The First Heterobimetallic Multifunctional Asymmetric Catalyst

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Abstract: The optically active lanthanum-sodium-BINOL complex (LSB), prepared from La(O-*i*-Pr)$_3$, (*R*)-BINOL (3 mol equiv), and NaO-*t*-Bu (3 mol equiv), is quite effective as an asymmetric catalyst for various Michael reactions to give adducts in up to 92% ee. X-ray crystallographic analysis of LSB shows that this catalyst consists of $LaNa_3C_{60}H_{36}O_6$·6THF·H_2O, in which three BINOL molecules, three sodium atoms, and one water molecule surround a lanthanum atom and two THF molecules coordinate to the each sodium atom. ^{1}H-NMR study indicates the coordination of cyclohexenone, acts as a Michael acceptor, to the lanthanum atom in LSB. Furthermore, Rappé's universal force field calculation of the LSB catalyzed reaction of cyclohexenone with dimethyl malonate supports that this basic LSB complex also acts as a Lewis acid to control the direction of the carbonyl function and enhance the reactivity of the enone. This is the first example of a multifunctional heterobimetallic asymmetric catalyst (chemzyme) in which two different metals play different roles.

Introduction

A key feature of enzymes is their ability not only to position substrates in proximity to each other but to enhance their reactivity by transition state stabilization by functional groups present at the appropriate positions in their asymmetric environment. Although numerous asymmetric metal complexes have been developed, the enantioselection and activation of substrates are meager as compared to those of enzymes. Thus, creation of synthetic enzymes (chemzymes) remains an intriguing and challenging goal of supramolecular chemistry. In this paper we report the first example of a multifunctional heterobimetallic asymmetric catalyst in which two different metals play different roles to enhance the reactivity of both reaction partners and to position them.[1]

Recently we have reported the syntheses of bimetallic rare earth-lithium-BINOL complexes (LnLB: Ln = rare earth, L = lithium, and B = BINOL, respectively) and their successful use in catalytic asymmetric nitroaldol reactions.[2,3] The LnLB prepared from rare earth trichlorides had not been crystallized, but the structures of LnLB were elucidated based on the analyses of both laser desorption/ionization time-of-flight mass spectra of various rare earth-alkali metal-BINOL complexes (Ln-MB: M = Li, Na, and/or K) and X-ray crystallographic data of three kinds of rare earth-sodium-BINOL catalysts (LnSB: Ln = Pr, Nd, and/or Eu, S = sodium, respectively).[2f] In addition, successful conversion of crystalline LnSB to LnLB on treatment with lithium chloride in THF also supported the structure of LnLB[2f]. Of various LnLB complexes available, LLB (L = La, L = Li, B = BINOL) has been found to be the most effective for catalytic asymmetric nitroaldol reactions.

Results and Discussions

We have now succeeded in obtaining the crystalline lanthanum-sodium-(*R*)-BINOL complex (LSB: L = La) prepared from La(O-*i*-Pr)$_3$, (*R*)-BINOL (3 mol equiv), and NaO-*t*-Bu (3 mol equiv).[2f] As shown in Figure 1, X-ray structure analysis of the LSB crystal[4] showed that the structure of LSB was similar to that of other LnSB complexes,[2f] but the inter atomic distances between the lanthanum and oxygens of BINOL were somewhat longer (La-O; 2.423 and 2.425 Å, cf. Pr-O; 2.365 and 2.386 Å, Nd-O; 2.338 and 2.363 Å, Eu-O; 2.286 and 2.312 Å, respectively).[2f]

Although LSB was ineffective as an asymmetric catalyst for nitroaldol reaction,[2f] we were pleased to find that LSB was quite effective in catalytic asymmetric Michael reaction of various enones with malonates to give Michael adducts in up to 92% ee in almost quantitative yield in spite of the ineffectiveness of LLB for catalytic asymmetric Michael reaction.[5] Typical results are summarized in Table 1.[6] Quite recently we had succeeded in developing the alkali metal free lanthanum BINOL complex as an effective catalyst for asymmetric Michael reactions.[5,7] Compared to the alkali metal free lanthanum BINOL catalyst,

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(1) An asymmetric heterobimetallic complex has been reported by Hayashi *et al.* However, the iron in their system does not enhance the reactivity of the substrates; see: Hayashi, T.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.*, **1974**, 4405-4408. See also the following review and the references cited therein: Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857-871.

