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Direct catalytic asymmetric aldol reactions promoted by novel heterobimetallic catalysts possessing strong Brønsted base: a new strategy for the development of Lewis acid–Brønsted base bifunctional catalysts

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This paper is dedicated to Professor Henri B. Kagan on the occasion of him being awarded the 1999 Tetrahedron Prize

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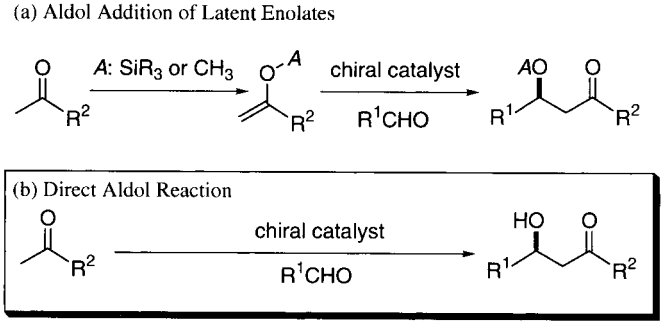
Abstract—Novel heterobimetallic catalysts possessing lithium alkoxide as Brønsted base have been developed. The catalysts were found to be effective in the direct asymmetric aldol reaction of less acidic dialkyl ketones as well as aromatic ketones, affording the aldol products in moderate yield and ee. Attempts at diastereo- and enantioselective direct catalytic aldol reaction of ethyl ketone using small molecule catalysts are reported for the first time. © 2001 Published by Elsevier Science Ltd.

1. Introduction

The development of a catalytic asymmetric aldol reaction is one of recent landmarks in organic chemistry. A number of excellent catalysts for asymmetric syntheses of aldol adducts from latent enolates such as enol silyl ethers or enol methyl ethers have been reported (Scheme 1).[1] In these reactions, however, latent enolates must be prepared prior to the reaction, and stoichiometric amounts of bases and reagents such as $(CH_3)_3SiCl$ are necessary. Therefore, the development of a *direct* catalytic asymmetric aldol reaction, in which the pre-activation of nucleophiles is no longer needed, has been worthy of notice. Nevertheless, no efficient catalysts for this method have been reported until recently,[2–5] presumably due to difficulties described below. For example, the catalyst must not only activate the aldehyde in order to get high ee but also has to abstract an α-hydrogen of the ketone to generate an enolate. Retro-aldol reactions and self-condensation of aldehydes must be prevented as well. Having established the system for Lewis acid–Brønsted base bifunctional catalysts,[6] we have achieved direct catalytic asymmetric aldol reactions using $LaLi_3$tris(binaphthoxide) (LLB),[7] and subsequently using a barium complex (BaB–M)[8] and a heteropolymetallic catalyst.[9] Another group has recently reported a proline-catalyzed reaction.[10] These reactions have excluded the



Scheme 1.

Keywords: direct catalytic asymmetric aldol reaction; lanthanide; heterobimetallic multifunctional catalyst.
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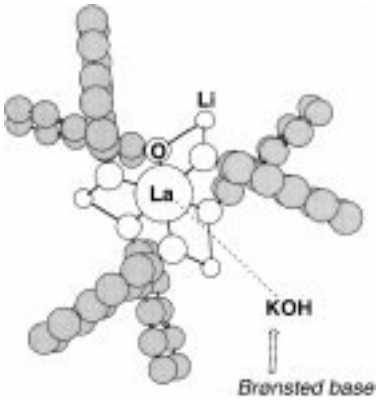
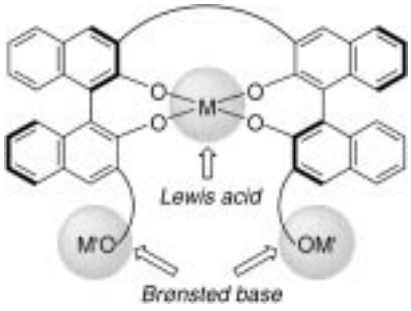


Figure 1. Structure of the heteropolymetallic catalyst.



Scheme 2.

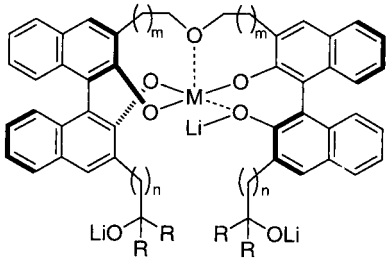
necessity of pre-activation of ketones for catalytic asymmetic aldol reactions. Modest to excellent results were obtained in the reactions between aldehydes and methyl ketones such as acetophenone or acetone. On the other hand, there is no report that these catalysts are capable of promoting the aldol reactions of esters or methylene ketones such as 3-pentanone. Thus we were prompted to develop novel catalysts to broaden the generality of the direct catalytic asymmetric aldol reaction. In this article, we report a novel strategy, which allows a flexible design of new catalysts. This strategy is applied to the development of direct asymmetric aldol reactions.

2. Results and discussions

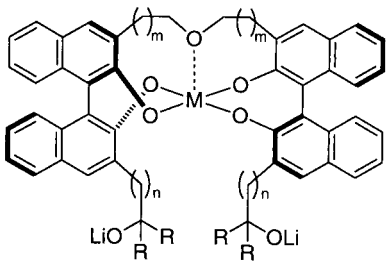
In 1999, we developed a heteropolymetallic catalyst by addition of potassium hydroxide (KOH) and H_2O to LLB.[9] The catalyst was found to accelerate the direct asymmetric aldol reaction of ketones with aldehydes. Fig. 1 shows the postulated structure of the heteropolymetallic catalyst. Potassium hydroxide was thought to coordinate to LLB and to act as Brønsted base for the abstraction of α-hydrogens of ketones. Since the rate-determining step proved to be the deprotonation of ketones on the basis of kinetic studies, the modification of Brønsted base seemed to be necessary to enhance the catalytic activity. Scheme 2 shows the possible design of new catalysts, which consist of a center metal (M) acting as a Lewis acid and metal-alkoxide moiety (OM′) acting as a strong Brønsted base. The novel strategy for designing catalysts is to attach the Brønsted base moiety covalently to the naphthyl ring through a carbon tether,[11] different from the cases of conventional heterobimetallic catalysts[6] and the heteropolymetallic catalyst.[9] We believe this strategy facilitates the optimization of bifunctional catalysts, since the Brønsted base moiety can be varied without changing the framework of the complexes.

2.1. Direct catalytic asymmetric aldol reactions of methyl ketones

Our first aim was to synthesize catalysts which possess two lithium alkoxide moieties, from ligand **6** (Scheme 3 shows an assumed structure).[12] Scheme 4 summarizes the sequence for the synthesis of ligand **6** starting from MOM-protected (*R*)-BINOL. Two hydroxyethyl groups were introduced at 3,3′-position of 1,1′-binaphthyl by treatment of lithiated MOM-BINOL with an excess amount of ethylene oxide in the presence of $BF_3{\cdot}OEt_2$.[13] After one of two hydroxyl functions was protected as allyl ether,[14] the MOM group was replaced with a benzyl group. The remaining hydroxyl group was oxidized to aldehyde using Dess–Martin periodinane to afford **5**. The formation of a symmetrical ether was achieved by reductive coupling of the aldehyde using triethylsilane in the presence of trimethylsilyl triflate.[15] The deprotection of the allyl group was performed



