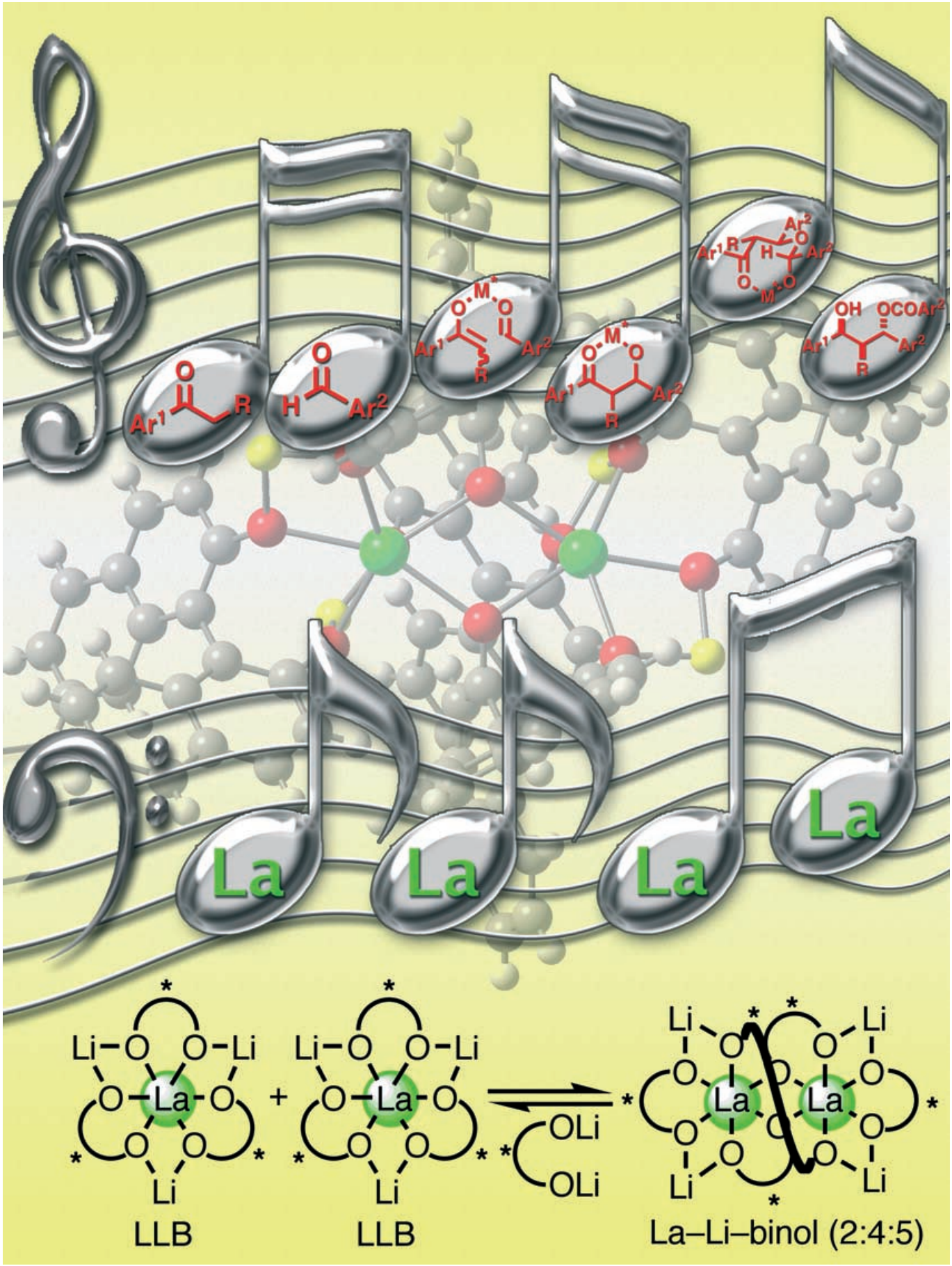


 DOI: 10.1002/chem.200500442

CHEMISTRY
A EUROPEAN JOURNAL

VIP

Dynamic Structural Change of the Self-Assembled Lanthanum Complex Induced by Lithium Triflate for Direct Catalytic Asymmetric Aldol–Tishchenko Reaction

Yoshihiro Horiuchi,[a] Vijay Gnanadesikan,[a] Takashi Ohshima,*[a] Hyuma Masu,[b] Kosuke Katagiri,[b] Yoshihisa Sei,[b] Kentaro Yamaguchi,[b] and Masakatsu Shibasaki*[a]

Abstract: The development of a direct catalytic asymmetric aldol–Tishchenko reaction and the nature of its catalyst are described. An aldol–Tishchenko reaction of various propiophenone derivatives with aromatic aldehydes was promoted by $[LaLi_3(binol)_3]$ (LLB), and reactivity and enantioselectivity were dramatically enhanced by the addition of lithium trifluoromethanesulfonate (LiOTf). First, we observed a dynamic structural change of LLB by the addition of LiOTf using ^{13}C NMR spectroscopy, electronspray ionization mass spectrometry (ESI-MS), and cold-spray ionization mass spectrometry (CSI-MS). X-ray crystallography revealed that the structure of the newly generated self-assembled complex was a binuclear $[La_2Li_4(binaphthoxide)_5]$ complex **6**. A reverse structural change of complex **6** to LLB by the addition of one equivalent of $Li_2(binol)$ was also confirmed by ESI-MS and experimental results. The drastic concentration effects on the direct catalytic asymmetric aldol–Tishchenko reaction suggested that the addition of LiOTf to LLB generated an active oligomeric catalyst species.

Keywords: aldol–Tishchenko reaction · asymmetric catalysis · lanthanum · self-assembly

Introduction

Some enzymes, such as tyrosinase monooxygenases, contain bimetallic centers, and cooperative effects between the two metal atoms are thought to be involved in enzyme activity.[1] Chemical transformations induced by bimetallic (or multimetallic) catalyst systems often have higher reaction rates and selectivities than those induced by monometallic and mononuclear complex catalysts.[2] The synergistic functions of the active metal sites make substrates more reactive and control their position in the transition state, so that the functional groups are proximal to each other. In contrast to bioinorganic catalytic chemistry, the synthesis and utilization of artificial chiral multimetallic catalysts in asymmetric reactions have not been well studied. As a result, the development of a chiral multimetallic catalyst is one of the most important topics in chemical science. The majority of the reported asymmetric catalyses, however, have used monometallic complexes, due to difficulties assembling the requisite metals and ligands in a well-organized manner.

Since the early 1990s, we have reported a series of rare-earth/alkali-metal heterobimetallic complexes that catalyze various asymmetric reactions, such as the nitro–aldol and direct aldol reactions.[3] These heterobimetallic complexes were determined to consist of one rare-earth metal (RE), three 1,1′-bi-2-naphtholates (binol), and three alkali metals (M) (abbreviated REMB) by X-ray crystallography, elemental analysis, mass spectrometry, and NMR spectroscopy (Figure 1).[4] Recently, several other groups also reported various excellent asymmetric catalyses promoted by chiral bi- or multimetallic complexes.[5] The self-assemblies of those systems are thermodynamically controlled to form one predominant assembled structure. On the other hand, dynamic assembly, which interconvert two or more self-assembled units by re-sorting or reorganizing the component species, is often observed in biologic systems. In chemical sys-

[a] Y. Horiuchi, V. Gnanadesikan, Dr. T. Ohshima, Prof. Dr. M. Shibasaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo, Hongo, Bunkyo-ku
Tokyo 113–0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: ohshima@mol.f.u-tokyo.ac.jp
mshibasa@mol.f.u-tokyo.ac.jp

[b] Dr. H. Masu, K. Katagiri, Dr. Y. Sei, Prof. Dr. K. Yamaguchi
Faculty of Pharmaceutical Sciences at Kagawa Campus
Tokushima Bunri University, Shido, Sanuki-city
Kagawa, 769–2193 (Japan)

