Linked-BINOL: An Approach towards Practical Asymmetric Multifunctional Catalysis

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Abstract: The development and application of a novel linked-1,1′-binaphthol (linked-BINOL) as an approach towards practical asymmetric multifunctional catalysis is described. Linked-BINOL was first designed to increase the stability of a Ga-Li-BINOL complex against ligand exchange with 4-methoxyphenol. An oxygen-containing linked-BINOL, which is a semi crown ether, was effective in both promoting the formation of a monomer complex and increasing the stability of the Ga-Li complex. A Ga-Li-linked-BINOL complex promoted the epoxide opening reaction in up to 96% enantiomeric excess (ee). Second, based on the X-ray structural information of the Ga-Li-linked-BINOL complex, we designed a more stable lanthanide linked-BINOL complex. An air-stable, storable, and reusable La-linked-BINOL complex promoted the Michael reaction in up to >99% ee. The catalyst activity remained unchanged after storage under air for 4 weeks. Calculations suggested that the linked-BINOL would function as a pentadentate ligand in a lanthanum complex, thus efficiently improving the stability of the complex. Finally, the linked-BINOL was applied to a new homobimetallic multifunctional catalysis. A dinuclear Zn-Zn-linked-BINOL complex promoted the enantio- and diastereoselective direct aldol reaction in up to 99% ee, where one Zn cation might function as a Lewis acid and the other Zn-phenoxide as a Brønsted base.

Keywords: asymmetric catalysis; BINOL; bridging ligands; bimetallic complex; lanthanum; multifunctional catalysis.

1 Introduction

Synthesis of chiral compounds using catalytic asymmetric processes is one of the most important and most rapidly growing areas in modern synthetic organic chemistry.[1] Such catalytic and asymmetric processes are more economic and more environmentally benign than processes that use stoichiometric amounts of reagents. In our continuing research project towards the development of practical and atom-economic[2] asymmetric catalysis, we have demonstrated the usefulness of multifunctional cooperative asymmetric catalysis in a variety of enantioselective transformations,[3] such as the nitroaldol reaction,[4] direct aldol reaction,[5] Michael reaction,[6] Michael-aldol reaction,[7] hydrophosphonylation,[8] hydrophosphination,[9] protonation,[10] epoxidation of enones,[11] epoxide opening reaction,[12] Diels – Alder reaction,[13] nitro-Mannich reaction,[14] cyanosilylation of aldehydes[15] and ketones,[16] Strecker reaction,[17] and Reissert reaction.[18] There have been great achievements in the field of asymmetric catalysis with regard to the concept of multifunctional cooperative catalysis, and many groups are now employing a multifunctional strategy in the development of new asymmetric catalysts.[19,20] From a practical point of view, however, some of the heterobimetallic multifunctional asymmetric complexes still have room for improvement, such as in catalyst amount and stability. To overcome these problems and to widen the scope of multifunctional bimetallic catalysis, we launched a new project for the development of a novel chiral ligand. This review focuses on our efforts towards the development and application of a novel linked-BINOL, which opened up the new possibility of multifunctional asymmetric catalysis.

2 Heterobimetallic Multifunctional Asymmetric Complexes

1,1′-Binaphthols (BINOLs) have an important role as chiral ligands in modern asymmetric catalysis,[21] incorporating various types of Lewis acidic metals. Our heterobimetallic complexes also consist of two or three BINOLs, Lewis acidic central metals, and alkali metals, the structures of which were unequivocally determined using NMR, LDI-TOF mass spectrometry, and X-ray crystal analysis (Figure 1).[22]

Mechanistic studies[22] suggest that the heterobimetallic complexes promote the various asymmetric reactions via dual activation of both substrates (nucleophiles and electrophiles). The Brønsted base moiety of the catalysts (alkali metal binaphthoxide) activates the nucleophiles, such as nitroal-

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Takashi Ohshima was born in 1968 in Ehime, Japan and received his Ph. D. from The University of Tokyo in 1996 under the direction of Professor Masakatsu Shibasaki. On the following year, he joined Otsuka Pharmaceutical Co., Ltd. for one year. After two years as a postdoctoral fellow at The Scripps Research Institute with Professor K. C. Nicolaou (1997–1999), he returned to Japan and joined Professor Shibasaki's group in The University of Tokyo as an assistant professor. He has received the Fujisawa Award in Synthetic Organic Chemistry, Japan (2001).

Masakatsu Shibasaki was born in 1947 in Saitama, Japan, and received his Ph. D. from the University of Tokyo in 1974 under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University. In 1977 he returned to Japan and joined Teikyo University as an associate professor. In 1983 he moved to Sagami Chemical Research Center as a group leader, in 1986 to Hokkaido University as a professor, and in 1991 to the University of Tokyo as a professor. He was a visiting professor at Philipps-Universität Marburg during 1995. He has received the Pharmaceutical Society of Japan Award for Young scientists (1981), the Inoue Prize for Science (1994), the Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (1998), the Pharmaceutical Society of Japan Award (1999), Molecular Chirality Award (1999) and the Naito Foundation Research Prize for 2001 (2001). He will receive ACS Arthur C. Cope Senior Scholar Award in 2002. His research interests include asymmetric catalysis, including asymmetric Heck reactions and reactions promoted by asymmetric bifunctional complexes, and also the medicinal chemistry of biologically significant compounds.

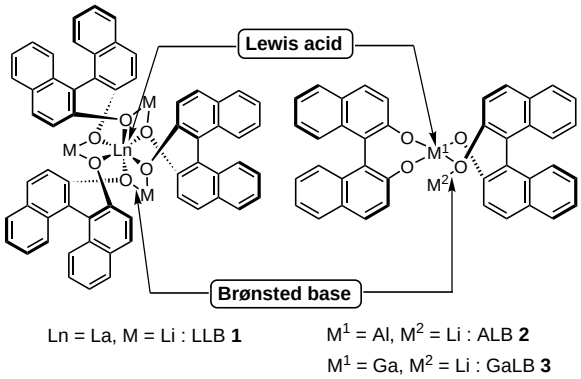


Figure 1. Heterobimetallic multifunctional complexes.

kanes, by deprotonation. At the same time, the Lewis acid moieties (lanthanides, aluminum or gallium center metals) activate the electrophiles. The dual activation occurs at positions controlled by the asymmetric catalyst, and so the substrates react with the other substrates from a defined direction, resulting in high enantioselectivity.

Although the heterobimetallic complexes work well in various asymmetric reactions,[3] the structural features of two or more ligands incorporated in the complexes sometimes cause a severe stability problem. In the worst cases, some heterobimetallic complexes decompose under the reaction conditions due to irreversible ligand exchange between BINOLs and nucleophiles, resulting in a lower chemical yield and/or enantiomeric excess of the desired products. For example, we previously reported the enantioselective epoxide opening reaction with 4-methoxyphenol promoted by the GaLibis(binaphthoxide) (GaLB) complex (Figure 1, **3**).[12b] In this reaction, GaLB afforded enantiomerically enriched 1,2-diol monoethers, which are versatile chiral building blocks, in only moderate chemical yields despite the use of more than 20 mol % of the catalyst. The poor reactivity of GaLB **3** was attributed to a ligand exchange between BINOL and 4-methoxyphenol, and the preparation of a more stable Ga complex was an effective solution to this problem. Thus, we first attempted to increase the stability of the GaLB complex **3** through the development of new chiral ligands.

