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Catalytic Asymmetric Michael Reactions Promoted by the La-Na-BINOL Complex (LSB). Enantioface Selection on Michael Donors

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Abstract: LSB can efficiently promote catalytic asymmetric Michael reactions in CH_2Cl_2, inducing high enantiomeric excesses on the Micheal donor side. The multifunctional character of LSB appears to give rise to high stereoselectivity, offering the most efficient asymmetric reaction of its type.

Catalytic asymmetric Michael reactions are one of the most important synthetic methods for affording asymmetric centers. 1,3-Dicarbonyl compounds in particular are greatly promising Michael donors for the enantioselective construction of carbon-carbon bonds. Catalytic asymmetric Michael reactions using 1,3-dicarbonyl compounds can be divided into two types (Figure 1). Type I reactions[1] induce the asymmetric center on the Michael donor side, while Type II reactions[2] give the asymmetric center on the Michael acceptor side. For Type I reactions, although the enantioselective additions of indan-1-one-2-carboxylate to methyl vinyl ketone have been well studied by using cinchona alkaloids and/or asymmetric crown ethers to give the adducts with high ees, these catalysts have not shown similarly high enantioselectivity with many other substrates. On the other hand, for Type II reactions several successful asymmetric catalysts with broad generality have been reported.[2] We have developed three kinds of efficient asymmetric catalyst for Type II reactions; the alkali metal free-La-BINOL complex,[2f] the La-Na-BINOL complex (LSB),[2g] and the Al-Li-BINOL complex (ALB).[2h] Mechanistic studies on LSB-catalyzed Michael reactions have revealed that LSB acting as a base catalyst (ONa), shows Lewis acid character (La) at the same time, making possible highly enantioselective reactions even at room temperature. It was thus not unreasonable to suppose that these catalysts could be successfully applied to Type I reactions, and in this paper we wish to report just such catalytic asymmetric Michael reactions, which are of broad generality.

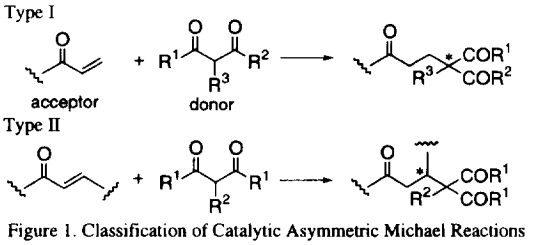
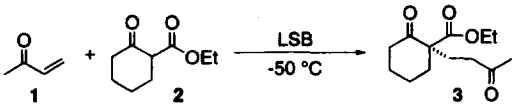


Figure 1. Classification of Catalytic Asymmetric Michael Reactions

As a preliminary study the catalytic activities of the alkali metal free-La-BINOL complex, LSB, and the Al-Li-BINOL complex (ALB) in Type I reactions were examined using methyl vinyl ketone (**1**) and the β-keto ester **2**.[3] Although, as shown in Table 1, the enantiomeric excesses of Michael adduct **3**[4] formed by the above asymmetric catalysts were low in THF, in toluene 10 mol % of LSB[5] provided 97% yield of **3** in 75% ee (the alkali metal free-La-BINOL complex: 82% yield, 5% ee; ALB: 31% yield, 14% ee). However, when the amount of LSB was reduced to 5 mol %, the enantiomeric excess of **3** declined to a more modest 25% ee. In an attempt to offset this decline while still maintaining the lower level of catalyst we next examined the effects of slow addition of **2**. As expected, the use of syringe pump methods gave **3** with high enantiomeric excess

(89% ee). In marked contrast to this result in toluene, we were very pleased to find that the asymmetric Michael reaction catalyzed by 5 mol % of LSB in CH_2Cl_2[6] gave **3** in 89% yield and with 91% ee, without the need for slow addition previously encountered. This is the first use of CH_2Cl_2 in the field of heterobimetallic asymmetric catalysis.

Table 1. LSB- Catalyzed Michael Reactions under Various Conditions



1 2 3

entry	solvent	catalyst amount (mol %)	time (h)	yield (%)	ee (%)
1	THF	10	21	81	23
2	toluene	10	14	97	75
3	toluene	5	14	83	25
4[a]	toluene	5	22	76	89
5	CH_2Cl_2	10	19	85	93
6	CH_2Cl_2	5	19	89	91
7	Et_2O	10	14	85	71

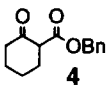
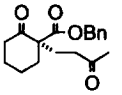
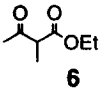
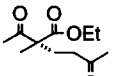
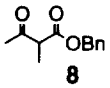
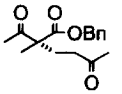
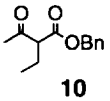
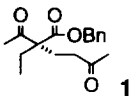
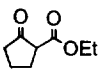
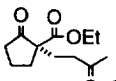
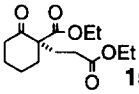
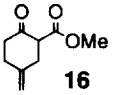
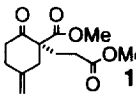
a) Compound **2** was added slowly using syringe pump methods over 8 h.

