Design and application of linked-BINOL chiral ligands in bifunctional asymmetric catalysis

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The design and application of linked-BINOLs investigated in our group are reviewed. Linked-BINOLs are a kind of semi-crown ether, thus they are flexible and applicable to metals having various ionic radii (Ga^{3+}, Li^{+}, Zn^{2+}, In^{3+}, La^{3+}, and Y^{3+}). The flexible linker segment, containing a coordinative heteroatom, has a crucial role in the construction of a unique and effective chiral environment that is not accessible from BINOL itself. Applications of linked-BINOLs to an epoxide opening reaction, Michael reactions, a direct aldol reaction, direct Michael reactions of a hydroxyketone, and direct Mannich-type reactions of hydroxyketones and *N*-acylpyrrole are described.

1. Introduction

The synthesis of chiral compounds using catalytic asymmetric processes is one of the most important and rapidly growing areas in modern synthetic organic chemistry.[1] Catalytic asymmetric processes are potentially more economical and more environmentally benign than processes using stoichiometric amounts of reagents. Asymmetric catalysis using chiral metal complexes provides general and flexible methods for asymmetric synthesis. In asymmetric metal catalysis, the design of chiral ligands for metals is key when new reactions. The activity and selectivity of metals are tuned by chiral ligands. A delicate balance between the steric and electronic properties of the catalyst determines the reaction efficiency.

Axially chiral 1,1′-bi-2-naphthol (BINOL: Fig. 1) and its derivatives have an important role for Lewis acidic metals as chiral ligands in modern asymmetric catalysis.[2] In our continuing research toward the development of practical and atom-economical[3] asymmetric catalysis, we have utilized various metal/BINOL complexes.[4,5] Among them, we reported heterobimetallic complexes that consist of two or three BINOLs, a Lewis acidic central metal, and additional alkali metals cations. The structures of some heterobimetallic complexes were determined using NMR, LDI-TOF mass spectrometry, and single crystal X-ray analysis. The structure of a group-13/alkali metal heterobimetallic complex is shown in Fig. 1.[4] Mechanistic studies suggest that heterobimetallic complexes of this class promote asymmetric reactions *via* dual activation of both nucleophiles and electrophiles. The Brønsted base moiety of the catalyst (the alkali metal

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Shigeki Matsunaga

Shigeki Matsunaga received his PhD, with a thesis on the development of a novel chiral ligand linked-BINOL, from the University of Tokyo under the direction of Prof. M. Shibasaki. He started his academic career in 2001 as an assistant professor in Prof. Shibasaki's group at the University of Tokyo. He is the recipient of the 2001 Yamanouchi Award of Synthetic Organic Chemistry, Japan. His current research interests lie in the development and mechanistic studies of new catalytic reactions, including asymmetric catalysis.

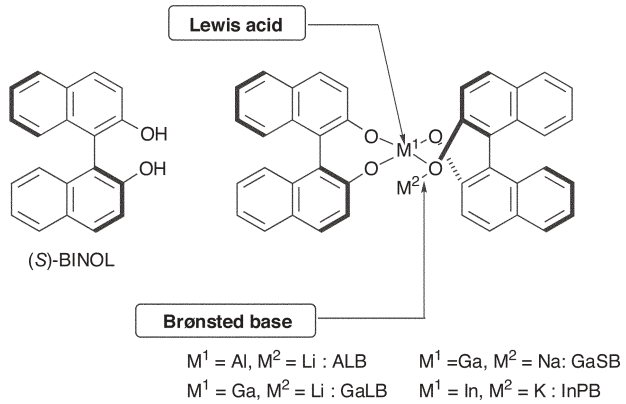


Fig. 1 Structures of (*S*)-BINOL and group-13 metal/alkali metal heterobimetallic bifunctional complexes.

binaphthoxide) activates nucleophiles, such as nitroalkanes and malonates, by deprotonation. At the same time, the Lewis acid moiety (an aluminium, gallium, indium or rare earth metal) activates the electrophile. The dual activation occurs at positions controlled by an asymmetric environment, and so nucleophiles react with electrophiles from a defined direction, resulting in high enantioselectivity.

Although heterobimetallic complexes work well in a variety of asymmetric reactions,[4] the necessity of simultaneous binding by two or more ligand molecules per complex creates a liability in so far as catalyst stability is concerned. Under certain conditions, some heterobimetallic complexes decompose due to irreversible ligand exchange between BINOLs and nucleophiles, resulting in lowered chemical yields and/or enantiomeric excesses. For example, we previously reported enantioselective epoxide ring-opening with 4-methoxyphenol promoted by GaLibis(binaphthoxide) (abbreviated as GaLB: Ga = gallium; L = lithium; B = BINOL) complex (Fig. 1).[6] In this reaction, GaLB afforded enantiomerically enriched 1,2-diol mono ethers, which are versatile chiral building blocks, in only moderate chemical yields despite the use of more than 20 mol% of the catalyst. The low reactivity of GaLB was attributed to a ligand exchange between BINOL and 4-methoxyphenol. A more stable Ga-complex was needed. To solve this problem and widen the scope of bifunctional 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 novel linked-BINOLs.

2. Ga-Li-linked-BINOL complex: design and development of a novel linked-BINOL

To increase the stability of GaLB, we considered linking its two BINOL units. Thereby, the complex would become more stable against ligand exchange while its asymmetric environment would remain unchanged. One of the key issues in designing a linked-BINOL is the length and flexibility of the linker. The linker should be relatively short in order to somewhat limit the flexibility of the BINOL units, maintaining the geometry crucial for enantioselectivity. However, the asymmetric environment would be negatively affected by a linker that is too rigid and, in the worst case scenario, even the formation of the desired 1 : 2 (gallium : BINOL unit) complex could be prevented.

We first designed carbon-linked-BINOLs (Fig. 2), **1a–1c** to evaluate the effect of various linkers.[7,8] We prepared Ga-Li-carbon-linked-BINOL complexes using $GaCl_3$ (1 mol equiv.), **1a**, **1b**, or **1c** (1 mol equiv.), and BuLi (4 mol equiv.). In contrast to our initial assumption, however, none of these gave results superior to GaLB in the enantioselective epoxide opening reaction of cyclohexene oxide with 4-methoxyphenol. Ga-Li-carbon-linked-BINOL complexes afforded the epoxide opening product in low yield and low ee (with **1a**: yield 28%, 27% ee; with **1b**: yield 43%, 10% ee; with **1c**: y. 40%, 1% ee), whereas 10 mol% of the original GaLB catalyst afforded the desired product in 48% yield and 93% ee. The unsatisfactory results may be attributed to the undesired oligomeric structure of these linked-BINOL complexes. With a carbon linker, each BINOL unit of linked-BINOLs **1a–1c** can rotate freely during the formation of Ga-complexes. As shown in Fig. 3, the *anti*

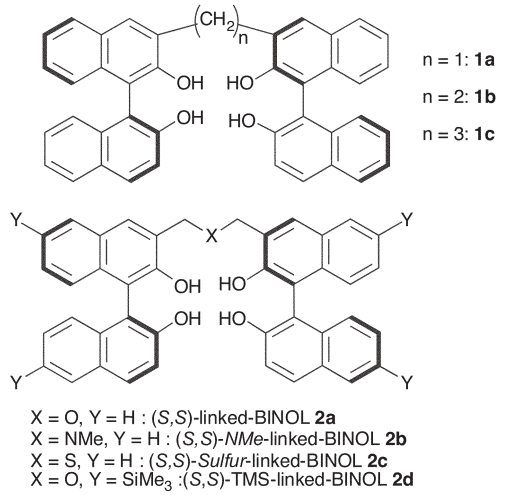


Fig. 2 Carbon-linked-BINOLs (**1a–1c**) and linked-BINOLs (**2a–2d**) with heteroatom linker.