3 Ga-Li-linked-BINOL Complex: Design and Development of a Novel Linked-BINOL

To increase the stability of the GaLB **3**, we hypothesized that by linking the two BINOL units in GaLB, the complex would become more stable against ligand exchange without any adverse effects on the asymmetric environment.[23,24] One of the key issues for designing a linked-BINOL is the length and flexibility of its linker. The linker should be relatively short to somewhat limit the flexibility of BINOL units, because the geometry is likely to be crucial for enantioselectivity. In addition, a linker that is too rigid would also be unfavorable, because the asymmetric environment would be negatively affected by a rigid linker and, in the worst cases, even the formation of the desired 1:2 (gallium:BINOL unit) complex would be prevented.

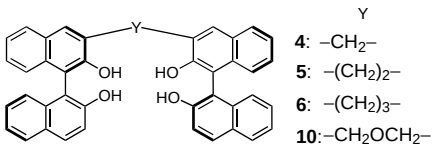


Figure 2. Carbon-linked-BINOLs (**4**–**6**) and linked-BINOL (**10**).

We first designed carbon-linked-BINOLs (Figure 2, **4**–**6**) to evaluate the effect of the linker. We prepared Ga-Li-carbon-linked-BINOL complexes using $GaCl_3$ (1 mol eq), **4**, **5**, or **6** (1 mol eq), and BuLi (4 mol eq). In contrast to our initial assumption, however, none of these were effective in the enantioselective epoxide opening reaction of cyclohexene oxide (**7a**) with 4-methoxyphenol (**8**). Ga-Li carbon-linked-BINOL complexes afforded the epoxide opening product **9a** in only low yield and enantiomeric excess (with **4**: yield 28%, 27% ee; with **5**: yield 43%, 10% ee; with **6**: yield 40%, 1% ee). These unsatisfactory results might be due to the undesired oligomeric structure of these linked-BINOL complexes. With a carbon linker, each BINOL unit of the linked-BINOLs can rotate freely during the formation of Ga complexes. As shown in Figure 3, the conformation (A) seems favored due to the steric and electronic repulsion, thus the Ga-Li-carbon-linked-BINOL would result in undesired oligomeric species, the asymmetric environment of which should be different from that of the monomeric GaLB **3**.

To overcome this problem, we designed a novel oxygen-containing linked-BINOL (Figure 2, **10**). This new linked-BINOL **10** was designed based on reports by Cram et al. regarding crown ethers incorporating chiral-BINOL units.[25] We assumed that the oxygen atom in the linker would coordinate to gallium during the Ga complex formation, thus helping the formation of the desired monomeric Ga complex. In contrast to crown ether-type cyclic ligands, this linked-BINOL, which is a kind of semi-crown ether linked only with one side of the BINOL units (3–3″ position), has a vacant coordination site around the gallium center metal. Thus, the Ga-Li-linked-BINOL complex should be active as a Lewis acid towards epoxides. The preparation of **10** is shown in Scheme 1.

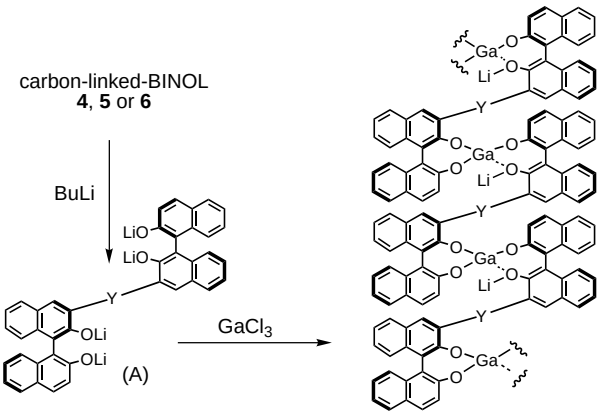
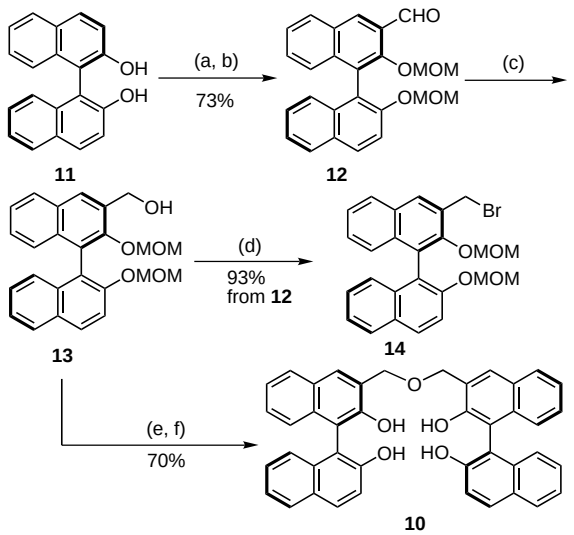


Figure 3. Possible oligomeric structure of Ga-Li carbon-linked-BINOL complexes.

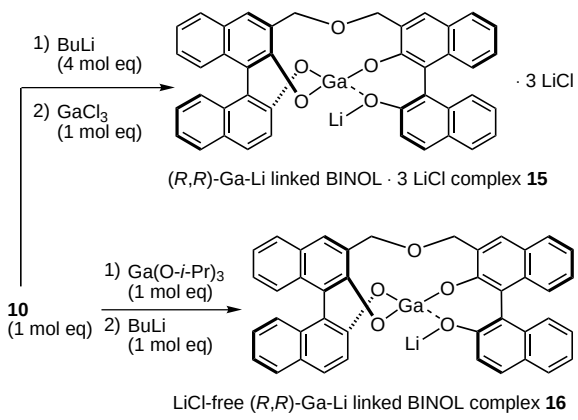


(a) NaH, MOMCl, DMF, 0 °C, 5 h; (b) i) BuLi, TMEDA, THF, –78 °C to 0 °C; ii) DMF, –78 °C to 0 °C; (c) $NaBH_4$, THF, MeOH, 0 °C, 15 min; (d) i) MsCl, toluene, AcOEt, 0 °C, 90 min; ii) LiBr, DMF, rt, 10 min; (e) i) NaH, THF, DMF, 0 °C, 60 min; ii) **14**, rt, 64 h; (f) TsOH–H_2O, CH_2Cl_2, MeOH, 40 °C, 36 h.

Scheme 1. Synthesis of the oxygen-containing (*R*,*R*)-linked-BINOL **10.**

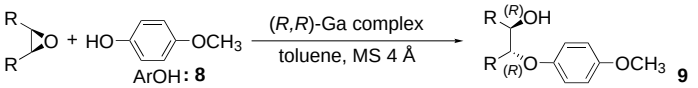
Starting from optically active (*R*)-BINOL,[26] the (*R*,*R*)-linked-BINOL **10** was obtained easily on a gram scale [7 steps, total yield 47% from (*R*)-BINOL].