We next examined the effects of rare earth metals on the catalytic asymmetric Michael reaction. We previously reported that rare earth-Li-BINOL complex (LnLB)-catalyzed asymmetric nitroaldol reactions are very sensitive to changes in the ionic radius of center rare earth metal.[3d] Moreover, LnSB-catalyzed asymmetric Michael reaction of cyclohexenone with dibenzyl malonate (Type II) was also greatly influenced by the choice of rare earth, revealing that only lanthanum as a center metal gave high enantioselection.[2g] On the other hand, the catalytic asymmetric Michael reaction for **3** (Type I) was not so affected by the choice of rare earth (for example, at -50 ℃ for 20 h in CH_2Cl_2 the following results were obtained: Pr, 91% ee in 90% yield; Sm, 90% ee in 83% yield; Gd, 92% ee in 79% yield; Dy, 85% ee in 83% yield).

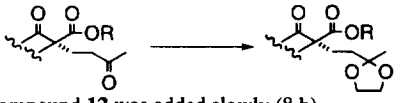
The optimized typical procedure is as follows; after concentrating a THF solution of 0.05 M (*R*)-LSB (0.5 ml, 0.025 mmol), the resulting (*R*)-LSB powder was redissolved in CH_2Cl_2 (2.0 ml). To this CH_2Cl_2 solution were added methyl vinyl ketone (50 μl, 0.60 mmol) and ethyl 2-oxocyclohexanecarboxylate (**2**) (80 μl, 0.50 mmol) at -50 ℃. After stirring for 19 h at the same temperature, the reaction mixture was treated with 1 N HCl (2.0 ml) followed by extraction with EtOAc (10 ml x 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 **3** (107 mg, 89%) in 91% ee as a colorless oil. Using the procedure described above, various substrates were subjected to a catalytic asymmetric Michael reaction. The representative results are given in Table 2,[7] showing that in CH_2Cl_2 a variety of Michael adducts were obtained in good enantiomeric excesses, ranging from 74 to 91 %, and in excellent yields. The following results are noteworthy. Firstly, not only the cyclic 6-membered ring containing β-keto esters **2** and **4** but also *acyclic* β-keto esters **6**, **8** and **10**, and 5-membered ring containing β-keto ester **12** are all good substrates for LSB-catalyzed asymmetric Michael reactions. However, in the case of 5-membered β-keto ester **12**, 20 mol % of LSB was required to give the Michael adduct **13** with satisfactory enantiomeric excess. As with the conversion of **2** to **3** in toluene, slow addition of the 1,3-dicarbonyl compound **12** was found to be effective in giving the product **13** with increased enantiomeric excess. Secondly, ethyl acrylate (**14**), which is a less reactive substrate than methyl vinyl ketone, gave the corresponding Michael adduct **15** in 76% ee and 60% yield even at room temperature. To the best of our knowledge, all the results shown in Table 2 are, respectively, the highest enantiomeric excesses obtained to date for their particular donor-acceptor pairs. Thus, LSB may be seen as the most practical catalyst for asymmetric Michael reactions of Type I.

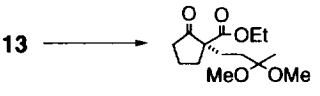
As shown in Table 1, slow addition of β-keto ester and the use of CH_2Cl_2 as solvent are generally quite effective in preventing reduction of enantiomeric excess for the various Michael adducts. On the other hand,

Table 2. Catalytic Asymmetric Michael Reactions Promoted by LSB in CH_2Cl_2

Michael donor	Michael acceptor	product	catalyst amount (mol %)	temp. (°C)	time (h)	yield (%)	ee[a] (%)
 **4**	**1**	 **5**	10	-50	12	73	91
 **6**	**1**	 **7**	5	-50	20	94	74
 **8**	**1**	 **9**	5	-50	16	93	83
 **10**	**1**	 **11**	5	-50	16	98	89
 **12**	**1**	 **13**	10 10[b] 20	-50 -50 -50	18 17 18	95 95 97	62 75 84
2	 **14**	 **15**	10	0→rt	17	60	76
 **16**	 **17**	 **18**	20	0→rt	93	69	89

a) For the determination of the enantiomeric excesses, Michael adducts **3**, **5**, **7**, **9**, and **11** were converted to the corresponding ethyleneketal derivatives as shown below, and **13** was converted to the dimethyl acetal. The enantiomeric excesses were determined by HPLC analysis using DAICEL CHIRALCEL OD or OJ. For **15** and **18**, enantiomeric excesses were directly determined by HPLC (CHIRALCELL OD) without any transformation.





b) Compound **12** was added slowly (8 h).

