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Direct Catalytic Asymmetric Mannich Reaction of Unmodified Ketones: Cooperative Catalysis of an AlLibis(binaphthoxide) Complex and $La(OTf)_3 \cdot nH_2O$†

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Abstract: The direct catalytic asymmetric Mannich reaction of unmodified ketones is described. This was achieved by the cooperative catalysis of a heterobimetallic asymmetric complex: AlLibis(binaphthoxide) (ALB) and $La(OTf)_3 \cdot nH_2O$ in the presence of molecular sieves 3A. The association of ALB and $La(OTf)_3 \cdot nH_2O$ was indicated by means of the Laser Desorption/Ionization Time-of-Flight Mass (LDI-TOF MS) spectrum.

The aminoalkylation of CH-acidic compounds such as enolizable ketones, so-called Mannich reaction, is one of the most powerful C–C bond forming reactions in organic chemistry. It is an invaluable method for the preparation of β-aminocarbonyl compounds (Mannich bases),[1] which are useful intermediates for the synthesis of numerous natural products. The Mannich reaction is also widely used in the field of medicinal chemistry.[2] The majority of Mannich bases are prepared in racemic form by a classical Mannich reaction, in which a CH-acidic compound, formaldehyde and an secondary amine hydrocholoride are heated in a protic solvent. The synthesis of optically pure pharmaceuticals is undoubtedly important to obtain better products in terms of therapeutic value and safety. Although various methods for the asymmetric synthesis of Mannich bases have been developed, enantioselective modes of the Mannich reaction itself, using achiral substrates are quite scarce even as non-catalytic methods.[3] The development of catalytic asymmetric Mannich-type reactions is thus a challenging theme in organic chemistry. In the past two years, four research groups have realized such catalytic asymmetric 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, 7] to imines, which are prepared by the treatment of aldehydes with amines. In all of these Mannich-type reactions, however, pre-conversion of the ketone or the ester moiety to a more reactive species as mentioned above is an unavoidable necessity. In addition, the aminomethylation, which is the classical Mannich reaction, appears to be difficult as such an imine

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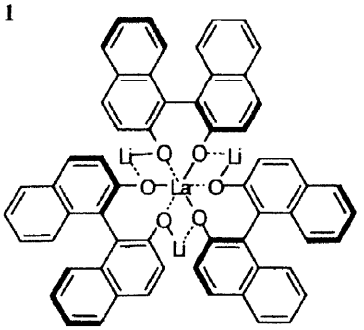
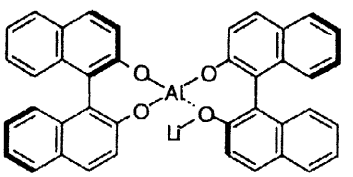
is hardly prepared from formaldehyde. In order to achieve *direct* catalytic asymmetric Mannich reactions of *unmodified* ketones, it would be necessary to discover an efficient catalysis, which overcomes the low reactivity of unmodified ketones and also controls overreaction of product ketones. As a preliminary solution to these problems, we present herein a detailed account of the development of the first direct catalytic asymmetric Mannich reaction: an aminomethylation of unmodified ketones utilizing the cooperative catalysis of a AlLibis((*R*)-binaphthoxide) complex ((*R*)-ALB) and $La(OTf)_3 \cdot nH_2O$. A preliminary report of this work has been published.[8]

Figure 1



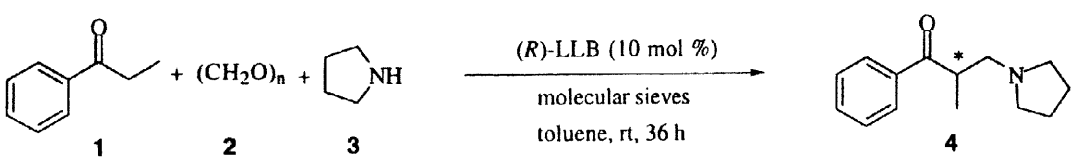
(*R*)-LaLi$_3$tris(binaphthoxide)((*R*)-LLB)



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

We have developed several heterobimetallic asymmetric catalysts containing both Lewis acidity and Brønsted basicity.[9] Among them, a LaLi$_3$tris(binaphthoxide) complex (LLB) (Figure 1) allowed us to use unmodified ketones for a direct catalytic asymmetric aldol reaction with aldehydes, affording various aldols with up to 94% ee.[10] The LLB complex turned out to be quite stable in the presence of a small amount of H_2O in organic solvents. Indeed, the monohydrated LLB efficiently catalyzed asymmetric nitroaldol reactions.[11] We thus envisaged that the LLB catalysis would also be applicable to a direct asymmetric Mannich reaction such as the reaction of propiophenone (**1**) with paraformaldehyde (**2**: $(CH_2O)_n$) and pyrrolidine (**3**), in which H_2O is unavoidably generated as a side product. The racemic form of Mannich base **4** is known as a compound with pharmacological activity (centrally acting muscle relaxant).[12] Indeed, the Mannich reaction proceeded in the presence of 10 mol % of LLB (rt, toluene), although the yield of **4** was only 5% and its enantiomeric excess (ee)