DOI: 10.1002/chem.200500442

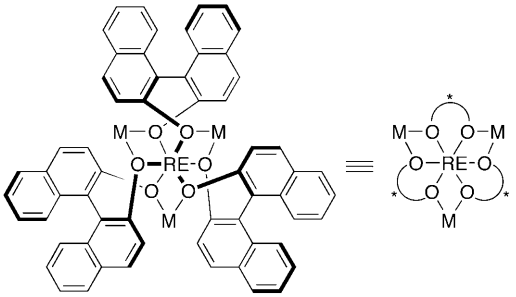


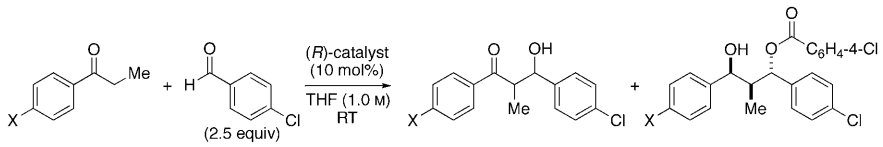
Figure 1. Structure of $[REM_3\{(S)\text{-binol}\}_3]$ ((*S*)-REMB).

tems, although there are several reports on the dynamic assembly of supramolecules,[6] dynamic assembly of asymmetric catalysts is rarely discussed, despite the usefulness of this concept for the development of new artificial chiral multimetallic catalysts.[7] In this manuscript, we report a dynamic structural change between the self-assembled $[LaLi_3(binol)_3]$ (LLB) complex and another unique self-assembled $[La_2Li_4(binol)_5]$ complex by the addition of lithium triflate (LiOTf). The structure of the $[La_2Li_4(binol)_5]$ complex was elucidated by X-ray crystallography. The catalyst development for the direct catalytic asymmetric aldol–Tishchenko reaction[8,9] and active species of the reaction are also discussed.

Results and Discussion

Catalyst development for the direct asymmetric aldol–Tishchenko reaction: The aldol reaction is one of the most powerful and efficient carbon–carbon bond-forming reactions.[10] From the viewpoint of atom economy, the development of a direct catalytic asymmetric aldol reaction is highly desirable.[11] Since our first successful intermolecular, direct catalytic, asymmetric aldol reaction of aldehydes with unmodified ketones using heterobimetallic asymmetric catalyst, we[3h–j] and other groups[12] have attempted this type of direct reaction with great success. In almost all of these direct asymmetric catalyses, however, only limited donors, such as methyl ketones, α-hydroxy ketones, and easily enolizable aliphatic aldehydes, are utilized. Thus, despite the high demand for the development of a direct aldol reaction of ethyl ketones, it remains uninvestigated. Considering the usefulness of the corresponding aldol product of ethyl ketones for the synthesis of 2-methyl-1,3-polyol arrays, we examined various reaction conditions using heterobimetallic asymmetric catalysts; however, all attempts were unsatisfactory. One major reason for this difficulty is a strong tendency toward retro-aldol reactions of the resulting product. Inspired by the earliest report of an SmI_2-catalyzed Tishchenko reaction of β-hydroxy ketone by Evans et al.,[9a] and cross-aldol–Tishchenko reaction catalyzed by an yttrium–salen complex by Morken et al.,[9j] we hypothesized that the metalated aldolates derived from our lanthanoid-based hetrobimetallic catalyst might be activated for the addition of another aldehyde molecule to provide Tishchenko adduct through [3,3]-bond reorganization. Thus, by coupling an irreversible Tishchenko reaction to a reversible aldol reaction of ethyl ketones, we recently overcame this issue and achieved a direct catalytic asymmetric aldol–Tishchenko reaction that provided high product yields and high enantioselectivities. To obtain satisfactory results, tuning of the LLB complex by the addition of LiOTf was essential (Table 1). Although 10 mol% of LLB, which was prepared from $[La(O\text{-}iPr)_3]$,[13] 1,1′-bi-2-naphthol (BINOL = binol-H_2), and BuLi in a ratio of 1:3:3, promoted the reaction with excellent diastereoselectivity (>98:2) and moderate enantioselectivity (64% *ee*), only 20% of the ketone **1a** was converted to a mixture of **3a**[14] and **4a** (~1:1) even after 48 h (Table 1, entry 1). To improve the reactivity, we examined the addition of metal salts. As shown in entries 2–6, all lithium salts greatly accelerated the reaction, but only

Table 1. Effects of lithium salt on direct catalytic asymmetric aldol–Tishchenko reaction.



1a: X = H
1b: X = CF_3

2a (2.5 equiv)

(*R*)-catalyst (10 mol%), THF (1.0 M), RT

3a: X = H
3b: X = CF_3

4a: X = H
4b: X = CF_3

Entry[a]	Ketone	Catalyst	Total yield [%][b]	**3**:**4**[c]	*ee* [%][d]
1	**1a**	(*R*)-LLB	20	~1:1	64
2	**1a**	(*R*)-LLB+LiI (1:3)	75	~1:1	60
3	**1a**	(*R*)-LLB+$LiBF_4$ (1:3)	50	~1:1	44
4	**1a**	(*R*)-LLB+$LiClO_4$ (1:3)	78	~1:1	64
5	**1a**	(*R*)-LLB+LiOTf (1:3)	60	~1:1	78
6	**1a**	(*R*)-LLB+$LiPF_6$ (1:3)	73	~1:1	64
7	**1a**	(*R*)-LLB+NaOTf (1:3)	70	~1:1	62
8	**1a**	(*R*)-LLB+KOTf (1:3)	65	~1:1	73
9	**1a**	(*R*)-LLB+CuOTf (1:3)	40	1:>10	9
10	**1a**	(*R*)-LLB+AgOTf (1:3)	42	1:9	28
11	**1a**	$La(OTf)_3$+(*R*)-BINOL+BuLi (1:3:6)	60	~1:1	86
12	**1b**	(*R*)-LLB+LiOTf (1:3)	89	2:>98	93
13	**1b**	$La(OTf)_3$+(*R*)-BINOL+BuLi (1:3:6)	75	2:>98	88
14	**1b**	$La(OTf)_3$+(*R*)-BINOL+BuLi (1:3:5.6)	80	2:>98	93

[a] All reactions were performed in THF (1.0 M) at room temperature (48 h for **1a**, 24 h for **1b**). [b] Total yield of **3** and **4** was determined by ^1H NMR analysis of the crude sample. [c] The ratio was determined by ^1H NMR analysis of the crude sample. [d] Enantiomeric excess of **4** was determined by HPLC analysis after hydrolysis using NaOMe/MeOH to produce the corresponding diol. Diastereoselectivity of **4** was generally below the detection limit of 500 MHz ^1H NMR (>98/2).

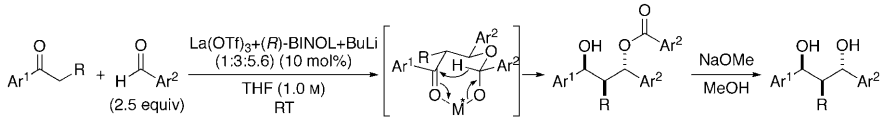
in the case of lithium triflate was the enantioselectivity improved (entry 5, 78% *ee*). Based on the results obtained using other metal triflates (entries 7–10), both lithium cations and triflates were indispensable for obtaining optimal reaction efficiency. The addition of at least three equivalents of LiOTf to one equivalent of LLB was necessary, because decreasing the amount of LiOTf decreased enantioselectivity. Alternatively, the same catalyst system as LLB·3 LiOTf can be prepared by the addition of six equivalents of BuLi to a 1:3 ratio mixture of $[La(OTf)_3]$ and BINOL. This new catalyst preparation method improved enantioselectivity (entry 11) and by changing the ketone to **1b** superior levels of substrate conversion, Tishchenko selectivity, and asymmetric induction were realized (entry 13). Because even a slight excess of BuLi resulted in decreased enantioselectivity, the 1:3:5.6 $[La(OTf)_3]$/BINOL/BuLi catalyst system was set as the standard condition (entry 14).

Under the optimized conditions, the direct catalytic asymmetric aldol–Tishchenko reaction of a variety of both aldehydes **2** and ketones **1** smoothly proceeded to give **4** and, after hydrolysis using NaOMe in MeOH, the corresponding diols **5** were obtained in up to 96% isolated yield and up to 95% *ee* (Table 2). It is worth noting that the reaction proceeded with the same efficiency even when propyl ketone **1h** (entry 16) and butyl ketone **1i** (entry 17) were used, achieving the asymmetric direct aldol-type reaction of propyl and butyl ketones for the first time.