(2) (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418-4420. (b) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851-854. (c) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* 1993, *34*, 855-858. (d) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657-2660. (e) Sasai, H.; Kim, W.-S.; Suzuki, T.; Shibasaki, M.; Mitsuda, M.; Hasegawa, J.; Ohashi, T. *Tetrahedron Lett.* **1994**, *35*, 6123-6126. (f) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372-10373.

(3) We believe that the multifunction of LnLB makes possible the first and effective catalytic asymmetric nitroaldol reactions. Evidence of the multifunction, however, has not been obtained.

(4) Crystal data for LSB collected at 298 K: $LaNa_3C_{60}H_{36}O_6$·6THF·H_2O, space group $P6_3$, a = 15.355(1) Å and c = 18.388(0) Å with Z = 2. The structure of the complex in 3-fold symmetry, as shown in Figure 1, was refined to a crystallographic R factor of 0.029 against 1364 observations.

(5) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571-1572.

(6) Regarding the absolute configurations of Michael adducts **3**, **5**, **7**, **9** and **11**, see reference 5.

(7) Treatment of LSB with three equiv of HCl in THF formed the alkali metal free lanthanum BINOL complex **1**. By the use of this complex (10 mol %) the Michael adduct **3** was obtained in the similar ee as that by the alkali metal free lanthanum complex prepared from La(O-*i*-Pr)$_3$ and BINOL. Further treatment of **1** with three equiv of BuLi gave LLB.

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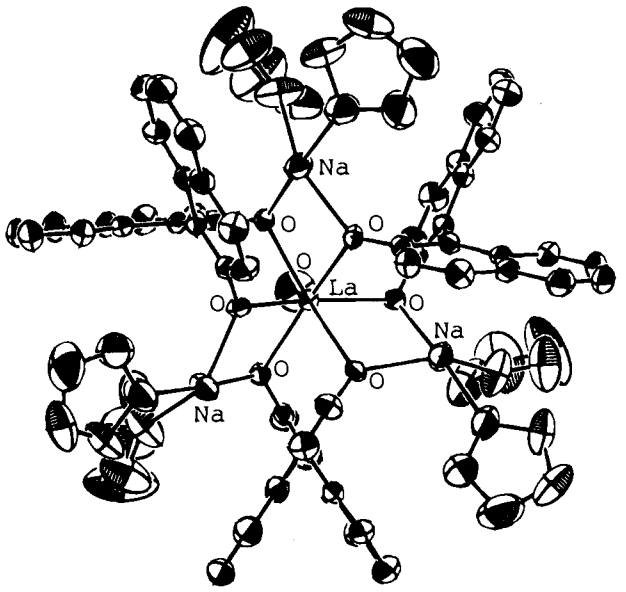
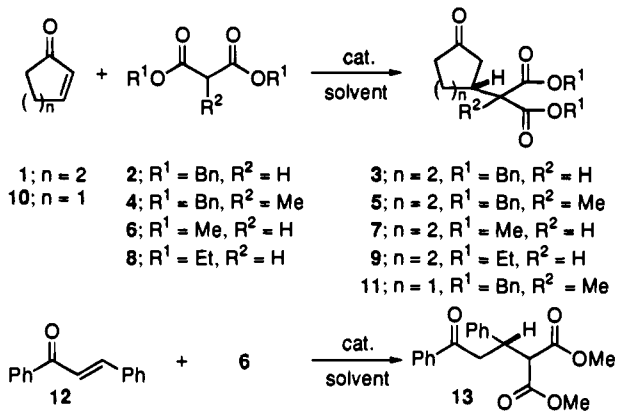


Figure 1. ORTEP representation of $LaNa_3$tris((*R*)-binaphthoxy)·6THF·H_2O ((*R*)-LSB).

Table 1. Catalytic Asymmetric Michael Reactions Promoted by (*R*)-LnMB (10 mol %)



entry	enone	Michael donor	product	cat.	solvent	temp. (°C)	time (h)	yield (%)	ee (%)
1	1	2	3	LSB	THF	0	24	97	88
2	1	2	3	LSB	THF	rt	12	98	85
3	1	2	3	LSB	toluene	rt	12	96	82
4	1	2	3	LLB	THF	rt	12	78	2
5	1	2	3	LPB	THF	rt	12	99	48
6	1	4	5	LSB	THF	0	24	91	92
7	1	4	5	LSB	THF	rt	12	96	90
8	1	6	7	LSB	THF	rt	12	98	83
9	1	8	9	LSB	THF	rt	12	97	81
10	10	4	11	LSB	THF	-40	36	89	72
11	12	6	13	LSB	THF	-50	36	62	0
12	12	6	13	LSB	toluene	-50	24	93	77
13	12	6	13	PrSB	toluene	-50	24	96	56
14	12	6	13	GdSB	toluene	-50	24	54	6