Table 1. The direct asymmetric Mannich reaction in the presence of several types of molecular sieves

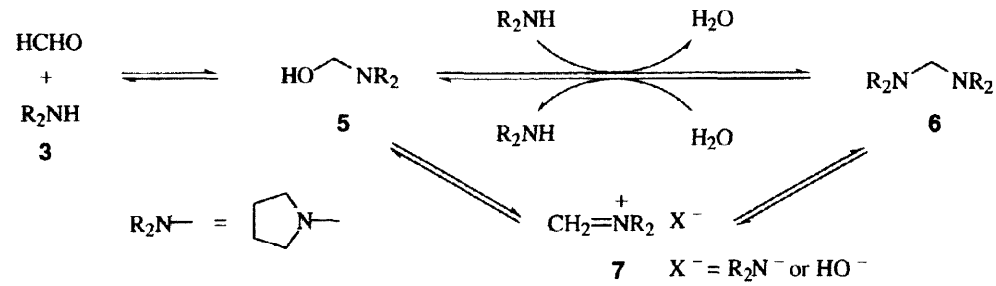


1 **2** **3** **4**

entry	molecular sieves	yield (%)	ee (%)
1	—	5	6
2	MS 3A	16	64
3	MS 4A	6	58
4	MS 5A	5	34
5	MS 13X	4	16

was only 6% (entry 1, Table 1). Under these conditions, a decomposition of LLB might occur due to the existence of too much H_2O being a contaminant of **2** and the reaction side product. Thus, the addition of several types of molecular sieves (MS) as dehydrating agent was examined (entries 2–5). The presence of MS 3A among them, drastically improved the ee of **4** (64% ee),[13] albeit in only 16% yield. The reason for the low yield is as follows: In genaral, formaldehyde (HCHO) and pyrrolidine (**3**) should be in equilibrium with a hemiaminal **5**, an iminium salt **7**, and an aminal **6** as shown in Scheme 1. The aminal **6** is likely to be generated by the dehydration of **5** assisted by the action of MS 3A in toluene and it seemed to be inactive under these conditions. Since the reaction of preformed **6** with **1**, in the presence of LLB and MS 3A, did not proceed at all, **6** and **7** should not be in equilibrium under these conditions. When the transformation into **6** was complete, further addition of paraformaldehyde (**2**) and **3** allowed further formation of **4**, although the resultant ee of **4** was lower. This is probably due to the existence of H_2O, more than MS 3A (1.11 g for 0.74 mmol of **1**) can trap in toluene (3.5 mL). Unfortunately, after further addition of MS 3A the stirring of the reaction mixture by a magnetic stirrer became problematic.

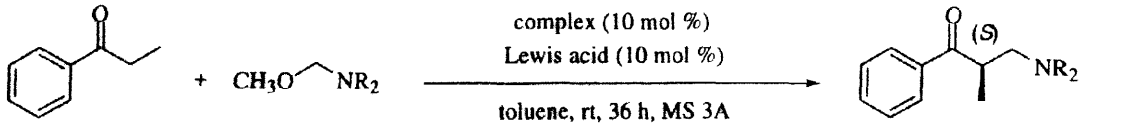
Scheme 1. Equilibrium between formaldehyde-pyrrolidine (**3**) and aminal **6**



We next focused on the use of isolable aminomethyl ethers such as **8**,[14] which would be an useful equivalent for $[R_2N{=}CH_2]^+$ in the presence of Lewis acids, instead of formaldehyde and secondary amines as the reactants.[1] If the heterobimetallic complex, LLB has enough Lewis acidity for the activation of the aminomethyl ether **8**, the reaction of **1** with **8** is likely to proceed. Unfortunately, the reaction (rt, toluene) using LLB (10 mol %) gave (*S*)-**9**[15] in only 12% yield, although modest ee (25%) was found (entry 1, Table 2). To improve the reactivity, a $YbLi_3$tris(binaphthoxide) complex (YbLB), which has a more strong Lewis acidic center metal compared to LLB, was examined. The reaction using (*R*)-YbLB (10 mol %), however, afforded (*S*)-**9** in only 14% yield and only 15% ee. As the Lewis acidity of LLB and YbLB appeared to be insufficient for the activation of **8**, the effects of additional achiral Lewis acids were examined. The addition of 10 mol % of rare earth metal triflates: $Ln(OTf)_3{\cdot}nH_2O$ (Ln = La, Yb), among various Lewis acids, produced slight improvement of the yield (18% and 23%, respectively), although the ee of **9** drastically decreased (9% ee and 0% ee, respectively) (entries 2 and 3), as the reactions were probably catalyzed by the achiral Lewis acid without participation of the chiral LLB moiety. An association of $Ln(OTf)_3{\cdot}nH_2O$ with LLB appears to be difficult because of the steric hindarance of LLB, which has three binaphthyl moieties.