Dynamic structural change of LLB induced by LiOTf—formation of a novel binuclear lanthanum complex: In our previous studies, the structure of several self-assembled REMB complexes, such as $[LaNa_3\{(S)\text{-binol}\}_3(thf)_6(H_2O)]$ (LSB), were elucidated by X-ray crystallography.[4c] Recently, Aspinall et al.[15] also reported the preparation of anhydrous crystal of several REMB. In all cases, the obtained crystals possessed the Λ configuration rather than the Δ configuration when the complex was prepared from (*S*)-BINOL. X-ray crystallography of LLB has not yet been achieved. Based on laser-desorption/ionization time-of-flight mass spectrometry (LDI-TOF MS) and NMR spectroscopy,[4a] the structure of LLB is similar to that of LSB (Figure 1) and even in solution phase one La^{3+} ions, three binol ligands, and three Li^+ ions are predominantly assembled to the structure. After obtaining excellent results in a direct catalytic asymmetric aldol–Tishchenko reaction by using the LLB·3 LiOTf catalyst system, we were interested in the effects of LiOTf on the catalyst structure. During the investigation of the above asymmetric catalysis, we observed the formation of a colorless prismatic crystal from the catalyst solution prepared from $La(OTf)_3$, BINOL, and BuLi in a ratio of 1:3:5.6 in THF (0.2 M) after a long storage period. The structure of the crystal was unequivocally determined by X-ray crystallography to be a novel binuclear $[La_2Li_4(binaphthoxide)_5]$ complex (**6**), which exists as a 1:1 mixture of adducts **6a** and **6b** (Figure 2) with eight and nine coordinated THF molecules, respectively. In the complex, two binol units and one THF coordinate to each La metal, and both La metals are bridged by another binol ligand. Another structural feature of the complex is that each oxygen atom of the binol moiety is bridged to the oxygen of another binol unit by La metal and/or Li metal. This is the first example from X-ray crystallography of rare-earth/alkali-metal/binol heterobimetallic complexes other than those with the REMB-type structure shown in Figure 1.

To further investigate the crystals of **6**, a new preparation method of **6** was developed. In the standard procedure for the preparation of the catalyst solution (Scheme 1, procedure A), after addition of hexane solution of BuLi to a mixture of $La(OTf)_3$ and BINOL in THF, all solvents were removed under reduced pressure, and the residual solid was dissolved by THF to make 0.2 M stock solution of the catalyst. In the new procedure for the preparation of the crystal (procedure B), the mixture of $La(OTf)_3$, BINOL, and BuLi[16] was allowed to stand in 0.15 M THF/hexane (7:8) without concentration. After 12 h storage at room temperature, identical colorless prismatic crystals of **6** were obtained in approximately 40% yield with high reproducibility. In spite of

Table 2. Direct catalytic asymmetric aldol–Tishchenko reaction of various substrates.



1 2 4 5

Entry	Ketone **1**	Aldehyde **2**	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**1b**: $Ar^1=C_6H_4$-4-CF_3, R = Me	**2a**: $Ar^2=C_6H_4$-4-Cl	60	95	93
2	**1b**: $Ar^1=C_6H_4$-4-CF_3, R = Me	**2b**: $Ar^2=C_6H_4$-4-Br	48	96	95
3	**1b**: $Ar^1=C_6H_4$-4-CF_3, R = Me	**2c**: $Ar^2=C_6H_4$-4-F	72	85	92
4	**1b**: $Ar^1=C_6H_4$-4-CF_3, R = Me	**2d**: $Ar^2=C_6H_4$-4-Me	94	67	92
5	**1b**: $Ar^1=C_6H_4$-4-CF_3, R = Me	**2e**: $Ar^2=C_6H_5$	84	95	91
6	**1b**: $Ar^1=C_6H_4$-4-CF_3, R = Me	**2f**: $Ar^2=C_6H_4$-3-Br	48	92	86
7	**1b**: $Ar^1=C_6H_4$-4-CF_3, R = Me	**2g**:$Ar^2=C_6H_4$-3-OMe	72	65	85
8	**1b**: $Ar^1=C_6H_4$-4-CF_3, R = Me	**2h**: Ar^2 = 2-naphthyl	80	67	88
9	**1b**: $Ar^1=C_6H_4$-4-CF_3, R = Me	**2i**: Ar^2 = 3-furyl	84	77	93
10	**1b**: $Ar^1=C_6H_4$-4-CF_3, R = Me	**2j**: Ar^2 = 3-thienyl	84	82	94
11	**1c**: $Ar^1=C_6H_4$-4-Br, R = Me	**2b**: $Ar^2=C_6H_4$-4-Br	48	70	85
12	**1d**: $Ar^1=C_6H_4$-3-Cl, R = Me	**2a**: $Ar^2=C_6H_4$-4-Cl	48	60	84
13	**1e**: $Ar^1=C_6H_4$-3,4-Cl_2, R = Me	**2a**: $Ar^2=C_6H_4$-4-Cl	48	81	88
14	**1f**: $Ar^1=C_6H_4$-3,5-Cl_2, R = Me	**2a**: $Ar^2=C_6H_4$-4-Cl	48	73	85
15	**1g**: $Ar^1=C_6H_4$-3,5-F_2, R = Me	**2a**: $Ar^2=C_6H_4$-4-Cl	48	77	87
16	**1h**: $Ar^1=C_6H_4$-4-CF_3, R = Et	**2b**: $Ar^2=C_6H_4$-4-Br	90	90	88
17	**1i**: $Ar^1=C_6H_4$-4-CF_3, R = Pr	**2b**: $Ar^2=C_6H_4$-4-Br	90	88	87

[a] Isolated yield of the corresponding diol **5**. [b] Determined by HPLC analysis after converting to the corresponding diol. The diastereoselectivity was generally below the detection limit of 500 MHz ^{1}H NMR (>98:2).

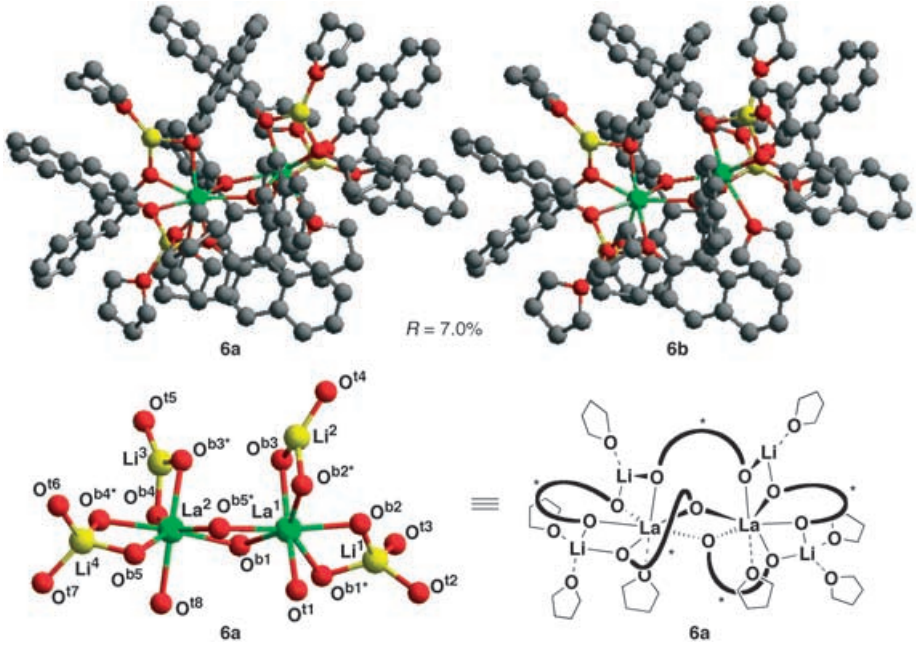
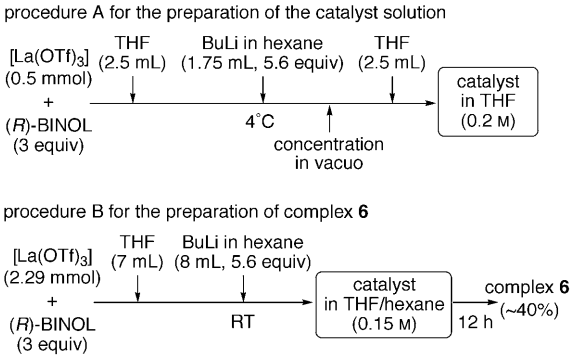