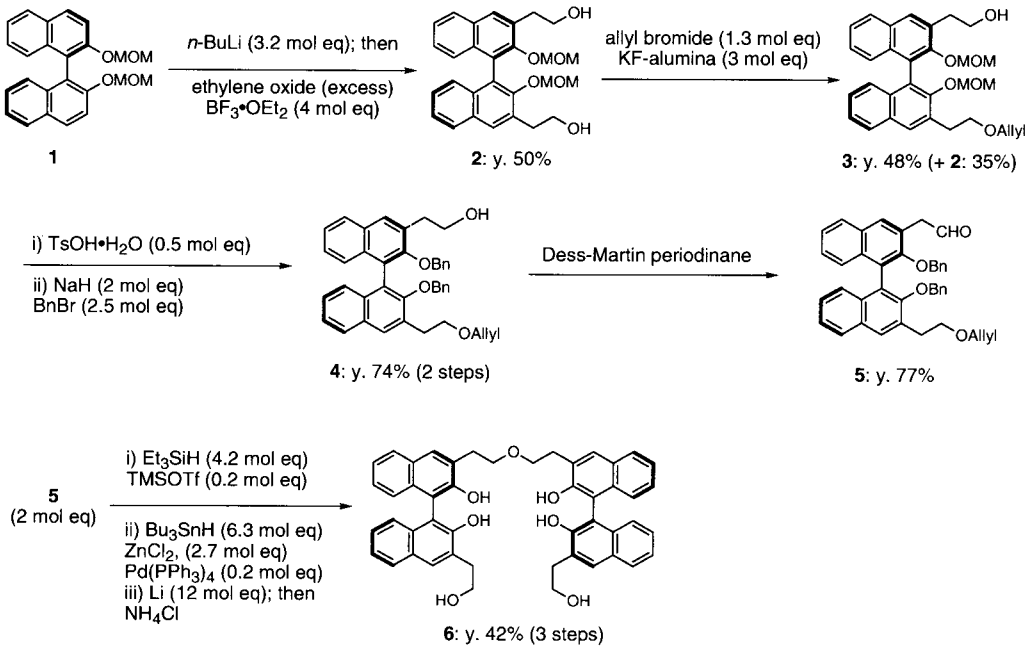
type A (M = La, Yb, Al)



type B (M = Ti, Zr)

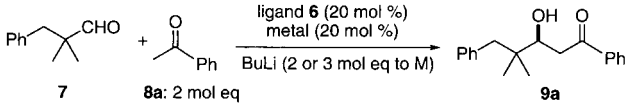
ligand **6**: m = 1, n = 1, R = H
ligand **10**: m = 1, n = 0, R = H
ligand **11**: m = 0, n = 0, R = H
ligand **15**: m = 1, n = 1, R = CH_3

Scheme 3.



Scheme 4. Synthetic route to ligand **6**.

Table 1. Effect of center metals and solvents

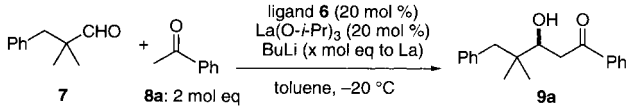


Entry	Metal (M) source	BuLi (equiv. to M)	Solvent	Temp. (°C)	Time (h)	Yield (%)	ee (%)
1	$Ti(O\text{-}i\text{-}Pr)_4$	2	THF	−20°C	28	Trace	–
2	Me_3Al	3	THF	−20°C	28	31	13
3	$Zr(O\text{-}i\text{-}Pr)_4$	2	THF	Rt	48	16	23
4	$La(O\text{-}i\text{-}Pr)_3$	3	THF	−20°C	0.75	75	6
5	$La(O\text{-}i\text{-}Pr)_3$	3	CH_3CN	−20°C	21	58	10
6	$La(O\text{-}i\text{-}Pr)_3$	3	CH_2Cl_2	−20°C	21	Trace	–
7	$La(O\text{-}i\text{-}Pr)_3$	3	Toluene	−20°C	0.75	61	22
8	$Yb(O\text{-}i\text{-}Pr)_3$	3	Toluene	−20°C	2	68	−1

by palladium-catalyzed reduction using tributyltin hydride and zinc chloride[16] to afford the alcohol. Ligand **6** was obtained after cleavage of the benzyl ethers under Birch's conditions in the absence of a proton source.

With the desired ligand in hand, we prepared several kinds of catalysts by treatment of ligand **6** with 1 mol equiv. of metal isopropoxide (or Me_3Al) and 2–3 mol equiv. of *n*-BuLi. Table 1 indicates that the reactivity strongly depends on the choice of center metal of the catalyst (M in Scheme 3). Although titanium (Ti) complex had been expected to show high catalytic activity, based on previous examples of asymmetric Mukaiyama–aldol reactions, the direct aldol reaction between aldehyde **7** and acetophenone (**8a**) was not promoted by Ti–Li complex (entry 1). Neither catalyst containing Al nor Zr as center metal was applicable (entries 2, 3). In contrast, moderate to good yields were achieved when the catalyst was prepared from **6**, $La(O\text{-}i\text{-}Pr)_3$ and BuLi. Toluene proved to be the best solvent, giving the product in 61% yield with 22% ee (entry 7). The reaction was completed in 45 min at −20°C. Using Yb, the complex gave unsatisfactory result (−1% ee) (entry 8).

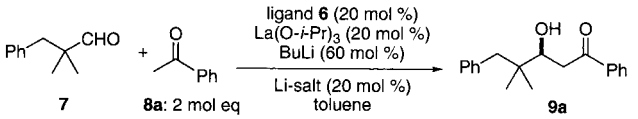
Table 2. Effect of the amount of base



Entry	BuLi (*x* mol equiv. to La)	Time (h)	Yield (%)	ee (%)
1	3 mol equiv.	0.75	61	22
2	2 mol equiv.	19	51	4
3	1 mol equiv.	19	0	–

With the best center metal, we turned our attention to the effect of the Brønsted base part of the catalyst. The importance of lithium alkoxide moiety bonded to naphthalene ring has been clearly demonstrated by varying the equivalent of BuLi used for the catalyst preparation. Table 2 shows the results of the aldol reaction promoted by La–Li catalysts in toluene. When only 2 mol equiv. of BuLi were used (the

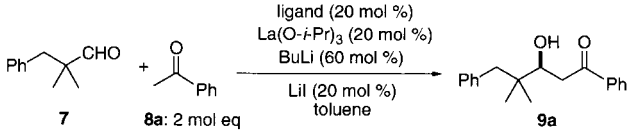
Table 3. Effect of lithium salts



Entry	Li-salit	Temperature (°C)	Time (h)	Yield (%)	ee (%)
1	–	−20°C	0.75	61	22
2	LiCl	−20°C	4	30	4
3	LiBr	−20°C	1	61	36
4	LiI	−20°C	1.5	84	34
5[a] (cat A)	–	−30°C	4	70	60
6[a] (cat A)	LiI	−30°C	4	70	67

[a] BuLi solution provided by Aldrich was used for the catalyst preparation.

Table 4. Aldol reactions using several types of ligands



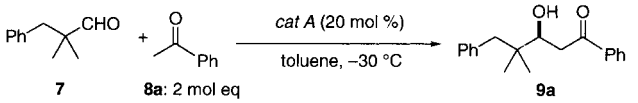
Entry	Ligand	Temperature (°C)	Time (h)	Yield (%)	ee (%)
1	**6** (cat A)	−30°C	4	70	67
2	**10**	−20°C	19	55	35
3	**11**	−20°C	22	48	3

BuLi solution provided by Aldrich was used for the catalyst preparation.

best catalyst is prepared from 3 mol equiv. of BuLi), the reaction time was prolonged to 19 h (cf. 0.75 h for the control experiment (entry 1)) and the enantiomeric excess decreased to 4% (entry 2). Moreover, a catalyst which lacks aliphatic alkoxide (entry 3) gave no product at all.