In order to find an alternative, we then paid our attention to the use of another type of heterobimetallic asymmetric complex: an AlLibis(binaphthoxide) complex (ALB),[16] which has only two binaphthyl moieties (Figure 1). The ALB complex also functions as both a Lewis acid and Brønsted base to be an efficient catalyst

Table 2. Direct catalytic Mannich reaction of propiophenone (**1**) with aminomethyl ethers



1 **8**: R = C_2H_5; **10**: R_2 = -$(CH_2)_4$- **9**: R = C_2H_5; **4**: R_2 = -$(CH_2)_4$-

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

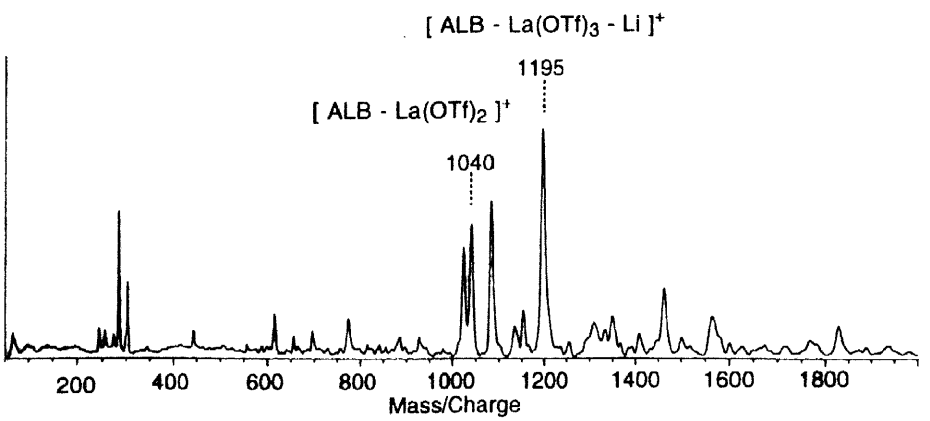
for several asymmetric syntheses,[17] although it was not efficient for the direct catalytic asymmetric aldol reaction of unmodified ketones. The ALB complex may provide more space than the LLB complex, enabling an association with $Ln(OTf)_3 \cdot nH_2O$ in the asymmetric environment. Thus the reaction of **1** with **8** (1.0 equiv) was examined in the presence of 10 mol % of (*R*)-ALB and MS 3A at rt in toluene. Although ALB (10 mol %) itself showed low activity (6% yield, 16% ee) similar to LLB (entry 4, Table 2), we were pleased to find that the combination with $Ln(OTf)_3 \cdot nH_2O$ (10 mol %) was extremely effective in increasing the yield of **9**: $Sc(OTf)_3 \cdot nH_2O$ (66% yield), $Yb(OTf)_3 \cdot nH_2O$ (55% yield), $La(OTf)_3 \cdot nH_2O$ (53% yield) (entries 5–7). Under similar conditions, the reaction of **1** with **10** instead of **8**, gave **11** in only 11% yield (2% ee) (entry 8), probably due to the deactivation of $La(OTf)_3 \cdot nH_2O$ by a relatively tight coordination by the nitrogen atom of the pyrrolidine ring. The addition of $La(OTf)_3 \cdot nH_2O$ was also beneficial, with respect to the asymmetric induction, resulting in the formation of (*S*)-**9** with 30% ee compared to 16% ee using only ALB. It is notable that the combination enhanced the enantioselectivity as well as the yield of **9** (53% yield), because the reaction using only $La(OTf)_3 \cdot nH_2O$ (10 mol %) afforded **9** in only 35% yield (entry 9). It is sure that the role of the aluminum complex (ALB) itself is important in terms of the asymmetric induction, based on the following results. The combination of $La(OTf)_3 \cdot nH_2O$ with (*R*)-binaphthol or its dilithium salt, instead of (*R*)-ALB, afforded (*S*)-**9** in only 13% yield or 15% yield, respectively, with much lower ee values. These results suggest that the ALB complex and $La(OTf)_3 \cdot nH_2O$ associate with each other to catalyze the direct asymmetric Mannich reaction cooperatively.