Figure 2. Crystal structure of $[La_2Li_4\{(R)\text{-binol}\}_5(thf)_8]$ **6a** (top left) and $[La_2Li_4\{(R)\text{-binol}\}_5(thf)_9]$ **6b** (top right). The crystal unit is composed of **6a** and **6b** (1:1). Hydrogen atoms are omitted for clarity. Selected bond lengths of **6a** (Å): La^1–O^{b1}, 2.474; La^1–O^{b1*}, 2.429; La^1–O^{b2}, 2.439; La^1–O^{b2*}, 2.467; La^1–O^{b3}, 2.417; La^1–O^{b5*}, 2.500; La^1–O^{t1}, 2.584; Li^1–O^{b1*}, 1.901; Li^1–O^{b2}, 1.894; Li^1–O^{b2}, 1.901; Li^1–O^{t2}, 1.936; Li^1–O^{t3}, 2.020; Li^2–O^{b2*}, 1.827; Li^2–O^{b3}, 1.862; Li^2–O^{t4}, 1.836.



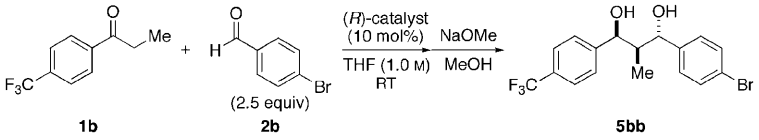
Scheme 1. Best preparative procedures for the catalyst solution (top) and the crystalline complex **6** (bottom).

intensive efforts, no crystal was obtained in the absence of LiOTf, suggesting that LiOTf was essential for crystal formation; however, LiOTf was not involved in the crystal.

Mechanistic studies: The results shown in Table 1 revealed that LiOTf had an important role in the highly enantioselective aldol–Tishchenko reaction. In addition, a new La/Li/binol (2:4:5) complex **6** was obtained from a catalyst solution prepared from $La(OTf)_3$, BuLi, and BINOL. Thus, we were interested in the role of LiOTf and the efficiency of crystalline complex **6** in the asymmetric catalysis. When ketone **1b** and aldehyde **2b** were used as substrates, clear beneficial effects of LiOTf were observed (Table 3, entries 1–4). On the other hand, the crystalline complex **6** on its own was a less effective catalyst (entry 5). This low selectivity might be due to the absence of LiOTf, and as expected, the addition of LiOTf to complex **6** greatly improved enantioselectivity of the reaction to 80% *ee* (entry 6). The addition of one equivalent of Li_2(binol) to complex **6** (entry 7), which was assumed to change the composition from La/Li/binol (2:4:5) to La/Li/binol (2:6:6 = 1:3:3 as in LLB), gave almost identical results to those achieved with LLB (entry 1). As shown in entries 8 and 9, the addition order of LiOTf to a mixture of (*R*)-**6**, (*R*)-BINOL, and BuLi did not affect either yield or enantioselectivity, suggesting rapid equilibrium of the lanthanum complexes. The addition of either extra BuLi (entry 10) or extra Li_2(binol) (entries 11 and 12) dramatically decreased enantioselectivity (vide infra).

To gain insight into the structure of the lanthanum complexes in solution, we performed NMR spectroscopy on the catalyst. Probably due to structural similarity and/or rapid equilibrium, there was almost no difference between the solution of LLB in $[D_8]$THF and that of crystalline complex **6** in $[D_8]$THF on the ^{1}H and ^{13}C NMR spectra (Figure 3a). On the other hand, following the addition of LiOTf to those solutions, a new set of signals appeared in the ^{13}C NMR spectra in both cases (Figure 3b), suggesting the generation of new species in the presence of LiOTf. To obtain more information on the lanthanum complexes, we performed electrospray ionization mass spectrometry (ESI-MS) and cold-spray ionization mass spectrometry (CSI-MS) analyses. Almost no peak was observed by ESI-MS of solutions of the lanthanum complexes in THF due to the low ionization efficiency in aprotic solvent; therefore, ESI-MS analysis was performed by using solution of the complex in a THF/*i*PrOH (2:1) mixture (ca. 0.7 mM due to limitations of the ESI apparatus). As shown in Figure 4a, the La/Li/binol (1:1:2) complex ($m/z = 721$) and LLB ($m/z = 1019$) were detected in the LLB solution as major peaks (see Table 3, entry 1). In the ESI-MS analysis of the solution of the crystalline complex **6**, a peak assigned to the La/Li/binol (2:4:5) complex **6** ($m/z = 1733$) was detected and the relative intensity of the peak of the LLB+binol−Li_2 complex ($m/z = 1317$) increased (Figure 4b, see also Table 3, entry 5). The addition of one equivalent of Li_2(binol) to complex **6** made the peak at 1733 disappear, resulting in an ESI-MS spectrum

Table 3. Direct asymmetric aldol–Tishchenko reaction catalyzed by several lanthanum complexes.



1b 2b 5bb

Entry	Catalyst	La/Li/binol/LiOTf	Yield [%][a]	*ee* [%][b]
1	(*R*)-LLB	1:3:3:0	75	79
2	(*R*)-LLB+LiOTf (1:3)	1:3:3:3	92	92
3	$La(OTf)_3$+(*R*)-BINOL+BuLi (1:3:6)	1:3:3:3	87	92
4	$La(OTf)_3$+(*R*)-BINOL+BuLi (1:3:5.6)	1:2.6:3:3	96	95
5[c]	(*R*)-**6**	2:4:5:0	83	59
6[c]	(*R*)-**6**+LiOTf (1:6)	2:4:5:6	92	80
7[c]	(*R*)-**6**+(*R*)-BINOL+BuLi (1:1:2)	2:6:6:0 (1:3:3:0)	79	81
8[c][d]	(*R*)-**6**+(*R*)-BINOL+BuLi+LiOTf (1:1:2:6)	2:6:6:6 (1:3:3:6)	90	92
9[c][e]	(*R*)-**6**+(*R*)-BINOL+BuLi+LiOTf (1:1:2:6)	2:6:6:6 (1:3:3:6)	93	90
10[c][e]	(*R*)-**6**+(*R*)-BINOL+BuLi+LiOTf (1:1:3:6)	2:7:6:6	98	34
11[e]	(*R*)-LLB+(*R*)-BINOL+BuLi+LiOTf (1:0.5:1:3)	1:4:3.5:3	82	68
12[e]	(*R*)-LLB+(*R*)-BINOL+BuLi+LiOTf (1:1:2:3)	1:5:4:3	88	24

[a] Isolated yield of the corresponding diol **5bb**. [b] Determined by HPLC analysis after converting to the corresponding diol. The diastereoselectivity was generally below the detection limit of 500 MHz ^{1}H NMR (> 98:2). [c] 5 mol% of crystalline complex **6** (10 mol% on La) was used. [d] LiOTf was added after the addition of BuLi to (*R*)-**6** and BINOL in THF. [e] LiOTf was added before the addition of BuLi.

