Self-Assembly of Heterobimetallic Complexes and Reactive Nucleophiles: A General Strategy for the Activation of Asymmetric Reactions Promoted by Heterobimetallic Catalysts

Takayoshi Arai, Yoichi M. A. Yamada, Noriyoshi Yamamoto, Hiroaki Sasai, and Masakatsu Shibasaki*

Abstract: Heterobimetallic asymmetric catalysts, such as the lanthanum–lithium–binaphthol complex (La Li–BINOL), the aluminum–lithium–binaphthol complex (Al Li–BINOL), and a newly prepared gallium–sodium–binaphthol complex (Ga Na–BINOL), have been self-assembled with reactive nucleophiles, such as lithium nitronates and sodium malonates, to generate more efficient catalysts than the parent heterobimetallic catalysts. For example, by the combined use of La Li–BINOL (1 mol%; contains one H_2O molecule) and BuLi (0.9 mol%) as the catalyst system, asymmetric nitroaldol reactions are greatly accelerated in all cases without a decrease in the optical purity of the nitroaldol products. Kinetic analyses have also been carried out on the Ga Na–BINOL-catalyzed Michael reaction of dibenzyl malonate with cyclohexenone, with or without NaO*t*Bu. The calculated rate constants show that the combined use of Ga Na–BINOL and NaO*t*Bu as the catalyst gives reaction rates that are about 50 times faster than with Ga Na–BINOL alone. This activation method should be useful for other asymmetric reactions catalyzed by heterobimetallic complexes.

Keywords
heterobimetallic catalysts · Michael additions · multifunctional catalysts · nitroaldol reactions · self-assembly

Introduction

Conventional bases such as NaO*t*Bu can generate reactive nucleophiles from suitably acidic starting materials, which can then react with electrophiles to give racemic products when both of the starting materials are achiral. However, in the presence of heterobimetallic asymmetric catalysts,[1–4] we have found that reactive nucleophiles and the aforementioned asymmetric catalysts self-assemble very quickly, thereby making possible the more rapid formation of chiral products with high enantiomeric excesses. To the best of our knowledge, this is the first reported example of such chemical phenomena. In this paper, we report exciting results concerning heterobimetallic asymmetric catalysts and reactive nucleophiles for catalytic asymmetric nitroaldol reactions and for catalytic asymmetric Michael reactions. We also report the development of new heterobimetallic asymmetric catalysts.

Results and Discussion

Recently we successfully developed several heterobimetallic asymmetric catalysts in which each metal plays a different role in controlling asymmetric reaction. Asymmetric nitroaldol reactions catalyzed by lanthanoid–lithium–BINOL (1,1′-bi-2-naphthol) complexes,[1] asymmetric Michael reactions catalyzed by lanthanoid–sodium–BINOL complexes,[2] asymmetric hydrophosphonylations of imines catalyzed by lanthanoid–potassium–BINOL complexes,[3] and asymmetric Michael–aldol reactions and hydrophosphonylation of aldehydes catalyzed by an aluminum–lithium–BINOL complex (Al Li–BINOL)[4] have been developed. Although these asymmetric reactions are highly stereoselective, most require 3 to 10 mol% of catalyst, and the reactions are rather slow. To develop more reactive catalysts, we prepared new asymmetric heterobimetallic catalysts using Group 13 elements other than aluminum. Boron–alkali metal–BINOL ((*R*)-BINOL was used in all asymmetric transformations) complexes did not promote the reaction of cyclohexenone (**1**) with dibenzyl malonate (**2**) at room temperature (Table 1, entries 1–3). However, the gallium–sodium–BINOL complex (Ga Na–BINOL) (entry 8) and the indium–potassium–BINOL complex (In K–BINOL) (entry 12) were rather effective catalysts for asymmetric Michael reactions. The former was better than the latter in terms of stereoselectivity. The Ga Na–BINOL catalyst was prepared from $GaCl_3$, NaO*t*Bu (4 molequiv to $GaCl_3$), and (*R*)-BINOL (2 molequiv to $GaCl_3$) in THF/ether. The structure, consisting of one Ga atom, one Na atom, and two molecules of BINOL, was determined from the ^{13}C NMR spectrum and LDI-TOF mass spectrum.

