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Direct Catalytic Asymmetric Mannich-type Reaction of Unmodified Ketones Utilizing the Cooperation of an AlLibis(binaphthoxide) Complex and $La(OTf)_3 \cdot nH_2O$

Shingo Yamasaki, Takehiko Iida and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
e-mail: mshibasa@mol.f.u-tokyo.ac.jp; fax:+81-(0)3-5684-5206.

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Abstract: The first example of a direct catalytic asymmetric Mannich-type reaction using unmodified ketones and an aminomethyl ether is described. This was achieved by the cooperative catalysis of a heterobimetallic asymmetric complex (AlLibis(binaphthoxide)) and $La(OTf)_3 \cdot nH_2O$.

Keywords: *Asymmetric reactions; Ketones; Lanthanides; Mannich reactions*

The asymmetric Mannich-type reaction is one of the most important C-C bond forming reactions in chiral synthesis. It provides optically active β-amino ketones and esters (Mannich bases) [1], which are versatile building blocks for the synthesis of numerous biologically significant compounds [2]. In fact, various other methods for the asymmetric synthesis of Mannich bases have been developed as well. However, enantioselective modes of the Mannich-type reaction itself, using achiral substrates are quite limited [3]. Recently, four research groups have realized such catalytic and enantioselective Mannich-type reactions: Mannich bases have been obtained by the addition of metal enolates [4], the addition of ketene silyl acetals [5], and the addition of enol silyl ethers [6] to imines. In these reactions, an aminomethylation appears to be difficult as their imines were not prepared from formaldehyde. Thus, we became interested in a catalytic asymmetric aminomethylation reaction. In addition, such *direct* enantionselective Mannich-type reactions of *unmodified* ketones have not yet been achieved, probably due to the low reactivity of unmodified ketones and the difficulty in controlling overreaction of product ketones. Herein, we report the first example of a direct catalytic asymmetric Mannich-type reaction of unmodified ketones utilizing the cooperative catalysis of a AlLibis((*R*)-binaphthoxide) complex ((*R*)-ALB) and $La(OTf)_3 \cdot nH_2O$.

We previously succeeded in developing various types of heterobimetallic asymmetric catalysts, which function at the same time as both a Lewis acid and a Brønsted base [7]. Among them, the $LaLi_3$tris(binaphthoxide) catalyst (LLB) (Figure 1) was effective for direct asymmetric aldol reactions of unmodified ketones [8]. We envisaged that the LLB catalysis would be applicable to a direct asymmetric Mannich reaction of propiophenone (1) with

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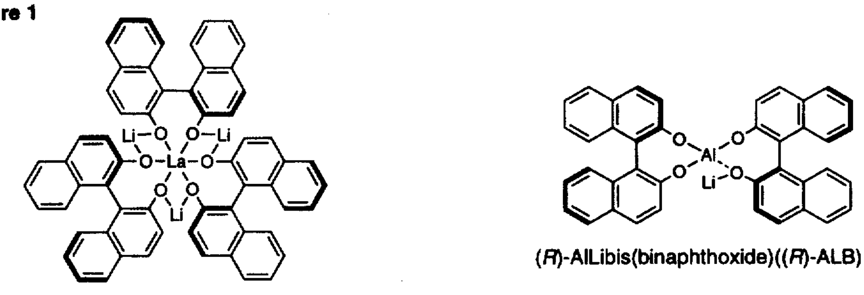
Figure 1

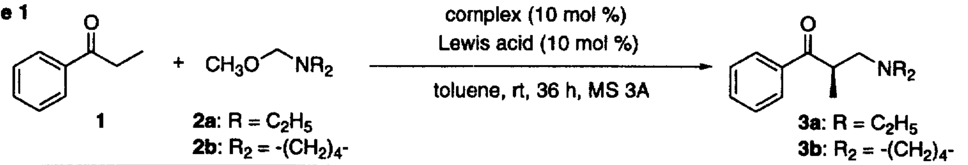


(*R*)-LaLi$_3$tris(binaphthoxide)((*R*)-LLB)

(*R*)-AlLibis(binaphthoxide)((*R*)-ALB)