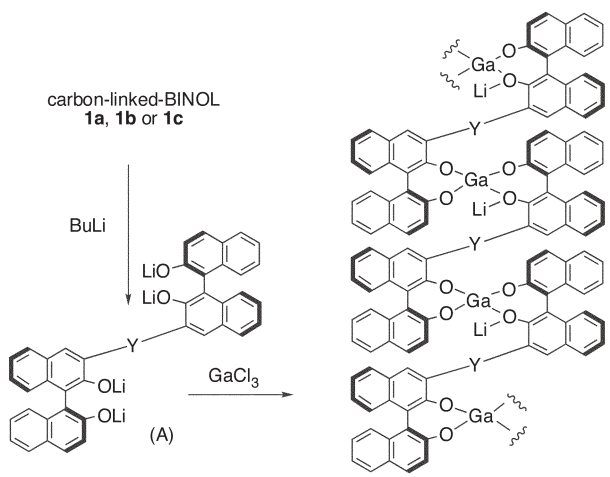


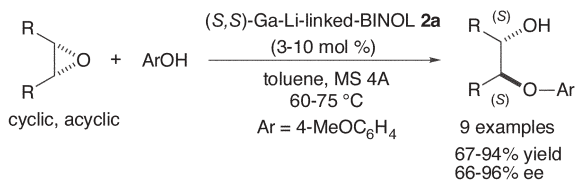
Fig. 3 Possible oligomeric structure of Ga-Li-carbon-linked-BINOL complex.

conformation (A) seems most favorable due to steric and electronic repulsion, thus Ga-Li-carbon-linked-BINOL would be expected to adopt an undesired oligomeric structure, the asymmetric environment of which should be different from that of monomeric GaLB.

To overcome this problem, we designed an oxygen-containing BINOL-linker (Fig. 2), **2a**.[9] The new linked-BINOL **2a** was designed based on reports by Cram *et al.* regarding crown ethers incorporating chiral BINOL units.[10] We assumed that the oxygen atom in the linker would coordinate to gallium during the Ga-complex formation, thus promoting the formation of the desired monomeric Ga-complex. In contrast to crown ether-type cyclic ligands, the linked-BINOL **2a**, which is a kind of semi-crown ether linked only to one side of the BINOL units (3–3″ position), leaves a vacant coordination site around the gallium metal. Thus, the Ga-Li-linked-BINOL **2a** complex should be active as a Lewis acid towards epoxides. Indeed, it worked nicely in the presence of 3 equiv. of 4-methoxyphenol, and epoxide opening adducts were obtained in good yield (67–94%) and ee (66–96% ee, Scheme 1). Catalyst loading was successfully reduced to 3 mol%. The results in Scheme 1 were attributed to the stability of the Ga-Li-linked-BINOL **2a** complex, obtained by linking the two BINOL units in GaLB. The stable complex remained unchanged during the course of the reaction, whereas GaLB decomposed gradually due to ligand exchange with 4-methoxyphenol. To summarize the present epoxide opening reaction, Ga functions as Lewis acid to activate epoxides, whereas the Li–OAr moiety (ArOH = linked-BINOL **2a**) functions as Brønsted base to generate 4-MeO-C_6H_4OLi as a nucleophile. The structure of Ga-Li-linked-BINOL **2a** complex was determined by X-ray single crystal analysis (Fig. 4), and a similar structure in solution phase was supported by ^{13}C NMR and mass analysis.[9] The X-ray crystal structure of the Ga-Li-linked-BINOL **2a** complex indicated that, in contrast to our initial assumption, the ether linker does not coordinate to the Ga metal center, at least in the absence of epoxide.

2. La(O-*i*-Pr)$_3$/linked-BINOL complex: application to the Michael reaction

In the four-coordinate tetrahedral structure of the Ga-Li-linked-BINOL **2a** complex (Fig. 4), the length of the ether linker seemed to be sufficient to accommodate metals of larger ionic radius. Because we had already reported the utility of various rare earth metal/BINOL complexes in asymmetric catalysis, we turned our attention to the application of linked-BINOL **2a** to rare earth metals.



Scheme 1 Catalytic asymmetric *meso*-epoxide opening reaction using Ga-Li-linked-BINOL complex.

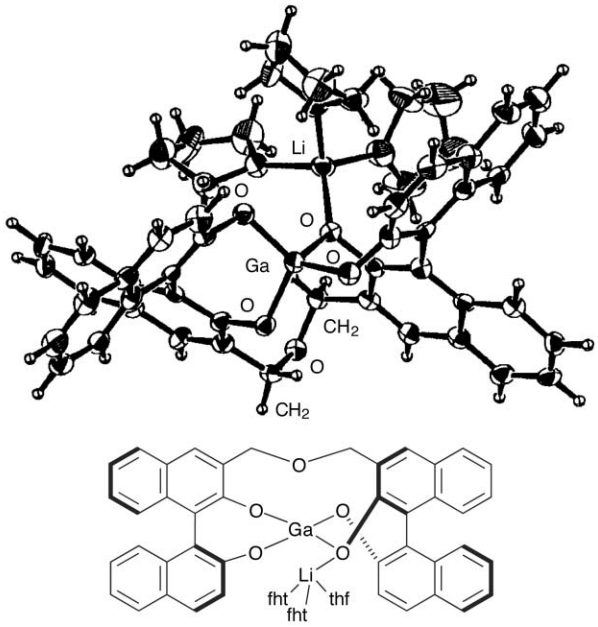


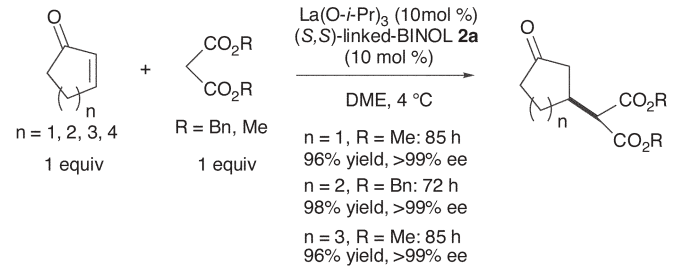
Fig. 4 Structure of Ga-Li-linked-BINOL **2a**(thf)$_3$.

We previously reported that a La(O-*i*-Pr)$_3$: BINOL = 1 : 1 complex promotes the Michael reaction of malonates with cyclic enones in up to 95% ee.[11,12] With the linked-BINOL **2a** as a ligand, Michael adducts were obtained in much higher ee (>99% ee) using 5–8 membered ring cyclic enones (Scheme 2).[13] In the Michael reaction, the La–OAr moiety functions as a Brønsted base to generate a lanthanum-enolate. La also acts as Lewis acid to activate enones. The La(O-*i*-Pr)$_3$: linked-BINOL **2a** = 1 : 1 complex is stable under air at room temperature, and is storable in the solid state for at least four weeks without loss of reactivity or enantioselectivity (Fig. 5). In the Michael reaction, a heterobimetallic La(O-*i*-Pr)$_3$/Et_2Zn/linked-BINOL catalyst was also effective, affording Michael adducts in up to 96% ee.[14] For the Michael reaction of β-keto esters, *NMe*-linked-BINOL **2b** (Fig. 2) was more effective than linked-BINOL **2a** (Scheme 3).[15]

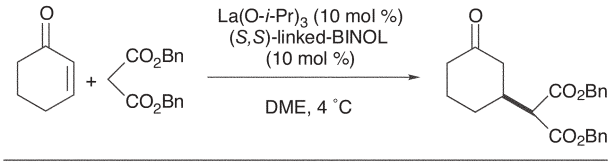
3. Et_2Zn/linked-BINOL complex

3.1. Direct aldol reaction of hydroxyketone

Because a La(O-*i*-Pr)$_3$/Et_2Zn/linked-BINOL **2a** complex showed high activity in the Michael reaction,[14] we investigated the utility of Et_2Zn/linked-BINOL **2a** complexes in other transformations. Among the asymmetric reactions screened, a Et_2Zn/linked-BINOL **2a** complex gave promising results for the direct aldol reaction of hydroxyketones.[16,17] The aldol reaction of cyclohexanecarboxaldehyde with hydroxyacetophenone gave the desired aldol adduct in 85% ee using 10 mol% of linked-BINOL **2a**-derived catalyst.[18,19] After optimization of reaction conditions, the use of hydroxyketone **3a** was shown to effectively improve both reaction rate and enantioselectivity, giving products in 87–99% ee using various aliphatic aldehydes (Scheme 4).[20] Reactions proceeded smoothly in the presence of as little as 1 mol% of linked-BINOL **2a** and 2 mol% of Et_2Zn. The methoxyphenyl group is useful as a template for



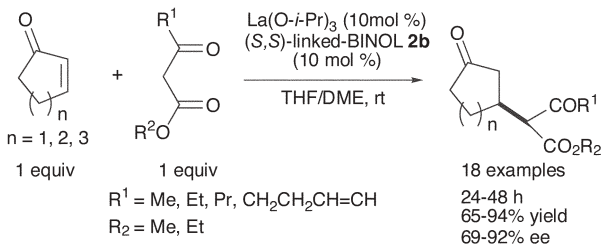
Scheme 2 Catalytic asymmetric Michael reaction of malonate using La(O-*i*-Pr)$_3$/linked-BINOL **2a** complex.