LSB catalyzed Michael reactions were found to proceed smoothly and with high enantioselectivities even at room temperature.[8] As shown in entry 12, LSB catalyzed the reaction of *trans*-chalcone (**12**) with **6** to give **13** in 77% ee (93% yield).[9] The previous method[5] using the alkali metal free lanthanum BINOL complex gave **13** only in 7% ee. In the nitroaldol reaction, the nature of both metals in the rare earth-alkali metal-BINOL complex influences the optical purity of products.[2d,e] Metal effects were also checked in the Michael reaction of **1** with **2**. Among the bimetallic complexes (LnSB, LnLB: Ln = La, Pr, Nd, Sm, Eu, Gd, Tb, Yb, and/or Y; LnPB: Ln = La, Pr, and/or Gd, P = potassium) we examined, LSB was found to give the best result in this Michael reaction (98% yield, 85% ee). Although LPB and PrSB also gave **3** in moderate optical purity, other rare earth-alkali metal-BINOL complexes gave almost racemic **3**, though the chemical yields were good. Effects of rare earth and alkali metals on the asymmetric induction (**1** + **2** → **3**) are summarized in Figure 2.

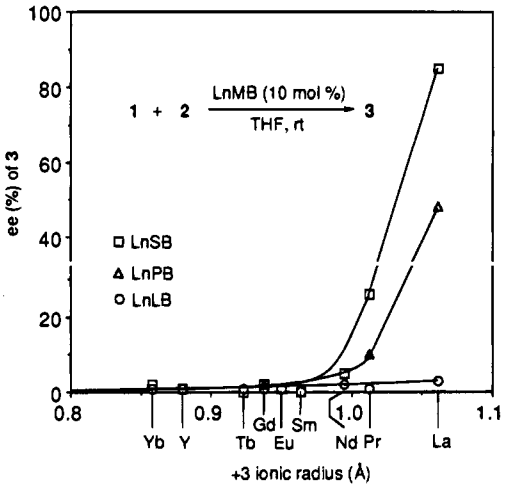


Figure 2. Effects of rare earth and alkali metals on the asymmetric induction.

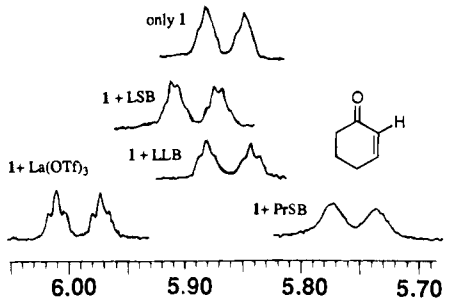


Figure 3. Chemical shift of α-proton on cyclohexenone (**1**).

What is the origin of catalytic activity and mode of enantioselection of LSB catalyzed Michael reaction?[10] In order to clarify the interaction between enone and the asymmetric catalyst, the nature of complexation was studied by ^{1}H-NMR after mixing cyclohexenone (**1**) and the asymmetric bimetallic complexes, to observe the chemical shift of α-proton of enone (Figure 3). In general, it is well-known that Pr complexes induce upfield shifts while Eu complexes induce downfield shifts.[11] In addition, ordinary Lewis acids such as $La(OTf)_3$ and Et_2AlCl were observed to induce downfield shifts. We were pleased to find that complexation with LSB induced a small downfield shift on the α-proton of **1** and PrSB induced a large

(8) For other catalytic asymmetric Michael reactions of this type, see: (a) Yamaguchi, M.; Shiraishi, T.; Igarashi Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233−8236 and references cited therein. (b) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805−8808 and references cited therein.

(9) Toluene was essential as a solvent to obtain high enantiomeric excess. When toluene was used as a solvent in the other Michael reactions, the enantiomeric excesses were almost same as those obtained in THF. The alkali metal free La-BINOL complex prepared from La(O-*i*-Pr)$_3$ and BINOL gave **13** of only 14% ee even in toluene at −50 °C.

(10) The reaction was controlled kinetically since a treatment of racemic **3** with (*R*)-LSB caused any changes in optical purity of **3**.