The use of anhydrous $La(OTf)_3$ instead of $La(OTf)_3 \cdot nH_2O$ was also examined, but the reaction gave less satisfactory results (18% yield, 7% ee) (entry 10, Table 2), presumably due to the polymeric structure and the low solubility of anhydrous $La(OTf)_3$. However, it is known that the ALB complex is very sensitive to small amounts of H_2O, and so it is interesting that the ALB complex could be used together with $La(OTf)_3 \cdot nH_2O$ without the decomposition of ALB. This is probably due to the strong coordination of H_2O to $La(OTf)_3$ and the

absence of free H_2O. The addition of MS 3A, however, was still required for the Mannich reaction of **1** with **8**, in which H_2O is not generated as a reaction side product. Interestingly, the reaction of **1** with **8** (toluene, rt), in the presence of $La(OTf)_3 \cdot nH_2O$ and in the absence of MS 3A, gave **9** in only 3% yield (cf. entry 9). It is remarkable that MS 3A has an important role in achieving the catalytic cycle of the direct Mannich reaction, although the role is not clear. Indeed, several catalytic asymmetric reactions have been carried out successfully in the presence of molecular sieves, which did not seem to act just as a dehydrating agent.[17d,e, 18]

To reveal the structure of the active species, we analyzed the mixture of ALB and $La(OTf)_3 \cdot nH_2O$ by Laser Desorption/Ionization Time-of-Flight Mass (LDI-TOF MS) spectrometry. As shown in Figure 2, the LDI-TOF(+) MS spectrum showed a peak at m/z = 1195 corresponding to $[ALB\text{-}La(OTf)_3\text{-}Li]^+$ and another peak at m/z = 1040 corresponding to $[ALB\text{-}La(OTf)_2]^+$. Thus we suggest that ALB and $La(OTf)_3 \cdot nH_2O$ associate with each other to result in the formation of a relatively tight complex and therefore create the cooperative catalysis, although the structure of the associated complex is not clear at the present time. This is in agreement with the results shown in Table 2. Furthermore, the ^{27}Al-NMR spectrum of ALB in toluene indicated the existence of at least three species (δ: 53, 36, and 14 ppm). The spectrum changed into a single peak (δ: 62 ppm) in the presence of $La(OTf)_3 \cdot nH_2O$ and MS 3A. On the other hand, the ^{27}Al-NMR spectrum of ALB itself in THF indicated the existence of only one species (δ: 75 ppm).[16] Although the ^{13}C-NMR spectrum of ALB in THF indicated only ten peaks corresponding to symmetrical naphthyl moieties, ^{13}C-NMR of ALB in toluene did not indicate detectable peaks. These results might be suggesting that the structural state of ALB is oligomeric in toluene and then it changes into a monomeric structure by association with $La(OTf)_3 \cdot nH_2O$.

Figure 2. LDI-TOF(+) MS spectrum of ALB-$La(OTf)_3 \cdot nH_2O$



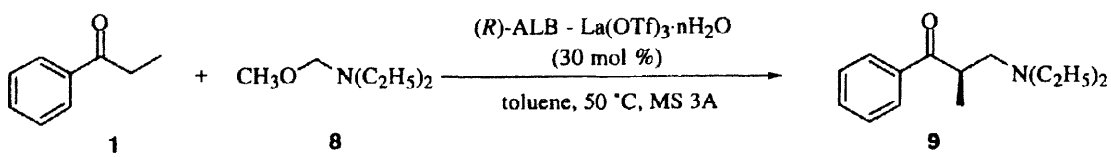
To obtain informations for further improvement of the Mannich reaction in terms of the enantioselectivity, the ee of **9** has been monitored during the reaction. It was found that the ee of **9** gradually increased to 30% ee (36 h) from 6% ee (1 h), as shown in Table 3. The reason is probably the decreasing concentration of the aminomethyl ether **8** which would cause a dissociation of $La(OTf)_3 \cdot nH_2O$ from ALB by means of the strong coordination of **8** itself. Therefore, a slow addition of **8** seemed to be advisable to keep the concentration of **8** low during the reaction. However, this method caused a drastic decrease of the reaction rate. Thus, now the reaction of **1** with **8** was optimized in presence of 30 mol % of (*R*)-ALB and $La(OTf)_3 \cdot nH_2O$, and carried out in