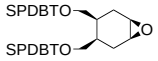
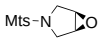
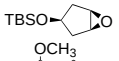
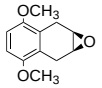
Complex **15** [prepared from $GaCl_3$ (1 mol eq), **10** (1 mol eq), and BuLi (4 mol eq): Scheme 2] was far more stable than GaLB **3**, and very effective for the epoxide opening reaction. The results are summarized in Table 1. Unlike GaLB, complex **15** was stable even in the presence of excess 4-methoxyphenol (**8**) and/or at higher temperature. By using complex **15**, the reaction proceeded smoothly with reduced levels of catalyst for the first time. Under optimized conditions (toluene, 75 °C, 3 eq of **8**), cyclohexene oxide (**7a**) reacts with 4-methoxyphenol (**8**) smoothly in the presence of 10 mol % catalyst, half the amount of GaLB, to afford **9a** (36 h, yield 94%, 85% ee, entry 4). Entries 1 through 5 show that the new catalyst **15** (10 mol %) afforded products (**9a**–**9e**) in analogous enantiomeric excess



Scheme 2. Preparation of (*R*,*R*)-Ga-Li-linked-BINOL · 3 LiCl complex **15** and the LiCl-free (*R*,*R*)-Ga-Li-linked-BINOL complex **16.**

Table 1. Enantioselective ring opening of various *meso*-epoxides with 4-methoxyphenol (**8**) promoted by the Ga-Li-linked-BINOL complex (**15**) and GaLB (**3**).



entry	epoxide		product	Ga-Li-linked-BINOL (10 mol %) ArOH (eq)	temp (°C)	time (h)	yield[a] (%)	ee[b] (%)	GaLB (20 mol %) ArOH (eq)	temp (°C)	time (h)	yield[a] (%)	ee[b] (%)
1[c]		**7a**	**9a**	3.0	75	96	72	91	1.2	50	72	48	93
2		**7b**	**9b**	3.0	60	63	88	85	1.2	50	72	75	86
3		**7c**	**9c**	3.0	75	108	82	66	1.2	50	72	31	67
4		**7d**	**9d**	3.0 (1.2)[d]	75 (75)[d]	36 (117)[d]	94 (80)[d]	85 (91)[d]	1.2	50	72	74	87
5		**7e**	**9e**	3.0	60	96	72	79	1.2	50	96	34	80
6		**7f**	**9f**	3.0	60	160	77[e]	78[e]	1.2	50	160	51[e]	90[e]
7		**7g**	**9g**	3.0	60	48	67	87	–	–	–	–	–
8		**7h**	**9h**	2.0	60	70	85	96	–	–	–	–	–
9		**7i**	**9i**	3.0	60	140	72	91	–	–	–	–	–

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The reaction was run on 0.5 mmol scale at 0.25 M in epoxide.
[d] 3 mol % of catalyst was used.
[e] 30 mol % of catalyst was used. Mts = 2,4,6-trimethylbenzenesulfonyl.

(66–91%) but in much higher chemical yields (72–94%) compared to GaLB (20 mol %, Table 1). After the reaction ligand **10** was recovered by extracting with 1M aqueous NaOH. This situation was very different from that with GaLB **3** because BINOL itself reacted with epoxide and the recovery of BINOL was impossible. The Ga-Li-linked-BINOL **15** was also effective for epoxides **7g**–**7i** (entries 7–9). Importantly, using only 3 mol % of catalyst **15**, epoxide **7d** gave **9d** in 80% yield (TON = 26.3) and 91% ee, however the reaction time was long (117 h, entry 4 in parenthesis). All of these results can be attributed to the stability of the Ga-Li-linked-BINOL complex **15**, obtained by linking the two BINOL units in GaLB **3**. The stable catalyst **15** remained unchanged during the course of the reaction, whereas GaLB **3** decomposed due to severe ligand exchange with 4-methoxyphenol (**8**) and the reaction then stopped.

Having improved stability of the Ga-Li complex against ligand exchange with the newly developed linked-BINOL **10**, we then attempted to determine the structure of the linked-BINOL complex because the structural information should provide clues for applying the linked-BINOL **10** to other catalytic asymmetric reactions. Although both ^{13}C NMR and (–)-LDI TOF mass spectrometry [Ga-Li-linked-BINOL **15**: $(M - Li^+) = 679$ for ^{69}Ga (base peak)] data suggested the assumed monomeric structures, all attempts to obtain X-ray grade crystals of the Ga-Li-linked-BINOL complex **15**, prepared from $GaCl_3$, were unsuccessful. After several trials, we obtained X-ray grade crystal of the LiCl-free Ga-Li-linked-BINOL complex **16**, prepared from $Ga(O\text{-}i\text{-}Pr)_3$ (1 mol eq), linked-BINOL **10** (1 mol eq), and BuLi (1 mol eq) (Scheme 2). The LiCl-free Ga-Li-linked-BINOL complex **16** also promoted the reaction to give **9a** in good yield (85%), although the enantiomeric excess (74%) was somewhat lower. As shown in Figure 4, Ga-Li-linked-BINOL complex has a monomeric tetracoordinated structure, which is similar to the structure of the Al-Li-bis(binaphthoxide)$(thf)_3$ complex (ALB: **2** in Figure 1).[6a] The crystal structure clearly indicates that, as planned initially, the linked-BINOL has no adverse effects on the asymmetric environment constructed by the two BINOL units in GaLB **3**. Instead, the linked-BINOL **10** provides stability against ligand exchange by linking the two BINOL units. On the other hand, in contrast to our initial assumption, the oxygen atom in the linker does not coordinate to the gallium metal center, at least in the ground state. The different results obtained by carbon-linked-BINOL **6** (**9a**, 1% ee) and linked-BINOL **10** (**9a**, 91% ee) indicate that the oxygen in the linker should have a key role in the present system. The oxygen in the linker might provide properties similar to a crown ether to the ligand, thus promoting formation of the desired monomeric species similar to GaLB **3** during the complex formation.

The proposed mechanism of the epoxide opening reaction with 4-methoxyphenol (**8**) is shown in Scheme 3. The gallium

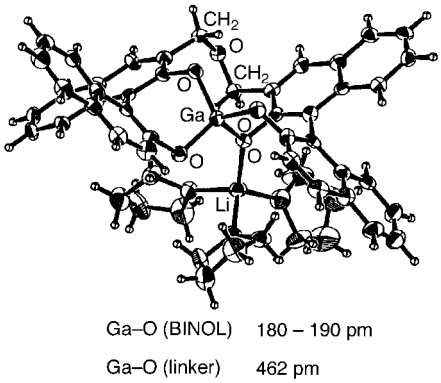
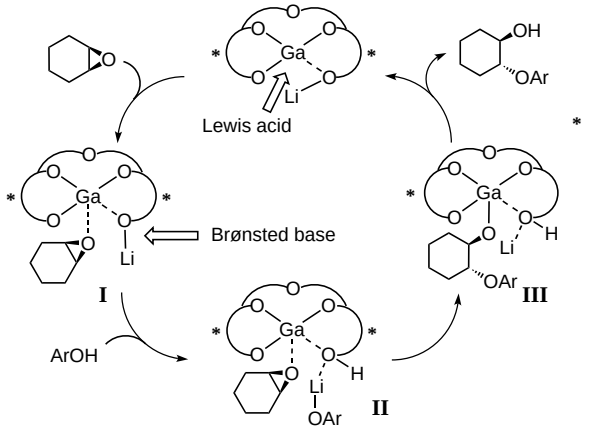


Figure 4. X-ray structure of LiCl-free Ga-Li-linked-BINOL **16.**

metal center acts as a Lewis acid and activates epoxides (I), while at the same time the lithium binaphthoxide moiety functions as a Brønsted base to activate 4-methoxyphenol (**8**: ArOH) (II). The activated nucleophile would then react with epoxide to give III. Proton exchange between gallium alkoxide and an aromatic hydroxy proton leads to the epoxide opening adduct and regeneration of the catalyst. On the basis of the X-ray structure of LiCl-free (*R*,*R*)-Ga-Li-linked-BINOL complex **16** and the absolute configuration of the product obtained using this catalyst [(*R*,*R*)-**9a**], enantiomeric induction in the present system is explained by assuming the transition state shown in Figure 5. Due to the steric hindrance, the epoxide coordinating to gallium would be fixed in the (A) form rather than the (B) form. Lithium binaphthoxide then activates and controls the orientation of 4-methoxyphenol (**8**: ArOH) so that lithium phenoxide attacks the epoxide selectively from one side to afford the (*R*,*R*)-1,2-diol monoether.