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

[a] La(O-*i*-Pr)$_3$/(*S*,*S*)-linked-BINOL complex was stored under air.

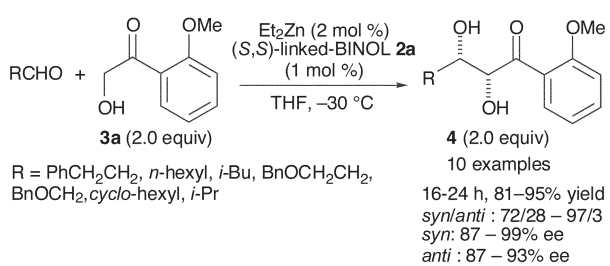
Fig. 5 Catalytic asymmetric Michael reaction promoted by stock catalyst.



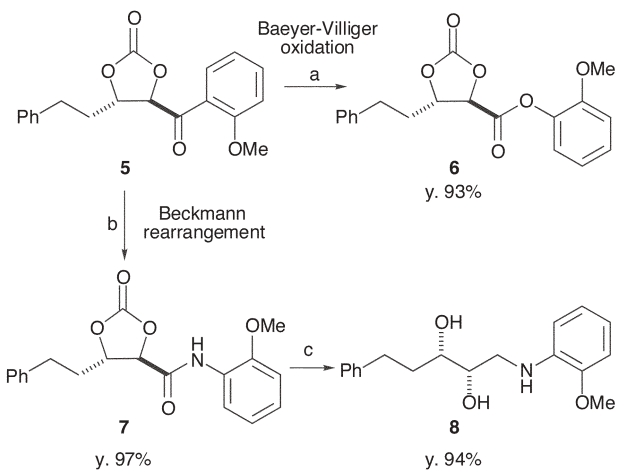
Scheme 3 Catalytic asymmetric Michael reaction of β-keto esters using La(O-*i*-Pr)$_3$/*NMe*-linked-BINOL **2b** complex.

the conversion of aldol adducts **4** into esters and amides. The anisole moiety assists Baeyer–Villiger oxidation and Beckmann rearrangements of **5** to afford ester **6** and amide **7** in 93% and 97% yield, respectively (Scheme 5).

The structure of the Et$_2$Zn/linked-BINOL **2a** complex, which was prepared from 2 equiv. of Et$_2$Zn and 1 equiv. of linked-BINOL **2a**, was clarified to be a trinuclear Zn$_3$(linked-BINOL **2a**)$_2$ complex by ^{1}H NMR, Cold-spray-ionization mass spectroscopy (CSI-MS), and single crystal X-ray analysis (Fig. 6).[21] The Zn$_3$(linked-BINOL **2a**)$_2$ complex forms even in the presence of a slight excess of Et$_2$Zn. Ethane gas emission measurements also supported a 3 : 2 stoichiometry, showing that 0.5 equiv. of Et$_2$Zn remained unchanged in a Et$_2$Zn : linked-BINOL **2a** = 2 : 1 solution. In the X-ray crystal structure, the ether oxygen of the linker in **2a** coordinates to zinc, and has a crucial role in the assembly of a Zn$_3$(linked-BINOL **2a**)$_2$ complex. Given that the aldol reaction shown in Scheme 4 gave only poor reactivity and enantioselectivity using Et$_2$Zn/BINOL catalysts, the structural changes induced by linked-BINOL **2a** seem to be crucial for effective catalysis. By monitoring aldol reactions catalyzed by isolated Zn$_3$(linked-BINOL **2a**)$_2$ and *in situ* generated catalyst using excess Et$_2$Zn, we recognized that the presence of unreacted Et$_2$Zn had beneficial effects on the reaction rate. Kinetic studies suggested that the addition of an excess amount of Et$_2$Zn accelerates the rate-determining product dissociation step. CSI-MS analysis in the presence of hydroxyketone **3a** suggested that the active species could be an oligomeric Zn/linked-BINOL **2a**/hydroxyketone **3a** complex. On the basis of mechanistic studies, the reaction conditions were further optimized, and Et$_2$Zn/linked-BINOL **2a** = 4 : 1 ratio in the presence of MS 3 Å gave the best results. Addition of 4 equiv. of Et$_2$Zn to linked-BINOL **2a** improved the reactivity without loss of enantioselectivity. The



Scheme 4 Direct catalytic asymmetric aldol reaction of hydroxyketone using Et$_2$Zn/linked-BINOL = 2/1 system.



Scheme 5 Transformations of aldol adducts. *Reagents and conditions*: (a) *m*CPBA, NaH_2PO_4, $ClCH_2CH_2Cl$, 50 °C, 2 h; (b) *O*-mesitylenesulfonylhydroxylamime, CH_2Cl_2, rt, 4 h; (c) DIBAL, −78 °C to rt, 2 h.

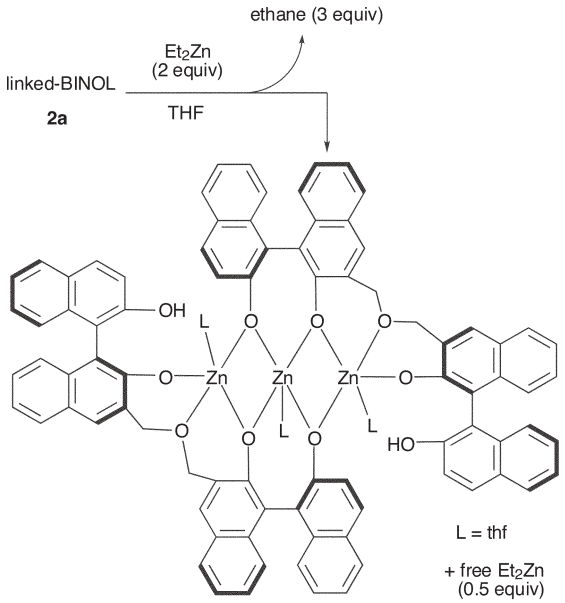
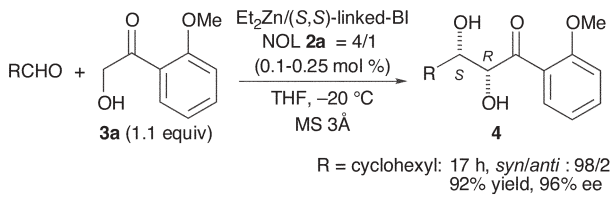


Fig. 6 Structure of Zn_3(linked-BINOL **2a**)$_2$(thf)$_3$ determined by X-ray crystal analysis.

aldol reaction proceeded with excellent results using 0.1–0.25 mol% of optimized catalyst and only 1.1 equiv. of hydroxyketone **3a** (Scheme 6).