almost identical to that of LLB (Figure 4c). In conjunction with results shown in Table 3 (entry 7), the addition of Li_2-(binol) to crystalline complex **6** promoted a dynamic structural change of the La/Li/binol (2:4:5) complex, returning to LLB. Similar to ^{13}C NMR analysis, the addition of LiOTf to the solution of LLB and the complex **6** produced several new peaks assigned to LLB+LiOTf ($m/z=1175$), LLB+2LiOTf ($m/z=1331$), LLB+HLi(binol)+LiOTf ($m/z=1467$), and so forth (Figure 4d and e, see also Table 3, entries 2 and 6, respectively). In addition, the ESI-MS spectrum of $[La(OTf)_3]$+BINOL+BuLi (1:3:5.6) (Figure 4f) was almost identical to those shown in Figure 4d and e.[17] Additional valuable information on the actual structure of the lanthanum complexes in solution was obtained by CSI-MS. CSI-MS was developed by one of the authors for the characterization of labile ionic compounds, such as labile self-assembling nanosize metal complexes.[18] Because the CSI apparatus features a drying gas (N_2) cooling device to maintain the temperature of the capillary and spray below −20 °C, CSI-MS allows for easy and precise characterization of labile self-assembling compounds. Another beneficial feature of CSI-MS is that highly concentrated solution of the sample in THF (2 mM) can be directly used for analysis without the addition of a protic solvent, although it is still a very dilute solution compared with that used for asymmetric catalysis (200 mM). CSI-MS of the solution of LLB in THF mainly showed peaks of LLB as several THF adducts ($n=0$–3) with peaks of LLB+Li_2(binol) (Figure 5a). In striking contrast to ESI-MS analysis, the relative intensity of the peak of LLB dramatically decreased in the presence of LiOTf (Figure 5b), indicating the formation of other self-assembling lanthanum complexes. In the case of a solution of the crystalline complex **6** in THF, very complicated spectra were obtained due to the existence of possible THF adducts of various self-assembled complexes in solution.[19]

The information obtained from the above-mentioned experimental and spectroscopic results allowed us to make the following deductions:

1) Based on the ^{13}C NMR spectra (Figure 3c) and ESI-MS (Figure 4d–f), the addition of LiOTf promoted a dynamic structural change in the LLB complex to generate several new self-assembled lanthanum complexes, presumably including the active species of the asymmetric catalysis. Moreover, CSI-MS (Figure 5b) indicated that the LLB complex underwent a high degree of structural change.

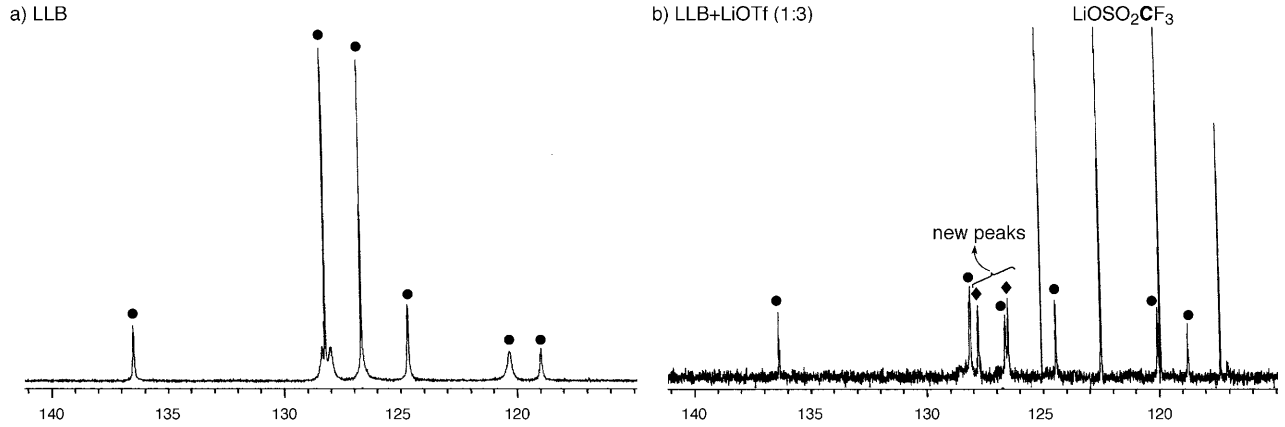


Figure 3. ^{13}C NMR spectra of the lanthanum complexes in [D_8]THF.

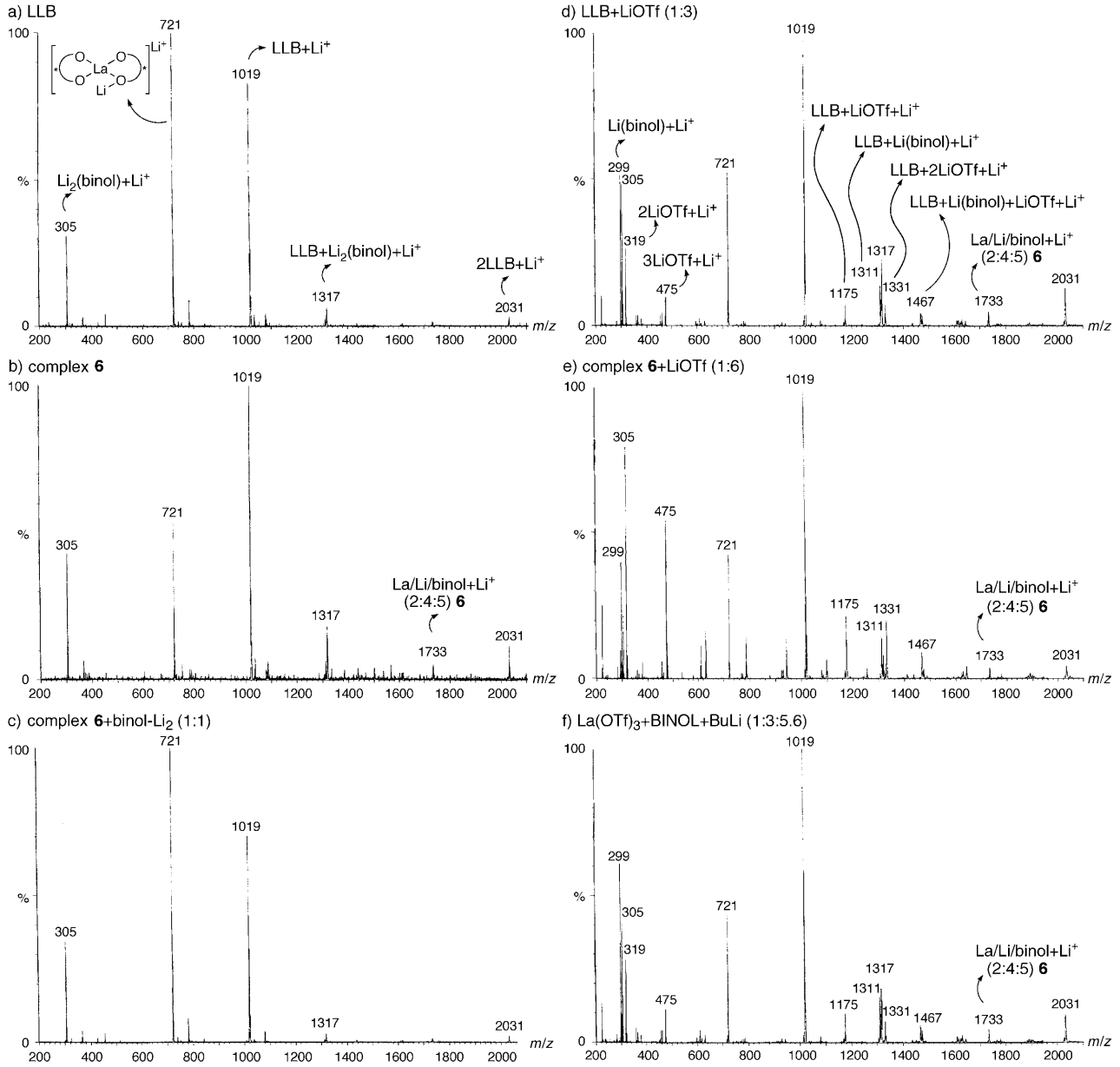


Figure 4. ESI-MS of the lanthanum complexes in THF/*i*PrOH. a) LLB; b) complex **6**; c) complex **6**+Li_2(binol) (1:1); d) LLB+LiOTf (1:3); e) complex **6**+LiOTf (1:6); f) $La(OTf)_3$+BINOL+BuLi (1:3:5.6). *m/z*: 299 $[HLi(binol)+Li]^+$, 305 $[Li_2(binol)+Li]^+$, 319 $[2LiOTf+Li]^+$, 475 $[3LiOTf+Li]^+$, 721 [La/Li/binol(1:1:2)+Li]$^+$, 1019 $[LLB+Li]^+$, 1175 $[LLB+LiOTf+Li]^+$, 1311 $[LLB+HLi(binol)+Li]^+$, 1317 $[LLB+Li_2(binol)+Li]^+$, 1331 $[LLB+2LiOTf+Li]^+$, 1467 $[LLB+HLi(binol)+LiOTf+Li]^+$, 1733 [La/Li/binol(2:4:5)+Li]$^+$, 2031 $[2LLB+Li]^+$.