Scheme 3. Working model for the ring opening of cyclohexene oxide with 4-methoxyphenol (**8**: ArOH) catalyzed by Ga-Li-linked-BINOL complex.

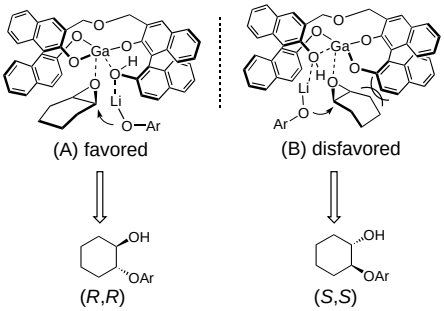
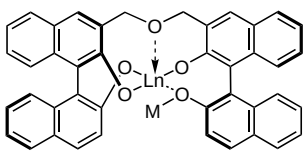


Figure 5. Working transition state model for *meso*-epoxide opening reaction promoted by Ga-Li-linked-BINOL (**15**).

4 La-linked-BINOL Complex: Development of Stable, Storable and Reusable Asymmetric Catalyst for Catalytic Asymmetric Michael Reaction

The development of efficient methods to facilitate the recovery and reuse of asymmetric catalysts remains an important goal in organic chemistry. To address this issue, intensive efforts have been devoted to develop soluble and insoluble polymer-supported asymmetric catalysts.[27,28] Only a few reusable non-polymer-supported homogeneous asymmetric catalysts[29] have been developed, however, due to the difficulty of recovery for recycling. In the previous section, we demonstrated that the linked-BINOL **10** effectively stabilized the Ga-Li complex against ligand exchange with a nucleophile under the reaction conditions.[23a] In terms of catalyst stability, however, group XIII metal complexes such as Al and Ga complexes are still unsatisfactory for recovery and reuse because of their high reactivity to moisture.[30]

To develop more stable, even against moisture, asymmetric catalysts, we examined a combination of rare earth metals (lanthanides: Ln) and the linked-BINOL **10**. We expected that rare earth metals would be useful as Lewis acidic metal centers in the linked-BINOL complex. This combination (Ln-M-linked-BINOL) should lead to much more stable complexes, considering the following aspects. (1) The Ln phenoxide complex is relatively stable against moisture.[31] (2) The ionic radius and coordination number of lanthanides are larger than that of gallium (Ga^{3+}: ionic radius 61 – 76 pm, coordination number 4 – 6, La^{3+}: ionic radius 103 – 136 pm, coordination number 6 – 12).[32] Thus, in contrast to the LiCl-free Ga-Li-linked-BINOL complex **16** (Figure 4), the oxygen in the linker is likely to coordinate to the rare earth metal in an Ln-M-linked-BINOL complex, and linked-BINOL **10** might function as a pentadentate ligand (Figure 6). To evaluate this hypothesis, we performed computational optimization of the Ln-linked-BINOL complex. On the basis of the structure of the Ga-Li-linked-BINOL complex **16**, a model compound (La linked biphenol complex) was computationally optimized.



	ionic radius	coordination site
La	103 – 136 pm	6 – 12
Ga	61 – 76 pm	4 – 6

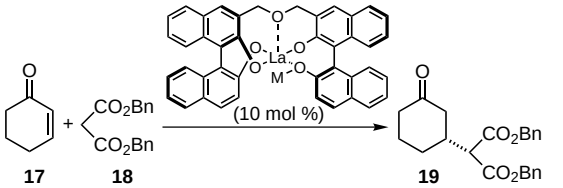
Figure 6. Expected structure of (*R*,*R*)-Ln-M-linked-BINOL complex.

First, the initial structure of the La-linked-BINOL complex was obtained by substitutions of the center metal (from Ga to La) and the counter cation of the phenolic oxygen (from Li to H) in the Ga-Li-linked-BINOL complex **16**. The lowest energy conformation of La-linked-BINOL was obtained by using several conformational search methods followed by molecular mechanics minimization [UNIVERSAL forcefield[33] (v. 1.02) calculation performed on Cerius[2] (Molecular Simulations Inc.)]. Next, the initial structure of the La-linked biphenol complex was obtained by simplifying the optimized structure of the La-linked-BINOL complex. The geometry optimization of the La-linked biphenol complex to minima was performed using *ab initio* calculation [HF/LanL2DZ[34] level with Gaussian 98[35] (Gaussian Inc.)]. Although the optimization did not reach a stationary point due to the high flexibility of La-linked biphenol, the distance between lanthanum and oxygen in the linker ranged from 262 to 269 pm after nine calculation steps (Figure 7). The result indicated that the distance between lanthanum and oxygen in the linker should be nearly equal to that between lanthanum and phenolic oxygen (258–265 pm). As we expected, the oxygen atom in the linker could also function as a coordinative moiety and thus, the linked-BINOL **10** could function as pentadentate ligand toward lanthanum.

In recent years, the catalytic asymmetric Michael reaction promoted by chiral metal complexes has been recognized as an efficient method for enantioselective carbon-carbon bond formations. Although efficient catalytic asymmetric Michael reactions have been achieved by our group[3d,6,7,36] and others,[37–39] there is still a big demand for improvement in terms of generality and stability of the catalyst. For example, AlLibis(binaphthoxide) complex (ALB: **2**)[7] is applicable only to cyclic enones and is also moisture sensitive.[30,40] Thus, we attempted to increase the stability of the ALB complex **2**. For preparation of an efficient linked-BINOL complex, lanthanum was chosen as a Lewis acidic metal center instead of aluminum based on the above-mentioned negative factors of group XIII metals. First, an asymmetric Michael reaction of 2-cyclohexen-1-one (**17**) with dibenzyl malonate (**18**) was examined with monometallic (La only) and heterobimetallic (La-Li, La-Na, La-K) complexes. The results are summarized in Table 2. The best result was obtained using alkali-metal free La-linked-BINOL complex **20** (entry 4), in which lanthanum metal should function as a Lewis acid and the lanthanum naphthoxide moiety should function as a Brønsted base to promote the reaction. The proposed mechanism of the catalytic asymmetric Michael reaction of enones with malonates using the La-linked-BINOL complex **20** is shown in Scheme 4. After optimization of the reaction conditions, we finally found that the use of DME as a solvent afforded **19** in 94% yield and >99% ee at room temperature (Table 2, entry 5).[41]

Next, we examined the scope and limitations of different substrates. In all cases, the reaction was run at 0.4 M in enone and malonate. As shown in Table 3, the complex **20** promoted the Michael reaction of a variety of cyclic enones (*from 5- to 9-membered rings!*) with various malonates to afford Michael adducts with good to excellent enantiomeric excess. The

Table 2. Catalytic asymmetric Michael reaction promoted by (*R,R*)-La-M-linked-BINOL complexes.



entry	M	solvent	temp. (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	Li	THF	0	24	21	35
2	Na	THF	0	24	41	43[c]
3	K	THF	–20	24	16	54[c]
4	H (**20**)	THF	0	45	53	85
5	H (**20**)	DME	rt	72	94	>99

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The mirror image enantiomer was formed.