Next, the effect of lithium salts[17] as additive was investigated (Table 3). When lithium chloride (LiCl) (1 mol equiv. to the catalyst) was added, the reactivity and the enantioselectivity dropped (entry 2). On the other hand, lithium bromide (LiBr) and lithium iodide (LiI) were found to improve the enantioselectivity slightly without significant drop of reactivity (entries 3, 4). When the catalyst was prepared from BuLi provided by Aldrich, which contains only trace amounts of lithium salts, to exclude LiCl, much higher enantiomeric excess (60% ee) was achieved (cat A, entry 5). The addition of LiI gave rise to a slightly higher ee (entry 6).[†,‡]

Table 5. Effect of catalyst amount



Entry	Catalyst (mol %)	Time (h)	Yield (%)	ee (%)
1	20	4	70	60
2	10	19	76	58
3	5	28	61	74
4	3	28	66	63

BuLi solution provided by Aldrich was used for the catalyst preparation.

We were encouraged by these results and attempted to tune the ligand by changing the length of the tether or the linker (m, n in Scheme 3). In fact, the length proved to affect both reactivity and selectivity significantly (Table 4). The use of a shorter tether of the alcohol (ligand **10**) was found to decrease the reactivity (entry 2). Moreover, a catalyst with a shorter linker (ligand **11**) showed much lower selectivity as well as lower reactivity (entry 3). Consequently, catalyst A proved to be the best catalyst.

With the best catalyst in hand, we tried to reduce the catalyst loading (Table 5). The reactions were examined using 2 mol equiv. of the ketone. As a result, we were glad to find that as little as 3 mol% of catalyst A promoted the reaction with comparable yield and ee (entry 4). In the presence of less than 3 mol% of catalyst, the reaction did not proceed well. The relatively low reactivity would be due to the decomposition of the catalyst since the lithium alkoxide part could be easily hydrolyzed by a small amount of water generated from dehydration of the product.

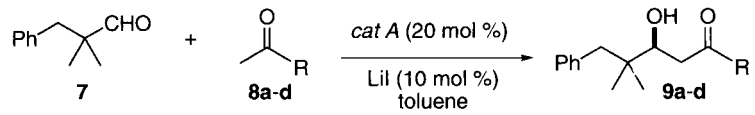
Compared to aromatic ketones such as acetophenone, it is more difficult to carry out the direct aldol reaction of aliphatic ketones such as 2-butanone or pinacolone, due to their lower acidity. To demonstrate the activity of catalyst A, several aliphatic ketones were tested. Table 6 shows that this catalyst can promote the reaction of less acidic aliphatic ketones as well as aromatic ketones (entries 2, 3). It is noteworthy that the aldol reaction of isopropyl methyl ketone (**8c**) gave the product (**9c**) in moderate yield (entry 3), since this substrate has not been reported as a good substrate for direct aldol reactions. It is well known that α,β-unsaturated ketones can form vinylogous enolates and undergo condensations at the γ-position under basic conditions. Catalyst A was found to be rather effective in the reaction of α,β-unsaturated ketone **8d** with aldehyde **7**. The ketone reacted smoothly and solely at the α-position to afford the corresponding product (**9d**) in 66% yield and 60% ee (entry 4).

On the basis of the observed effects of the center metal (Table 1) and the lithium alkoxide moiety (Table 2), the reaction seems to be promoted by the cooperation of the Lewis acid and the Brønsted base, similar to the conventional catalyses.[7–9] We describe below a postulated mechanism for the catalysis (Scheme 5). A molecular model of catalyst A suggests that an intramolecular coordination of the linker oxygen[12a] and a lithium alkoxide moiety to the center metal can take place, thus stabilizing the monomeric structure (**I**). The remaining alkoxide moiety abstracts a proton from the α-position of the ketone to give an alcohol and the corresponding lithium enolate. A chelation of Li to the alcohol and to an oxygen atom of BINOL would fix the lithium enolate inside the cavity of the catalyst to form

[†] The moderate yields are due to unreacted aldehyde and a small amount of dehydrated product.

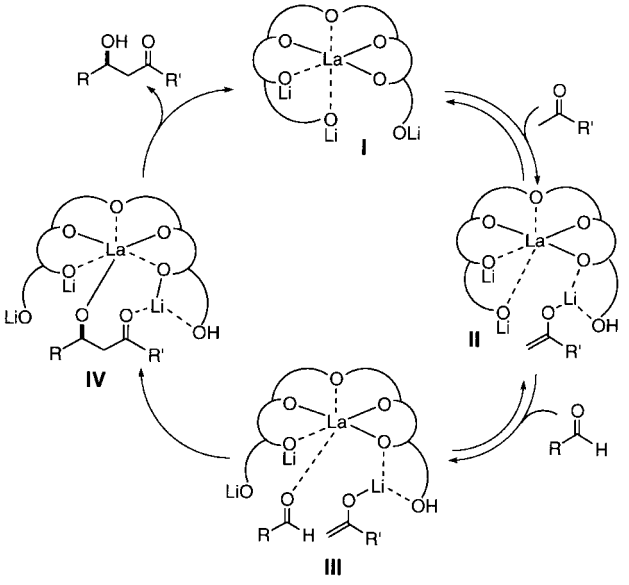
[‡] Several enolizable aldehydes (e.g. isobutyraldehyde) instead of **7** were also tested. However, they suffered from poor enantioselectivities and lower chemical yields.

Table 6. Aldol reactions of several kinds of ketones



Entry	Ketone		Temp. (°C)	Product	Time (h)	Yield (%)	ee (%)
1		**8a** (2 mol equiv.)	−30°C	**9a** (R=Ph)	4	70	67
2		**8b** (5 mol equiv.)	−20°C	**9b** (R=Et)	14	71	40
3		**8c** (5 mol equiv.)	−20°C	**9c** (R=*i*-Pr)	71	62	45
4		**8d** (5 mol equiv.)	−30°C	**9d** (R=CHC(CH$_3$)$_2$)	50	66	60
5			−20°C		14	70	52

BuLi solution provided by Aldrich was used for the catalyst preparation.



Scheme 5. Postulated catalytic cycle.

intermediate **II**. The aldehyde replaces the lithium alkoxide by coordination to the center metal to form intermediate **III**, in which the aldehyde is activated by the Lewis acidity of the center metal[18] and the relative position of the aldehyde and the enolate is arranged suitably. The enolate then attacks the *Si* face of the aldehyde to afford the corresponding aldolate (**IV**). As the last step protonation of the aldolate by the alcohol moiety of the catalyst gives the (*S*)-aldol adduct and regenerates the catalyst (**I**).[§] The mechanism of the enantioselection at the stage of intermediate **III** is tentatively described in Fig. 2.

2.2. Attempts at diastereo- and enantioselective direct catalytic aldol reaction of 3-pentanone

The aldol reaction between aldehydes and methylene ketones or propionates should provide a powerful tool for the construction of two continuous chiral centers as well as for the formation of carbon–carbon bonds. Catalytic asymmetric syntheses of *syn*- and *anti*-aldols from latent enolates have already been well investigated.[1] In contrast, the diastereo- and enantioselective synthesis of aldols, starting from methylene ketones, by means of direct catalytic asymmetric aldol reaction has not been reported.[19] The bulkiness of methylene ketones was anticipated to make it more difficult for the catalysts to abstract an α-hydrogen of the ketones. We expected that the new catalysts could be applicable to diastereoselective direct aldol reactions.