The absolute and relative configurations of aldol adducts **4** provide useful information regarding the mechanism of the present aldol reaction. Absolute configurations of products at the position alpha to the carbonyl were identical (2*R*) in both *syn*- and *anti*-aldol adducts (Fig. 7A). Both *syn*- and *anti*-**4** were obtained in similarly high ee (>87% ee), suggesting that the present catalyst differentiates the enantioface of the zinc enolate very well and aldehydes are attacked preferentially from the *Re*-face of the zinc enolate (Fig. 7A). *Syn*/*anti*-selectivity can be explained by assuming the transition state shown in Fig. 7B.

The postulated catalytic cycle for the direct aldol reaction is shown in Scheme 7. Therein, the zinc complex functions as a bifunctional catalyst. In the presence of hydroxyketone **3a**, the oligomeric putative active complex (I) is generated, as observed by CSI-MS analysis. A Zn–OAr* (Ar*OH = linked-BINOL **2a**) moiety functions as a Brønsted base to deprotonate hydrokyketone **3a** and form zinc enolate (II). Aldehyde approaches the *Re*-face of the enolate selectively to be activated by a Lewis acidic zinc center, and 1,2-addition takes place (IV). Protonation by the phenolic proton of



Scheme 6 Direct catalytic asymmetric aldol reaction of hydroxyketone using Et_2Zn/linked-BINOL = 4/1 with MS 3Å system.

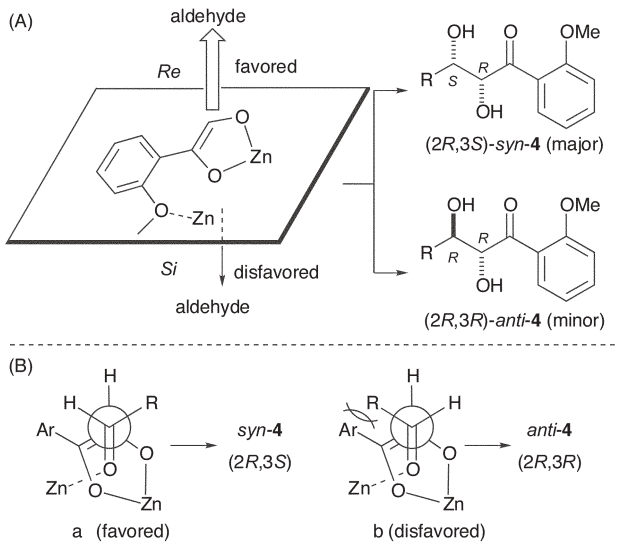
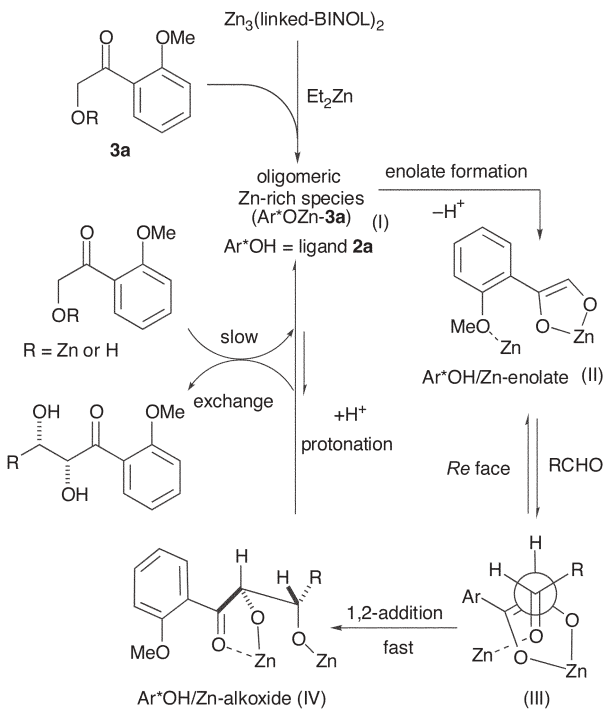


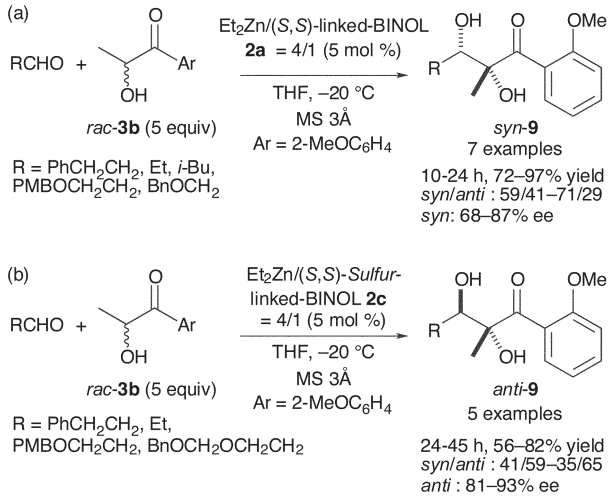
Fig. 7 (A) Relative and absolute configurations of aldol adducts. (B) Postulated transition state model.

linked-BINOL **2a** (Ar*OH) followed by ligand exchange with hydroxyketone **3a** regenerates (I).

Catalytic asymmetric construction of chiral tetrasubstituted carbon stereocenters is one of the most important topics in recent synthetic organic chemistry.[22] We envisioned that the present asymmetric zinc catalysis could also be used to differentiate the enantioface of a fully substituted enolate derived from 2-hydroxy-2′-methoxypropiophenone (**3b**, Scheme 8). The aldol reaction of **3b** would then afford product **9** bearing a chiral tetrasubstituted carbon stereocenter. Using



Scheme 7 Postulated catalytic cycle for the direct aldol reaction.

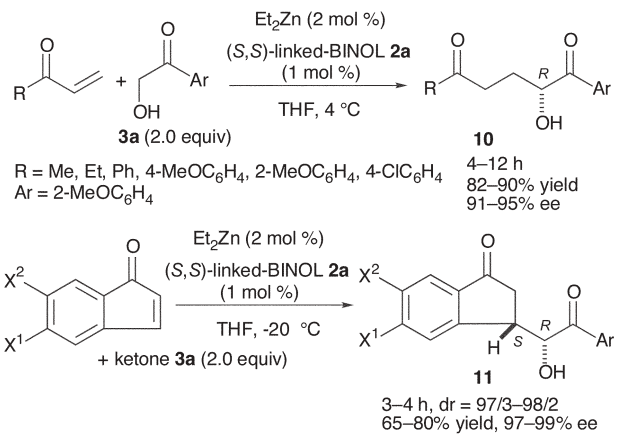


Scheme 8 Construction of tetrasubstituted carbon stereocenter by direct catalytic asymmetric aldol reaction with hydroxyketone **3b**.

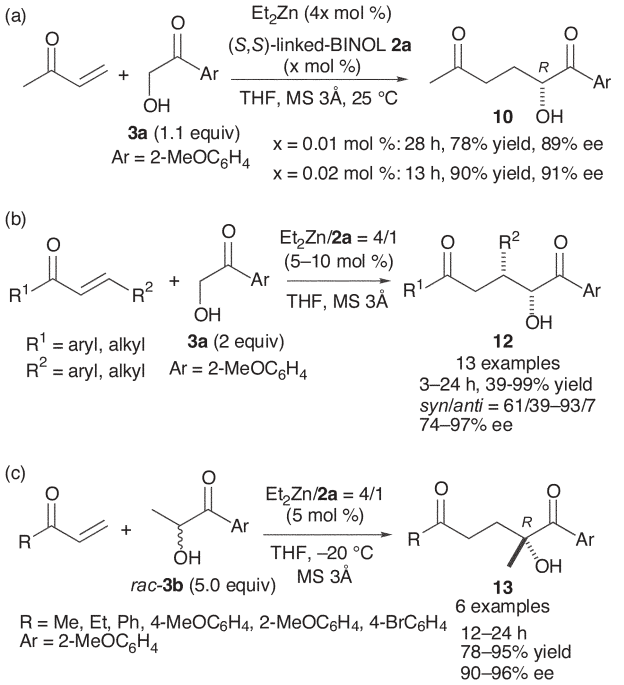
5 mol% of linked-BINOL **2a** the reaction proceeded in modest to good ee, although the *syn*/*anti* ratio was modest (Scheme 8a). By altering the linker heteroatom of linked-BINOL from oxygen to sulfur (*Sulfur*-linked-BINOL **2c**, Fig. 2), the reaction proceeded *anti*-selectively and *anti*-**9** was obtained in 81–93% ee (Scheme 8b).[21]