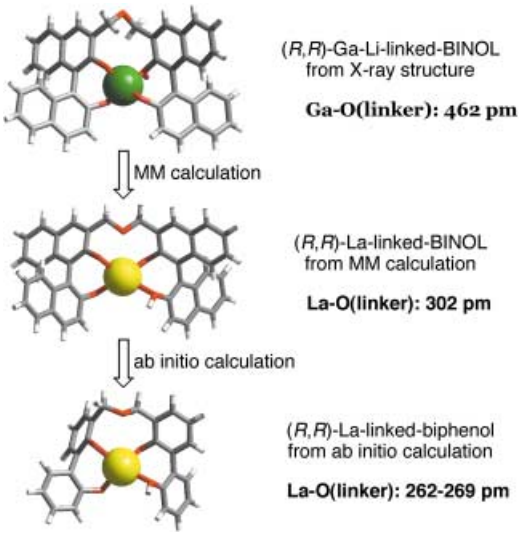
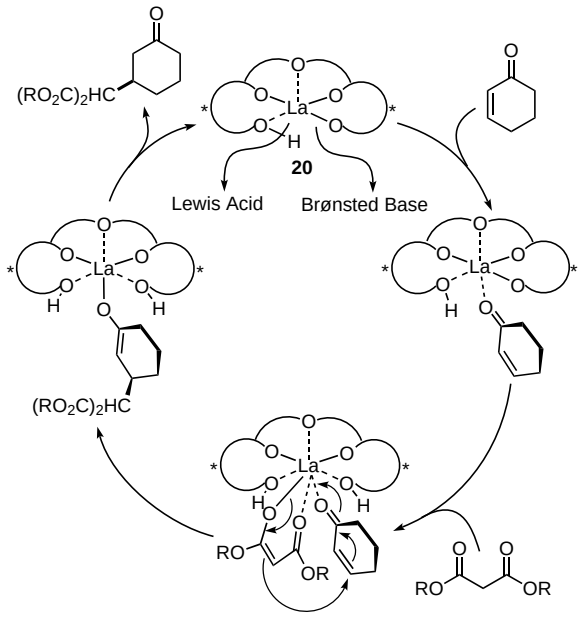
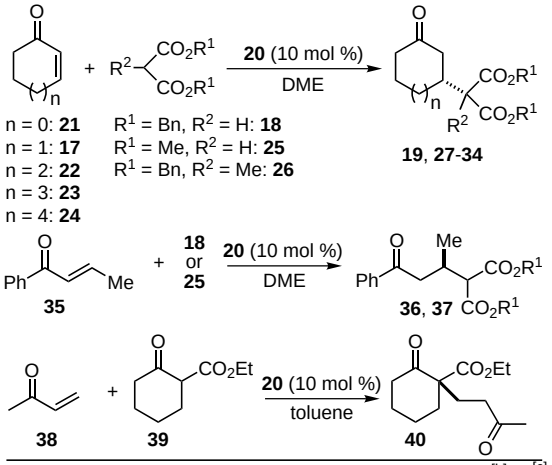


Figure 7. Computational optimization of La-linked-BINOL complex.



Scheme 4. Proposed mechanism for the Michael reaction of enones with malonates.

Table 3. Catalytic asymmetric Michael reactions promoted by (*R,R*)-La-linked-BINOL **20.**[a]



entry	enone	β-dicarbonyl compounds	temp. (°C)	time (h)	product	yield[b] (%)	ee[c] (%)
1	**21**	**18**	4	85	**27**	85	>99
2	**21**	**25**	4	85	**28**	96	>99
3	**17**	**18**	rt	72	**19**	94	>99
4	**17**	**18**	4	85	**19**	98	>99
5	**17**	**25**	rt	72	**29**	95	>99
6[d]	**17**	**26**	rt	84	**30**	84	98
7	**22**	**18**	4	85	**31**	96	>99
8	**22**	**25**	4	85	**32**	97	>99
9[d]	**23**	**25**	rt	96	**33**	82	99
10	**24**	**18**	4	120	**34**	61	82
11	**35**	**18**	–40	56	**36**	97	78
12	**35**	**25**	–40	56	**37**	95	74
13[e]	**38**	**39**	–30	36	**40**	97	75

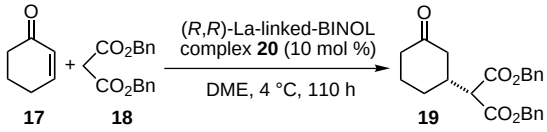
[a] In all cases, the reaction was run on 0.6 mmol scale at 0.4 M in enone and malonate.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] The reaction was carried out in DME/THF (9:1).
[e] **24** was added dropwise over 24 h.

complex **20** was also effective for the Michael reaction of acyclic enones such as **35** with **18** (97%, 78% ee) and **25** (95%, 74% ee). In addition, the Michael reaction of **38** with **39** gave **40** in 97% yield and 75% ee, where a newly formed chiral center was induced by the Michael donor moiety.[6b] To the best of our knowledge no efficient catalytic Michael reaction of 8- and 9-membered ring enones with malonates has been reported and this is the first example of a Michael reaction where the catalyst has such broad generality.

The novel La-linked-BINOL complex **20** was very stable even in air and storable over a long time, probably because the linked-BINOL **10** can function as pentadentate ligand toward lanthanum. The complex **20** was easily prepared from La(O-*i*-Pr)$_3$[42] and 1.0 equivalent of the linked-BINOL **10**, which were mixed in THF followed by removal of the solvent under reduced pressure to afford **20** as a pale-yellow powder, which has no deliquescent properties (Figure 8). This air-stable complex **20** is storable without any care at ambient temperature for at least 4 weeks. As shown in Table 4, there was no change in catalytic activity in terms of either chemical yield or

Figure 8. Preparation of the stock air-stable powdered (*R,R*)-La-linked-BINOL complex **20.**

Table 4. Catalytic asymmetric Michael reaction promoted by stock (*R,R*)-La-linked-BINOL complex **20.**



storage time (week)[a]	0	1	2	3	4
yield (%)[b]	94	93	94	94	95
ee (%)[c]	>99	>99	>99	>99	>99

[a] (*R,R*)-La-linked-BINOL complex **20** was stored under air.
[b] Isolated yield.
[c] Determined by HPLC analysis.

enantiomeric excess, using stock catalyst. After 4 weeks storage, **19** was obtained in 95% yield and >99% ee.

Finally, we succeeded in the recovery and reuse of the La-linked-BINOL **20** from the reaction mixture by utilizing the large difference in solubility between the complex **20** and product **19**. The successful implementation of this strategy is shown in Figure 9. After completion of the reaction [A], the complex **20** was precipitated by the addition of pentane at 0 °C [B]. Supernatant liquid, which contained product **19** and only trace amounts of **20**, was simply separated via cannula [C], [D]. The residual precipitate was dried under reduced pressure to afford the powdered complex **20** again [E].[43] After treatment with THF, the recovered La-linked-BINOL complex **20** was reused several times (Table 5). Although there was some loss of activity, the recovered complex **20** promoted the Michael reaction to afford the desired product **19** in very high enantiomeric excess, even after the fourth use.

The structure of La-linked-BINOL **20** has not yet been clarified. Instead, an X-ray crystal structure analysis of the La(binaphthoxide)$_2$($Ph_3As=O$)$_3$ complex **41** was recently achieved,[11] which was the first X-ray analysis of an alkali metal-free lanthanoid BINOL complex (Figure 10). We believe that the La-linked-BINOL **20**, which also consists of La and two BINOL units, may have a structure related to the La(binaphthoxide)$_2$($Ph_3As=O$)$_3$ complex **41**. Studies elucidating the structure of the La-linked-BINOL **20** are currently in progress.

