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Review

Metal/linked-BINOL complexes: Applications in direct catalytic asymmetric Mannich-type reactions

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Abstract

Development of metal/linked-BINOL complexes and their applications in direct catalytic asymmetric Mannich-type reactions of hydroxyketones are reviewed. A Et_2Zn/linked-BINOL complex was effective for diastereo- and enantioselective synthesis of β-amino alcohols. By choosing the proper protective groups on the imine nitrogen, either *anti*- or *syn*-β-amino alcohol was obtained in excellent enantioselectivity (up to >99.5% ee) using the same zinc catalysis. $Y\{N(SiMe_3)_2\}_3$/linked-BINOL complex was effective for various hydroxyketones, affording *syn*-β-amino alcohols with high enantioselectivity (up to 98% ee). To broaden the nucleophile scope to carboxylic acid derivatives, *N*-acylpyrrole was utilized as an ester equivalent donor. $In(O\text{-}iPr)_3$/linked-BINOL complex was effective for generating an In-enolate from *N*-acylpyrrole in situ, giving Mannich adducts with high enantioselectivity (up to 98% ee).

Keywords: Asymmetric catalysis; Asymmetric synthesis; Bifunctional catalysis; Linked-BINOL; Mannich reaction; β-amino alcohol; Zinc; Yttrium; Lewis acid; Brønsted base

Contents

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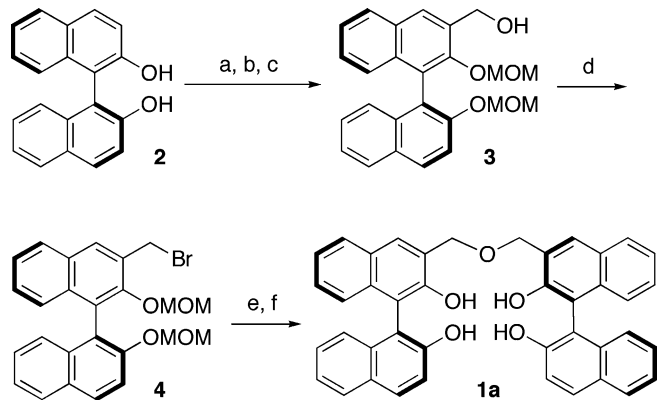
1. Introduction

Asymmetric catalysis using chiral metal complexes is one of the most general and flexible methods for asymmetric synthesis [1]. In asymmetric metal catalysis, the design of chiral ligands for metals is key when developing highly enantioselective and reactive catalytic reactions. The activity and selectivity of metals are tuned by the chiral ligand [2]. A delicate balance between the steric and electronic properties of the catalyst determines the reaction efficiency.

We recently reported a series of chiral ligands termed linked-BINOLs (**1a**–**1d**, Fig. 1) [3,4]. Linked-BINOLs consist of two chiral 1,1′-bi-2-naphthol units connected by a flexible linker at the 3 and 3″-positions, and one heteroatom in the linker. The heteroatom in the linker affects catalytic activity and stereoselectivity. Linked-BINOLs often provide a better chiral environment than 1,1′-bi-2-naphthol (BINOL **2**, Fig. 1), which was demonstrated for various catalytic asymmetric reactions, such as an epoxide opening reaction [3a], a direct aldol reaction [3b,5], Michael reactions [6,7], and direct Mannich-type reactions [8–10]. The linked-BINOL **1a** was designed based on reports by Cram et al. [11] regarding crown ethers incorporating chiral BINOL units. In contrast to crown ether-type cyclic ligands, the linked-BINOL **1a**, 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 Lewis acidic metal center. In addition, linked-BINOLs afford a suitable chiral environment for various metals with a different ionic radius because the linker is relatively flexible. Starting from optically active (*S*)-BINOL **2**, (*S*,*S*)-linked-BINOL **1a** was synthesized easily on a greater than 30 g scale (6 steps, total yield 57% from (*S*)-BINOL) as shown in Scheme 1 [12]. In this manuscript, we review our recent applications of metal/linked-BINOL **1a** complexes in direct catalytic asymmetric Mannich-type reactions.

2. Catalytic asymmetric Mannich-type reaction for β-amino alcohol synthesis

Chiral β-amino alcohol units are useful chiral building blocks found in various natural products, compounds with pharmacologically important activity, chiral auxiliaries, and chiral ligands [13], Various methods have been developed over the last decade for enantioselective and diastereoselective preparation of β-amino alcohols [14]. Among the methods available for their catalytic enantioselective syntheses [15], catalytic asymmetric Mannich-type reactions [16] of α-alkoxy enolate are of particular interest because two adjacent stereocenters are constructed simultaneously with a concomitant carbon-carbon bond formation. As shown in Scheme 2, either *anti*- or *syn*-β-amino alcohol is obtained in an optically active form using suitable chiral catalysts, imines, and nucleophiles. Toward this end, Kobayashi [17] reported pioneering work on Zr catalysis using preformed α-TBSO- and α-BnO-ketene silyl acetals, which selectively provided either *anti*- or *syn*-β-amino alcohol, respectively. Akiyama et al. [18] reported a *syn*-selective Mannich-type reaction of an α-Ph_3SiO-ketene silyl acetal using a chiral Brønsted acid catalyst. Although these methods are synthetically useful, they are not atom-economical [19]. Preparation of latent enolates such as ketene silyl acetals from esters requires stoichiometric amounts of a strong base and silylating reagents, and therefore the formation of salt as waste is unavoidable. The use of unmodified substrates as donors would be more atom-economical [20]. Toward this goal, the direct additions of