While determining the optimal amounts of starting materials to construct the Ga Na–BINOL catalyst, we were very surprised to observe that almost one molar excess of NaO*t*Bu did not reduce the optical purity of the Michael adducts, but en-

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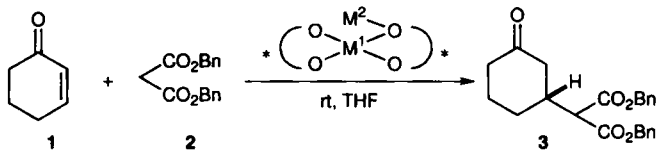
Table 1. Catalytic asymmetric Michael reaction of **1** with **2** in the presence of heterobimetallic asymmetric catalysts (10 mol%).



1 2 3

Entry	M^1	M^2	t (h)	Yield (%)	*ee* (%)
1	B	Li	17	0	–
2	B	Na	21	0	–
3	B	K	15	0	–
4	Al	Li	72	88	99
5	Al	Na	72	50	98
6	Al	K	72	43	87
7	Ga	Li	43	71	49
8	Ga	Na	143	45	98
9	Ga	K	44	50	86
10	In	Li	24	77	2
11	In	Na	95	25	10
12	In	K	168	61	84

hanced the reactivity of the catalyst. For example, the asymmetric Michael reaction of **1** with **2** catalyzed by 10 mol% of GaNa–BINOL required 143 h at room temperature to give **3** with 98% *ee* in 45% yield (Table 2, entry 1); treatment of **1** and **2** with 10 mol% GaNa–BINOL and 9 mol% NaO*t*Bu at room temperature for only 21 h gave **3** with 98% *ee* in 87% yield (entry 2). Addition of the sodium salt of dibenzyl malonate (9 mol%) instead of NaO*t*Bu gave almost the same result (96% *ee*, quant; entry 5). The asymmetric Michael reaction of cyclopentenone (**4**) with **2** in the presence of 10 mol% of GaNa–BINOL and 9 mol% NaO*t*Bu also proceeded smoothly to give **5** with 98% *ee* in 96% yield (room temperature, 22 h; entry 7). Moreover, an effective catalytic asymmetric synthesis of **7** was also realized for the first time (>99% ee, 79% yield; entry 9).[5]

Typical time courses of the Michael reaction of **1** with **2** in the presence of GaNa–BINOL, GaNa–BINOL + NaO*t*Bu, or NaO*t*Bu are shown in Figure 1. The reaction was controlled

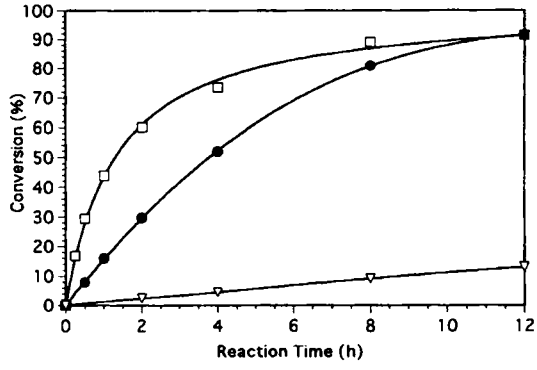
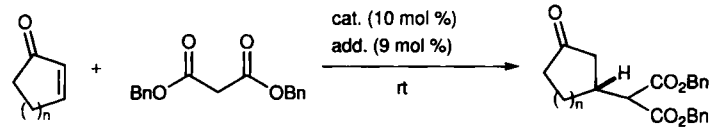


Fig. 1. Typical time course of the Michael reaction of cyclohexenone (392 mM) with dibenzyl malonate (392 mM) in THF in the presence of 10 mol% of the catalyst at 24°C. □ GaNa-BINOL + NaO*t*Bu; ● NaO*t*Bu; ▽ GaNa-BINOL.

kinetically since treatment of racemic **3** with GaNa–BINOL or GaNa–BINOL + NaO*t*Bu resulted in only racemic **3**. The reactions catalyzed by GaNa–BINOL and GaNa–BINOL + NaO*t*Bu were second-order for up to ca. 70% of the reaction with a linear correlation coefficient of r of over 0.998. The calculated rate constants for the reactions catalyzed by GaNa–BINOL and GaNa–BINOL + NaO*t*Bu were 0.031 and 1.78 $M^{-1}h^{-1}$, respectively. As expected, reaction of **1** with **2** in the presence of 10 mol% of the sodium salt of dibenzyl malonate at room temperature for 12 h gave racemic Michael adduct **3** in 91% yield. These results clearly suggest that the sodium salt of dibenzyl malonate binds to GaNa–BINOL much more quickly than it reacts with the enone, thereby producing Michael adducts with high enantiomeric excess. No free sodium dibenzyl malonate should be present in the reaction medium. The malonate anion can be transferred to cyclohexenone from the resulting assembly with an enantiomeric excess similar to that in the case of GaNa–BINOL itself. This result appears to suggest that cyclohexenone also coordinates with Ga metal under the conditions described above.[4a,6]

