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Catalytic Asymmetric Michael Reactions Promoted by a Lithium-Free Lanthanum-BINOL Complex

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Recently considerable work concerning new reactions mediated by rare earth metal reagents has been reported.[1] We too have investigated the reactivity of rare earth metal alkoxides as basic reagents. As a result, we have found that rare earth metal alkoxides such as $La_3(O\text{-}t\text{-}Bu)_9$,[2a] $Y_3(O\text{-}t\text{-}Bu)_8Cl$,[2a] and $Y_5(O\text{-}i\text{-}Pr)_{13}O$[2b] can be used as bases in catalytic aldol, cyanosilylation, nitroaldol, and Michael reactions.[3a,4] In the process, we have succeeded in developing several asymmetric BINOL–rare earth metal–lithium bimetallic complexes (e.g., **16**), which have been quite effective in catalytic asymmetric nitroaldol reactions.[3] In the case of a catalytic asymmetric Michael reaction, which is another important carbon–carbon bond-forming reaction, however, these bimetallic complexes have been found to be quite ineffective.[5] For example, treatment of cyclopentenone (**1**) with dibenzyl methylmalonate (**2**) in the presence of 3 mol % of the BINOL–lanthanum–lithium bimetallic complex **16** gave the Michael adduct **3** of only 13% ee in 26% yield. In this communication we report about a new lithium-free BINOL–lanthanum complex, which is quite effective in catalytic asymmetric Michael reaction to give the adduct **3** of up to 95% ee in 97% yield.

Initial studies focused on the preparation of a lithium-free lanthanum–BINOL complex which should form a structurally different lanthanum ester enolate from that generated with the BINOL–lanthanum–lithium bimetallic complex **16**. The lithium-free lanthanum ester enolate was expected to lead to Michael adducts with higher ee's. Thus, to a stirred solution of $La(O\text{-}i\text{-}Pr)_3$[6] (1.0 mmol) in anhydrous THF (5 mL) was added 1 molar equiv of (*S*)-BINOL at 0 °C, which resulted in rapid formation of a suspension. The white precipitate **I** (138 mg) thus obtained was immediately used for the Michael reaction as an asymmetric base catalyst. We were very pleased to find that treatment of dibenzyl methylmalonate (**2**) with cyclopentenone (**1**) (1.1 equiv) in anhydrous THF containing 10 mol %[7] of the lanthanum–BINOL complex **I** at –20 °C for 48 h gave the Michael adduct **3** of 70% ee in 86% yield.[8] Solvent effects were next investigated and showed that the use of THF gave the best result (cf.: toluene, 64% ee in 70% yield, –20 °C, 21 h; CH_2Cl_2, 43% ee in 42% yield, –20 °C, 72 h; Et_2O, 46% ee in 17% yield, –20 °C, 72 h). The following results were also noteworthy. Firstly the use of the supernatant[7] as a base catalyst gave **3** of 35% ee in 41% yield, suggesting that the active asymmetric base catalyst was the precipitate itself. Secondly, combined use of inductively coupled plasma spectroscopy (ICPS) analysis of lanthanum and the recovered amount of BINOL showed that the lanthanum–BINOL complex **I** consisted of lanthanum and the BINOL moiety in a ratio of ca. 2:3.[9] Thirdly, addition of dibenzyl methylmalonate (**2**) to a suspension of the lanthanum–BINOL complex **I** in THF resulted in the rapid formation of a homogeneous solution.