(11) Cockerill, A. F.; Davies, L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 553−588 and references cited therein.

upfield shift (Figure 3). Interestingly, in the case of either europium−sodium−BINOL complex (EuSB) or LLB, which gave only almost racemic Michael adducts, the ^{1}H-NMR spectra showed no changes in chemical shift of the α-proton of **1**. These NMR studies indicated that carbonyl group of enone coordinated to lanthanum and/or praseodymium metal in the LnSB molecule, while the enone did not coordinate to LLB and/or EuSB.[12] These changes of chemical shift were observed even in the presence of **6**. In addition, the small electronegativity value (0.9) of sodium compared to that (1.1) of lanthanum suggests that sodium enolate of **2, 4, 6,** and/or **8** should be generated.

Based on the X-ray structures of LnSB, computational simulations of enantioselection were made by the aid of Rappé's universal force field (UFF).[13,14] As shown in Scheme 1, when enone **1** coordinated to lanthanum metal, the plane of the cyclohexenone ring should be occupied in parallel to one of the naphtyl ring in LSB. Then the enone should be attacked by sodium-enolate of **6** to give Michael adduct **7**. UFF calculation and conformational search of the models for pro-(*R*)- and pro-(*S*)-adducts showed that the (*R*)-LSB complex complexes better as a pro-(*R*) adduct than a pro-(*S*)-adduct (ΔE = 4.9 kcal/mol).[15−17] Namely LSB can generate the intermediate such as top in Scheme 1 to give high ee. Furthermore, resulting sodium enolates of optically active Michael adducts appear to abstract a hydrogen from an acidic OH to regenerate the LSB catalyst. *Thus, the basic LSB complex also acts as a Lewis acid to control the direction of the carbonyl function and to activate the enone.* The proposed catalytic cycle is shown in Scheme 2.

Conclusions

The catalytic amount of heterobimetallic LSB promoted Michael reactions in a highly enantioselective manner. Mechanistic study on the LSB catalyzed reaction revealed that LSB, acting as a base catalyst, showed Lewis acid character at the same time. We believe that the multifunction of LSB catalyst makes possible the formation of Michael adducts with high ees even at room temperature. Further studies on this concept are currently under way.

Experimental Section

Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 diffraction grating infrared spectrophotometer. NMR spectra were measured on JEOL JNM-EX-270 spectrometers, operating at 270 MHz for ^{1}H and 68 MHz for ^{13}C NMR. Chemical shifts, in $CDCl_3$ solution, are reported downfield from TMS (δ 0) for ^{1}H and relative to the central $CDCl_3$ resonance (δ 77.00) for ^{13}C spectra. Optical rotation was measured on a JASCO DIP-140 polarimeter. In general, reactions were carried out in dry solvents under an argon atmosphere, unless otherwise mentioned. IR, NMR, MS data were obtained on all Michael adducts described herein using chromatographically homogeneous samples.

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Toluene was distilled from sodium.

Synthesis of (*R*)-LSB Complex. To a stirred solution of (*R*)-BINOL (859 mg, 3.0 mmol) in THF (11.3 mL) was added a solution of La(O-*i*-Pr)$_3$ (1.0 mmol; purchased from Soekawa Chemical Co., Ltd., Japan) in THF (5 mL) at 0 °C. After being stirred for 0.5 h at room temperature, a solution of NaO-*t*-Bu (3.0 mmol) in THF (3.8 mL) was added to the above reaction mixture at 0 °C. The colorless clear solution thus obtained was directly used as a catalyst (0.05 M).

Preparation of the Crystal of (*R*)-LSB. An X-ray grade crystal of (*R*)-LSB (brown needles, 266 mg) was grown from the THF solution (0.05 M, 20 mL) at room temperature.

IR (KBr) 3434, 3052, 2974, 2870, 1611, 1588, 1549, 1499, 1461, 1422, 1345, 1276, 1246, 1211, 1173, 1142, 1055, 993, 958, 934, 910, 859, 826, 751 cm^{-1}; ^{13}C NMR (THF) δ 119.7, 124.6, 125.9, 127.8, 128.3, 136.1 (Chemical shifts are reported relative to the THF resonance (δ 67.4) for ^{13}C spectra.).