The reaction between aldehyde **12** and 3-pentanone (**13**) (Table 7) can produce the *syn*- or *anti*-aldol adduct (**14**), which has been utilized as an intermediate in a total synthesis of epothilone A by our group.[20] First of all we carried out the reaction in the presence of the heteropolymetallic catalyst (20 mol%); however, no reaction proceeded and the starting materials were recovered. In contrast, catalyst A was found to promote the aldol reaction to afford the corresponding products, albeit in 15% yield (entry 1). In order to improve the reactivity, we designed a different catalyst (cat B), which possesses a tertiary alkoxide instead of a primary alkoxide (ligand **15**, Scheme 3). The catalyst (cat B) was prepared from La(O-*i*-Pr)$_3$, BuLi, and ligand **15** possessing tertiary alcohols. As a result, catalyst B was found to improve the reactivity to give the products in 38% yield (entry 2). The diastereoselectivity was found to be opposite to that observed in the case of catalyst A. Furthermore, asymmetric induction (28% ee) has been achieved for the first time by addition of LiI (20 mol%) (entry 3). Although further addition of LiI increased the ee (up to 51%), the chemical yield dropped to 5% (entries 4, 5). The addition of other lithium salts gave less satisfactory results (entries 6, 7). Unfortunately, catalyst B was found to be less effective than catalyst A in the reaction of aldehyde **7** with ketone **8a**. The product (**9a**) was obtained in only 24% ee and 33% yield (catalyst B, 20 mol%; −30°C; 90 min). When LiI was added, an improvement on the solubility of the catalyst in toluene was observed. This phenomenon implies the association of LiI with the catalyst. However, its role is still not clear at the moment.

[§] Another catalytic cycle could also be reasonable: starting from the catalyst (**I**), first coordination of the aldehyde could take place. After deprotonation of the ketone, again intermediate **III** could be formed.

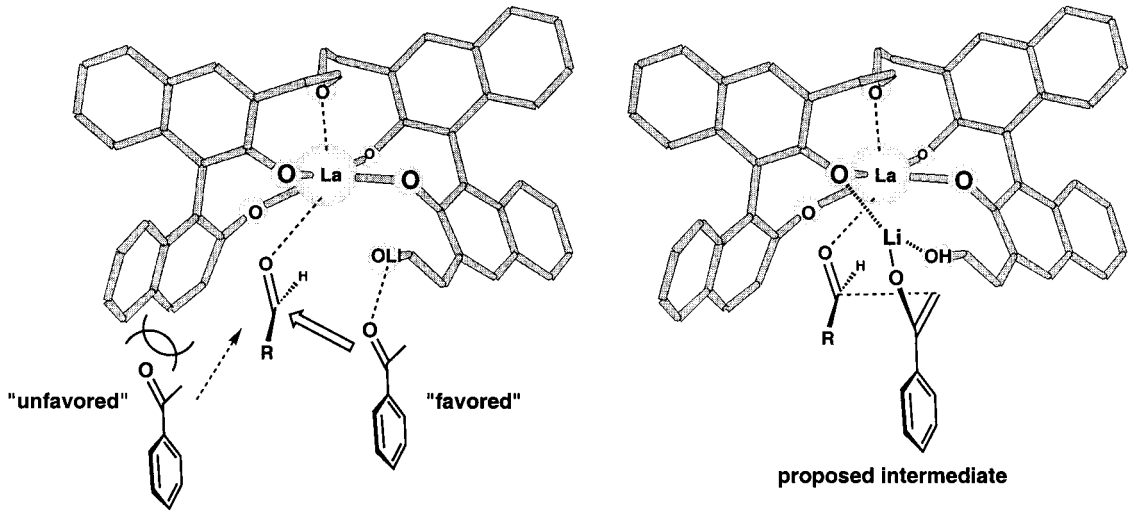
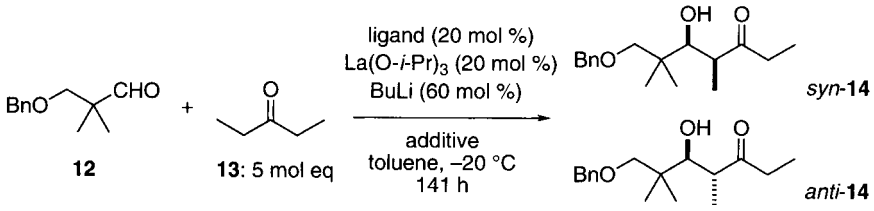


Figure 2. Postulated intermediate. Several atoms and groups are omitted for clarity.

Table 7. Aldol reaction of 3-pentanone



Entry	Ligand	Additive	Yield (%)	*syn*/*anti*	ee of *syn*	ee of *anti*
Cf	(Heteropolymetallic catalyst[a])		No reaction	–	–	–
1[b]	**6** (cat A)	LiI (10 mol %)	15	75/25	<10	–
2	**15** (cat B)	–	**38**	26/74	−1	−4
3	**15** (cat B)	LiI (20 mol %)	21	19/81	8	**28**
4	**15** (cat B)	LiI (40 mol %)	11	36/64	10	**36**
5	**15** (cat B)	LiI (60 mol %)	5	40/60	9	**51**
6	**15**	LiOH (20 mol %)	24	21/79	4	−6
7	**15**	$LiBF_4$ (20 mol %)	Trace	–	–	–

BuLi solution provided by Aldrich was used for the catalyst preparation.
[a] The reaction was carried out in THF.
[b] The reaction was carried out for 114 h.

3. Conclusions

In summary, we have demonstrated a novel concept which enables flexible design of Lewis acid–Brønsted base bifunctional catalysts. Lithium alkoxide was introduced as Brønsted base function to enhance the catalytic activity. The lithium alkoxide moiety was covalently bonded to the catalysts to prevent undesired background reactions, which might form racemic products. In line with this concept, several novel catalysts have been developed for direct asymmetric aldol reactions. A catalyst possessing two primary alkoxides was found to promote the aldol reactions of dialkyl ketones as well as aromatic ketones, giving the aldol products in moderate yield and ee, whereas a catalyst lacking the alkoxide moieties gave no aldol products. On the other hand, a different catalyst possessing tertiary alkoxide moieties has been found to be applicable to the aldol reaction of 3-pentanone, which should provide a powerful method for the construction of continuous chiral centers. Since this kind of reaction is totally unexploited, it is notable that the *anti*-aldol product was obtained with up to 51% ee, albeit in low chemical yield.

Investigations into the role of lithium salts and further studies on the development of diastereo- and enantioselective direct catalytic aldol reaction in accordance with the methodology reported herein, for instance seeking a more suitable Brønsted base, are now in progress.[23]

4. Experimental

4.1. General methods and materials

Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for

^{13}C NMR. Chemical shifts in $CDCl_3$ are reported on the δ scale relative to $CHCl_3$ (7.26 ppm for ^1H NMR and 77.00 ppm for ^{13}C NMR) as an internal reference. The following abbreviations are used to report multiplicities: 's' (singlet), 'd' (doulet), 'dd' (doublet of doublets), 't' (triplet), 'dq' (doublet of quartets), 'm' (multiplet), 'br' (broad). Optical rotations were measured on a JASCO P-1010 polarimeter. EIMS were measured on a JEOL JMS-BU20 GCmate. Column chromatography was carried out with silica gel Merck 60 (230–400 mesh ASTM). Preparative thin layer chromatography (preparative TLC) was performed on Merck Art. 5715, Silica gel 60 F_{254} plates. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UVIDEC-100-IV, measured at 254 nm; column, DAICEL CHIRALPAK AS, AD, DAICEL CHIRALCEL OD or OJ; mobile phase, hexane-2-propanol; flow rate, 0.3–1.0 mL/min. Reactions were carried out in dry solvents under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Toluene was distilled from sodium. BuLi solution in hexane was purchased from Kanto Chemical, Japan unless otherwise stated. Lanthanum triisopropoxide ($La(O\text{-}i\text{-}Pr)_3$) was purchased from Kojundo Chemical Laboratory, 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (fax: +81-492-84-1351). Other reagents were purified by usual methods.