The usefulness of this activation strategy has also been demonstrated in catalytic asymmetric Michael reactions promoted by AlLi–BINOL. The structure of AlLi–BINOL itself has been unequivocally determined by X-ray analysis (Fig. 2).[4] Representative results are summarized in Table 2 (entries 10–15). The reactions catalyzed by AlLi–BINOL and AlLi–

Table 2. Enhancement of catalyst efficiency for asymmetric Michael reactions using Ga or Al complexes.



1: n = 2
4: n = 1
6: n = 3

2

3: n = 2
5: n = 1
7: n = 3

Entry	Enone	Catalyst	Add. [a]	t (h)	Yield (%)	*ee* (%)
1	**1**	GaNa-BINOL	–	143	45	98
2	**1**	GaNa-BINOL	A	21	87	98
3	**1**	GaNa-BINOL	A [b]	6	81	84
4	**1**	GaNa-BINOL	A [c]	6	91	60
5	**1**	GaNa-BINOL	C	21	quant	96
6	**4**	GaNa-BINOL	–	72	32	89
7	**4**	GaNa-BINOL	A	22	96	98
8	**6**	GaNa-BINOL	–	73	trace	–
9	**6**	GaNa-BINOL	A	73	79	>99
10	**1**	AlLi-BINOL	–	72	88	99
11	**1**	AlLi-BINOL	B	12	quant	97
12	**1**	AlLi-BINOL	C	24	99	98
13 [d]	**1**	AlLi-BINOL	C	48	98	98
14	**6**	AlLi-BINOL	–	72	34	97
15	**6**	AlLi-BINOL	C	72	83	96

[a] Additives: A: NaO*t*Bu; B: Li-hexamethyldisilazide; C: Na-malonate. [b] 2 molequiv of NaO*t*Bu was used to GaSB. [c] 3 molequiv of NaO*t*Bu was used to GaNa-BINOL. [d] 5 mol% of AlLi-BINOL and 4.5 mol% of Na-malonate were used.

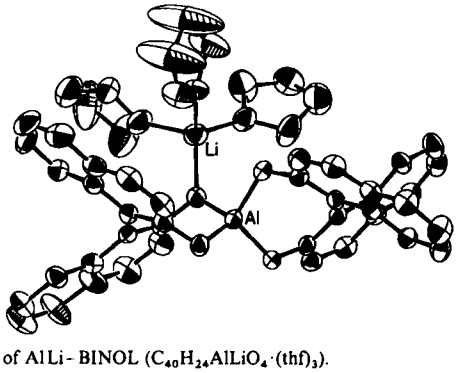
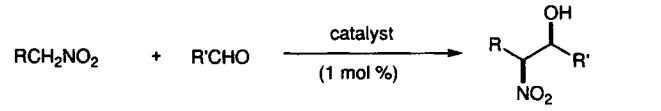


Fig. 2. Crystal structure of AlLi-BINOL ($C_{40}H_{24}AlLiO_4 \cdot (thf)_3$).

BINOL + Na-malonate were also second-order with a linear correlation coefficient r of over 0.995. The calculated rate constants for these two reactions were 0.273 and 1.66 $M^{-1}h^{-1}$, respectively. This strategy has also made possible the use of 5 mol% AlLi-BINOL for efficient catalytic asymmetric Michael reactions (entry 13).