3.2. Direct Michael reaction of hydroxyketone

We anticipated that efficient enantiofacial selection of zinc enolates would be applicable to other electrophiles, such as enones. The resulting Michael adducts are chiral 2-hydroxy-1,5-dicarbonyl compounds. As shown in Scheme 9, the Michael reaction of hydroxyketone **3a** to vinyl ketones and indenones proceeded smoothly to afford the desired products in 91–95% ee and 97–99% ee, respectively.[23] The reactions proceeded with little, if any, polymerization of vinyl ketones, demonstrating the high chemoslectivity of the zinc catalyst toward hydroxyketone **3a**. Under the optimized reaction conditions using the Et_2Zn/linked-BINOL **2a** = 4 : 1 with MS 3Å system, the catalyst loading was reduced to 0.01 mol%



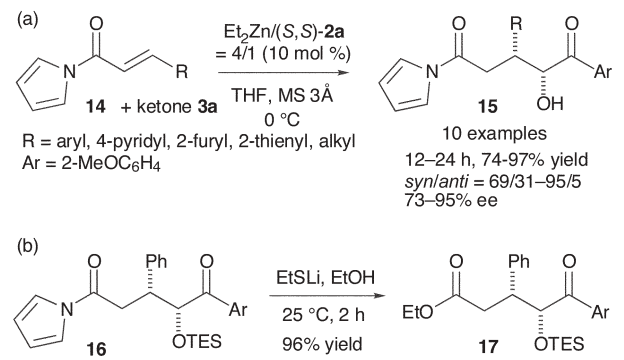
Scheme 9 Direct catalytic asymmetric Michael reaction of hydroxyketone **3a** using the Et_2Zn/linked-BINOL = 2/1 system.



Scheme 10 Direct catalytic asymmetric Michael reaction of hydroxyketones **3a** and **3b** using the Et_2Zn/linked-BINOL = 4/1 with MS 3Å system.

(Scheme 10a).[24] The Et_2Zn/linked-BINOL **2a** = 4 : 1 with MS 3Å system was also effective for β-substituted enones, and the Michael adducts **12** were obtained *syn*-selectively with good yield and ee (Scheme 10b). Cyclic enones were less reactive, and 10 mol% of linked-BINOL **2a** was required. Hydroxyketone **3b** was also effective for the reaction of vinyl ketones, affording Michael adducts **13** with tetrasubstituted carbon stereocenters in 90–96% ee (Scheme 10c).[24]

To broaden the substrate scope to carboxylic acid derivatives, we used α,β-unsaturated *N*-acylpyrrole **14** (Scheme 11) as a monodentate activated ester surrogate.[25,26] Because the lone pair on the nitrogen in the pyrrole ring is delocalized in an aromatic system, the reactivity of α,β-unsaturated *N*-acylpyrrole **14** is expected to be similar to that of enones. Because the metal coordination mode of *N*-acylpyrroles is



Scheme 11 Direct catalytic asymmetric Michael reaction using α,β-unsaturated N-acylpyrrole **14** as an ester surrogate.

similar to that of aromatic ketones, the chiral environment optimized for enones should be applicable for *N*-acylpyrroles. Using our optimal catalyst systems, the reactivity of α,β-unsaturated *N*-acylpyrroles **14** was found to be slightly lower than enones. Nevertheless, when the reaction was performed at 0 °C, expected products **15** were afforded in good *syn*-selectivity and ee (Scheme 11a). The *N*-acylpyrrole moiety of **16** was readily converted into ester **17** by treatment with EtSLi in EOH at 25 °C for 2 h (Scheme 11b).

3.3. Direct Mannich-type reaction of hydroxyketone

Chiral β-amino alcohols are useful chiral building blocks found in various natural products, compounds with pharmacologically important activity, chiral auxiliaries, and chiral ligands.[27] We anticipated that efficient enantiofacial selection of zinc enolates could be useful for additions to imines. A Mannich-type reaction of hydroxyketones would afford chiral β-amino alcohols.[28] Face selection of imines is important for achieving high diastereoselectivity. We hypothesized that either *anti*- or *syn*-Mannich adducts could be selectively obtained by choosing proper imine protecting groups that favor *Si*-face or *Re*-face approach to the zinc enolate, respectively (Fig. 8).

Screening of various imines revealed that Dpp-imines **18** afforded *anti*-β-amino alcohol **19** in high enantioselectivity (98 to >99% ee, Scheme 12a).[29,30] Imines derived from aromatic aldehydes with various substituents afforded products with high *anti*-selectivity (dr: 94/6 to >98/2). Imines derived from α,β-unsaturated aldehydes had less *anti*-selectivity despite high enantioselectivity. In all cases, the reactions were complete within 24 h using 1 mol% of linked-BINOL **2a**. Catalyst loading was successfully reduced to 0.02 mol% without reduction in yield/selectivity. On the other hand, the Mannich-type reaction proceeded *syn*-selectively with Boc-imines **20** (Scheme 12b).[31] *syn*-Adducts **21** were obtained in good yield (80–100%), diastereomeric ratio (*syn*/*anti* = 83/17–95/5), and ee (98 to >99.5% ee) using imines prepared from aromatic aldehydes. Diastereoselectivities observed for α,β-unsaturated imines were, however, poor (*syn*/*anti* = 58/42–80/20). With Boc-imines **20**, reactions generally proceeded smoothly with 1–5 mol% of

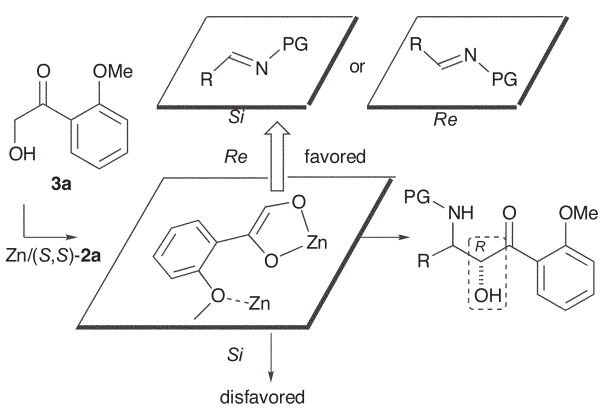
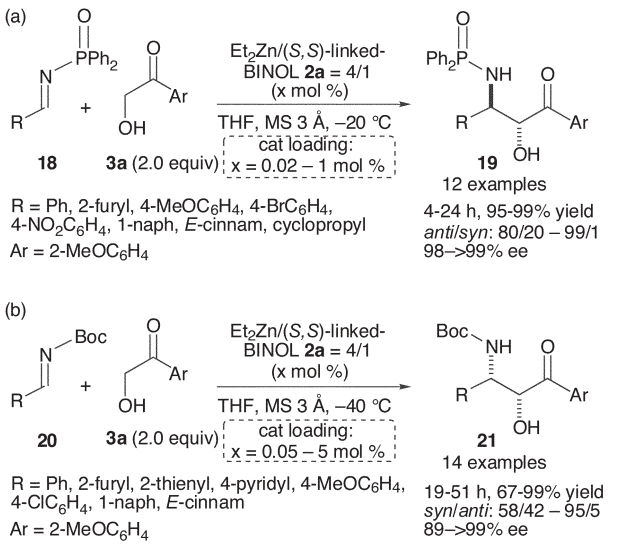


Fig. 8 Strategy to achieve enantio- and diastereoselective Mannich-type reaction producing β-amino alcohol.