4.1.1. (*R*)-3,3′-Bis(2-hydroxyethyl)-2,2′-bis(methoxymethyloxy)-1,1′-binaphthyl (2). To a solution of MOM-protected BINOL **1** (20 g, 0.0534 mol) in 600 mL of anhydrous ether, was added *n*-butyllithium (*n*-BuLi) in hexane (110 mL, 0.171 mol, 1.56 N) at room temperature, and the resulting mixture was stirred for 3.5 h. During the stirring, an ether solution of ethylene oxide was prepared in another flask according to the procedure described below. A dispersion of sodium hydride (21.4 g, 60–72% in mineral oil) was suspended in 400 mL of anhydrous ether, and 2-chloroethanol (32.2 mL, 0.481 mol, distilled from Na_2SO_4) was added slowly over 20 min with stirring at 0°C. The resulting mixture was stirred at the same temperature for 2.5 h and the supernatant was used as ethylene oxide solution. Tetrahydrofuran (200 mL) and the ether solution of ethylene oxide prepared above were added to a cooled suspension of the lithiated MOM-BINOL at −96°C (acetone/liq.N_2 bath). The mixture was stirred for 10 min and boron trifluoride ethyl ether complex ($BF_3{\cdot}OEt_2$) (26.9 mL, 0.214 mol) was added in one portion. The stirring was continued at −96°C for 25 min until the bath temperature was raised to −78°C. After stirring for 15 min, the reaction mixture was poured into a mixture of saturated aq. $NaHCO_3$ (800 mL), water (800 mL) and ether (800 mL). The aqueous layer was separated, saturated with NaCl and extracted with ether (500 mL) and then ethyl acetate (500 mL×5). The organic layers were combined, washed with brine (500 mL×2) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate=1/1) to afford alcohol **2** (12.3 g, y. 50%) as a colorless oil; ^1H NMR ($CDCl_3$) δ 7.85 (s, 2H), 7.82 (d, *J*=7.8 Hz, 2H), 7.39–7.35 (m, 2H), 7.23–7.19 (m, 2H), 7.14 (d, *J*=8.0 Hz, 2H), 4.52 (d, *J*=5.4 Hz, 2H), 4.39 (d, *J*=5.4 Hz, 2H), 4.03–4.00 (m, 4H), 3.22 (dd, *J*=6.0, 13.5 Hz, 2H), 3.15 (dd, *J*=6.5, 13.5 Hz, 2H), 2.97 (s, 6H), 2.12 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 153.23, 133.18, 132.38, 130.86, 129.98, 127.51, 126.13, 125.91, 125.28, 125.12, 99.01, 63.23, 56.68, 34.45; FTIR (neat) ν 3398, 2935, 1236, 1157, 1070 cm^{-1}; MS (*m*/*z*) 338 (base peak), 430, 462 (M^+); $[\alpha]_D^{22}=-152.6$ (*c* 0.97, CH_2Cl_2); HRMS calcd for $C_{28}H_{30}O_6$ 462.2042, found 462.2040.

4.1.2. (*R*)-4-(3-(2-Allyloxyethyl)-2-methoxymethyloxy-1-naphthyl)-3-methoxymethyloxy-2-naphthaleneethanol (3). To a solution of **2** (19.4 g, 0.0419 mol) in acetonitrile (210 mL), were added KF-alumina[14] (25.6 g, containing 0.126 mol of KF) and allyl bromide (4.72 mL, 0.0545 mol). The resulting mixture was stirred vigorously at room temperature for 20 h and filtered through a pad of Celite. The filtrate was evaporated to dryness and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate=2/1) to afford allyl ether **3** (10.1 g, y. 48%) as a colorless oil; ^1H NMR ($CDCl_3$) δ 7.86 (d, *J*=9.3 Hz, 2H), 7.82 (d, *J*=7.9 Hz, 2H), 7.38–7.34 (m, 2H), 7.22–7.18 (m, 2H), 7.14–7.12 (m, 2H), 5.96–5.88 (m, 1H), 5.29–5.25 (m, 1H), 5.18–5.15 (m, 1H), 4.55 (d, *J*=5.4 Hz, 1H), 4.51 (d, *J*=5.6 Hz, 1H), 4.41–4.38 (m, 2H), 4.05–4.00 (m, 4H), 3.88–3.78 (m, 2H), 3.28–3.13 (m, 4H), 2.96 (s, 3H), 2.90 (s, 3H), 2.15 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 153.27, 153.12, 134.89, 133.27, 133.10, 132.46, 132.38, 130.87, 130.80, 129.93, 129.90, 127.52, 127.47, 126.04, 126.01, 125.99, 125.91, 125.5, 125.10, 125.07, 124.96, 116.81, 99.05, 98.92, 71.87, 70.30, 63.28, 56.68, 56.58, 34.45, 31.41; FTIR (neat) ν 3446, 2933, 1158, 1070, 976, 922 cm^{-1}; MS (*m*/*z*) 338 (base peak), 426, 502 (M^+); $[\alpha]_D^{25}=-172.7$ (*c* 2.27, $CHCl_3$); HRMS calcd for $C_{31}H_{34}O_6$ 502.2355, found 502.2357. Further elution with hexane/acetone (1/1) gave the starting alcohol (**2**) (6.79 g, 35%).

4.1.3. (*R*)-4-(3-(2-Allyloxyethyl)-2-benzyloxy-1-naphthyl)-3-benzyloxy-2-naphthaleneethanol (4). A mixture of allyl ether **3** (26.4 g, 0.0525 mol) and *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) (5.00 g, 0.0263 mol) in CH_2Cl_2/MeOH (530/530 mL) was stirred at room temperature for 6.5 h. The resulting solution was poured into a mixture of saturated aq. $NaHCO_3$ (500 mL) and water (500 mL). After stirring for 1 h, the aqueous layer was separated and extracted with CH_2Cl_2 (300 mL×3). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (100 mL×2) and brine (200 mL) and dried over Na_2SO_4. Removal of the solvent gave crude phenol, which was used without further purification for the next alkylation. The crude phenol was dissolved in THF/DMF (250/250 mL) and sodium hydride (2.52 g, 0.105 mol) was added to the solution at 0°C. The mixture was stirred at room temperature for 30 min and then cooled to 0°C. After the addition of benzyl bromide (15.6 mL, 0.131 mol) the temperature was allowed to raise to room temperature and the mixture was stirred for 3.5 h. Water (600 mL) and ether (100 mL) were added and the aqueous layer was extracted with ether (200 mL×3). The combined organic layers were washed with water (200 mL×2) and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by flash silica gel column

chromatography (hexane/ethyl acetate=3/1) to afford benzyl ether **4** (22.8 g, y. 73%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.89–7.83 (m, 4H), 7.41–7.36 (m, 2H), 7.27–7.20 (m, 4H), 7.15–7.07 (m, 6H), 6.72–6.68 (m, 4H), 5.93–5.81 (m, 1H), 5.26–5.21 (m, 1H), 5.15–5.12 (m, 1H), 4.63 (d, J=10.8 Hz, 1H), 4.57 (d, J=10.9 Hz, 1H), 4.30–4.26 (m, 2H), 3.96–3.94 (m, 2H), 3.88–3.80 (m, 2H), 3.79–3.73 (m, 1H), 3.70–3.64 (m, 1H), 3.23–3.09 (m, 3H), 3.03–2.97 (m, 1H), 1.62 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 154.74, 154.57, 137.36, 137.13, 134.92, 133.50, 133.30, 132.63, 132.52, 130.87, 129.99, 129.88, 128.03, 127.97, 127.66, 127.65, 127.60, 127.52, 127.46, 126.05, 125.95, 125.82, 125.72, 125.57, 125.18, 124.98, 124.84, 116.77, 74.99, 74.94, 71.78, 70.50, 63.13, 34.87, 31.39; FTIR (neat) ν 3423, 2931, 2866, 1235, 1101, 749 cm^{-1}; MS (m/z) 91 (Bn^+, base peak), 445, 594 (M^+); $[\alpha]_D^{23}=-159.6$ (c 0.80, $CHCl_3$); HRMS calcd for $C_{41}H_{38}O_4$ 594.2770, found 594.2752.