Table 3. Progress of the ee of **9** during the Mannich reaction of **1** with **8** catalyzed by ALB and $La(OTf)_3 \cdot nH_2O$

reaction time (h)	1	12	24	36
yield of **9** (%)	2	22	42	53
ee of **9** (%)	6	20	25	30

toluene at 50 °C, as ALB appeared to decompose at higher temperature (70 °C). Under these conditions, the reaction using 1 equiv of **8** to **1**, without slow addition, resulted in the formation of (*S*)-**9** with relatively high ee value (66%), albeit in only 12% yield (36 h) (entry 1, Table 3). The use of increased amount (5 equiv) of **8** improved the yield of **9** to 78% but remarkably decreased the ee to 18% (36 h) (entry 2). On the other hand, the slow addition of 5 equiv of **8** over 48 h, to a mixture of **1**, ALB, $La(OTf)_3 \cdot nH_2O$, and MS 3A in toluene, afforded **9** in 65% yield with 35% ee (entry 3). After several attempts, the combination of pre-addition (1 equiv of **8**) with slow addition (2 equiv of **8**) over 18 h was found to give the best result, providing **9** in 65% yield with 40% ee (entry 4). The slow addition over a longer period (36 h) was not effective, giving **9** in 41% ee with lower yield (56%) (entry 5).

Table 4. Optimization of the direct catalytic asymmetric Mannich reaction of **1** with **8**

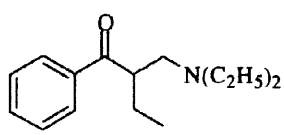


1 **8** **9**

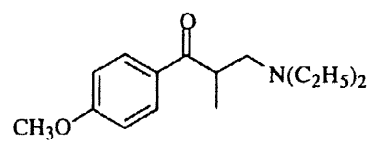
	equivalent of **8**				
entry	pre-addition	slow addition	a period of slow addition (h)	yield (%)	ee (%)
1	1	0	—	12 [a]	66
2	5	0	—	78 [a]	18
3	0	5	48	65	35
4	1	2	18	65	40
5	1	2	36	56	41

a) Reaction time was 36 h.

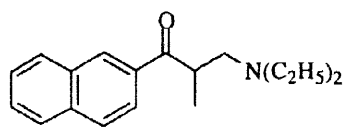
Figure 3



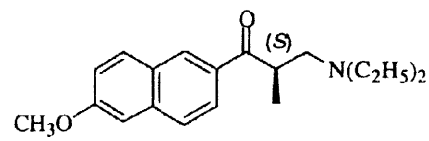
11: y. 69%, 34% ee



12: y. 76%, 31% ee



13: y. 61%, 44% ee



14: y. 69%, 44% ee

Next, other aryl ketones were also subjected to the reaction with **8** under the above-mentioned optimimum conditions (18 h for slow addition of **8**). As shown in Figure 3, several kinds of β-amino aryl ketones **11**–**13**[19] and (*S*)-**14** were obtained with 31–44% ee in good yields (61–76%), without over-Mannich reaction of **11**–**14** with **8**. These compounds were prepared by simple extraction after the reaction without further purification by column chromatography.[20]

In conclusion, we have succeeded in developing a direct catalytic asymmetric Mannich reaction of unmodified ketones by using an aminomethyl ether. This has been achieved by the cooperative catalysis of a heterobimetallic asymmetric complex, AlLibis(binaphthoxide) (ALB) and $La(OTf)_3 \cdot nH_2O$ in the presence of molecular sieves 3A. Although the enantiomeric excesses of the Mannich bases are still moderate, we believe that the present results will pave the way for further progress. Further improvement in the enantiomeric excess of the Mannich bases, and further applications using dialkyl ketones and/or carboxylic acid esters, are under study.

Experimental

Genaral Notes:

Infrared (IR) spectra were recorded on a JASCO FT/IR-410 fourier transform infrared spectrometer. NMR spectra were measured in a JEOL JNM-LA 500 spectrometer, operating at 500 MHz for ^{1}H-NMR, at 125.65 MHz for ^{13}C-NMR, and 139.29 MHz for ^{27}Al-NMR. Chemical shifts are reported on the δ scale relative to C_6D_6 as an internal reference (7.15 ppm for ^{1}H-NMR and 128.00 ppm for ^{13}C-NMR), or relative to $Al(NO_3)_3$ as an external standard (0.00 ppm for ^{27}Al-NMR). Mass spectra (MS) were measured on a JMS-GCMATE mass spectrometer for EI-MS, and on a Shimadzu KOMPACT MALDI IV mass spectrometer for Laser Desorption/Ionization Time-of-Flight Mass (LDI-TOF MS). Optical rotation was measured on a JASCO P-1010 polarimeter. Thin layer chromatography (TLC) analysis was performed on commercial glass plates bearing 0.25 mm layer of Merck silica gel 60 F_{254} (Merck Art. No. 5715). Column chromatography was carried out with silica gel, Merck Type 60 (230–400 mesh ASTM). HPLC analysis was performed on a JASCO HPLC system consisting of the following: pump, 880-PU; detector, 875-UV, measured at 254 nm.