Scheme 12 Direct catalytic asymmetric Mannich-type reaction of hydroxyketone **3a** using the Et_2Zn/linked-BINOL = 4/1 with MS 3 Å system.

linked-BINOL **2a**. Under the optimized conditions, catalyst loading was successfully reduced to 0.05 mol%, still affording Mannich adducts in good yields and ee. Postulated transition state models that explain the observed diastereoselectivity are shown in Fig. 9. To avoid steric repulsion between the Dpp-group and zinc enolate, the Mannich-type reaction of Dpp-imine **18** might proceed *via* transition state (A) in Fig. 9, preferentially affording *anti*-adducts **19**. When using less sterically demanding Boc-imine **20**, the facial selectivity of the imine would be opposite. To avoid steric repulsion between the substituent (R) of the imine and the zinc enolate, the Mannich-type reaction would proceed *via* transition state (B) in Fig. 9, preferentially giving *syn*-adducts **21**.

Facile methods for deprotection of the *N*-Dpp and *N*-Boc groups, and transformation of the anisyl ketone to an ester make the present Mannich-type reactions synthetically useful. As shown in Scheme 13, *anti*-Mannich adduct **19** was readily converted to a cyclic carbamate after removal of the *N*-Dpp

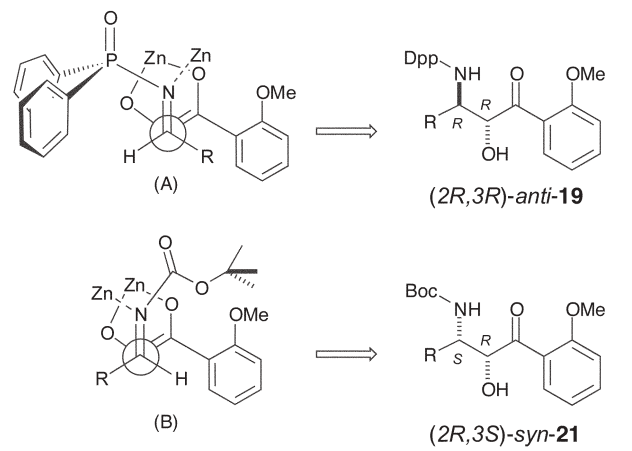
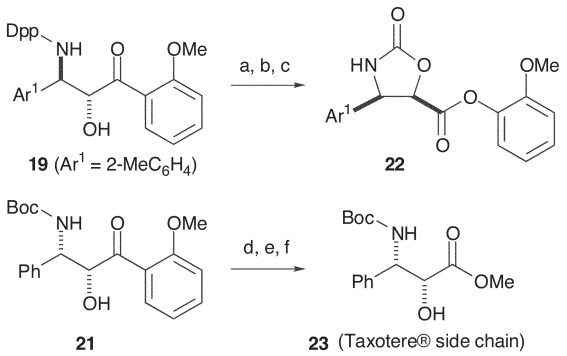


Fig. 9 Proposed transition state models of Mannich-type reaction.



Scheme 13 Transformations of Mannich adducts: *Reagents and conditions*: (a) *conc*. HCl*aq*/THF, rt, 1 h; (b) triphosgene, pyridine, CH_2Cl_2, −78 °C, 0.5 h, y. 84% (2 steps); (c) *m*CPBA, NaH_2PO_4, $Cl(CH_2)_2Cl$, 60 °C, 3 h, y. 88%; (d) Ac_2O, cat. DMAP, Py, 25 °C, 12 h, y. 94%; (e) *m*CPBA, Na_2HPO_4, 4,4′-thiobis(6-*tert*-butyl-*m*-cresol), $Cl(CH_2)_2Cl$, 60 °C, 10 h, y. 97%; (f) K_2CO_3, CH_3OH, 25 °C, y. quant.

group under acidic conditions, followed by treatment with triphosgene. Baeyer–Villiger oxidation of cyclic carbamate gave ester **22**. *syn*-Mannich adducts can be manipulated with equal ease, especially because the Boc group is one of the most frequently used amine protecting groups. *syn*-Mannich adduct **21** was readily converted to a side chain of Taxotere **23** through Baeyer–Villiger oxidation.[31]

4. Non-C_2-symmetric linked-BINOL

As mentioned in the introductory part, the delicate balance between steric and electronic properties of a catalyst determines reaction efficiency. Thus, a chiral ligand with a readily tunable framework is desirable. The Zn_3/(linked-BINOL)$_2$ structure shown in Fig. 6 suggested to us that 1) C_2-symmetry of linked-BINOL **2a** is not important, and 2) one phenolic OH group is not required for formation of the active zinc complex. Mechanistic studies revealed that while the active Zn-catalyst is not monomeric species, there is, however, a linear relationship between the enantiomeric excess of Mannich adduct **19** and the ee of chiral ligand **2a** used in the Mannich-type reaction of Dpp-imine **18** and hydroxyketone **3a** (Fig. 10), suggesting that 3) a homo-chiral complex is both more stable and more catalytically active than a hetero-chiral complex. We hypothesized that one of the chiral binaphthol units in linked-BINOL **2a** could be replaced by an achiral unit such as a biphenol or phenol derivative. Chirality would be transferred to the flexible achiral unit upon complexation to zinc and a similar chiral environment would be obtained with a chirally economical ligand.[32,33]

The structures of the evaluated ligands (**24a**–**24k**) are summarized in Fig. 11. These ligands were evaluated in a direct catalytic asymmetric Mannich-type reaction of Dpp-imine **18** and hydroxyketone **3a** using 5 mol% of ligand **24** and 20 mol% of Et_2Zn at −20 °C. With the original linked-BINOL **2a**, the reaction completed within 1 h, and Mannich-adduct **19** was obtained in 99% yield, *anti*/*syn* = 98/2, and >99% ee. A control experiment with 10 mol% of simple BINOL required much longer reaction time and gave inferior enantiomeric excess (68 h, 24% ee). Ligand **24a**, which lacks one phenolic OH group, gave

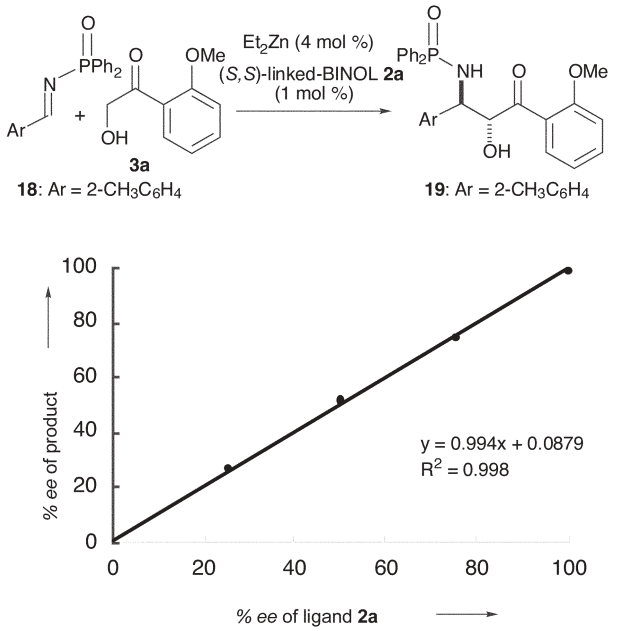


Fig. 10 Linear-relationship between Mannich-adduct **19** and (*S*,*S*)-linked-BINOL **2a** observed in direct Mannich-type reaction.

results similar to those obtained with **2a**. Ligand **24b** with an *atropisomeric*-biphenol unit was also efficient, suggesting that the chirality of the biphenol unit was controlled by complexation with zinc metals. Even a ligand containing an achiral unit, like **24c**, gave excellent results (1 h, 99% yield, 99% ee), while ligand **24d**, which has a phenolic-OH group in the 2′-position, required a long reaction time and gave poor enantioselectivity (23 h, 74% yield, 9% ee). On the other hand, ligands **24e** and **24f** also produced an unsatisfactory reaction rate and only modest enantioselectivity. These results imply that both the phenolic-OH group, at the proper position, and a biphenyl or sterically equivalent structure are required.