Catalytic asymmetric nitroaldol reactions can also be improved by using a similar activation strategy. Generally, about 3 mol% of the lanthanum-lithium-BINOL complex (LaLi-BINOL) is essential for efficient catalytic asymmetric nitroaldol reactions. However, we were very pleased to find that 1 mol% of second-generation LaLi-BINOL (LaLi-BINOL + H_2O + BuLi) prepared from LaLi-BINOL, 1 molequiv of H_2O, and 0.9 molequiv of butyllithium, efficiently promoted catalytic asymmetric nitroaldol reactions. For example, exposure of hydrocinnamaldehyde (**12**) to nitropropane (**14**) in THF containing 1 mol% of second-generation LaLi-BINOL*[ih] (LaLi-BINOL* + H_2O + BuLi; BINOL* = 6,6'-bis(triethylsilylethynyl)BINOL) at −40°C for 166 h gave rise to nitroaldol **15** in 84% yield (*syn*:*anti* = 95:5, *ee* of *syn* 95%) (Table 3, entry 8).[1] The use of other additives was examined: H_2O + NaO*t*Bu gave **15** in 87% yield (*syn*:*anti* = 88:12, *ee* of *syn* 85%); the corresponding figures for H_2O + KO*t*Bu and for H_2O + Ca(O*i*Pr)$_2$ were 82% (88:12, 81% *ee*) and 28% (93:7, 91% *ee*), respectively. The use of additives such as Et_3N, LiCl, and HMPA had little effect on the acceleration of the catalytic asymmetric nitroaldol reaction. Only a trace amount of nitroaldol **15** was formed with only 1 mol% of LaLi-BINOL* under similar reaction conditions. Furthermore, treatment of lithium nitronate (0.9 mol%), generated from **14** and BuLi, with LaLi-BINOL* (1 mol%), **12**, and **14** under the above reaction conditions gave comparable results (59% yield, *syn*:*anti* = 94:6, 94% ee). This result suggests that a similar heteropolymetallic intermediate is formed to that proposed for improved catalytic asymmetric Michael reactions. Although the molecular ion peak was not observed, a fragment ion peak for the complex of LaLi-BINOL and lithium propanenitronate was observed at m/z = 816 by FAB mass spectrum (Fig. 3). The structure of the second-generation LaLi-BINOL has not yet been unequivocally determined. However, we propose here that the structure is a complex of LaLi-BINOL and LiOH. Representative results for the catalytic asymmetric nitroaldol reactions are summarized in Table 3.

Table 3. Comparison of the catalytic activity of LaLi-BINOL and second-generation LaLi-BINOL in asymmetric nitroaldol reactions.

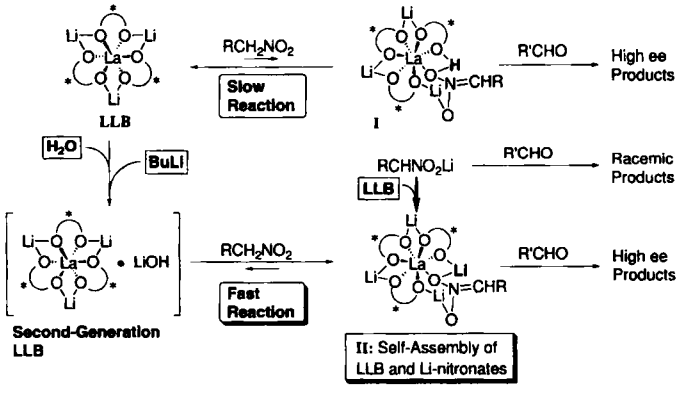


8: R = H
11: R = Me
14: R = Et
16: R = CH_2OH
9: R' = C_6H_{11}
12: R' = CH_2CH_2Ph
10: R = H, R' = C_6H_{11}
13: R = Me, R' = CH_2CH_2Ph
15: R = Et, R' = CH_2CH_2Ph
17: R = CH_2OH, R' = CH_2CH_2Ph

Entry	SM	Catalyst [a]	t (h)	T(°C)	Prod.	Yield (%) (*syn*/*anti*)	*ee* (%) of *syn*
1	**8** + **9**	LaLi-BINOL	24	−50	**10**	5.6	88
2	**8** + **9**	LaLi-BINOL + H_2O + BuLi	24	−50	**10**	73	89
3	**8** + **9**	LaLi-BINOL + H_2O + BuLi [b]	42	−50	**10**	86	51
4	**8** + **9**	LaLi-BINOL + H_2O + BuLi [c]	42	−50	**10**	94	40
5	**11** + **12**	LaLi-BINOL*	113	−30	**13**	25 (70/30)	62
6	**11** + **12**	LaLi-BINOL* + H_2O + BuLi	113	−30	**13**	83 (89/11)	94
7	**14** + **12**	LaLi-BINOL*	166	−40	**15**	trace	–
8	**14** + **12**	LaLi-BINOL* + H_2O + BuLi	166	−40	**15**	84 (95/5)	95
9	**16** + **12**	LaLi-BINOL*	154	−50	**17**	trace	–
10	**16** + **12**	LaLi-BINOL* + H_2O + BuLi	154	−50	**17**	76 (94/6)	96

[a] BINOL*: 6,6'-bis(triethylsilylethynyl)BINOL. [b] 1 molequiv of H_2O and 2 molequiv of BuLi were used to generate LaLi-BINOL. [c] 1 molequiv of H_2O and 3 molequiv of BuLi were used to generate LaLi-BINOL.