4.1.4. (*R*)-4-(3-(2-Allyloxyethyl)-2-benzyloxy-1-naphthyl)-3-benzyloxy-2-naphthaleneacetaldehyde (5). Benzyl ether **4** (22.6 g, 0.0380 mol) was dissolved in CH_2Cl_2 (170 mL) and Dess–Martin periodinane (19.3 g, 0.0456 mol) was added at 0°C. The resulting mixture was stirred at room temperature for 2 h and then cooled to 0°C. The mixture was diluted with CH_2Cl_2 (200 mL) before saturated aq. $NaHCO_3$ (300 mL) and $Na_2S_2O_3{\cdot}5H_2O$ (20 g) were added. The mixture was stirred at room temperature for 30 min and filtered through a pad of Celite. The filtrate was evaporated to dryness and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate=6/1) to afford aldehyde **5** (17.3 g, y. 77%) as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.58–9.57 (m, 1H), 7.90 (s, 1H), 7.86–7.84 (m, 2H), 7.79 (s, 1H), 7.42–7.36 (m, 2H), 7.28–7.23 (m, 4H), 7.15–7.04 (m, 6H), 6.71–6.69 (m, 4H), 5.93–5.84 (m, 1H), 5.26–5.21 (m, 1H), 5.15–5.12 (m, 1H), 4.61 (d, J=10.8 Hz, 1H), 4.43 (d, J=10.6 Hz, 1H), 4.27 (d, J=10.6 Hz, 1H), 4.26 (d, J=10.8 Hz, 1H), 3.96–3.94 (m, 2H), 3.84–3.65 (m, 4H), 3.23–3.16 (m, 1H), 3.15–3.08 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 199.68, 154.81, 154.19, 137.20, 136.75, 134.91, 134.08, 133.22, 132.70, 130.88, 130.83, 130.74, 130.10, 128.09, 128.00, 127.78, 127.76, 127.72, 127.58, 127.53, 126.74, 126.58, 126.10, 125.89, 125.66, 125.57, 125.21, 124.94, 124.79, 116.80, 75.08, 74.89, 71.80, 70.46, 45.94, 31.38; FTIR (neat) ν 2859, 2726, 1723, 1235, 1102, 751 cm^{-1}; MS (m/z) 91 (Bn^+, base peak), 443, 592 (M^+); $[\alpha]_D^{22}=-161.4$ (c 1.20, $CHCl_3$); HRMS calcd for $C_{41}H_{36}O_4$ 592.2613, found 592.2639.

4.1.5. (*R*,*R*)-3,3″-Oxydiethylene-di-(2,2′-dihydroxy-3′-(2-hydroxyethyl)-1,1′-binaphthyl) (6). To a cooled solution of triethylsilane (Et_3SiH) (6.2 mL, 39.0 mmol) in CH_2Cl_2 (40 mL) were added trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.336 mL, 1.86 mmol) and a solution of aldehyde **5** (11.0 g, 18.6 mmol) in CH_2Cl_2 (30 mL+10 mL rinse) at 0°C. After stirring for 1 h, the reaction was quenched by addition of saturated aq. $NaHCO_3$ (40 mL) and CH_2Cl_2 (40 mL) at 0°C. The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were washed with saturated aq. $NaHCO_3$ (30 mL) and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography (hexane/acetone=8/1→6/1) to afford alcohol **4** (1.30 g, 12%) and the symmetrical ether (7.58 g), which contained inseparable impurity. A THF solution of zinc chloride ($ZnCl_2$) (37.2 mL, 0.5 M) and tetrakis(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$) (1.59 g, 1.38 mmol) were added to a solution of the symmetrical ether (8.08 g) in THF (35.6 mL). Under stirring, tributyltin hydride (11.7 mL, 43.5 mmol) was added slowly (over 1 h) to the mixture before ethyl acetate (60 mL) and water (60 mL) were added. The aqueous layer was separated and extracted with ethyl acetate (20 mL×2). The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent the residue was dissolved in 400 mL of acetonitrile and the solution was extracted with hexane (100 mL×2). The acetonitrile layer was evaporated to dryness and the resulting residue was purified by flash silica gel column chromatography (hexane→hexane/acetone 5/2, and then hexane/ethyl acetate 2/1→1/1) to afford the desired alcohol (6.4 g) as a colorless foam, which contained inseparable impurity. To a solution of the alcohol (300 mg, 0.275 mmol) in THF/liquid ammonia (3 mL/ca. 3 mL) was added lithium (22.9 mg, 3.30 mmol) at −78°C. The resulting deep blue solution was stirred at −78°C for 13 min and the reaction was quenched by addition of ammonium chloride (2 g). After the evaporation of ammonia, water and CH_2Cl_2 were added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography (CH_2Cl_2/acetone 15/1) to afford ligand **6** (234 mg, y. 70%) as a colorless powder. This sample contained 0.06% (w/w) of CH_2Cl_2 and 5% (w/w) of acetone; ^{1}H NMR ($CDCl_3$): δ 7.76 (d, J=7.9 Hz, 2H), 7.67 (d, J=8.2 Hz, 4H), 7.63 (d, J=7.9 Hz, 2H), 7.27–7.21 (m, 4H), 7.17–7.12 (m, 4H), 7.03–7.00 (m, 4H), 6.70 (br, 2H), 6.22 (br, 2H), 3.91–3.74 (m, 8H), 3.16–3.04 (m, 6H), 2.97–2.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 151.82, 151.37, 132.95, 132.89, 130.64, 130.57, 129.15, 128.14, 127.96, 127.65, 126.42, 126.27, 124.43, 124.32, 123.72, 123.66, 113.82, 113.50, 71.65, 62.91, 34.76, 32.23; FTIR (KBr) ν 3511, 3289, 2926, 1626, 1502, 1436, 1200, 1146, 1100, 750 cm^{-1}; MS (m/z) 712 (M^+-H_2O), 730 (M^+); $[\alpha]_D^{22}=+23.9$ (c 1.13, $CHCl_3$); HRMS calcd for $C_{48}H_{42}O_7$ 730.2931, found 730.2921.