General Procedure for the Catalytic Asymmetric Synthesis of Michael Adducts. (*R*)-3-[bis(benzyloxycarbonyl)methyl]cyclohexanone (3). To a stirred solution of (*R*)-LSB (0.05 mmol) in THF (1.0 mL) was successively added cyclohexenone (**1**) (48 μL, 0.5 mmol) and dibenzyl malonate (**2**) (125 μL, 0.5 mmol) at 0 °C. After being stirred for 24 h at the same temperature, the reaction mixture was treated with 1 N HCl (2.0 mL) followed by extraction with EtOAc (10 mL × 3). 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** (189 mg, 97% yield) in 88% ee.

IR (KBr) 1740, 1261 cm^{-1}; mp 43 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (dddd, J = 3.0, 11.5, 11.5, 11.5 Hz, 1 H), 1.62 (ddddd, J = 2.2, 4.4, 12.3, 12.3, 12.3 Hz, 1 H), 1.84−2.08 (m, 2 H), 2.12−2.64 (m, 5 H), 3.41 (d, J = 7.6 Hz, 1 H), 5.14 (s, 2 H), 5.16 (s, 2 H), 7.25−7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 24.4, 28.6, 38.0, 40.9, 45.0, 56.6, 67.2, 128.2, 128.4, 128.5, 135.0, 167.4, 167.5, 209.3; MS *m/z* 289 (M^+ − Bn), 91 (base peak); Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36; Found: C, 72.40; H, 6.13; $[\alpha]^{24}_D$ +1.10° (*c* 2.21, $CHCl_3$) (88% ee).

The optical purity of **3** was determined by chiral HPLC analysis (DAICEL CHIRALPAK AS, *i*-PrOH-hexane/1:9).

(*R*)-3-[1,1-bis(benzyloxycarbonyl)ethyl]cyclohexanone (5). According to the general procedure for the synthesis of **3**, 179 mg of **5** (91%) was obtained from **1** (48 μL, 1.0 mmol) (0 °C, 24 h).

IR (neat) 1732, 1231 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18−1.38 (m, 1H), 1.44 (s, 3 H), 1.50−1.62 (m, 1 H), 1.74−1.84 (m, 1 H), 1.96−2.08 (m, 1 H), 2.08−2.25 (m, 2 H), 2.30−2.43 (m, 2 H), 2.48−2.62 (m, 1 H), 5.08−5.13 (m, 4 H), 7.20−7.35 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 16.8, 24.6, 26.6, 41.0, 42.6, 43.2, 57.0, 67.1, 67.2, 128.1, 128.4, 128.5, 135.3, 170.5, 170.6, 210.0; MS *m/z* 303 (M^+ − Bn), 91 (base peak); HRMS calcd for $C_{17}H_{19}O_5$ (M^+ − Bn) 303.1233, Found 303.1232; $[\alpha]^{24}_D$ +0.34° (*c* 3.93, $CHCl_3$) (92% ee).

The optical purity of **5** was determined by chiral HPLC analysis (DAICEL CHIRALPAK AS, *i*-PrOH-hexane/1:9).

(*R*)-3-[bis(methoxycarbonyl)methyl]cyclohexanone (7). According to the general procedure for the synthesis of **3**, 229 mg of **7** (98%) was obtained from **1** (48 μL, 1.0 mmol) (rt, 12 h).

IR (neat) 1732, 1259 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1.46 (dddd, J = 2.6, 12.2, 12.2, 12.2 Hz, 1 H), 1.62 (ddddd, J = 2.6, 4.2, 12.2, 12.2, 12.2 Hz, 1 H), 1.86−1.97 (m, 1 H), 1.98−2.11 (m, 1 H), 2.15−2.31 (m, 2 H), 2.31−2.59 (m, 3 H), 3.32 (d, J = 7.9 Hz, 1 H), 3.71 (s, 3 H), 3.72 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 24.4, 28.7, 37.9, 38.0, 40.9, 45.0, 52.5, 56.5, 168.1, 168.2, 209.4; MS *m/z* 228 (M^+), 197 (M^+ − OMe), 97 (base peak); Anal. calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07; Found: C, 57.70; H, 7.01; $[\alpha]^{24}_D$ +3.33° (*c* 2.10, $CHCl_3$) (83% ee).

The optical purity of **7** was determined by chiral HPLC analysis (DAICEL CHIRALPAK AS, *i*-PrOH-hexane/1:9).

(12) Mono- and di-alkali metal salts of BINOL and BINOL itself made no change on the chemical shift of α-proton. At present, the reason why the enone can not coordinate to LLB is not known.