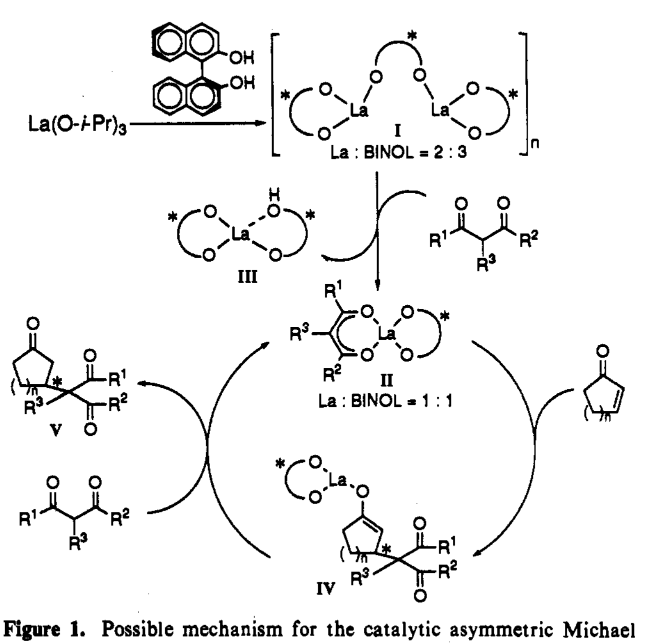

Figure 1. Possible mechanism for the catalytic asymmetric Michael reaction promoted by alkali metal free La–(*S*)-BINOL complex.

Further studies were carried out to find a more effective catalyst in asymmetric Michael reactions. A possible mechanism for the above-mentioned Michael reaction is proposed in Figure 1. Although the structure of the new lanthanum–BINOL complex **I**[10] was not unequivocally determined, it seemed likely that reaction of dibenzyl methylmalonate (**2**) with the lanthanum complex **I** would give the BINOL–lanthanum ester enolate **II** together with the lanthanum complex **III** consisting of lanthanum and the BINOL moiety in a ratio of 1:2. This lanthanum ester enolate **II** would react with cyclopentenone (**1**), giving the lanthanum enolate **IV** in an enantioselective manner. Further reaction of this enolate **IV** with **2** would lead to the Michael adducts **V** together with the lanthanum ester enolate **II** due to the difference in their pK_a values, thus making the catalytic cycle possible. The above-mentioned mechanistic consideration suggested that the intermediary lanthanum ester enolate **II**, the real asymmetric catalyst,

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(1) For application of rare earth elements in organic synthesis, see following reviews and references cited therein. (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68. (b) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573–6614.

(2) (a) Evans, W. J.; Sollberger, M. S.; Hanusa, T. P. *J. Am. Chem. Soc.* **1988**, *110*, 1841–1850. (b) Poncelet, O.; Sartain, W. J.; Hubert-Pfalzgraf, L. G.; Folting, K.; Caulton, K. G. *Inorg. Chem.* **1989**, *28*, 263–267. (c) Review for rare earth metal alkoxides; see: Mehrotra, R. C.; Singh, A.; Tripathi, M. *Chem. Rev.* **1991**, *91*, 1287–1303 and references cited therein.

(3) (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.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372–10373.

(4) Various catalytic Michael reactions have been found to proceed smoothly using $La(O\text{-}i\text{-}Pr)_3$. Sasai, H.; Arai, T.; Shibasaki, M. Unpublished results.

(5) For catalytic asymmetric Michael reactions, see: (a) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295–8296. (b) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176–1178. (c) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625–627. (d) Takasu, M.; Wakabayashi, H.; Furuta, K.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 6943–6946. (e) Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7229–7230. (f) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057–4060. (g) Sera, A.; Takagi, K.; Katayama, H.; Yamada, H.; Matsumoto, K. *J. Org. Chem.* **1988**, *53*, 1157–1161. (h) Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* **1988**, 1025–1026. (i) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806 and references cited therein.

(6) Alkali metal free $La(O\text{-}i\text{-}Pr)_3$ can be purchased from Soekawa Chemical Co., Ltd., Tokyo, Japan.

(7) The lanthanum metal contents in the catalyst were analyzed with inductively coupled plasma spectroscopy (ICPS).