$(CH_2O)_n$ and pyrrolidine (C_4H_8NH). As we had hoped, the reaction proceeded (rt, toluene, molecular sieves 3A as a dehydrating agent) and afforded **3b** with 64% enantiomeric excess (ee), albeit in only 16% yield. The low yield was caused by the cessation of the reaction due to the formation of $C_4H_8NCH_2NC_4H_8$, which was inactive under the conditions. To avoid its formation, we focused on the use of aminomethyl ethers such as **2a** [9], which are useful equivalents for $[R_2NCH_2]^+$ in the presence of Lewis acids [1]. Unfortunately, in the reaction of **1** with **2a**, (*R*)-LLB (10 mol %) showed only low activity to afford (*S*)-**3a**[1] (12% yield), although modest ee (25%) was found (Table 1, entry 1). As the Lewis acidity of LLB appeared to be insufficient for the activation of **2a**, the effect of additional achiral Lewis acids was examined. Among various Lewis acids, rare earth metal triflates: $Ln(OTf)_3 \cdot nH_2O$ (Ln = La, Yb) slightly improved the yield of **3a**, but the ee drastically decreased (entries 2, 3). Presumably the reactions were catalyzed by the achiral Lewis acid without participation of the LLB moiety.

Table 1



entry	complex	Lewis acid	aminomethyl ether	yield (%)	ee (%)
1	(*R*)-LLB	–	**2a**	12	25
2	(*R*)-LLB	$La(OTf)_3 \cdot nH_2O$	**2a**	18	9
3	(*R*)-LLB	$Yb(OTf)_3 \cdot nH_2O$	**2a**	23	0
4	(*R*)-ALB	–	**2a**	6	16
5	(*R*)-ALB	$Sc(OTf)_3 \cdot nH_2O$	**2a**	66	2
6	(*R*)-ALB	$Yb(OTf)_3 \cdot nH_2O$	**2a**	55	10
7	(*R*)-ALB	$La(OTf)_3 \cdot nH_2O$	**2a**	53	30
8	–	$La(OTf)_3 \cdot nH_2O$	**2a**	35	–
9	(*R*)-ALB	$La(OTf)_3 \cdot nH_2O$	**2b**	11	2

In order to find an alternative, we paid attention to another type of heterobimetallic asymmetric complex: AlLibis(binaphthoxide) (ALB) [10] (Figure 1). It was thought that ALB may provide more space than LLB, enabling an association with $Ln(OTf)_3 \cdot nH_2O$.

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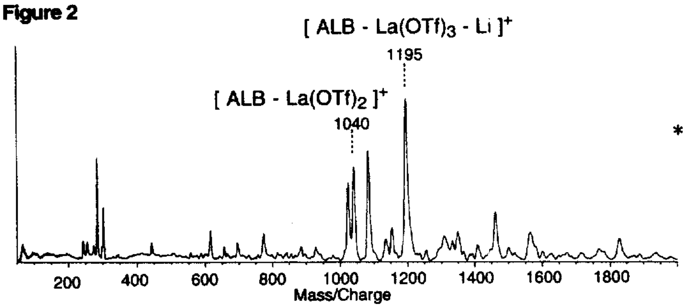
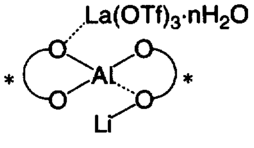
[1] The ee of **3a** was determined by chiral stationary phase HPLC: DAICEL CHIRALCEL OJ; hexane–2-propanol–diethylamine (100:1:0.1, v/v); flow rate: 0.5 mL/min; retention times, 10.5 min for (*R*)-**3a** and 14.0 min for (*S*)-**3a**. The absolute configuration of (*S*)-**3a** was determined by Mosher's method [Mosher HS, J. Am. Chem. Soc. 1973; 95: 512–519] after the reduction of **3a** by $LiAlH_4$.

Although ALB (10 mol %) itself showed low activity (6% yield, 16% ee) similar to LLB (entry 4), we were pleased to find that the combination with Ln(OTf)$_3$·nH$_2$O was extremely effective in increasing the yield of **3a** (53–66%) (entries 5–7). The addition of La(OTf)$_3$·nH$_2$O [2] (10 mol %) was also beneficial, with respect to asymmetric induction, resulting in the formation of (*S*)-**3a** with 30% ee. It is quite interesting that the combined addition enhanced the enantioselectivity as well as the yield of **3a** (53% compared to 35% when only using La(OTf)$_3$·nH$_2$O, entry 8)[3], while **2b** gave less satisfactory results (entry 9).

To reveal the structure of the active species, we analyzed the mixture of ALB and La(OTf)$_3$·nH$_2$O by Laser Desorption/Ionization Time-of-Flight Mass (LDI-TOF MS) spectrometry. The LDI-TOF(+) MS spectrum showed a peak at *m/z* = 1195 corresponding to [ALB-La(OTf)$_3$-Li]$^+$ and another peak at *m/z* = 1040 corresponding to [ALB-La(OTf)$_2$]$^+$ (Figure 2). Thus, we suggest that ALB and La(OTf)$_3$·nH$_2$O associate as indicated in structure **4**, therefore creating the cooperative catalyst. This is in agreement with the results shown in Table 1.