(13) Transition structure searches for the reaction of metal coordinated enone **1** with the sodium enolate of **6** by *ab initio* calculations indicate that the cationic enone and anionic enolate couple without any stable intermediate or transition state.

(14) (a) Rappé, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard III, W. A.; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024−10035. (b) Casewit, C. J.; Colwell, K. S.; Rappé, A. K. *J. Am. Chem. Soc.* **1992**, *114*, 10035−10046. (c) Casewit, C. J.; Colwell, K. S.; Rappé, A. K. *J. Am. Chem. Soc.* **1992**, *114*, 10046−10053. (d) Rappé, A. K.; Colwell, K. S.; Casewit. C. J. *Inorg. Chem.*, **1993**, *32*, 3438−3450.

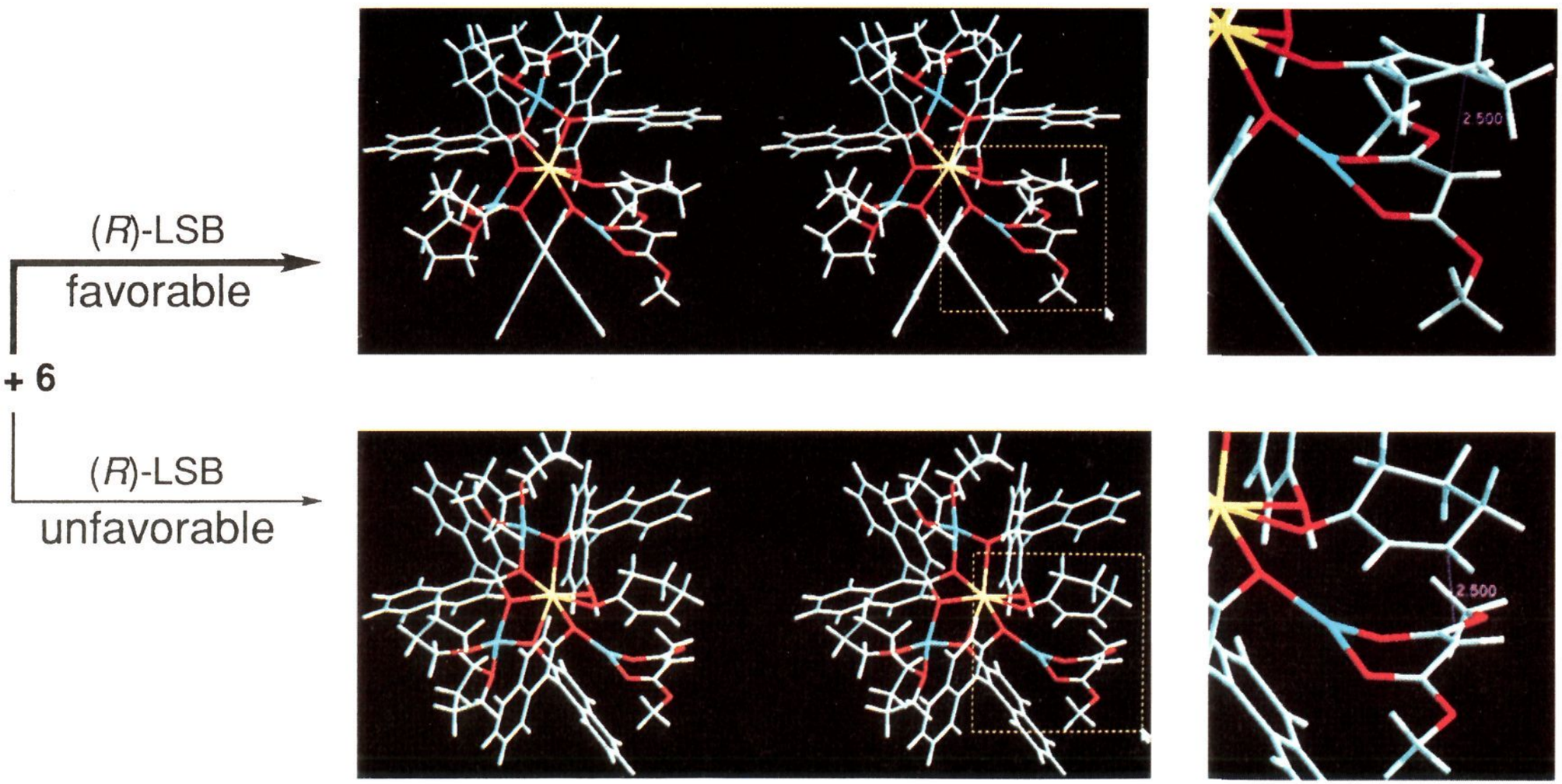
(15) The UFF calculation was performed on Cerius 2 (Molecular Simulations Inc.).