(8) Using other substrates, the following ee's and yields were obtained: **5**, 74% ee in 87% yield (–20 °C, 48 h); **7**, 74% ee in 69% yield (–20 °C, 48 h); **8**, 77% ee in 77% yield (–20 °C, 48 h). These enantiomeric excesses of the Michael adducts were determined by chiral HPLC assay, and their absolute configurations were determined by transformation to corresponding authentic samples; see: (a) Posner, G. H.; Weitzberg, M.; Hamill, T. G.; Asirvatham, E.; Cun-Heng, H.; Clardy, J. *Tetrahedron* **1986**, *42*, 2919–2929. (b) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269–1277 and supplementary material.

(9) This complex appears to be obtained in good yield since it is barely soluble in anhydrous THF.

(10) The ^{13}C NMR spectrum of this catalyst was quite obscure; in general, rare earth complexes exist as oligomers.

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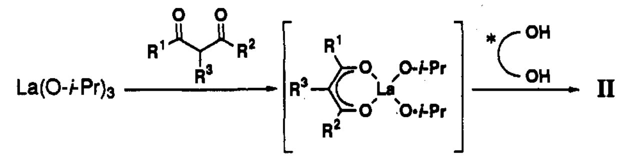
Scheme 1



would be more effectively prepared starting with La(O-*i*-Pr)$_3$, dibenzyl methylmalonate (**2**), and BINOL.[11] This indeed proved to be the case.

The BINOL–lanthanum ester enolate **II** as an asymmetric base catalyst was first prepared as follows (Scheme 1). To a stirred solution of La(O-*i*-Pr)$_3$ (0.1 mmol) in THF (0.5 mL) was added dibenzyl methylmalonate (**2**) (0.1 mmol) in anhydrous THF (1.0 mL) gradually at 0 °C, and the resulting solution was stirred at 0 °C for 0.5 h. In this instance no precipitate was observed. To this lanthanum ester enolate solution was then added (*S*)-BINOL (0.1 mmol) in THF (1.0 mL) at 0 °C, and the whole solution was further stirred for 0.5 h at the same temperature. This THF solution was directly used as an asymmetric base catalyst. Thus, to a stirred solution of the above-prepared ester enolate **II**[10] were successively added dibenzyl methylmalonate (**2**) (0.9 mmol) and cyclopentenone (**1**) (1.0 mmol) at −20 °C, and the whole reaction mixture was stirred for 60 h at the same temperature. This afforded the Michael adduct **3** of 90% ee in 75% yield. It was further observed that the asymmetric ester enolate catalyst **II**, which was prepared through removal of THF and *i*-PrOH, followed by a readdition of THF (1.0 mL), showed better reactivity and gave **3** of 95% ee in 97% yield.[12,13] To our knowledge this is the best example of a catalytic asymmetric Michael reaction.[5] Using the procedure described above, various substrates were further subjected to a catalytic asymmetric Michael reaction. The results summarized in Table 1 showed that various Michael adducts were obtained in good enantiomeric excesses, ranging from 62% to 95% ee, and in excellent yields.[14]

In conclusion, we have succeeded in developing effective asymmetric base catalysts, in particular, asymmetric ester enolate catalysts for asymmetric Michael reactions. Very interestingly, the use of the lithium-free ester enolate complex **II** gave very unsatisfactory results in catalytic asymmetric nitroaldol reactions (Table 2). In any case, two asymmetric lanthanum complexes are now available, namely, BINOL–lanthanum–lithium complex **16**, which is quite effective in catalytic asymmetric nitroaldol reactions, and a new lithium-free BINOL–lanthanum ester enolate complex, **II**, that is very effective in catalytic asymmetric Michael reactions. The two complexes complement each other in their ability to catalyze asymmetric nitroaldol and asymmetric Michael reactions. Elucidation of the structure of the complex **II** and mechanistic studies are in progress.