4.1.6. (*R*,*R*)-3,3″-Oxydiethylene-di-(2,2′-dihydroxy-3′-(2-hydroxy-2,2-dimethylethyl)-1,1′-binaphthyl) (15). To a solution of the alcohol which was obtained after the deprotection of allyl ethers in the synthesis of ligand **6** (608 mg, 0.557 mmol), in CH_2Cl_2 (2.9 mL), was added Dess–Martin periodinane (543 mg, 1.28 mmol) at 0°C. The resulting mixture was stirred at room temperature for 5 h. The reaction was quenched by the addition of $Na_2S_2O_3{\cdot}H_2O$ (500 mg), saturated aq. $NaHCO_3$ (5 mL) and CH_2Cl_2. After stirring for 1 h, the mixture was filtered through a pad of Celite. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aq. $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was evaporated to dryness and the residue was purified by flash silica gel column chromatography (hexane/acetone 4/1) to afford the aldehyde (496 mg, y. 82%). The aldehyde was dissolved in THF

(6 mL) and the solution was added to a cooled solution of methylmagnesium bromide (1.00 mmol) in THF (3 mL) at 0°C. The mixture was stirred at 0°C for 15 min and quenched by adding aq. HCl (1N, 5 mL). The mixture was extracted with CH_2Cl_2, and the extract was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 2/1→1/1) to afford the secondary alcohol as a mixture of diastereomers (325 mg, y. 73%). This alcohol (325 mg) was then treated with Dess–Martin periodinane (283 mg) in CH_2Cl_2 (5.8 mL) at 0°C, and the stirring was continued for 4 h until saturated aq. $NaHCO_3$ was added. The mixture was filtered and the aqueous layer was extracted with CH_2Cl_2. The extract was washed with saturated aq. $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 3/1) to afford the desired ketone (262 mg, y. 81%) (This ketone was very unstable and should be subjected to the next reaction immediately). Cerium chloride[21] (anhydrous, 326 mg, 0.325 mmol) was dried under reduced pressure for 40 min at 90°C and then for 3 h at 140°C. After suspending cerium chloride in THF (800 μL), it was sonicated for 1 h. The resulting slurry was vigorously stirred for 11 h. A solution of methyllithium (1.16 mL, 1.32 mmol, 1.14 M in ether) was added at −40°C and the resulting mixture was stirred at the same temperature for 2.5 h. The mixture was cooled to −78°C and a solution of the ketone (262 mg) in THF (1.5 mL) was added −78°C. The stirring was continued at −40°C for 10 min until the reaction was quenched by addition of saturated aq. NH_4Cl (3 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were washed with water (twice) and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by flash silica gel column chromatography (hexane/ethyl acetate=3/1) to afford the tertiary alcohol (233 mg). The tertiary alcohol (1.01 g) was dissolved in THF (10 mL)/liq. NH_3 (ca. 10 mL) in a cooled flask (−78°C). Lithium (73.3 mg) was added and the resulting blue solution was stirred at −78°C for 10 min. Ammonium chloride (6 g) was added to quench the reaction and ammonia was allowed to evaporate. Dichloromethane and water were added to the mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, purification was performed by flash silica gel column chromatography (hexane/ethyl acetate and then hexane/acetone) to afford ligand **15** (400 mg) as a pale yellow powder. This sample contained 3% (w/w) of diethyl ether; ^{1}H NMR ($CDCl_3$): δ 7.80 (d, J=7.9 Hz, 2H), 7.71–7.62 (m, 6H), 7.32–7.28 (m, 2H), 7.24–7.13 (m, 6H), 7.09–7.02 (m, 4H), 3.93–3.84 (m, 4H), 3.20–3.03 (m, 8H), 1.30 (s, 6H), 1.24 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 151.94, 151.25, 133.28, 132.93, 132.07, 130.20, 129.17, 129.03, 128.15, 127.69, 127.36, 126.33, 126.14, 124.67, 124.49, 123.61, 123.48, 114.95, 114.73, 72.85, 71.93, 45.44, 32.34, 29.79, 29.57; FTIR (KBr) ν 3520, 3229, 2970, 1626, 1501, 1435, 1203, 1099, 749 cm^{-1}; MS (*m/z*) 750 (M^+ - $2H_2O$), 768 (M^+-H_2O), 786 (M^+); $[\alpha]_D^{23}$=+35.6 (*c* 0.60, $CHCl_3$); HRMS calcd for $C_{48}H_{42}O_7$ 786.3557, found 786.3572.

4.2. General procedure for the aldol reactions promoted by catalyst A

Ligand **6** (27.9 mg, calculated on the basis of ^{1}H NMR; 0.0381 mmol), which contained trace amount of diethyl ether and acetone, was dissolved in toluene/CH_2Cl_2. The solvents were evaporated together with trace amount of diethyl ether and acetone at room temperature under reduced pressure. The residue was dried at room temperature under reduced pressure for 1 h and dissolved in THF (200 μL). This solution was cooled to 0°C, and a solution of lithium iodide (0.0381 mmol, 0.5 M in THF) was added. A solution of lanthanum triisopropoxide (La(O-*i*-Pr)$_3$) (0.0381 mmol, 0.2 M) in THF was added at 0°C and the resulting mixture was stirred for 40 min at the same temperature. Addition of *n*-BuLi (0.114 mmol, 1.62N in hexanes, Aldrich) to this solution was followed by stirring for 30 min at 0°C, and the solvent was evaporated to dryness at the same temperature under reduced pressure. Toluene (200 μL) was added to the residue and the resulting mixture was stirred at room temperature for 10 min. The solvent was evaporated and the residue was dried under reduced pressure at room temperature for 10 min. Toluene (300 μL) was again added to the residue and the resulting mixture was cooled to −30 or −20°C (see Table 6). The ketone (**8a**–**8d**) (2–5 mol equiv. with respect to the aldehyde (0.191 mmol), see Table 6) was added to the stirred mixture of the catalyst. After stirring for 20 min, 2,2-dimethyl-3-phenylpropanal (**7**) (32 μL, 0.191 mmol) was added and the resulting mixture was stirred at −30 or −20°C (see Table 6). The reaction was quenched by addition of aq. HCl (1N, 2 mL) and CH_2Cl_2 (2 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2. The organic layers were combined, washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash silica gel column chromatography to afford the corresponding product (**9a**–**9d**). The ligand (**6**) was recovered by elution with CH_2Cl_2/acetone. The enantiomeric excess was determined by HPLC analysis. Aldol products **9a** and **9b** have been reported (Ref. 9). The absolute configurations of **9c** and **9d** were determined to be *S* on the basis of ^{1}H NMR analysis of the corresponding MTPA esters.[22]

4.2.1. (*S*)-3-Hydroxy-4,4-dimethyl-1,5-diphenyl-1-pentanone (9a, Table 6, entry 1). Yield 70%, 67% ee; mixture of colorless solid and colorless oil; flash column (SiO_2): hexane/ether 15/1; HPLC: DAICEL CHIRALPAK AD, 2-propanol/hexane 1/9, flow 1.0, t_R 8.4 min (*S*) and 10.2 min (*R*).

4.2.2. (*S*)-6,6-Dimethyl-5-hydroxy-7-phenyl-3-heptanone (9b, Table 6, entry 2). Yield 71%, 40% ee; colorless oil; flash column (SiO_2): hexane/ether 10/1; HPLC: DAICEL CHIRALPAK AD, 2-propanol/hexane 5/95, flow 0.2, t_R 37.2 min (*R*) and 42.6 min (*S*).