(16) Hybridized atom parameter for lanthanum was set to 2.05Å for bond and 90° for angle in order to reproduce the X-ray structure of LSB.

(17) On the computer graphics, after the removal of two THF molecules which were coordinated to one of the sodium metals in LSB, **6** was located to form sodium enolate. Then **1** was located where the carbonyl group of **1** took a direction to the lanthanum atom. These two molecules **6** and **1** were restrained to have 2.5 Å in bond forming carbon−carbon atom distance and Monte Carlo conformational analyses were carried out to search energy minima.

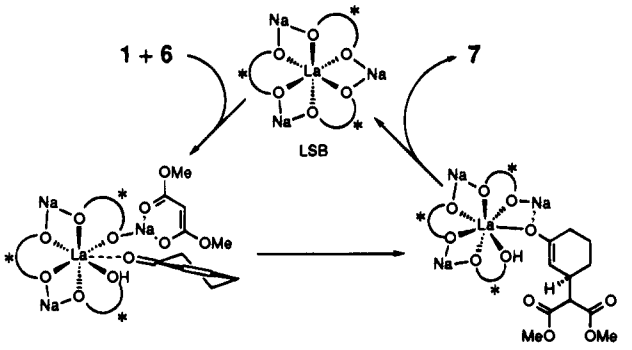
(18) (a) Kubota, H.; Koga, K. *Tetrahedron Lett.*, **1994**, *35*, 6689−6692. (b) Trost, B. M.; Murphy, D. J. *Organometallics*, **1985**, *4*, 1143−1145.

Scheme 1. UFF Computational Simulations of the Michael Reaction of **1** with **6** Catalyzed by (*R*)-LSB[a]



[a] Top: Pro-(*R*)-model (favorable model). Bottom: Pro-(*S*)-model (unfavorable model). Enlarged pictures of the reaction sites are drawn in the each right side of the stereoviews (yellow: lanthanum, blue: sodium, red: oxygen, white: carbon and hydrogen, respectively).

Scheme 2. Proposed Catalytic Cycle of the Asymmetric Michael Reaction Promoted by LSB



(*R*)-3-[bis(ethoxycarbonyl)methyl]cyclohexanone (9). According to the general procedure for the synthesis of **3**, 123 mg of **9** (97%) was obtained from **1** (48 μL, 0.5 mmol) (rt, 12 h).

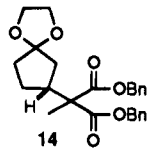
IR (neat) 1731, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, J = 7.3 Hz, 3 H), 1.21 (t, J = 7.3 Hz, 3 H), 1.44 (dddd, J = 3.2, 12.1, 12.1, 12.1 Hz, 1 H), 1.62 (ddddd, J = 3.2, 5.0, 12.1, 12.1, 12.1 Hz, 1 H), 1.83–1.95 (m, 1 H), 1.95–2.07 (m, 1 H), 2.11–2.28 (m, 2 H), 2.28–2.54 (m, 3 H), 3.23 (d, J = 7.9Hz, 1 H), 4.13 (q, J = 7.3 Hz, 2 H), 4.14 (q, J = 7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 24.5, 28.7, 38.0, 40.9, 45.0, 56.8, 61.5, 167.7, 167.8, 209.6; MS *m/z* 256 (M^+), 211 (M^+ – OEt), 97 (base peak); Anal. calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87; Found: C, 60.64; H, 7.62; $[\alpha]^{24}_D$ +2.89° (*c* 2.56, $CHCl_3$) (81% ee).

The optical purity of **9** was determined by chiral HPLC analysis (DAICEL CHIRALPAK AS, *i*-PrOH-hexane/1:9).

(*R*)-3-[1,1-bis(benzyloxycarbonyl)ethyl]cyclopentanone (11). According to the general procedure for the synthesis of **3**, 169 mg of **11** (89%) was obtained from **10** (42 μL, 0.5 mmol) (–40 °C, 36 h).