A proposed reaction course for an improved catalytic asymmetric nitroaldol reaction is shown in Scheme 1.[7] The activation strategy shown presents several conceptually new chemical



Scheme 1. Proposed mechanism of catalytic asymmetric nitroaldol reaction promoted by LaLi-BINOL (further abbreviated to LLB) and lithium nitronates.

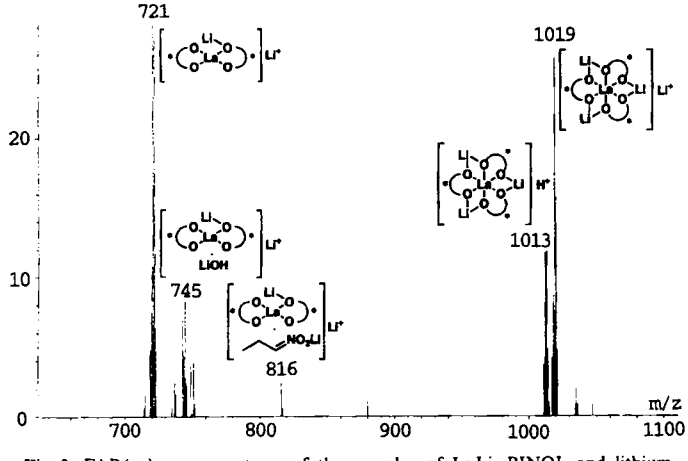


Fig. 3. FAB(+) mass spectrum of the complex of LaLi-BINOL and lithium propanenitronate.

phenomena, which may be interesting when applied to supramolecular chemistry. First, the tight complex of LaLi-BINOL and LiOH or the high rate of aggregation between LaLi-BINOL and lithium nitronates results in the formation of products with high enantiomeric excesses.[8] Second, much higher reaction rates were observed in all cases; this suggests that heteropolymetallic intermediates such as **II** react with carbonyl compounds much more quickly than heterobimetallic intermediates such as **I**, or that the rate of reverse reactions of the type **II** to LaLi-BINOL is much lower than the rate of reactions of the type **I** to LaLi-BINOL.[9]

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Conclusion

Complete self-assembly of heterobimetallic asymmetric catalysts and reactive nucleophiles (e.g., the sodium salt of dibenzyl malonate or lithium nitronates) was realized for the first time. The resulting catalyst was capable of promoting catalytic asymmetric reactions more efficiently. We believe that the approach described here may be very useful for other asymmetric reactions catalyzed by heterobimetallic complexes. Further studies are in progress.

Experimental Procedure

Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 diffraction grating infrared spectrophotometer. NMR spectra were measured on JEOL JNM-EX-270 spectrometer, operating at 270 MHz for ^{1}H NMR and at 67.8 MHz for ^{13}C NMR. Chemical shifts, in $CDCl_3$ solution, are reported downfield from TMS ($\delta = 0$) for ^{1}H NMR. For ^{13}C NMR spectra, chemical shifts in $CDCl_3$ or THF are reported relative to the central $CDCl_3$ resonance ($\delta = 77.00$) and upfield THF resonance ($\delta = 25.2$), respectively. Optical rotations were measured on a JASCO DIP-140 polarimeter. Mass spectra were measured on JEOL JMS-SX102A, JEOL JMS-DX303, and Shimadzu MALDI IV for FAB-Mass, EIMS, and LDI-TOF Mass, respectively. In the catalytic asymmetric Michael addition, reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. IR, NMR, and MS data were obtained for all of the Michael adducts described here using chromatographically homogeneous samples. Tetrahydrofuran (THF) and Et_2O were distilled from sodium benzophenone ketyl.