2) Because of the formation of a large quantity of the complex **6** from the LiOTf-containing catalyst solution (Figure 2), a certain amount of this La/Li/binol (2:4:5) complex would exist in the active solution [Eq. (1)], although the precise abundance ratio of **6** is unclear (Table 3, Entry 5).
3) Based on the experimental results (Table 3, entry 7) and ESI-MS (Figure 4c), the addition of one equivalent of Li_2(binol) to the complex **6** in the absence of LiOTf promotes a reverse dynamic structural change of **6** to LLB [Eq. (2)].
4) As in Equation (1), with the formation of complex **6** from two equivalents of LLB, the same amount of Li_2(binol) is generated. Li_2(binol) promotes the aldol–Tishchenko reaction to give almost racemic products, so that Li_2(binol) itself does not exist in the active catalyst solution and transforms to a more oligomeric complex such as the $(LLB)_l$·**6**$_m$·$\{Li_2(binol)\}_n$·$(LiOTf)_x$ complex, as detected on ESI-MS (Figure 4d–f). When Li_2(binol) was added to a solution of LLB+LiOTf (1:3), there was a significant decrease in enantioselectivity (Table 3, entry 11, 0.5 equiv of Li_2(binol), 68% *ee* and entry 12, 1 equiv of Li_2(binol), 24% *ee*).

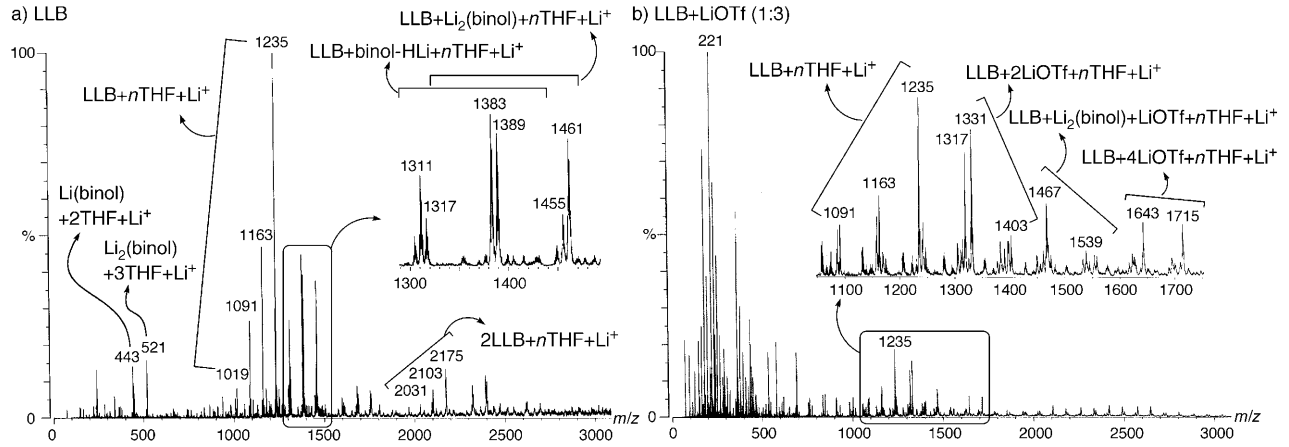
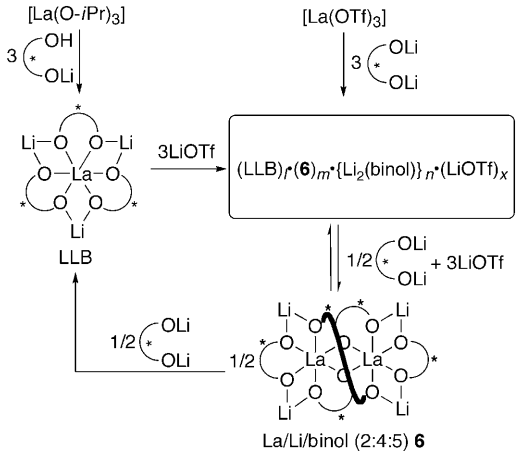


Figure 5. CSI-MS of the lanthanum complexes in THF. a) LLB; b) LLB+LiOTf (1:3). *m*/*z*: 443 $[HLi(binol)+2THF+Li]^+$, 521 $[Li_2(binol)+3THF+Li]^+$, 1019 $[LLB+Li]^+$, 1091 $[LLB+THF+Li]^+$, 1163 $[LLB+2THF+Li]^+$, 1235 $[LLB+3THF+Li]^+$, 1311 $[LLB+HLi(binol)+Li]^+$, 1317 $[LLB+Li_2(binol)+Li]^+$, 1331 $[LLB+2LiOTf+Li]^+$, 1383 $[LLB+HLi(binol)+THF+Li]^+$, 1389 $[LLB+Li_2(binol)+THF+Li]^+$, 1403 $[LLB+2LiOTf+THF+Li]^+$, 1455 $[LLB+HLi(binol)+2THF+Li]^+$, 1461 $[LLB+Li_2(binol)+2THF+Li]^+$, 1467 $[LLB+Li_2(binol)+LiOTf+Li]^+$, 1539 $[LLB+Li_2(binol)+LiOTf+THF+Li]^+$, 1643 $[LLB+4LiOTf+Li]^+$, 1403 $[LLB+4LiOTf+THF+Li]^+$.

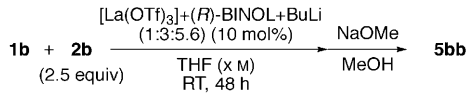
From the above deductions, we propose a scheme of dynamic self-assembling of the lanthanum complexes with LiOTf and the candidates of active species of the asymmetric aldol–Tishchenko reaction (Scheme 2). One reasonable



Scheme 2. Proposed dynamic self-assembling of the lanthanum complexes and active species.

candidate for the active species is an LLB–LiOTf complex such as the LLB•LiOTf and LLB•2 LiOTf complexes detected by ESI-MS and CSI-MS. Other possible candidates are some oligomeric species, which consist of LLB, Li_2(binol), the complex **6**, and LiOTf, or a cooperative catalyst system of all of those species. In addition, the results of the drastic concentration effects on both reactivity and enantioselectivity support the possibility of an oligomeric active species (Table 4).[20]

Table 4. Concentration effects on the direct catalytic asymmetric aldol–Tishchenko reaction.



Entry	Conc [M]	Yield [%][a]	*ee* [%][b]
1	1.0	96	95
2	0.7	82	86
3	0.5	66	78
4	0.2	22	77

[a] Isolated yield of the corresponding diol **5bb**. [b] Determined by HPLC analysis after converting to the corresponding diol. The diastereoselectivity was generally below the detection limit of 500 MHz ^{1}H NMR (>98:2).

Conclusion

We successfully developed a direct catalytic aldol–Tishchenko reaction using the lanthanum catalyst as a useful method to overcome the retroaldol reaction problem of a direct aldol reaction of ethyl ketone. LiOTf promoted a dynamic structural change of LLB to generate a novel binuclear [La_2Li_4(binaphthoxide)$_5$] complex (**6**), whose structure was determined by X-ray crystallography. We demonstrated that the self-assembled lanthanum complex **6** dynamically changed its structure to that of LLB (by the addition of Li_2(binol)) and an active species of the asymmetric catalysis (by the addition of Li_2(binol) and LiOTf). Results of ESI-MS, CSI-MS, ^{13}C NMR spectroscopy, and experiments of concentration effects suggested that the active species is an oligomeric species $(LLB)_r$•**6**$_m$•$\{Li_2(binol)\}_n$•$(LiOTf)_x$.