In this section, the successful extension of the linked-BINOL **10** to the lanthanide complex to achieve an air-stable, storable, and reusable asymmetric catalyst was described.[41] These results suggest that the linked-BINOL **10** is flexible enough to incorporate metals with various ionic radii like Ga (61 pm) and

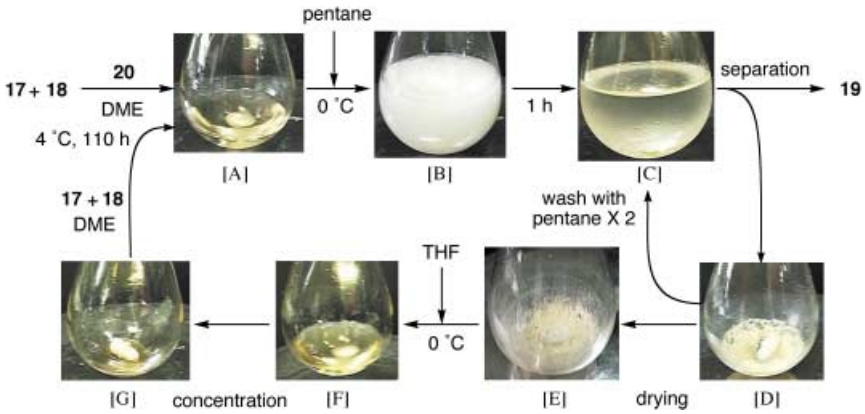
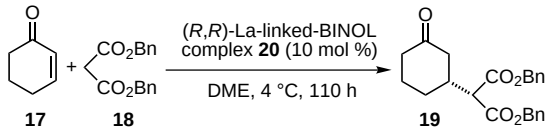


Figure 9. Experimental procedure for catalytic asymmetric Michael reaction with catalyst recycling.

Table 5. Catalytic asymmetric Michael reaction with catalyst recycling.



cycle	1	2	3	4
yield (%)[a]	82	94	68	50
ee (%)[b]	>99	>99	99	98

[a] Isolated yield.
[b] Determined by HPLC analysis.

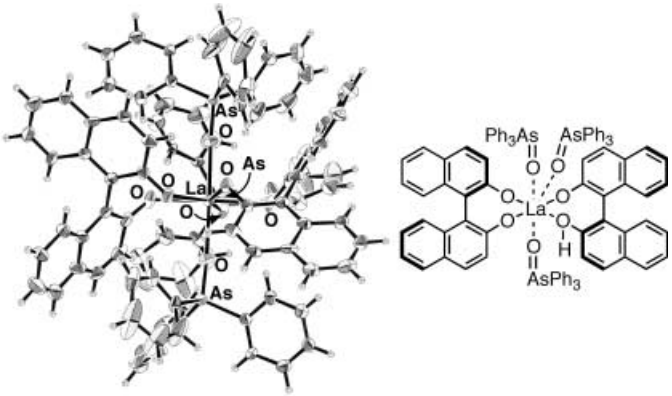
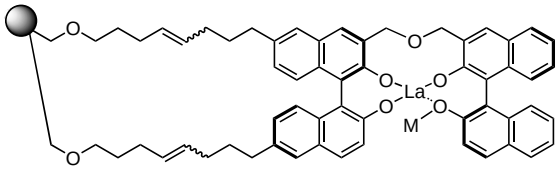


Figure 10. X-ray structure of La(binaphthoxide)$_2$($Ph_3As=O)_3$.

La (103 pm).[32] Application of the linked-BINOL **10** to other Lewis acidic metals to increase their stability is under investigation in our group.

We now have two types of practical asymmetric multifunctional catalysts for the Michael reaction of cyclic enones. (1) ALB (Figure 1, **2**) is suitable for large-scale synthesis on account of its cost efficiency, reaction temperature (room temperature), and catalyst loading (0.3 – 1 mol %, TON = up to 313) as well as chemical yield and enantiomeric excess, although one should avoid moisture.[36a,40] (2) On the other hand, La-linked-BINOL **20** requires rather high catalyst loading (10 mol %, TON = 9.7), but is suitable for small, laboratory-scale synthesis, because La-linked-BINOL **20** is stable, storable under air, and is very easy to handle.[41] While



M = H: polymer-supported La-linked-BINOL **42**
M = ZnEt: polymer-supported La-Zn-linked-BINOL **43**

Figure 11. Polymer-supported La-linked-BINOL complex **42** and La-Zn-linked-BINOL complex **43.**

investigating the La-linked-BINOL complex, we also examined the immobilization of the La-linked-BINOL complex **20** to an insoluble polymer. Although there was a severe decrease in reactivity and selectivity with polymer-supported La-linked-BINOL complex **42**, the use of a new polymer-supported La-Zn-linked-BINOL complex **43** (Figure 11) improves reactivity in the Michael reaction.[44] A homogeneous La-Zn-linked-BINOL complex was also effective in the Michael reaction of cyclic enones with malonates to afford products in good enantiomeric excess.[44] In the case of La-Zn-linked-BINOL complex, the Zn-naphthoxide moiety is considered to function as a Brønsted base. The use of mild and selective Zn species finally led to the development of a new multifunctional asymmetric catalysis, which will be discussed in the next section.

5 Zn-Zn-linked-BINOL Complex: A New *Homobimetallic* Multifunctional Catalysis for the Practical Direct Aldol Reaction

The aldol reaction is generally regarded as one of the most powerful and efficient carbon-carbon bond forming reactions. Many efforts have been devoted to develop catalytic asymmetric aldol reactions,[45] but almost all of these reactions require preconversion of the ketone or ester moiety into a more reactive species such as an enol silyl ether or a ketene silyl acetal by using no less than stoichiometric amounts of bases and reagents like $(CH_3)_3SiCl$. For the development of practical, economic, and environmentally benign processes, it is ideal to perform the aldol reaction with unmodified ketones and aldehydes using only *catalytic* amount of reagents. Our success

in performing direct catalytic asymmetric aldol reactions with unmodified ketones[4] has attracted much interest in this potentially advantageous strategy, especially in terms of atom economy.[2] List, [46a, 46b] Barbas,[46a,46c] and Trost[20f] have also reported direct asymmetric aldol reactions using amino acids or a chiral semi-crown Zn complex as catalysts. Moreover, several groups recently reported enantio- and diastereoselective direct aldol reactions using biological-type catalysts[47] or small molecular catalysts,[48,49] which considerably widened the scope of the field. We also reported an enantio- and diastereoselective direct aldol reaction with 2-hydroxyacetophenone (**44a**), which provided *anti*-α,β-dihydroxy ketones using a $LaLi_3$tris(binaphthoxide) · KOH (LLB · KOH) complex (Figure 12 and Scheme 5).[50] We hypothesized that a unique property inherent in the linked-BINOL **10** would also provide an effective direct aldol reaction.

Many catalysts, such as Ln-linked-BINOL (Ln = La, Gd, or Yb)[41] and Ln-Zn-linked-BINOL (Ln = La, Gd, Y, or Yb), [44] were examined and a new *homobimetallic* (*S*,*S*)-Zn-Zn-linked-BINOL complex **45** prepared from linked-BINOL and 2 equivalents of Et_2Zn (Figure 12) showed promising results.[50,51] Although the structure of **45** has not yet been clarified, we propose the ate complex depicted as $[Zn(OAr)_4]^{2-}Zn^{2+}$ (Figure 12) based on the property of this semi-crown ether type ligand and the X-ray structure of the Ga-Li-linked-BINOL complex ($[Ga(OAr)_4]^-Li^+$). Attempts to obtain X-ray grade crystals of Zn-Zn-linked-BINOL are currently underway in our laboratory. After optimization of the reaction conditions, the *syn*-aldol **47a** was selectively obtained in a ratio of 2 (*syn*, 81% ee) to 1 (*anti*, 81% ee) on treatment of 3-phenylpropanal (**46a**) with 2-hydroxyacetophenone (**44a**, 2 equiv.) in the presence of **45** (10 mol %) and triphenylphosphine oxide (20 mol %; entry 1, Table 6). As shown in Table 6, the reaction of **44a** with a variety of aldehydes afforded the