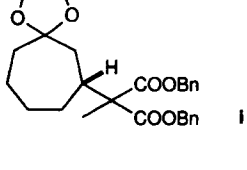
Preparation of 0.05 M InK–BINOL: A THF solution of K-hexamethyldisilazide (14.0 mL, 8.0 mmol) was added to a THF solution of (*R*)-BINOL (9 mL, 4.0 mmol) at room temperature. After having been stirred for 1 h, the suspension of (*R*)-BINOL dipotassium salt (23 mL, 4.0 mmol) was added to a solution of $InCl_3$ in THF (17 mL, 2.0 mmol), and the mixture was stirred for 1 h at room temperature. The resulting suspension was used directly.

Preparation of 0.05 M GaNa–BINOL in THF/ether solution: A THF solution of NaO*t*Bu (7 mL, 4.0 mmol) was added to a THF solution of (*R*)-BINOL (6 mL, 2.0 mmol) at room temperature. After having been stirred for 0.5 h, the resulting THF solution of (*R*)-BINOL disodium salt (13 mL, 2.0 mmol) was added to a solution of $GaCl_3$ in THF/ether (5:2) (7 mL, 1.0 mmol), and the mixture was stirred for 2 h at room temperature. The solution was allowed to stand for one day to precipitate NaCl salt, and the supernatant was used as the 0.05 M solution of GaNa-BINOL in THF/ether. ^{13}C NMR (THF, external D_2O was used for lock signal): δ = 157.4, 134.7, 129.0, 128.5, 127.4, 126.2, 124.6, 123.6, 121.8, 120.6. LDI-TOF (+) mass (reflectron mode): *m/z*: 685 and 683 [M^+ + Na], 662 and 660 [M^+].

Typical experimental procedure for asymmetric Michael reactions catalyzed by GaNa–BINOL + NaO*t*Bu: To a stirred solution of GaNa-(*R*)-BINOL (0.10 mmol) in THF/ether (9:1, 2.0 mL) was added NaO*t*Bu (0.09 mmol) in THF (0.2 mL) at room temperature. To this THF/ether solution was added cyclohexenone (**1**) (97 μL, 1.0 mmol) and dibenzyl malonate (**2**) (250 μL, 1.0 mmol) at room temperature. After having been stirred for 21 h at the same temperature, the reaction mixture was treated with 1 N HCl (2.0 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to give an oily residue. Purification by flash chromatography (SiO_2, 25% acetone/hexane) gave the Michael adduct **3** (330 mg, 87%) in 98% *ee*.

Catalytic asymmetric Michael reaction with GaNa–BINOL + Na-malonate: To a stirred solution of GaNa-(*R*)-BINOL (0.10 mmol) in THF/ether (9:1, 2.0 mL) was added the sodium salt of dibenzyl malonate (0.09 mmol) in THF (1.0 mL), which was prepared from NaH and **2** in THF at room temperature. To this THF/ether solution was added **1** (97 μL, 1.0 mmol) and **2** (227 μL, 0.91 mmol) at room temperature. After having been stirred for 21 h at the same temperature, the reaction mixture was quenched by 1 N HCl (2.0 mL). Purification was performed as above. Michael adduct **3** (392 mg, quant) was obtained in 96% *ee*.

(*R*)-3-[1,1-Bis(benzyloxycarbonyl)methyl]cycloheptanone (7): According to the general procedure for the synthesis of **3**, 312 mg of **7** (79%) was obtained from **6** (111 μL, 1.0 mmol) (RT, 73 h). $[\alpha]_D^{25}$ = + 27.4 (*c* = 0.70, $CHCl_3$) (>99% *ee*); ^{1}H NMR ($CDCl_3$): δ = 7.36–7.26 (m, 10H, aromatic), 5.15 (s, 4H, benzyl), 3.42 (d, 1H, *J* = 6.9 Hz), 2.57–2.46 (m, 5H), 1.91–1.81 (m, 3H), 1.56–1.41 (m, 3H) ; ^{13}C NMR ($CDCl_3$): δ = 212.3, 167.8, 135.1, 128.5, 128.4, 128.3, 67.2, 57.4, 47.2, 43.5, 35.7, 34.0, 28.6, 24.3; IR (neat): $\tilde{\nu}$ = 3020, 2935, 1732, 1700, 1216, 1152 cm^{-1}; EIMS: *m/z*: 395 [M^+ + 1], 197 (base peak), 153, 111, 91. The optical purity of **7** was determined by chiral HPLC analysis (Daicel Chiralcel OD, *i*PrOH:hexane/1:9) after conversion to the corresponding methylated acetal derivative **i**. The absolute configuration of **7** was determined by preparing an authentic sample, as described in ref. [5a].