Table 1. Catalytic Asymmetric Michael Reactions Promoted by Lithium-Free La–(*S*)-BINOL Ester Enolate **II** (10 mol %)

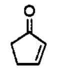
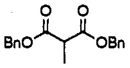
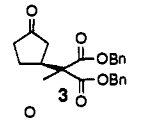
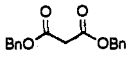
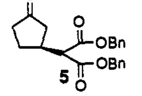
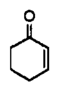
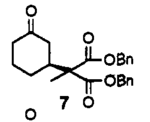
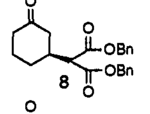
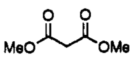
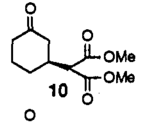
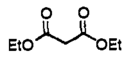
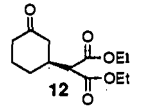
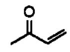
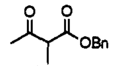
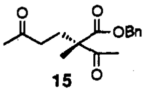
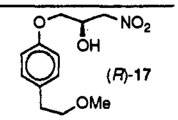
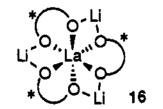
entry	enone	Michael donor	product	temp. (°C)	time (h)	yield (%)	ee (%)
1	 **1**	 **2**	 **3**	-20	60	97	95
2	**1**	 **4**	 **5**	-20	72	96	92
3	 **6**	**2**	 **7**	0	84	83	87
4	**6**	**4**	 **8**	-10	84	94	92
5	**6**	 **9**	 **10**	-10	84	100	75
6	**6**	 **11**	 **12**	-10	84	97	78
7	 **13**	 **14**	 **15**	-50	48	86	62

Table 2. Comparison of the Catalytic Behavior of La–BINOL Complexes

Catalyst	Michael	Nitroaldol
Alkali Metal Free La (*S*)-BINOL Complex	(*S*)-**3** 97%, 95% ee (-20 °C, 60 h)	 (*R*)-**17** 48%, 6% ee (-10 °C, 72 h)
 **16** (*S*)-BINOL-La-Li Complex[3]	(*R*)-**3** 26%, 13% ee (-40 °C, 60 h)	(*R*)-**17** 90%, 94% ee (-50 °C, 62 h)

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Supplementary Material Available: Experimental procedures for the preparation of the La–BINOL complex **I**, general procedures for the syntheses of Michael adducts using the complex **II**, spectral and analytical data for the La–BINOL complex **I** and compounds **3**, **5**, **7**, **8**, **10**, **12**, and **15**, and schematic procedures for determination of absolute configurations of Michael adducts (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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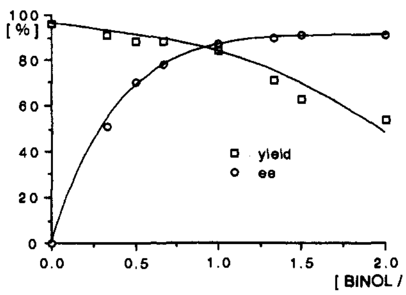
(11) It was expected that the reactivity of the complex consisting of lanthanum and the BINOL moiety in a ratio of 1:2 would be low; cf. ref 13.

(12) It seems likely that removal of THF and *i*-PrOH gives the more satisfactory oligomeric ester enolate due to the resulting higher chemical yield and slightly improved ee.

(13) Increasing the ratio of BINOL in the La–BINOL ester enolate complex formation resulted in a decrease in the reactivity of the complex. It is noteworthy that using less than 1 molar equiv of BINOL gave the Michael adduct **3** in enantiomeric excesses better than those calculated by assuming La(O-*i*-Pr)$_3$ and the La–BINOL ester enolate promoted the Michael reaction independently.



(14) In the case of entry 7, La–(*S*)-BINOL enolate complex was prepared by an addition of La(O-*i*-Pr)$_3$ to a mixture of the *β*-keto ester derivative **14** and BINOL. This method proved to be much more effective for obtaining **15** in good optical purity. See supplementary material.