IR (neat) 1734, 1262 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 3 H), 1.58–1.77 (m, 1 H), 1.97–2.42 (m, 5 H), 2.75–2.95 (m, 1 H), 5.11 (s, 2 H), 5.12 (s, 2 H), 7.20–7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 17.7, 24.4, 38.3, 40.5, 41.4, 55.6, 67.2, 128.1, 128.2, 128.4, 128.5, 135.1, 135.2, 170.8, 170.9, 217.3; MS *m/z* 381 (M^+ + 1), 289, 107 (base peak), 91; Anal. calcd for $C_{22}H_{24}O_5$: C, 72.61; H, 6.36; Found: C, 72.36; H, 6.48. $[\alpha]^{24}_D$ +28.35° (*c* 1.89, $CHCl_3$) (72% ee).

The optical purity of **11** was determined by chiral HPLC analysis (DAICEL CHIRALCEL OD, *i*-PrOH-hexane/1:9) after converting to the corresponding acetal derivative **14** shown below.

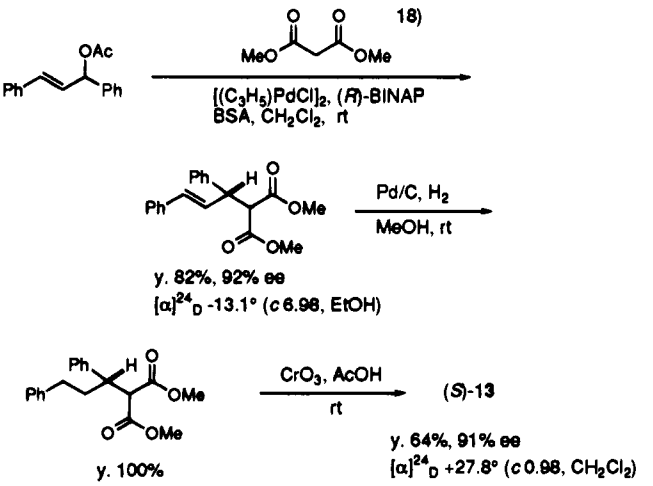


(*S*)-Methyl 3,5-Diphenyl-2-methoxycarbonyl-5-oxopentanoate (13). After concentrating a THF solution of (*R*)-LSB (0.05 M, 1.0 mL), the resulting (*R*)-LSB powder was redissolved in toluene (1.0 mL). To this toluene solution was added *trans*-chalcone (**12**) (104.1 mg, 0.5 mmol) at room temperature, and the mixture was further stirred for 1 h at –50 °C. Dimethyl malonate (**6**) (57 μL, 0.5 mmol) was then added to the above mixture at –50 °C. After being stirred for 24 h at the same temperature, the reaction mixture was treated with 1 N HCl (2.0 mL) followed by extraction with EtOAc (10 mL × 3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to give a residue. Purification by flash chromatography (SiO_2, 20% acetone/hexane) gave the Michael adduct **13** (157 mg, 93%) in 77% ee as a colorless solid (mp = 78 °C).

IR (KBr) 1730, 1682, 1236 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.51 (s, 3 H), 3.52 (dd, J = 5.3, 7.9 Hz, 1 H), 3.71 (d, J = 5.3 Hz, 1 H), 3.73(s, 3 H), 3.86 (d, J = 9.2 Hz, 1 H), 4.20 (dt, J = 5.3, 9.2 Hz, 1 H), 7.17–7.56 (m, 8 H), 7.88–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 40.7, 42.3, 52.4, 52.7, 57.3, 125.6, 127.2, 127.9, 128.1, 128.5, 133.1, 136.8, 140.4, 168.1, 168.7, 197.5; MS *m/z* 340 (M^+), 309, 308, 105 (base peak), Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92; Found: C, 70.40; H, 6.04. $[\alpha]^{24}_D$ +25.64° (*c* 2.00, $CHCl_3$) (77% ee).

The optical purity of **13** was determined by chiral HPLC analysis (DAICEL CHIRALPAK AS, *i*-PrOH-hexane/1:9).

The absolute configuration of **13** was determined by preparing an authentic sample as shown below.



NMR Experiments. To a NMR tube containing (*R*)-LSB (0.1 M in THF, 0.5 mL) was added cyclohexenone (5 μL, 0.05 mmol) under argon. The ^1H-NMR spectra were measured at room temperature by using an external D_2O tube (for locking). Chemical shifts, in THF solution, are reported relative to the THF resonance (δ 3.60) for ^1H spectra.

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