All reactions were carried out in dry solvents under an argon atmosphere, unless otherwise mentioned. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. Molecular sieves (MS) 3A was purchased from Fluka Chemie AG and dried at 160 ℃ under reduced pressure for 4 h prior to use. A solution of (*R*)-ALB[16] or (*R*)-LLB[9a] in THF was prepared according to the reported procedure. The aminomethyl ether **8** was prepared from paraformaldehyde ($(CH_2O)_n$), $(C_2H_5)_2NH$ and CH_3OH in the presence of K_2CO_3, according to the reported procedure.[14] $La(OTf)_3 \cdot nH_2O$ (n = about 8 to 9) was purchased from Aldrich Co.,Ltd. The following abbreviations are used: d = doublet, dd = doublet-of-doublets, dq = doublet-of-quartets, m = multiplet, q = quartet, s = singlet, t = triplet.

General Procedure for the Direct Catalytic Asymmetric Mannich Reactions;

(*S*)-3-(Diethylamino)-2-methyl-1-phenyl-1-propanone [(*S*)-9]:

To a mixture of MS 3A (1.11 g) and $La(OTf)_3 \cdot nH_2O$ (162 mg, 0.222 mmol) was added a 0.075 M solution of (*R*)-ALB in THF (2.96 mL, 0.222 mmol). THF was removed by evaporation under reduced pressure. To the residue were added toluene (3.5 mL), **8** (107 μL, 0.74 mmol) and propiophenone (**1**) (98 μL, 0.74 mmol) at

rt, and the mixture was heated at 50 °C and then **8** (214 μL, 1.48 mmol) was further added over 18 h at 50 °C. After a removal of MS 3A by filtration, the filtrate was extracted with 5N HCl (3 x 3 mL). The combined extracts were washed with Et_2O (2 x 20 mL), alkalized with 5% NH_4OH (40 mL) and then extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over Na_2SO_4, and then evaporated at rt *in vacuo* to afford (*S*)-**9**[15] (105 mg, 65% yield) as slightly yellow oil without further purification;[20] $[\alpha]_D^{20}$ + 9.76 (*c* 1.11, $CHCl_3$) (40% ee); ^{1}H-NMR: 0.90 (t, *J* = 7.0, 6H, $(NCH_2CH_3)_2$), 1.17 (d, *J* = 6.7, 3H, $CHCH_3$), 2.37 (q, *J* = 7.0, 4H, $(NCH_2CH_3)_2$), 2.39 (dd, *J* = 6.4, 12.8, 1H) and 2.94 (dd, *J* = 5.2, 12.8, 1H) ($COCHCH_2$), 3.52–3.59 (m, 1H, COCH); 7.08–7.21 (m, 3H, Ar), 7.93–8.00 (m, 2H, Ar); ^{13}C-NMR: 12.3, 16.2, 39.9, 47.8, 57.9, 128.3, 128.5, 132.5, 138.1, 203.3; IR (neat) cm^{-1}: 2969, 1684, 1262, 1222, 970; LR-MS *m/z*: 219 (M^+), 204, 105, 86, 77; HR-MS *m/z*: calcd for $C_{14}H_{21}NO$, 219.1623; found, 219.1627. The ee of **9** was determined by chiral stationary phase HPLC analysis: DAICEL CHIRALCEL OJ; hexane–2-propanol–Et_2NH (100 : 1 : 0.1, v/v); flow rate: 0.5 mL/min; retention times, 10.5 min for (*R*)-**9** and 14.0 min for (*S*)-**9**.

2-(Diethylamino)methyl-1-phenyl-1-butanone (11):