Although many of the ligands shown in Fig. 11 gave high enantioselectivity, it is more difficult to precisely compare their performance in terms of reaction rate. Generally, catalyst concentration is rather low when catalyst loading is reduced to less than 0.1 mol%, due to substrate solubility limitations. Thus, high turnover frequency (TOF) and turnover number (TON) under diluted conditions are required to reduce catalyst loading. To evaluate new ligands quantitatively in terms of reaction rate, the reaction profile for each ligand was monitored under diluted conditions ([imine] = 31 mM, [ligand **24**] = 0.31 mM, 1 mol%). The reaction profiles derived from ligands **2a**, BINOL, **24c**, **24j**, and **24k** are shown in Fig. 12. Ligands with achiral units gave better reaction rates than the original linked-BINOL **2a**, containing two chiral units. With ligand **24c**, catalyst loading was successfully reduced to as little as 0.01 mol% (TON = 8600, Scheme 14).

5. Y{N(SiMe$_3$)$_2$}$_3$/linked-BINOL complex: application in Mannich-type reaction

Although high catalyst turnover number and high ee were achieved in the Mannich-type reaction catalyzed by Et_2Zn and

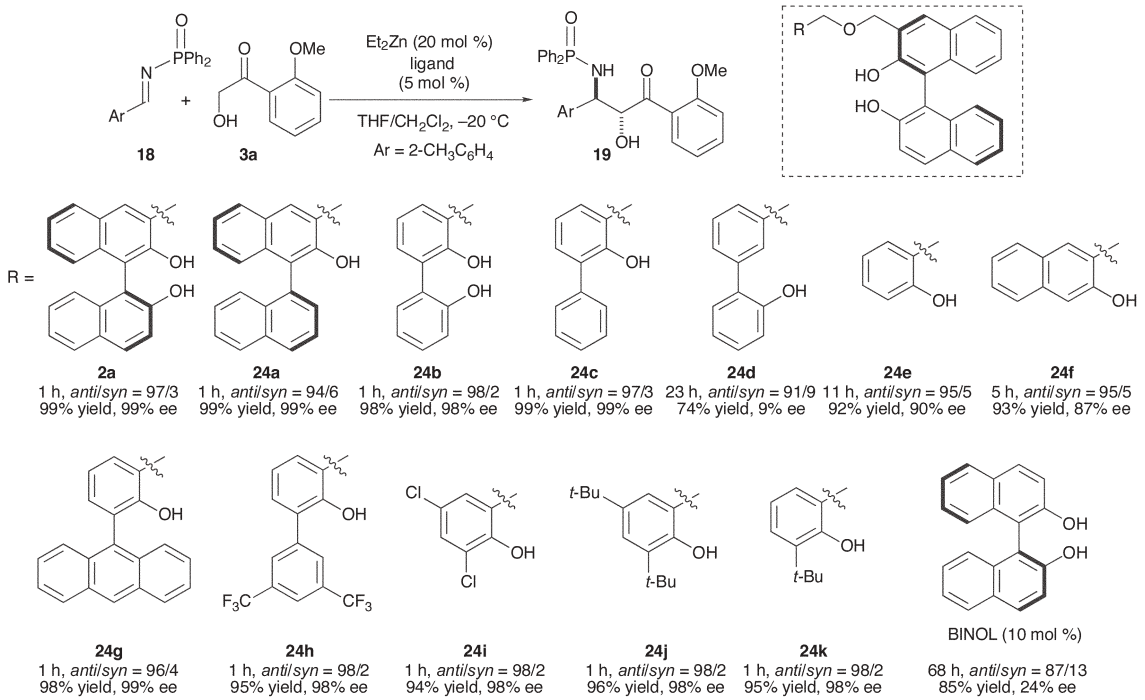


Fig. 11 Structures of linked-BINOL derivatives **24** and their application in Mannich-type reaction.

linked-BINOL, a few problems remained. 1) Only modest *syn*-selectivity was obtained with Boc-imines and diastereoselectivity strongly depended on the imine used.[31] Especially, α,β-unsaturated imines gave poor *syn*-selectivity (58/42–80/20). 2) The use of 2-hydroxy-2′-methoxyacetophenone **3a** was essential to achieve good selectivity. The methoxy phenyl group is synthetically useful, because the methoxy group facilitates efficient conversion of the Mannich adducts into β-amino-α-hydroxy esters *via* Baeyer–Villiger oxidation; however, zinc catalysis is not suitable for the synthesis of various β-amino-α-hydroxy ketones.

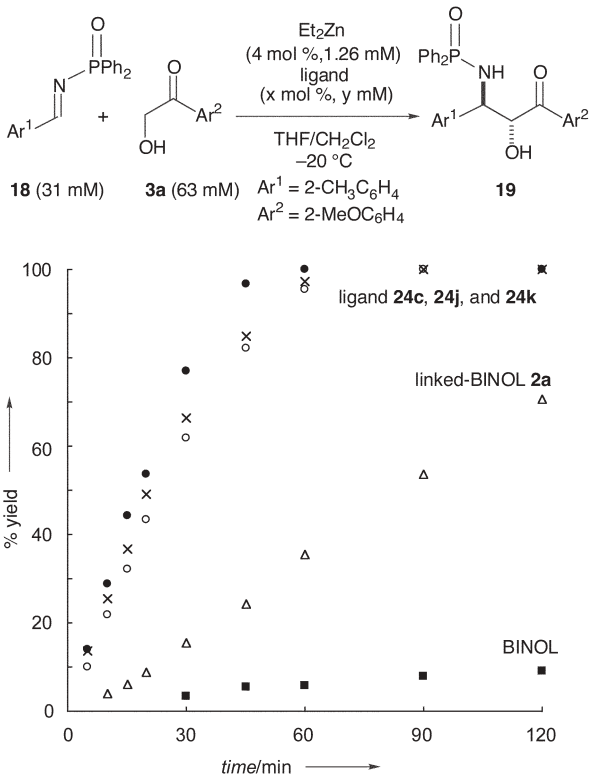
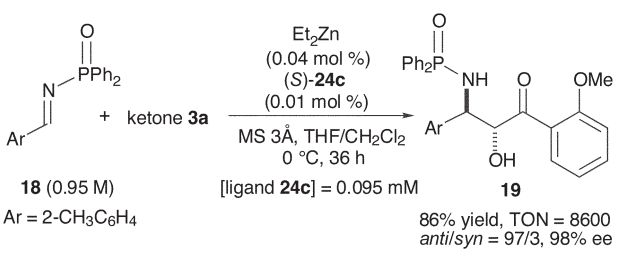


Fig. 12 Reaction profiles with linked-BINOL **2a** (△, 0.31 mM), BINOL (■, 0.62 mM), **24c** (○, 0.31 mM), **24j** (×, 0.31 mM), and **24k**(●, 0.31 mM)

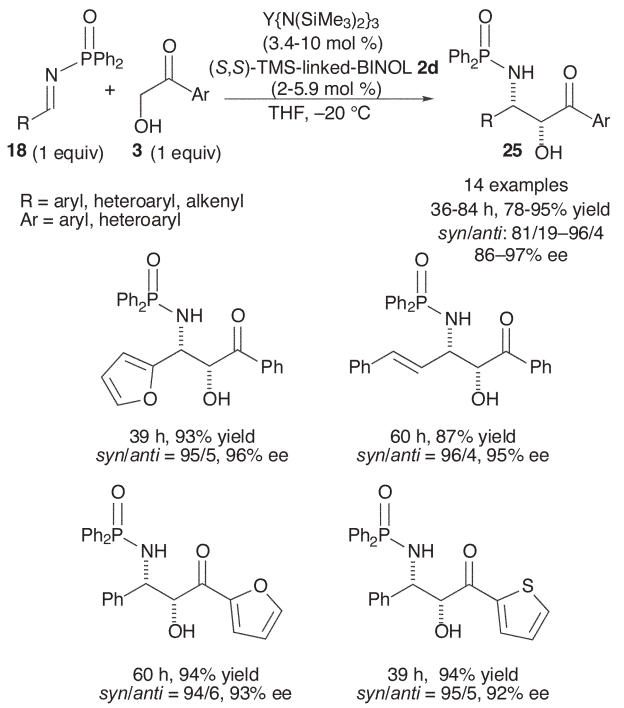
Because rare earth metal/linked-BINOL complexes are effective for other asymmetric reactions, we re-investigated these complexes for the Mannich-type reaction. In contrast to our expectations, the reaction of Dpp-imine **18** proceeded *syn*-selectively with rare earth metal/linked-BINOL complexes. Among the catalysts tested, the best diastereo- and enantioselectivity were obtained with $Y\{N(SiMe_3)_2\}_3$/linked-BINOL **2a** = 1.7 : 1. Rare earth metal alkoxides were not suitable for the present Mannich-type reaction. Modifications at the 6,6′,6″,6‴-positions of the linked-BINOL further improved stereoselectivity. When using TMS-linked-BINOL **2d** (Fig. 2), Mannich adduct **25** was obtained in 98% yield, *syn*/*anti* = 94/6,



Scheme 14 Mannich-type reaction with 0.01 mol% of ligand **24c**.