Experimental Section

General: 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 spectra. For ^{1}H NMR spectra chemical shifts in $CDCl_3$ were reported downfield from TMS ($\delta = 0$ ppm) or relative to $CHCl_3$ ($\delta = 7.26$ ppm) or THF ($\delta = 3.58$ ppm) as internal references. For ^{13}C NMR spectra, chemical shifts were reported downfield from TMS ($\delta = 0$ ppm) or relative to $CHCl_3$ ($\delta = 77.00$ ppm) or THF ($\delta = 67.40$ ppm) as internal references. Optical rotations were measured on a JASCO P-1010 polarimeter. EI mass spectra were measured on JEOL JMS-DX303, JEOL JMS-AX505W or JMS-BU20 GCmate. CSI Mass spectral measurements were performed by two-sector(BE) mass spectrometer (JMS-700,JEOL) equipped with a cold-spray ionization(CSI) source. The X-ray crystallographic analysis was under taken using Bruker Samrt1000 CCD diffractometer with $Mo_{K\alpha}$ radiation at 90 K. The enantiomeric excess (*ee*) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980: detector, 875-UV or UV-970. Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise stated. [La(O-*i*Pr)$_3$] was purchased from Kojundo Chemical Laboratory Co., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214 (Japan). Other reagents were purified by the usual methods.

Procedure for the formation of complex 6: Lanthanum trifluoromethanesulfonate (1.342 g, 2.29 mmol, purity 99.999%, Aldrich) and (*R*)-(+)-1,1′-bi-2-naphthol (1.964 g, 6.86 mmol) were placed in a 30 mL flask under air. The flask was charged with argon and THF (7 mL) was added. *n*BuLi in hexanes (8 mL, 12.8 mmol, 1.6 M, Aldrich) was then added dropwise to the mixture at room temperature over a period of 50 min, while maintaining the reaction temperature below 35 °C. After stirring for 10 min, the reaction mixture was left standing for 12 h; prismatic crystals were formed. Under argon atmosphere, the supernatant was removed by syringe (20 G) and then the crystals were washed with THF (2 mL × 3). The residual crystals were dried for 1 h by means of a needle (21 G) attached to a vacuum pump. The crystals were collected and stored under argon atmosphere. The absence of LiOTf was confirmed by ^{13}C NMR analysis of this product.

X-ray crystallographic analysis: A crystal coated with paratone-N was mounted on glass fiber. The crystal structure was solved by using SHELXS 97 (Sheldrick, 1997). Refinement was carried out by full-matrix least-squares methods (on F^2) with anisotropic temperature factors for non-hydrogen atoms after omission of redundant and space-group-forbidden data. In all of the structures H atoms were included as their calculated positions. For refinement of the structure and structure analysis, the program package SHELXTL was used. CCDC 269103 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data request/cif.

Preparation of catalyst solution of complex 6+BINOL+BuLi+LiOTf (Table 3, entry 9): In a glovebox under argon atmosphere, (*R*)-BINOL (51 mg, 0.178 mmol) and LiOTf (167 mg, 1.068 mmol) were added to the complex **6** (384 mg, 0.178 mmol) in a 20 mL round-bottom flask. THF (4 mL) was added to the mixture. After stirring for 10 min at room temperature, *n*BuLi (0.22 mL, 0.356 mmol, 1.6 M in hexanes, Aldrich) was added dropwise at 4 °C to give a white suspension. The reaction mixture was gradually warmed to room temperature and after 12 h became a homogeneous solution. The solution was cooled to −78 °C and the solvent was slowly removed by means of a needle (21 G) attached to a vacuum pump. The cooling bath was then removed and the reaction mixture was slowly allowed to come to room temperature. After the reaction mixture became a dry solid (approximately 2 h), the vacuum was replaced with argon gas and THF (1.8 mL) was added to make a 0.2 M catalyst solution based on lanthanum metal.

General procedure for the direct catalytic asymmetric aldol–Tishchenko reaction: A solution of the catalyst (0.25 mL, 0.2 M in THF based on lanthanum metal) was slowly added to a mixture of **1b** (101 mg, 0.50 mmol) and **2b** (231 mg, 1.25 mmol) in THF (0.25 mL) at 4 °C. After stirring for 48 h at room temperature, the reaction mixture was quenched by the addition of 1 M aqueous HCl. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/acetone 25:3) to afford aldol–Tishchenko ester **4bb** as a colorless oil. The product was dissolved in MeOH (3 mL), NaOMe (100 mg, 1.85 mmol) was added, and the resulting mixture was stirred for 1 h. The reaction mixture was poured into brine and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 400:70 to 400:30) to afford the diol **5bb** as a single diastereomer (96% yield for 2 steps). HPLC analysis conditions [column: DAICEL CHIRALPAK AD-H, eluent: hexane/isopropanol 92:8, flow rate: 1.0 mL min^{-1}, detector: 254 nm, $t_R = 11.0$ (minor (1*R*,2*R*,3*R*)) 14.9 min (major (1*S*,2*S*,3*S*))].

Mass spectrometry analyses: The 0.1 M LLB solution (20 μL) was diluted with dry THF (3 mL) and dry 2-propanol (1 mL). The diluted solution was directly used for ESI-MS analysis. ESI-MS analysis was performed in cation mode under the following conditions: capillary: 3.5 kV; cone: 150 V; source temp: 90 °C; desolvation temp: 90 °C; syringe pump: 30 μL min^{-1}. For CSI-MS the LLB solution (0.1 M) was diluted with THF to give a 2 mM solution, which was directly used for CSI-MS analysis. Typical measurement conditions were as follows: acceleration voltage: 5.0 kV; needle voltage: 3.4 kV; orifice voltage: 248 V; ringlens voltage: 283 V; resolution (10% valley definition): 1000; sample flow-rate: 17 μL min^{-1}; spray temperature: −25 to 0 °C.

Acknowledgements

This work was supported by RFTF, Grant-in-Aid for Encouragement for Young Scientists (A), and Grant-in-Aid for Specially Promoted Research from the Japan Society for the Promotion of Science (JSPS) and Ministry of Education, Culture, Sports, Science and Technology (MEXT). We thank Ryo Takita for his ESI-MS technical support.

[1] a) E. I. Solomon, U. M. Sundaram, T. E. Machonkin, *Chem. Rev.* **1996**, *96*, 2563; b) E. I. Solomon, M. D. Lowery, *Science* **1993**, *259*, 1575; c) R. H. Holm, P. Kennepohl, E. I. Solomon, *Chem. Rev.* **1996**, *96*, 2239; d) K. A. Magnus, H. Ton-That, J. E. Carpenter, *Chem. Rev.* **1994**, *94*. 727.

[2] a) T. Ooi, M. Takahashi, K. Maruoka, *J. Am. Chem. Soc.* **1996**, *118*, 11307; b) Y. Yamaguchi, N. Suzuki, T. Mise, Y. Wakatsuki, *Organometallics* **1999**, *18*, 996; c) A. K. El-Qisairi, H. A. Qaseer, *J. Organomet. Chem.* **2002**, *659*, 50; d) P. L. Gendre, M. Picquet, P. Richard, C. Moïse, *J. Organomet. Chem.* **2002**, *643–644*, 231.

[3] For general reviews, see: a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187; b) *Multimetallic Catalysts in Organic Synthesis* (Eds.: M. Shibasaki, Y. Yamamoto), Wiley-VCH, Weinheim, **2004**; for nitroaldol reactions, see: c) H. Sasai, T. Suzuki, N. Itoh, S. Arai, M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 2657; d) H. Sasai, T. Suzuki, N. Itoh, M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 851; e) H. Sasai, N. Itoh, T. Suzuki, M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 855; f) H. Sasai, W.-S. Kim, T. Suzuki, M. Shibasaki, *Tetrahedron Lett.* **1994**, *35*, 6123; g) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388; for direct aldol reactions, see: h) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871; i) N. Yoshikawa, T. Suzuki, M. Shibasaki, *J. Org. Chem.* **2002**, *67*, 2556; j) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168; for other reactions, see: k) E. Emori, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 4043; l) K. Funabashi, Y. Saida, M. Kanai, T. Arai, H. Sasai, M. Shibasaki, *Tetrahedron Lett.* **1998**, *39*, 7557; m) J. Tian, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Org.*

Lett. **2003**, *5*, 3021; n) H. Sasai, E. Emori, T. Arai, M. Shibasaki, *Tetrahedron Lett.* **1996**, *37*, 5561.