The compound **11** was obtained as slightly yellow oil (**8** was added over 36 h); $[\alpha]_D^{20}$ + 2.81 (*c* 3.18, $CHCl_3$) (34% ee); ^{1}H-NMR: 0.85 (t, *J* = 7.5, 3H, $CHCH_2CH_3$), 0.87 (t, *J* = 7.3, 6H, $(NCH_2CH_3)_2$), 1.51-1.60 (m, 1H) and 1.82-1.90 (m, 1H) ($CHCH_2CH_3$), 2.32 (dq, J = 7.3, 13.1, 2H) and 2.37 (dq, J = 7.3, 13.1, 2H) ($N(CH_2CH_3)_2$), 2.43 (dd, *J* = 7.3, 12.8, 1H) and 2.97 (dd, *J* = 8.7 12.8, 1H) ($COCHCH_2N$), 3.51-3.56 (m, 1H, CH), 7.12-7.19 (m, 3H, Ar), 8.01-8.04 (m, 2H, Ar); ^{13}C-NMR: 12.1, 12.2, 24.5, 47.0, 47.8, 56.8, 128.4, 128.6, 132.4, 139.2, 203.6; IR (neat) cm^{-1}: 2967, 1680, 1264, 1217; LR-MS *m/z*: 234 (M^+ + 1), 233 (M^+), 204, 105, 86; HR-MS *m/z*: calcd for $C_{15}H_{23}NO$ + H, 234.1858; found, 234.1855. The ee of **11** was determined by chiral stationary phase HPLC analysis: DAICEL CHIRALCEL OJ; hexane–2-propanol–Et_2NH (100 : 1 : 0.1, v/v); flow rate: 0.5 mL/min; retention times, 9.0 min for a minor enantiomer and 10.0 min for a major enantiomer.

3-(Diethylamino)-1-(4-methoxyphenyl)-2-methyl-1-propanone (12):

The compound **12** was obtained as slightly yellow oil (**8** was added over 18 h); $[\alpha]_D^{20}$ + 5.54 (*c* 4.19, $CHCl_3$) (31% ee); ^{1}H-NMR: 0.88 (t, *J* = 7.3, 6H, $(NCH_2CH_3)_2$), 1.16 (d, *J* = 6.7, 3H, $CHCH_3$), 2.36 (q, *J* = 7.3, 4H, $(NCH_2CH_3)_2$), 2.37 (dd, *J* = 6.7, 12.8, 1H) and 2.91 (dd, *J* = 7.6, 12.8, 1H) ($COCHCH_2N$), 3.29 (s, 3H, OCH_3), 3.49-3.56 (m, 1H, COCH); 6.67-6.70 (m, 2H, Ar), 7.94-7.97 (m, 2H, Ar); ^{13}C-NMR: 12.3, 16.5, 39.6, 47.8, 54.9, 58.0, 113.9, 130.8, 131.0, 163.4, 201.7; IR (neat) cm^{-1}: 2968, 1672, 1461, 1258, 1227, 971; LR-MS *m/z*: 249 (M^+), 135, 107, 86; HR-MS *m/z*: calcd for $C_{15}H_{23}NO_2$, 249.1729; found, 249.1726. The ee of **12** was determined by chiral stationary phase HPLC analysis: DAICEL CHIRALCEL OJ; hexane–2-propanol–Et_2NH (100 : 1 : 0.1, v/v); flow rate: 0.5 mL/min; retention times, 17.5 min for a minor enantiomer and 28.0 min for a major enantiomer.

3-(Diethylamino)-2-methyl-1-(2-naphthyl)-1-propanone (13):

The compound **13** was obtained as colorless oil (**8** was added over 18 h); $[\alpha]_D^{22}$ – 0.55 (*c* 5.90, $CHCl_3$) (44% ee); ^{1}H-NMR: 0.86 (t, *J* = 7.0, 6H, $(NCH_2CH_3)_2$), 2.53 (d, *J* = 7.0, 3H, $CHCH_3$), 2.33 (dq, *J* = 7.0,

13.1, 2H) and 2.37 (dq, J = 7.0, 13.1, 2H) ($(NCH_2CH_3)_2$), 2.39 (dd, J = 6.1, 13.1, 1H) and 2.96 (dd, J = 7.7, 13.1, 1H) ($COCHCH_2N$), 3.66–3.73 (m, 1H, COCH), 7.21–7.25 (m, 2H, Ar), 7.51–7.65 (m, 3H, Ar), 8,13–8,18 (m, 1H, Ar), 8.46 (s, 1H, Ar); ^{13}C-NMR: 12.2, 16.4, 40.0, 47.8, 58.1, 124.8, 126.7, 128.0, 128.2, 128.6, 129.7, 129.9, 133.1, 135.4, 135.8, 203.3; IR (neat) cm^{-1}: 2968, 1675, 1275, 1235, 980; LR-MS *m/z*: 269 (M^+), 155, 127, 86; HR-MS *m/z*: calcd for $C_{18}H_{23}NO$, 269.1780; found, 269.1786. The ee of **13** was determined by chiral stationary phase HPLC analysis: DAICEL CHIRALCEL OJ; hexane–2-propanol–diethylamine (1000 : 1 : 1, v/v); flow rate: 1.0 mL/min; retention times, 13.5 min a major enantiomer and 15.5 min a minor enantiomer.