Figure 2





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To obtain information enabling the further improvement of the Mannich-type reaction in terms of the enantioselectivity, we monitored the ee of **3a** during the reaction. Interestingly, the ee of **3a** gradually increased [6% ee (1 h), 20% ee (12 h), 30% ee (36 h)], presumably due to the decrease in concentration of the aminomethyl ether **2a**. Therefore, a slow addition method seemed to be advisable to keep the concentration of **2a** low during the reaction. However, this caused a drastic decrease of the reaction rate. Thus, **2a** was added slowly over 18 h to the reaction mixture, now using 30 mol % of ALB and La(OTf)$_3$·nH$_2$O and at 50 °C in toluene[4]. The reaction resulted in the formation of (*S*)-**3a** in 65% yield and

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[2] La(OTf)$_3$·nH$_2$O (n = about 8 to 9) was purchased from Aldrich Co.,Ltd. Anhydrous La(OTf)$_3$ gave less satisfactory results, presumably due to its polymeric structure.

[3] The use of (*R*)-binaphthol, or its dilithium salt, instead of (*R*)-ALB afforded **3a** in only 13% and 15% yield, respectively, with ee values much less than 30% ee.

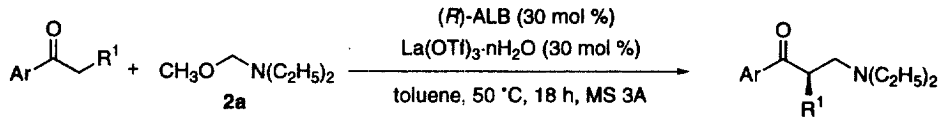
[4] General procedure: To a mixture of MS 3A (1.11 g), La(OTf)$_3$·nH$_2$O (0.222 mmol), and (*R*)-ALB (0.222 mmol) in toluene (3.5 mL) were added **1** (0.74 mmol) and **2a** (0.74 mmol)[5] at rt, and then **2a** (1.48 mmol) was added over 18 h at 50 °C. After removal of MS 3A by filtration, the filtrate was extracted with 5N HCl (3 x 3 mL). The combined extracts were washed with Et$_2$O (2 x 20 mL), alkalized with 5% NH$_4$OH (40 mL) and then extracted with Et$_2$O (3 x 30 mL). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over Na$_2$SO$_4$, and then evaporated at rt *in vacuo* to afford **3a** (105 mg, 65% yield) as slightly yellow oil without column choromatography[6]; ^{1}H-NMR (C$_6$D$_6$; 500 MHz): d 0.90 (t, *J* = 7.0, 6H, (NCH$_2$C*H*$_3$)$_2$); 1.17 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$); 2.37 (q, *J* = 7.0, 4H, (NC*H*$_2$CH$_3$)$_2$); 2.39 (dd, *J* = 6.4, 12.8, 1H) and 2.94 (dd, *J* = 5.2, 12.8, 1H) (COCHC*H*$_2$); 3.52-3.59 (m, 1H, CH); 7.08-7.21 (m, 3H, Ar); 7.93-8.00 (m, 2H, Ar); ^{13}C-NMR (C$_6$D$_6$; 125 MHz): d 12.3, 16.2, 39.9, 47.8, 57.9, 128.3, 128.5, 132.5, 138.1, 203.3.

[5] The reaction of **1** with **2a** (1 mol eq) gave **3a** in only 12 % yield.

[6] **3a** showed a tendency to racemize during column chromatography (silica gel or alumina).

40% ee (Table 2, entry 1). Under the optimized conditions, other unmodified aryl ketones were also subjected to the reaction with **2a**. As shown in Table 2, those reactions gave the corresponding β-amino ketones with 31–44% ee in good yields.

Table 2



entry	Ar	R^1	yield (%)	ee (%)
1	Ph	CH_3	65	40
2 *)	Ph	C_2H_5	69	34
3	4-CH_3O-phenyl	CH_3	76	31
4	2-naphtyl	CH_3	61	44
5	6-CH_3O-2-naphtyl	CH_3	69	44

*) **2a** was added over 36 h.

In conclusion, we have succeeded in developing the first direct catalytic asymmetric Mannich-type reaction of unmodified ketones with an aminomethyl ether. This has been achieved by the cooperative catalysis of a heterobimetallic asymmetric complex (ALB) and $La(OTf)_3 \cdot nH_2O$. Although the enantiomeric excesses of the Mannich bases are still moderate, we believe that the present results will pave the way for further progress.

Acknowledgments

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