[4] a) H. Sasai, T. Suzuki, N. Itoh, K. Tanaka, T. Date, K. Okamura, M. Shibasaki, *J. Am. Chem. Soc.* **1993**, *115*, 10372; b) T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai, M. Shibasaki, *Chem. Eur. J.* **1996**, *2*, 1368; c) H. Sasai, T. Arai, Y. Satow, K. N. Houk, M. Shibasaki, *J. Am. Chem. Soc.* **1995**, *117*, 6194.

[5] a) B. M. Trost, A. Fettes, B. T. Shireman, *J. Am. Chem. Soc.* **2004**, *126*, 2660; b) B. M. Trost, V. S. C. Yeh, *Angew. Chem.* **2002**, *114*, 889; *Angew. Chem. Int. Ed.* **2002**, *41*, 861; c) J. Gao, R. A. Zingaro, J. H. Reibenspies, A. E. Martell, *Org. Lett.* **2004**, *6*, 2453; d) S. Kii, K. Maruoka, *Tetrahedron Lett.* **2001**, *42*, 1935; e) S. Kii, T. Hashimoti, K. Maruoka, *Synlett* **2002**, 931; f) V. Annamalai, E. F. DiMauro, P. J. Carroll, M. C. Kozlowski, *J. Org. Chem.* **2003**, *68*, 1973; g) K. Ohno, Y. Kataoka, K. Mashima, *Org. Lett.* **2004**, *6*, 4695; h) C. J. Sander, K. M. Gillespie, D. Bell, P. Scott, *J. Am. Chem. Soc.* **2000**, *122*, 7132.

[6] a) T. Yamamoto, A. M. Arif, P. J. Stang, *J. Am. Chem. Soc.* **2003**, *125*, 12309; b) Y. K. Kryschenko, S. R. Seidel, D. C. Muddiman, A. I. Nepomuceno, P. J. Stang, *J. Am. Chem. Soc.* **2003**, *125*, 9647; c) A. Petitjean, H. Nierengarten, A. van Dorosselaer, J.-M. Lehn, *Angew. Chem.* **2004**, *116*, 3781; *Angew. Chem. Int. Ed.* **2004**, *43*, 3695; d) B. Hasenknopf, J.-M. Lehn, N. Boumediene, E. Leize, A. van Dorsselaer, *Angew. Chem.* **1998**, *110*, 3458; *Angew. Chem. Int. Ed.* **1998**, *37*, 3265; e) A. Hori, K. Yamashita, M. Fujita, *Angew. Chem.* **2004**, *116*, 5126; *Angew. Chem. Int. Ed.* **2004**, *43*, 5016.

[7] Some self-assembled catalysts are known, see: a) V. F. Slagt, P. W. M. N. Leeuwen, J. N. H. Reek, *Chem. Commun.* **2003**, 2474; b) S. J. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 12948; c) H. Jiang, A. Hu, W. Lin, *Chem. Commun.* **2003**, 96; d) Y. N. Belokon', A. J. Blacker, P. Carta, L. A. Clutterbuck, M. North, *Tetrahedron* **2004**, *60*, 10433; e) X. Li, G. Lu, W. H. Kwok, A. S. C. Chan, *J. Am. Chem. Soc.* **2002**, *124*, 12636; f) M. D. Rossa, M. R. Acocella, A. Soriente, A. Scettri, *Tetrahedron: Asymmetry* **2001**, *12*, 1529; g) K. Daikai, T. Hayano, R. Kino, H. Furuno, T. Kagawa, J. Inanaga, *Chirality* **2003**, *15*, 83; h) J. M. Takacs, D. S. Reddy, S. A. Moteki, D. Wu, H. Palencia, *J. Am. Chem. Soc.* **2004**, *126*, 4494.

[8] V. Gnanadesikan, Y. Horiuchi, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 7782.

[9] a) D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447; b) C. M. Mascrenhas, M. O. Duffy, S. Y. Liu, J. P. Morken, *Org. Lett.* **1999**, *1*, 1427; c) P. M. Bodnar, J. T. Shaw, K. A. Woerpel, *J. Org. Chem.* **1997**, *62*, 5674; d) I. Simpura, V. Nevalainen, *Tetrahedron Lett.* **2001**, *42*, 3905; e) R. Mahrwald, B. Costisella, *Synthesis* **1996**, 1087; f) O. Loog, U. Maeorg, *Tetrahedron: Asymmetry* **1999**, *10*, 2411; g) C. Schneider, M. Hansch, *Chem. Commun.* **2001**, 1218; h) T. Ooi, T. Miura, Y. Itagaki, H. Ichikawa, K. Maruoka, *Synthesis* **2002**, 279; i) C. Schneider, M. Hansch, T. Weide, *Chem. Eur. J.* **2005**, *11*, 3010; for asymmetric aldol–Tishchenko reactions, see: j) C. M. Mascarenhas, S. P. Miller, P. S. White, J. P. Morken, *Angew. Chem.* **2001**, *113*, 621; *Angew. Chem. Int. Ed.* **2001**, *40*, 601; k) C. Schneider, M. Hansch, *Synlett* **2003**, 837; l) J. Mlynarski, M. Mitura, *Tetrahedron Lett.* **2004**, *45*, 7549; for a review, see: m) R. Mahrwald, *Curr. Org. Chem.* **2003**, *7*, 1713.

[10] General reviews, see: a) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2004**, *33*, 65; b) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325; c) A. Bernardi, C. Gennari, J. M. Goodman, I. Paterson, *Tetrahedron: Asymmetry* **1995**, *6*, 2613.

[11] a) P. W. H. Chan, Y. Yamamoto, *Chemtracts* **2000**, *13*, 14; b) M. Shibasaki, H. Sasai, T. Arai, T. Iida, *Pure Appl. Chem.* **1998**, *70*, 1027; c) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570; d) W. Notz, F. Tanaka, C. F. Barbas, *Acc. Chem. Res.* **2004**, *37*, 580.

[12] a) B. M. Trost, E. R. Silcoff, H. Ito, *Org. Lett.* **2001**, *3*, 2497; b) B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367; c) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003; d) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798; e) B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395; f) T. Ooi, M. Kameda, M. Taniguchi, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 9685.

[13] [La(O-*i*Pr)$_3$] was purchased from Kojundo Chemical Laboratory Co., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214 (Japan).

[14] Aldol products were racemic with no diastereoselectivity, determined by ^{1}H NMR analysis and HPLC analysis.

[15] a) H. C. Aspinall, J. L. M. Dwyer, N. Greeves, A. Steiner, *Organometallics* **1999**, *18*, 1366; b) H. C. Aspinall, J. F. Bickley, J. L. M. Dwyer, N. Greeves, R. V. Kelley, A. Steiner, *Organometallics* **2000**, *19*, 5416.

[16] 1.6 M *n*BuLi in hexanes from Aldrich was used. It contains trace amounts of LiCl; information on the exact amount of LiCl was not available.

[17] In comparison of Figure 4d and f with Figure 4e, there were several additional peaks appeared in Figure 4e. The reason why the reaction with complex **6** and LiOTf gave lower enantioselectivity might be that a racemic reaction was promoted by unknown species.

[18] a) S. Sakamoto, M. Fujita, K. Kim, K. Yamaguchi, *Tetrahedron* **2000**, *56*, 955; b) Y. Yamanoi, Y. Sakamoto, T. Kusukawa, M. Fujita, S. Sakamoto, K. Yamaguchi, *J. Am. Chem. Soc.* **2001**, *123*, 980.

[19] On CSI-MS of the complex **6**+LiOTf and La(OTf)$_3$+BINOL+BuLi (1:3:5.6), only small peaks were detected in high-molecular-weight region (MW > 1000).

[20] The present direct catalytic asymmetric aldol–Tishchenko reaction involves two individual reactions (a non-selective aldol reaction and a highly enantio- and diastereoselective Tishchenko reaction), thus kinetic studies were difficult.

Received: April 20, 2005
Published online: July 8, 2005