(*S*)-3-(Diethylamino)-1-(6-methoxy-2-naphthyl)-2-methyl-1-propanone [(*S*)-14]:

The compound (*S*)-**14** was obtained as slightly yellow oil (**8** was added over 18 h); $[\alpha]_D^{18}$ −2.14 (*c* 2.37, $CHCl_3$) (44% ee); ^{1}H-NMR: 0.89 (t, J = 7.0, 6H, $(NCH_2CH_3)_2$), 1.25 (d, J = 6.7, 3H, $CHCH_3$), 2.36 (dq, J = 7.0, 12.8, 2H) and 2.39 (dq, J = 7.0, 12.8, 2H) ($(NCH_2CH_3)_2$), 2.43 (dd, J = 6.4, 12.8, 1H) and 3.00 (dd, J = 7.6, 12.8, 1H) ($COCHCH_2N$), 3.35 (s, 3H, OCH_3), 3.69–3.76 (m, 1H, COCH), 6.83 (d, J = 2.5, 1H, Ar(5)-H), 7.10 (dd, J = 2.5, 8.8, 1H, Ar(7)-H), 7.52 (d, J = 8.8, 1H, Ar(8)-H), 7.54 (d, J = 8.5, 1H, Ar(4)-H), 8.25 (dd, J = 1.8, 8.5, Ar(3)-H), 8.43 (d, J = 1.8, Ar(1)-H), ^{13}C-NMR: 12.2, 16.5, 39.9, 47.8, 54.9, 58.1, 106.0, 119.8, 125.6, 127.4, 128.4, 130.0, 131.4, 133.5, 137.5, 159.9, 202.9; IR (neat) cm^{-1}: 2967, 1671, 1481, 1267, 1235, 984; LR-MS *m/z*: 299 (M^+), 185, 157, 86; HR-MS *m/z*: calcd for $C_{19}H_{25}NO_2$, 299.1885; found, 299.1882. The absolute configuration of (*S*)-**14** was determined by Mosher's method[21] after the reduction of **14** by $LiAlH_4$. The ee of **14** was determined by chiral stationary phase HPLC analysis: DAICEL CHIRALCEL OJ; hexane–2-propanol–Et_2NH (1000 : 1 : 1, v/v); flow rate: 1.0 mL/min; retention times, 50 min for (*S*)-**14** and 56 min for (*R*)-**14**.

The three component asymmetric Mannich reaction using the (R)-LLB complex

2-Methyl-1-phenyl-3-(*N*-pyrrolidinyl)-1-propanone (4):

The mixture of 0.075 M solution of (*R*)-LLB in THF (0.99 mL, 0.074 mmol) and MS 3A (1.11 g) was evaporated to remove THF under reduced pressure. To the residue were successively added toluene (3.5 mL), propiophenone (**1**) (98 μL, 0.74 mmol), pyrrolidine (**2**) (74 μL, 0.88 mmol) and paraformaldehyde (**3**) (33mg, 0.88mmol) at rt, and the mixture was stirred at rt for 36 h. 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_2O (2 x 20 mL), alkalized with 5% NH_4OH (40 mL) and then extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over Na_2SO_4, and then evaporated at rt *in vacuo* to afford **4** (25.7 mg, 16% yield) as slightly yellow oil without further purification[20]; $[\alpha]_D^{20}$ + 9.41 (*c* 0.80, $CHCl_3$) (64% ee); ^{1}H-NMR: 1.18 (d, J = 6.7, 3H, CH_3), 1.46–1.49 (m, 4H, $N(CH_2CH_2)_2$), 2.31–2.35 (m, 4H, $N(CH_2CH_2)_2$), 2.50 (dd, J = 6.8, 11.9, 1H) and 2.93 (dd, J = 7.0, 11.9, 1H) ($COCHCH_2$), 3.49–3.56 (m, 1H, COCH); 7.06–7.18 (m, 3H, Ar), 7.94–7.96 (m, 2H, Ar); ^{13}C-NMR: 16.4, 23.9, 40.6, 54.6, 59.9, 128.5, 128.7, 132.6, 137.6, 202.6; IR (neat) cm^{-1}: 2966, 1682, 1219, 975, 707; LR-MS *m/z*: 217 (M^+), 202, 105, 84, 77; HR-MS *m/z*: calcd for $C_{14}H_{19}NO$, 217.1467; found, 217.1465. The ee of **4** was determined by chiral stationary phase HPLC analysis: DAICEL CHIRALCEL OJ; hexane–2-propanol–Et_2NH (100 : 1 : 0.1, v/v); flow rate: 0.5 mL/min; retention times, 15.0 min for a minor enantiomer and 20.5 min for a major enantiomer.

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