4.2.3. (*S*)-5-Hydroxy-2,6,6-trimethyl-7-phenyl-3-heptanone (9c, Table 6, entry 3). Yield 62%, 45% ee; colorless oil; flash column (SiO_2): hexane/ether 15/1; ^{1}H NMR ($CDCl_3$) δ 7.26–7.16 (m, 5H), 3.73 (dd, J=1.5, 10.0 Hz, 1H), 3.22 (brs, 1H), 2.79 (d, J=12.3 Hz, 1H), 2.66 (dd, J=1.5, 16.8 Hz, 1H), 2.63–2.55 (m, 1H), 2.51 (dd,

J=10.0, 16.8 Hz, 1H), 2.48 (d, J=12.3 Hz, 1H), 1.09 (d, J=6.7 Hz, 3H), 1.03 (d, J=6.6 Hz, 3H), 0.89 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 216.80, 138.68, 130.81, 127.74, 125.90, 72.94, 44.50, 41.68, 41.33, 37.90, 23.33, 22.25, 18.11, 18.06; FTIR (neat) ν 3502, 2967, 2930, 1703, 1081 cm^{-1}; MS (m/z) 91 (Bn^+, base peak), 115, 230 (M^+-H_2O), 248 (M^+); $[\alpha]_D^{22}$=−10.9 (c 0.4, $CHCl_3$) (40% ee); HRMS calcd for $C_{17}H_{26}O_3$ 248.1776, found 248.1777; HPLC: DAICEL CHIRALPAK AD, 2-propanol/hexane 2/98, flow 0.3, t_R 32.8 min (R) and 35.5 min (S).

4.2.4. (*S*)-6-Hydroxy-2,7,7-trimethyl-8-phenyl-2-octen-4-one (9d, Table 6, entry 4). Yield 66%, 60% ee; colorless solid; flash column (SiO_2): hexane/ether 15/1; ^{1}H NMR ($CDCl_3$) δ 7.26–7.23 (m, 2H), 7.19–7.14 (m, 3H), 6.06–6.05 (m, 1H), 3.76 (d, J=10.1 Hz, 1H), 3.42 (brs, 1H), 2.80 (d, J=12.3 Hz, 1H), 2.62 (dd, J=1.7, 16.7 Hz, 1H), 2.49 (dd, J=10.1, 16.7 Hz, 1H), 2.47 (d, J=12.3 Hz, 1H), 2.14 (d, J=0.8 Hz, 3H), 1.88 (d, J=0.8 Hz, 3H), 0.89 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.10, 156.80, 138.79, 130.85, 127.69, 125.83, 124.02, 73.11, 44.80, 44.50, 37.86, 27.75, 23.30, 22.28, 20.93; FTIR (KBr) ν 3458, 2969, 2929, 1687, 1620 cm^{-1}; MS (m/z) 83 (base peak), 91 (Bn^+), 127, 242 (M^+-H_2O), 260 (M^+); $[\alpha]_D^{24}$=−7.8 (c 0.65, $CHCl_3$) (60% ee); HRMS calcd for $C_{17}H_{24}O_2$ 260.1776, found 260.1764; HPLC: CHIRALPAK AD, 2-propanol/hexane 5/95, flow 1.0, t_R 7.2 min (S) and 11.2 min (R).

4.3. Procedure for the aldol reaction promoted by catalyst B (Table 7)

Ligand **15** (30 mg; 0.0381 mmol, containing 1 mg of diethyl ether on the basis of ^{1}H NMR) was dissolved in toluene. The solution was evaporated to remove diethyl ether at room temperature under reduced pressure. The residue was dried at room temperature under reduced pressure for 1 h and dissolved in toluene (300 μL). The solution was cooled to 0°C and a solution of lithium iodide (0.0381 mmol, 0.5 M in THF) was added. A solution of La(O-i-Pr)$_3$ (191 μL, 0.0381 mmol, 0.2 M in toluene) was added and the resulting mixture was stirred at 0°C for 30 min. The solvent was removed at 0°C under reduced pressure. After drying at 0°C for 40 min, toluene (0.45–1 mL) was added to the resulting residue. The mixture was stirred for 15 min and n-BuLi (71 μL, 0.114 mmol, 1.62N in hexanes) was added at 0°C. After stirring at 0°C for 30 min, the mixture was cooled to −20°C. 3-Pentanone (**13**) (101 μL, 0.953 mmol) was added and the mixture was stirred at −20°C for 20 min. After the addition of 3-benzyloxy-2,2-dimethylpropanal (**12**) (37 μL, 0.191 mmol), the mixture was stirred at −20°C for 141 h. The reaction was quenched by addition of 1N aq. HCl (2 mL) and ether (2 mL). The aqueous layer was separated and extracted twice with ether. The organic layers were combined and washed with brine. After drying over Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was purified by flash silica gel column chromatography to afford *syn*-**14** (2.1 mg, y. 4%) and *anti*-**14** (9 mg, y. 17%). Ligand **15** was eluted with hexane/acetone. The ee of each product was determined by HPLC analysis. The absolute configuration of *anti*-**14** was determined by Mosher's method on the basis of ^{1}H NMR analysis of the corresponding MTPA ester.[22] (±)-*Anti*-**14** was reported in Ref. 20.

4.3.1. (4*R*,5*S*)-7-Benzyloxy-5-hydroxy-4,6,6-trimethyl-3-heptanone (*anti*-14). Colorless oil; purification: flash column (SiO_2), hexane/ethyl acetate=15/1 then preparative TLC, hexane/ether=4/1; ^{1}H NMR ($CDCl_3$) δ 7.35–7.26 (m, 5H), 4.44 (d, J=7.9 Hz, 1H), 4.43 (s, 2H), 3.44 (dd, J=2.8, 7.9 Hz, 1H), 3.26−3.21 (m, 2H), 2.87 (dq, J=2.8, 7.0 Hz, 1H), 2.50 (dq, J=7.0, 18.0 Hz, 1H), 2.44 (dq, J=7.0, 18.0 Hz, 1H), 1.26 (d, J=7.0 Hz, 3H), 0.95 (t, J=7.0 Hz, 3H), 0.91 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 218.53, 138.31, 128.32, 127.55, 127.51, 81.66, 77.22, 73.17, 44.31, 39.87, 35.94, 22.90, 21.50, 17.94, 7.29; FTIR (neat) ν 3462, 2972, 2935, 2875, 1964, 1455, 1102 cm^{-1}; MS (m/z) 91 (Bn^+), 149, 167 (base peak), 279 (MH^+); $[\alpha]_D^{22}$=+4.5 (c 0.28, $CHCl_3$); HRMS calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1883; HPLC: CHIRALCEL OJ, 2-propanol/hexane 2/98, flow 0.5, t_R 15.3 min (5*S*) and 17.1 min (5*R*).

4.3.2. (4*R,5*R**)-7-Benzyloxy-5-hydroxy-4,6,6-trimethyl-3-heptanone (*syn*-14).** Colorless oil; purification: flash column (SiO_2), hexane/ethyl acetate=15/1 then preparative TLC, hexane/ethyl acetate=4/1;^{1}H NMR ($CDCl_3$) δ 7.36–7.27 (m, 5H), 4.49 (s, 2H), 3.89–3.87 (m, 1H), 3.36 (d, J=8.8 Hz, 1H), 3.28 (d, J=8.8 Hz, 1H), 3.26 (d, J=4.1 Hz, 1H), 2.75 (dq, J=4.1, 7.0 Hz, 1H), 2.53 (dq, J=7.1, 17.8 Hz, 1H), 2.47 (dq, J=7.1, 17.8 Hz, 1H), 1.15 (d, J=7.0 Hz, 3H), 1.03 (t, J=7.1 Hz, 3H), 0.93 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 215.11, 137.88, 128.43, 127.74, 127.57, 79.69, 76.17, 73.59, 47.64, 39.19, 34.20, 22.97, 20.79, 12.46, 7.81; FTIR (neat) ν 3495, 2971, 2936, 2875, 1709, 1455 cm^{-1}; MS (m/z) 91 (Bn^+, base peak), 149, 167, 279 (MH^+); HRMS calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1893; HPLC: CHIRALPAK AS, 2-propanol/hexane 1/9, flow 0.5, t_R 9.8 and 11.6 min.

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