i

Typical experimental procedure for asymmetric Michael reaction catalyzed by AlLi–BINOL + Na-malonate: To a stirred solution of AlLi-(*R*)-BINOL (0.1 mmol) in THF (1.0 mL) was added the sodium salt of **2** (0.09 mmol) in THF (1.0 mL), which was prepared from NaH and **2** in THF at room temperature. To this THF solution was added **1** (97 μL, 1.0 mmol) and **2** (250 μL, 1.0 mmol) at room temperature. After having been stirred for 24 h at the same temperature, the reaction mixture was treated with 1 N HCl (2.0 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to give an oily residue. Purification by flash chromatography (SiO_2, 25% acetone/hexane) gave the Michael adduct **3** (377 mg, 99%) in 98% *ee*.

Catalytic asymmetric Michael reaction with AlLi–BINOL + Li-hexamethyldisilazide: To a stirred solution of AlLi-(*R*)-BINOL (0.1 mmol) in THF (1.0 mL) was added Li-hexamethyldisilazide (0.09 mmol) in THF (0.9 mL), which was prepared from BuLi and hexamethyldisilazane in THF at room temperature. To this THF solution was added **1** (97 μL, 1.0 mmol) and **2** (250 μL, 1.0 mmol) at room temperature. After having been stirred for 12 h at the same temperature, the reaction mixture was treated with 1 N HCl (2.0 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to give an oily residue. Purification by flash chromatography (SiO_2, 25% acetone/hexane) gave the Michael adduct **3** (379 mg, 100%) in 97% ee.

Preparation of the LaLi–BINOL* + H_2O + BuLi catalyst: To a stirred solution of (*R*)-6,6'-bis(triethylsilylethynyl)BINOL (1.69 g, 3.0 mmol) in THF (92.2 mL) was added a solution of La(O*i*Pr)$_3$ (1.0 mmol; Kojundo Chemical Laboratory, Japan) in THF (5.0 mL) at 0 °C. To this THF solution was added a solution of BuLi (3.0 mmol) in hexane (1.84 mL) at 0 °C. After 12 h of stirring at room temperature, H_2O (1.0 mmol) in THF (1.0 mL) and BuLi (0.9 mmol) in hexane (0.55 mL) were added in succession. The resulting clear yellow solution was used as a LaLi–BINOL* + H_2O + BuLi catalyst.

Typical experimental procedure for asymmetric nitroaldol reactions catalyzed by LaLi–BINOL* + H_2O + BuLi: LaLi–BINOL* + H_2O + BuLi catalyst (382 μL, 3.8 mmol) was diluted with THF (1.13 mL). To this diluted solution was added nitropropane (**14**) (339 μL, 3.80 mmol) at − 40 °C, and the mixture was further stirred for 0.5 h at − 40 °C. Hydrocinnamaldehyde (**12**) (50.0 μL, 380 mmol) was then added to the above mixture at − 40 °C. After having been stirred for 166 h at the same temperature, the reaction mixture was treated with 1 N HCl (2.0 mL) and extracted with Et_2O (3 × 10 mL), washed with brine, dried (Na_2SO_4) and concentrated to give an oily residue. Purification by flash chromatography (SiO_2, 15% Et_2O/hexane) gave the nitroaldol adducts **15** (71.7 mg, 84%, *syn/anti* = 95/5) in 95% *ee*.

Catalytic asymmetric nitroaldol reaction with LaLi–BINOL* + Li-propanenitronate: To a stirred solution of lithium propanenitronate, which was prepared from **14** (3.80 mmol) in THF (1.13 mL) and BuLi (3.42 μmol) in hexane (2.1 μL) at − 40 °C, was added a solution of LaLi-(*R*)-BINOL* (3.8 mmol) in THF (0.380 mL) at − 40 °C. After 30 min of stirring at the same temperature, **12** (50.0 μL, 380 mmol) was then added to the above LaLi–BINOL* + Li-propanenitronate solution at − 40 °C, and the mixture was stirred for 166 h. The reaction was quenched with 1 N HCl (2.0 mL), and worked up as usual to give **15** (49.7 mg, 59%, *syn/anti* = 94/6) in 94% *ee*.

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