding adducts **3da**,**ed**,**ea**,**fa**,**ga**,**hc** in good yield with a high enantioselectivity, although dibenzyl 2-isopropylmalonate required 20 mol% catalyst to achieve a smooth reaction.

In summary, we developed an enantioselective Michael addition of malonates to maleates, catalyzed by chiral lithium binaphtholate. This is the first example of an enantioselective Michael addition using maleates as the acceptors. High enantioselectivities were observed, especially in the reactions of 2-alkylmalonic esters as donors. Further studies designed to enhance the enantioselectivity and explore the reaction mechanism are in progress and will be reported in due course.

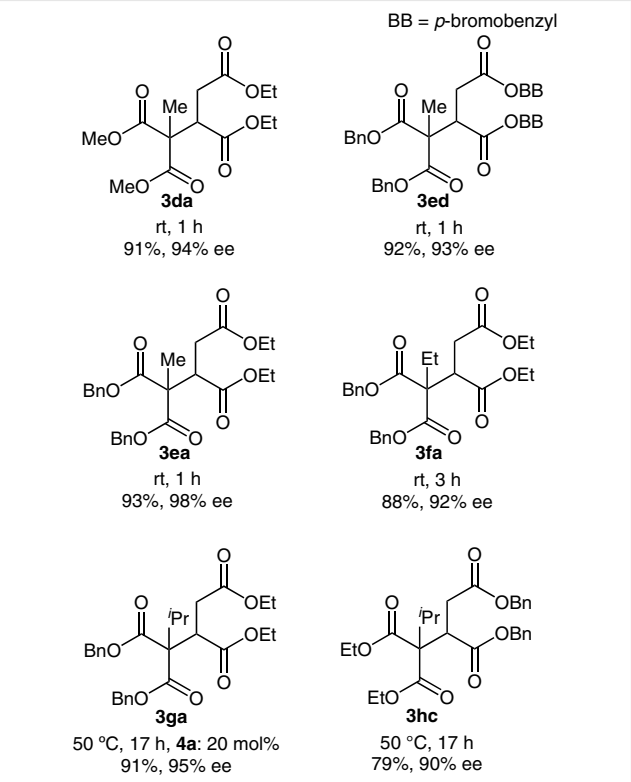


Figure 2 Enantioselective Michael addition of 2-alkylmalonate esters catalyzed by **4a** (10 mol%)

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562691.

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(7) Lithium salt prepared from the corresponding naphthol and lithium hydroxide gave lesser result (68% yield, 75% ee under the conditions given in Table 1, entry 7).

(8) **Typical Experimental Procedure for the Enantioselective Michael Addition Catalyzed by Lithium Binaphtholate**
Under argon atmosphere, *n*-BuLi (0.10 mmol, 20 mol%) in hexane (0.15 M, 0.67 mL) was added to the solution of (*R*)-Cl_2BINOL (**4a**, 17.8 mg, 0.050 mmol, 10 mol%) in TBME at r.t. After stirring for 1 min, dibenzyl malonate (**1a**, 0.13 mL, 0.5 mmol) and diethyl maleate (**2a**, 0.10 mL, 0.6 mmol, 1.2 equiv) were successively added to the reaction mixture. After stirring for 1 h, the reaction was quenched with sat. NH_4Cl aq (2 mL). The aqueous layer was extracted with EtOAc (20 mL), and the combined organic layers were washed with brine (20 mL). After drying over Na_2SO_4, filtration, and concentration, the crude product was purified by silica gel column chromatography (hexane–EtOAc = 9:1, SiO_2 10 g) to give the adduct **3aa** as a colorless oil (214 mg, 94% yield, 90% ee). $[\alpha]_{435}^{27}$ +11.5 (*c* 1.03, $CHCl_3$) for 90% ee. IR (film): 3066, 3033, 1731, 1159 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.23 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3), 2.66 (dd, *J* = 17.0, 5.2 Hz, 1 H, CH_2CO), 2.79 (dd, *J* = 17.0, 7.6 Hz, 1 H, CH_2CO), 3.60–3.62 (m, 1 H), 4.04–4.12 (m, 5 H), 5.14 (s, 2 H, CH_2Ph), 5.15 (s, 2 H, CH_2Ph), 7.28–7.37 (m, 10 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 14.1, 33.4, 40.4, 52.3, 60.8, 61.4, 67.4, 128.2, 128.3, 128.4 128.5, 134.9, 135.0, 167.3, 167.5, 171.1, 171.5 (3 C overlapped). MS–FAB: *m/z* = 457 (M + H^+), 91. HRMS: *m/z* calcd for $C_{25}H_{29}O_8$: 457.1862; found: 457.1868.

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(13) **Compound 3ea (Representative Product)**

$[\alpha]_D^{29}$ –11.4 (*c* 1.0, $CHCl_3$) for 98% ee. IR (ATR): 2983, 1728, 1213 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.24 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3), 1.50 (s, 3 H, CCH_3), 2.56 (dd, *J* = 16.6, 3.2 Hz, 1 H, CH_2CO), 2.77 (dd, *J* = 16.6, 10.4 Hz, 1 H, CH_2CO), 3.76 (dd, *J* = 10.4, 3.2 Hz, 1 H, CHCO), 4.03 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 4.10 (q, *J* = 7.6 Hz, 2 H, CH_2CH_3), 5.08 (d, *J* = 12.4 Hz, 1 H, CH_2Ph), 5.12 (s, 2 H, CH_2Ph), 5.14 (d, *J* = 12.4 Hz, 1 H, CH_2Ph), 7.22–7.25 (m, 4 H, ArH), 7.30–7.32 (m, 6 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.1, 17.9, 32.9, 45.5, 55.6, 60.8, 61.2, 67.5, 128.1, 128.2, 128.3, 128.3, 128.5, 128.5, 135.1, 169.9, 170.1, 171.5, 171.5 (two carbons overlapped). MS–FAB: *m/z* = 471 [M + H^+], 91. HRMS: *m/z* calcd for $C_{26}H_{31}O_8$: 471.2019; found: 471.2022.