malonates give the adducts with high ees regardless of the solvent used.[2g] These results can be rationalized by comparison of the p*K*a of a β-keto ester with that of a malonate; the former is significantly more acidic than the latter. Thus, the concentration of the resulting Na-enolate can be expected to be greater in the case of the β-keto ester, and moreover this Na-enolate will react with an enone more slowly than the Na-enolate derived from a malonate. We suggest that this combination of more rapid formation and longer lifetime increases the likelihood of dissociation of the Na-enolate from the chelated ensemble, thus giving a product of lower ee.[8] On the other hand, in less polar CH_2Cl_2 the Na-enolate would, even in this case, remain part of the ensemble,

thereby affording the product with high ee.[9] Furthermore, we believe that slow addition of the β-keto ester acts to limit undesired ligand exchange between BINOL moieties and the Michael donor.

In conclusion, we have succeeded in developing catalytic asymmetric Michael reactions of Type I with broad generality.

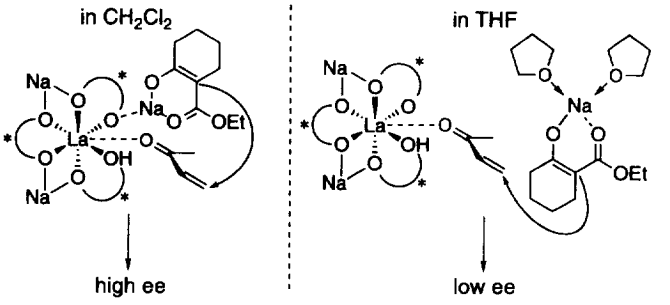


Figure 2. Proposed Mechanism for the Catalytic Asymmetric Michael Reaction Promoted by LSB

References and Notes

1. For previously reported catalytic asymmetric Michael reactions of Type I, see: (a) Helder, R.; Wynberg, H. *Tetrahedron Lett.* **1975**, 4057-4060. (b) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238-2244. (c) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625-627. Brunner, H.; Hammer, B. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 312-313. (d) Sera, A.; Takagi, K.; Katayama, H.; Yamada, H.; Matsumoto, K. *J. Org. Chem.* **1988**, *53*, 1157-1161. (e) Tamai, Y.; Kamifuku, A.; Koshiishi, E.; Miyano, S. *Chem. Lett.* **1995**, 957-958. (f) Desimoni, G.; Dusi, G.; Faita, G.; Quadrelli, P.; Righetti, P. *Tetrahrdron* **1995**, *51*, 4131-4144. And see also: (g) Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7229-7230. (h) Sawamura, M. Hamashima, H.; Shinoto, H.; Ito, Y. *Tetrahedron Lett.* **1995**, *36*, 6479-6482 and references cited therein.
2. For previously reported catalytic asymmetric Michael reactions of Type II, see: (a) Takasu, M.; Wakabayashi, H.; Furuta, K.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 6943-6946. (b) Aoki, S.; Sasaki, S.; Koga, K. *Heterocycles* **1992**, *33*, 493-495. (c) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem. Int. Ed Engl.* **1993**, *32*, 1176-1178. (d) Yamaguchi, M.; Shiraishi, T.; Igarashi Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233-8236. (e) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805-8808. (f) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571-1572. (g) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194-6198. (h) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 104-106.
3. For La-Li-BINOL complex (LLB), see: (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.; Yamada, Y. M. A.; Suzuki, T.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 12313-12318. (g) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372-10373. (h) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki M. *J. Org. Chem.* **1995**, *60*, 7388-7389. For La-K-BINOL complex (LPB), see (i) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656-6657.
4. Enantiomeric excess was determined as described in the footnote of Table 2.
5. LSB was prepared from either La(O-*i*-Pr)$_3$ or $LaCl_3$-$7H_2O$.
6. CH_2Cl_2 solvent was also effective in catalytic asymmetric Michael reactions of Type II. In the Michael reaction of cyclohexenone and dibenzyl malonate, 10 mol % of LSB gave the corresponding Michael adduct with 75% ee in 86% yield after 20 h at 0 °C in CH_2Cl_2 (88% ee in 97% yield for 24 h at 0 °C in THF).
7. The absolute configurations of the Michael adducts were determined by comparison of their optical rotation values with those reported in the literature. For **3**, **7**, and **15**, see: Tomioka, K.; Seo, W.; Ando, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 6637-6640. The absolute configuration of **5** was also determined after **5** had been converted into **3**. For the absolute configurations of **9** and **13**, see references 2f and 1e, respectively. The absolute configurations of **11** and **18** were presumed to be the same as for **9** and **15**, on the basis of their optical rotation data.
8. When 18-Crown-6 (3.6 mol eq to LSB) was added to the Michael reaction in CH_2Cl_2, **3** was obtained in only 5% ee.
9. Although the ^{13}C-NMR spectrum of LSB in CH_2Cl_2 was obscure, the LDI-TOF mass spectrum gave the peak at 1085 as LSB+Na^+.

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