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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<sub>2</sub>Cl<sub>2</sub>, inducing high enantiomeric excesses on the Michael donor side. The multifunctional character of LSB appears to give rise to high stereoselectivity, offering the most efficient asymmetric reaction of its type. Copyright © 1996 Elsevier Science Ltd

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<sup>1</sup> induce the asymmetric center on the Michael donor side, while Type

II reactions<sup>2</sup> 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



Figure 1. Classification of Catalytic Asymmetric Michael Reactions

other substrates. On the other hand, for Type II reactions several successful asymmetric catalysts with broad generality have been reported.<sup>2</sup> We have developed three kinds of efficient asymmetric catalyst for Type II reactions; the alkali metal free-La-BINOL complex,<sup>2t</sup> the La-Na-BINOL complex (LSB),<sup>2g</sup> and the Al-Li-BINOL complex (ALB).<sup>2h</sup> 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.

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  $\beta$ -keto ester 2.<sup>3</sup> Although, as shown in Table 1, the enantiomeric excesses of Michael adduct 3<sup>4</sup> formed by the above asymmetric catalysts were low in THF, in toluene 10 mol % of LSB<sup>5</sup> 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.

We next examined the effects of rare earth metals on the catalytic asymmetric Michael reaction. We previously reported that rare earth-Li-



_	↓ ↓ ↓		LSB -50 °C			
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 <sup>a</sup>	toluene	5	22	76	89	
5	CH <sub>2</sub> Cl <sub>2</sub>	10	19	85	93	
6	CH <sub>2</sub> Cl <sub>2</sub>	5	19	89	91	
7	Et <sub>2</sub> O	10	14	85	71	

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

BINOL complex (LnLB)-catalyzed asymmetric nitroaldol reactions are very sensitive to changes in the ionic radius of center rare earth metal.<sup>3d</sup> 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.<sup>2g</sup> 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 °C for 20 h in CH<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub> (2.0 ml). To this CH<sub>2</sub>Cl<sub>2</sub> solution were added methyl vinyl ketone (50  $\mu$ l, 0.60 mmol) and ethyl 2-oxocyclohexanecarboxylate (2) (80  $\mu$ l, 0.50 mmol) at -50 °C. 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<sub>2</sub>SO<sub>4</sub>) and concentrated to give a residue. Purification by flash chromatography (SiO<sub>2</sub>, 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<sub>2</sub>Cl, 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  $\beta$ -keto esters 2 and 4 but also acyclic  $\beta$ keto esters 6, 8 and 10, and 5-membered ring containing  $\beta$ -keto ester 12 are all good substrates for LSBcatalyzed asymmetric Michael reactions. However, in the case of 5-membered  $\beta$ -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% vield 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  $\beta$ -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,

Michael donor	Michael acceptor	product	catalyst amount (mol %)	temp. (°C)	time (h)	yield (%)	ee <sup>a</sup> (%)
OBn 4	1	OBn OBn 5	10	-50	12	73	91
O O OEt 6	1		5	-50	20	94	74
O OBn 8	1	OBn OBn 9	5	-50	16	93	83
OBn 10	1		5	-50	16	98	89
ပ္ ပ္	1	0 0	10	-50	18	95	62
OEt			10 <sup>b</sup>	-50	17	95	75
12		Ő 13	<b>3</b> 20	-50	18	97	84
2	EtO		10 5	0 <del>⊶</del> rt	17	60	76
о ОМе 16	о мео 17		20	0 <del>⊸r</del> t	93	69	89

Table 2. Catalytic Asymmetric Michael Reactions Promoted by LSB in CH<sub>2</sub>Cl<sub>2</sub>

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.



malonates give the adducts with high ees regardless of the solvent used.<sup>28</sup> These results can be rationalized by comparison of the pKa of a  $\beta$ -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  $\beta$ -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.<sup>8</sup> On the other hand, in less polar CH<sub>2</sub>Cl, the Na-enolate would, even in this case, remain part of the ensemble,

thereby affording the product with high ee.<sup>9</sup> Furthermore, we believe that slow addition of the  $\beta$ -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.



Asymmetric Michael Reaction Promoted by LSB

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- 4. Enantiomeric excess was determined as described in the footnote of Table 2.
- 5. LSB was prepared from either La(O-i-Pr)<sub>3</sub> or LaCl<sub>3</sub>-7H<sub>2</sub>O.
- 6. CH<sub>2</sub>Cl<sub>2</sub> 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 ℃ in CH<sub>2</sub>Cl<sub>2</sub> (88% ee in 97% yield for 24 h at 0 ℃ 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<sub>2</sub>Cl<sub>2</sub>, 3 was obtained in only 5% ee.
- Although the <sup>13</sup>C-NMR spectrum of LSB in CH<sub>2</sub>Cl<sub>2</sub> was obscure, the LDI-TOF mass spectrum gave the peak at 1085 as LSB+Na<sup>+</sup>.

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