95% ee. Although the precise reason for the positive effects of ligand **2d** is not yet clear, bulky substituents at the 6,6′-position of binaphthyl might slightly affect the dihedral angle of the ligand, thereby improving stereoselectivity. Reactions proceeded smoothly with an equimolar amount of the nucleophile and electrophile. The $Y\{N(SiMe_3)_2\}_3$/TMS-linked-BINOL **2d** = 1.7/1 complex was applicable to various aromatic and heteroaromatic hydroxyketones as well as various aromatic and α,β-unsaturated imines.[34,35] High ee and high *syn*-selectivity were achieved (Scheme 15).

In the direct Mannich-type reaction of Dpp-imines **18**, the $Y\{N(SiMe_3)_2\}_3$/linked-BINOL **2a** or **2d** complexes gave *syn*-adducts **25**, while the Et_2Zn/linked-BINOL complex gave *anti*-adducts **19**. In order to explain this contrast, we assume that the coordination mode of Dpp-imine **18** to the Lewis acidic metal is different. With more oxophilic rare earth metals, Dpp-imine **18** would coordinate to yttrium through the oxygen atom. The reaction might then proceed *via* the acyclic *anti*-periplanar transition state to minimize gauche interactions between imine **18** and yttrium enolate (Fig. 13), affording the *syn*-product **25**.



Scheme 15 Direct catalytic asymmetric Mannich-type reactions of various hydroxyketones using $Y\{N(SiMe_3)_2\}_3$/TMS-linked-BINOL **2d** complex.

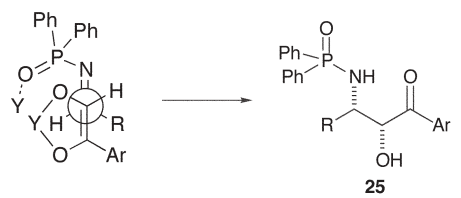
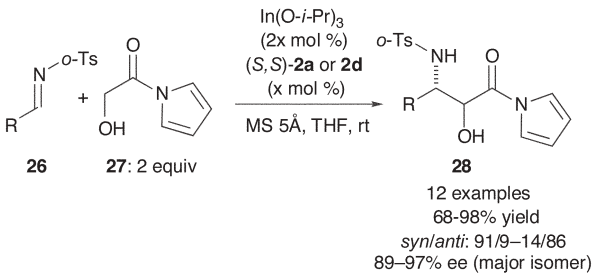


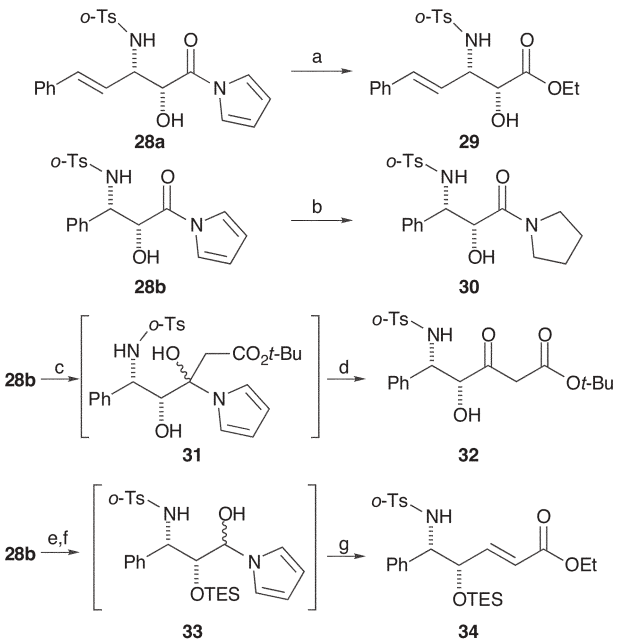
Fig. 13 Postulated transition model to give *syn*-Mannich adduct **25**.

6. In(O-*i*-Pr)$_3$/linked-BINOL complex: application in Mannich-type reaction

The Et_2Zn and $Y\{N(SiMe_3)_2\}_3$/linked-BINOL complexes afforded various β-amino-α-hydroxyketones in high enantio- and diastereoselectivity using hydroxyketones **3** as donors. On the other hand, the use of donor substrates with the oxidation state of carboxylic acid is still a formidable task due to the much higher pK_a value of the α-proton in carboxylic acid derivatives compared to ketones. Catalytic *in-situ* generation of enolates from carboxylic acid derivatives is much less favorable. The development of a suitably activated ester



Scheme 16 Direct catalytic asymmetric Mannich-type reactions using *N*-acylpyrrole as an activated carboxylic acid derivative donor.



Scheme 17 Transformations of *N*-acylpyrrole moiety: *Reagents and conditions*: a) NaOEt, EtOH, 0 °C to room temperature, 5 min, y. quant.; b) pyrrolidine, DBU, THF, 40 °C, 1 h, y. quant.; c) LDA, *t*-Bu-acetate, THF, −78 °C, 10 min; d) DBU, CH_2Cl_2, room temperature, 5 min, y. 62% (2 steps); e) TESCl, imidazole, DMF, 0 °C, 30 min, y. 87%; f) $LiBH_4$, THF, room temperature, 30 min; g) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, CH_3CN, room temperature, 7 h, y. 67% (2 steps).

equivalent donor and/or a new asymmetric catalyst are required to realize direct carbon–carbon bond-forming reactions using ester equivalent donors. As a donor substrate for investigation, we selected *N*-acylpyrrole because its aromaticity would assist enolate formation.

The Et_2Zn/linked-BINOL complex promoted the reaction of *N*-acylpyrrole **27** with Ts-imine, albeit in low yield. Better results were obtained by using an In(O-*i*-Pr)$_3$/linked-BINOL **2a** or **2d** complex. Rare earth metals were not suitable for generating the metal enolate of *N*-acylpyrrole **27**. As shown in Scheme 16, the Mannich-type reaction of α,β-unsaturated imines **26** proceeded *syn*-selectively in good yield and ee.[36] With aromatic imines, diastereoselectivity was modest. As shown in Scheme 17, the *N*-acylpyrrole moiety of Mannich adduct **28** was readily transformed into various functional groups, such as ester **29** (quant. yield), amide **30** (quant. yield) and so on.

7. Summary

The design and application of linked-BINOLs investigated in our group were reviewed. Linked-BINOLs are a kind of semi-crown ether, thus they are flexible and applicable to metals having various ionic radii (Ga^{3+}, Li^{+}, Zn^{2+}, In^{3+}, La^{3+}, and Y^{3+}). The flexible linker segment, containing a coordinative heteroatom, has a crucial role in the construction a unique and effective chiral environment that is not accessible from BINOL itself. Using linked-BINOLs as ligands, various catalytic asymmetric reactions can be realized by modifying central metals, linker heteroatom, and peripheral substituents.

Acknowledgements

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