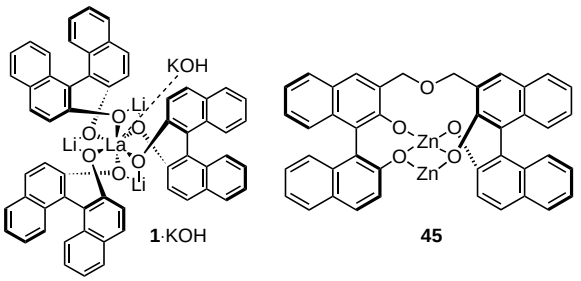
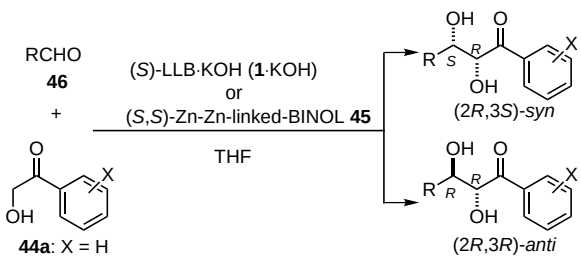
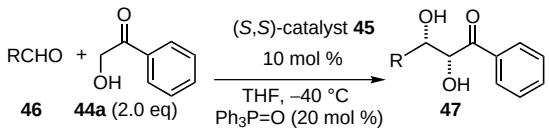


Figure 12. (*S*)-$LaLi_3$tris(binaphthoxide) · KOH (LLB · KOH) complex **1** · KOH and (*S*,*S*)-Zn-Zn-linked-BINOL complex **45.**



Scheme 5. General scheme for direct aldol reaction with hydroxyacetophenones.

Table 6. Direct aldol reaction of various aldehydes with 2-hydroxyacetophenone (**44a**).[a]



entry	R	product	time (h)	yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (*syn*/*anti*)
1	Ph **46a**	**47a**	48 (48)[e]	89 (81)[e]	72/28 (67/33)[e]	81/81 (78/76)[e]
2	**46b**	**47b**	60	80	67/33	77/73
3	**46d**	**47d**	36	80	67/33	83/79
4	**46e**	**47e**	60	81	67/33	79/75
5	**46h**	**47h**	36	92	83/17	86/67
6	**46i**	**47i**	48	79	88/12	79/72
7	**46j**	**47j**	48	89	85/15	85/78

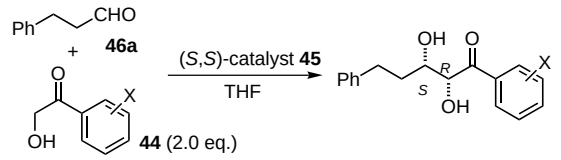
[a] All reactions were run on 0.3 mmol scale at 0.15 M in aldehyde.
[b] Isolated yield after conversion to acetonides.
[c] Determined by ^1H NMR of crude mixture.
[d] Determined by chiral HPLC.
[e] In the absence of $Ph_3P(O)$.

corresponding *syn*-aldols **47** stereoselectively in moderate to good enantiomeric excess.

From a practical perspective, there remains much room for improvement in the present reaction with respect to catalyst amount (10 mol %), diastereomeric ratio (*syn*/*anti* = 67/33 to 88/12), enantiomeric excess (77 – 86% for *syn* isomer), reaction rate, and yield. Our previous results suggested that substituents on the aromatic ring of acetophenones should affect both diastereoselectivity and enantioselectivity.[5b] We chose methoxy-substituted acetophenones, based on the following: from a synthetic point of view, the use of aryl ketones is potentially advantageous over the use of dialkyl ketones such as acetone and hydroxyacetone, because the aromatic ring functions as a placeholder for further conversions via regioselective rearrangements. Electron-rich methoxy-substituted acetophenones facilitates conversions such as a Baeyer – Villiger oxidation.

We investigated the direct aldol reaction of 3-phenylpropanal (**46a**) using methoxy-substituted 2-hydroxyacetophenones **44b** – **44d**. The aldol adducts were isolated after their conversion into the corresponding acetonides. As shown in Table 7, the reaction rate, yield, diastereomeric ratio, and enantiomeric excess all were improved when using 2-hydroxy-2′-methoxyacetophenone (**44d**) (entry 4). In contrast to **44a**, $Ph_3P(O)$ as an additive had no positive effects (entry 5). It is noteworthy that the aldol reaction of **44d** still proceeded smoothly even when the catalyst amount was reduced. The reaction was completed within 4 h with 3 mol % of catalyst **45**

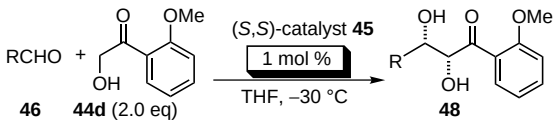
Table 7. Direct aldol reaction of **46a** with methoxy-substituted 2-hydroxyacetophenone **44** catalyzed by (*S*,*S*)-Zn-Zn-linked-BINOL **45**.[a]



entry	X		catalyst (mol %)	temp. (°C)	time (h)	yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (*syn*/*anti*)
1	H	**44a**	10	–40	48	81	67/33	78/76
2	4'-MeO	**44b**	10	–20	24	73	60/40	86/86
3	3'-MeO	**44c**	10	–30	12	85	70/30	77/77
4	2'-MeO	**44d**	10	–30	3	93	89/11	86/88
5[e]	2'-MeO	**44d**	10	–30	3	93	86/14	86/77
6	2'-MeO	**44d**	3	–30	4	94	90/10	90/89
7	2'-MeO	**44d**	1	–30	20	94	89/11	92/89
8	2'-MeO	**44d**	1	–30	16	94	87/13	93/91

[a] Reactions were run on 0.30 mmol scale (entries 1 - 5), 0.67 mmol scale (entry 6), 1.0 mmol scale (entry 7), and 8.0 mmol scale (1.05 g of **46a**, entry 8) at 0.2 M in aldehyde.
[b] Isolated yield after conversion to acetonides.
[c] Determined by ^{1}H NMR of crude mixture.
[d] Determined by chiral HPLC analysis of diols.
[e] In the presence of $Ph_3P(O)$ (20 mol %).

Table 8. Direct aldol reaction of various aldehydes with 2'-methoxy-2-hydroxyacetophenone (**44d**).[a]



entry	R	product	time (h)	yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (*syn*/*anti*)
1	Ph **46a**	**48a**	20	94	89/11	92/89
2	**46b**	**48b**	18	88	88/12	95/91
3	**46c**	**48c**	18	84	87/13	96/87
4	**46d**	**48d**	18	84	84/16	93/87
5	**46e**	**48e**	24	94	86/14	87/92
6	BnO **46f**	**48f**	18	81	86/14	95/90
7	BnO **46g**	**48g**	16	84	72/28	96/93
8	**46h**	**48h**	24	83	97/3	98/—
9	**46i**	**48i**	16	92	96/4	99/—
10	**46j**	**48j**	18	95	97/3	98/—

[a] All reactions were run on 1.0 mmol scale at 0.2 M in aldehyde.
[b] Isolated yield after conversion to acetonides.
[c] Determined by ^{1}H NMR of crude mixture.
[d] Determined by chiral HPLC analysis of diols.

(entry 6). Moreover, satisfactory yield (94%), diastereomeric ratio (*syn*/*anti* = 89/11), and enantiomeric excess (*syn* = 92%, *anti* = 89%) were achieved after 20 h with as little as 1 mol % of **45** (entry 7), and the reaction proceeded smoothly without any problem on a gram scale (entry 8). To the best of our knowledge, this is the most effective small molecular catalyst for direct asymmetric aldol reactions in terms of catalyst loading (TON = 94). In combination with the successful gram-scale experiment, the simple protocol proves the present reaction to be practically useful. The catalyst was prepared by just mixing commercially available Et_2Zn in hexanes and easily available linked-BINOL[23] in THF without any other additives, followed by the addition of ketone **44d** and the aldehyde.

Zn-Zn-linked-BINOL **45** was also applicable to various primary (α-unsubstituted) and secondary (α-monosubstituted) aldehydes (Table 8). In all cases, *1 mol % of catalyst **45** was sufficient to complete the reaction within 24 h* (TON = 81 – 95). Both normal (entries 1 – 3 and 5 – 7) and branched (entry 4) primary aldehydes afforded good results (yield: 81 – 94%, dr: *syn*/*anti* = 72/28 to 89/11, ee: *syn* = 87 – 96%, *anti* = 87 – 93%). It should be mentioned that primary (α-unsubstituted) aldehydes gave the corresponding aldol adducts in good to excellent yields and enantiomeric excess without forming any self-condensation products. The results demonstrate that the present catalysis has high chemoselectivity. Remarkably, secondary (α-monosubstituted) aldehydes (entries 8 – 10) showed good yield (83 – 95%), excellent diastereomeric ratio (*syn*/*anti* = 96/4 to 97/3), and enantiomeric excess (98 – 99%).[52]

The observed stereoselectivity of the aldol adducts **48** [(2*R*,3*S*)-*syn* and (2*R*,3*R*)-*anti* from (*S*,*S*)-catalyst **45**, Scheme 5] obtained with ketone **44d** is explained by assuming the following reaction mechanism. The formation of a chelate complex between the (*S*,*S*)-catalyst **45** and the enolate generated from **44d** results in an efficient shielding of the *Si*-face of the enolate (Figure 13), so that both *syn*- and *anti*-aldol adducts are obtained with an identical configuration at the α-position (2*R*) after the attack towards the aldehyde.

Moreover, the electron donating substituent (methoxy group) on the aromatic ring should increase the preference of one chelate complex (shielding *Si*-face) to the other (shielding *Re*-face) through participation of the 2'-methoxy group in chelate formation (Figure 13). Thus, the *Si*-face shielding would become more effective, resulting in higher enantiomeric excess of both *syn*- and *anti*-products. On the other hand, enhanced *syn*-selectivity is explained by the steric hindrance of the aromatic ring in the enolate against aldehydes. Considering the positions of the two Zn atoms in the proposed structure of **45**, it seems reasonable to assume that the enolate coordinates to one Zn metal and the aldehyde coordinates to the other in a manner as shown in (A) or (B) (Figure 13). The transition state (A), which leads to *syn*-diols, is sterically more favorable than (B). By using ketone **44d** instead of non-substituted **44a**, the steric bias should increase, thus resulting in the higher *syn*-selection. Detailed mechanistic studies are currently in progress.

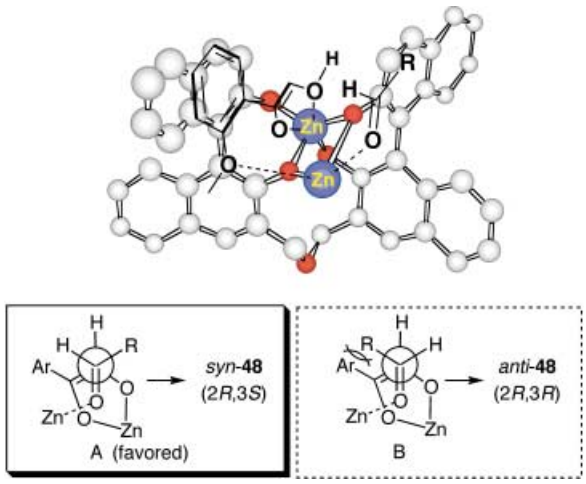
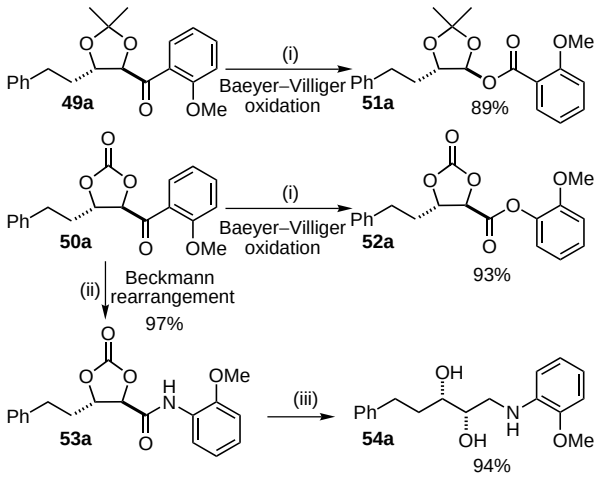


Figure 13. Working model for transition state.

As mentioned previously, the usefulness of the aldol adducts increases if the 2-methoxyphenyl moiety functions as a placeholder for further conversions. As shown in Scheme 6, the Baeyer – Villiger oxidation proceeded smoothly by treating the ketones **49a** and **50a** with *m*CPBA, probably with the aid of neighboring oxygen atoms. Interestingly, benzoate **51a** was obtained in 89% yield when acetonide **49a** was used. On the other hand, phenyl ester **52a** was obtained in 93% yield when a carbonate analogue **50a** was subjected to the same conditions. No regioisomer was observed in either case. Furthermore, **50a** afforded amide **53a** exclusively in 97% yield in one step via the Beckmann rearrangement with *O*-mesitylenesulfonylhydroxylamine (MSH).[53] The amide **53a** was readily transformed into **54a** by reduction with DIBAL; **54a** can be converted into an amino-diol after oxidative removal of the 2-methoxyphenyl group.[54]

A new homobimetallic multifunctional asymmetric catalysis was achieved using linked-BINOL **10**.[50,52] The results suggest a novel use for linked-BINOL in addition to stabilization of asymmetric catalysts. Further application of this homobimetallic system, especially to the efficient carbon-carbon bond forming reaction, such as a catalytic asymmetric aldol reaction with an unmodified ester as a donor, has been launched in our laboratory.



(i) *m*CPBA, NaH_2PO_4, $ClCH_2CH_2Cl$, 50 °C, 2h
(ii) *O*-mesitylenesulfonylhydroxylamine, CH_2Cl_2, rt, 4 h
(iii) DIBAL, –78 °C to rt, 2 h.

Scheme 6. Transformations of aldol adducts via regioselective rearrangement.

6 Conclusions

We have developed a novel linked-BINOL as an approach towards practical asymmetric catalysis. The linked-BINOL efficiently stabilized the *heterobimetallic* multifunctional asymmetric catalyst, Ga-Li complex, against ligand exchange with the nucleophile, thus greatly improving the chemical yield in the epoxide opening reaction. Further application of linked-BINOL to La metal led to an air-stable, storable, and reusable *monometallic* multifunctional asymmetric catalyst, La-linked-BINOL, [55] for the Michael reaction. Finally, the *homobimetallic* multifunctional asymmetric catalysis was realized by utilizing the unique property of linked-BINOL. An Zn-Zn-linked-BINOL complex provided a practical process for the synthesis of *syn*-1,2-diols. We believe that the successful development and applications of linked-BINOL has opened up a new possibility of multifunctional asymmetric catalysis towards practical catalytic asymmetric processes. However, it is obvious that further intensive investigations based on novel and more sophisticated concepts are still required to develop really practical, especially environmentally benign, processes. Our research projects on multifunctional asymmetric catalysis are ongoing towards this goal.

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