Scheme 1. Synthesis of linked-BINOL **1a**. Conditions: (a) NaH, MOMCl, DMF, 0 °C, 98%; (b) (i) BuLi, TMEDA, THF, −78–0 °C; (ii) DMF, −78–0 °C; (c) $NaBH_4$, THF, MeOH, 0 °C, 79% (2 steps); (d) (i) Ms_2O, CH_2Cl_2, Et_3N, 0 °C; (ii) LiBr, CH_2Cl_2, r.t., 97%; (e) **3**, NaH, THF, DMF, 0 °C to r.t., 88%; (f) $TsOHH_2O$, CH_2Cl_2, MeOH, 40 °C, 86%.

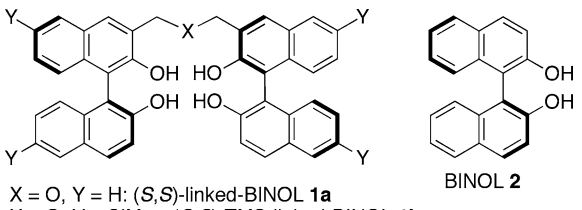
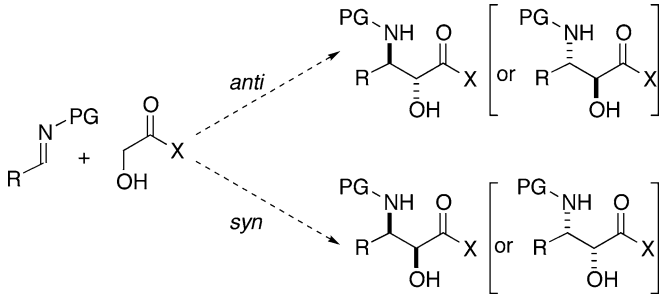


Fig. 1. Structures of (*S*,*S*)-linked-BINOLs (**1a**–**d**), and (*S*)-1,1′-bi-2-naphthol (BINOL **2**).



Scheme 2. Catalytic enantio- and diastereoselective synthesis of β-amino alcohol via Mannich-type reaction.

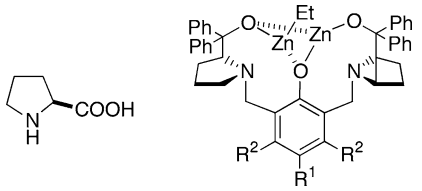


Fig. 2. Other highly enantioselective catalysts for *syn*-selective direct catalytic asymmetric Mannich(-type) reactions to produce *syn*-β-amino alcohols.

unmodified α-hydroxyketones [8,9,21], α-oxyaldehydes [22], and α-hydroxy-*N*-acylpyrrole as an ester surrogate [10] to imines were recently realized using either organocatalysts or metal catalysts [23,24]. Effective chiral catalysts for direct Mannich-type reactions producing *syn*-β-amino alcohols are shown in Fig. 2 [21,22], but are not covered in this review.

3. Et_2Zn/linked-BINOL complex [8]

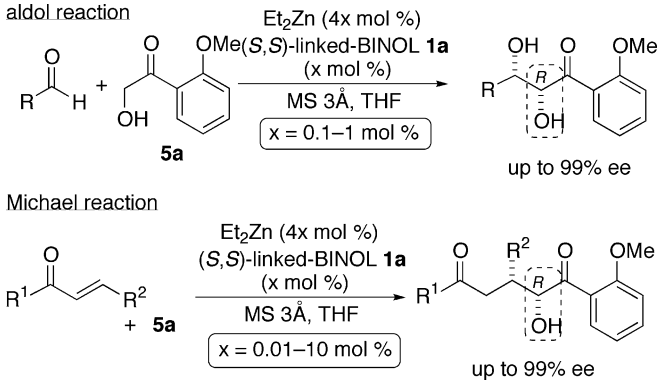
3.1. Mannich type reactions using the Et_2Zn/linked-BINOL *1a* complex

In our continuing investigation of direct catalytic asymmetric aldol reaction [5] and a Michael reaction [6] of hydroxyketones, a Et_2Zn/linked-BINOL **1a** complex was determined to be effective for shielding the *Si*-face of the zinc-enolate generated from ketone **5a**. Absolute configurations of products at the α-position of the carbonyl group were identical (2R) in aldol adducts and Michael adducts (Scheme 3). We anticipated that an efficient enantioface selection of the zinc-enolate would be applicable to other electrophiles, such as imines. Face selection of imines is important for achieving high diastereoselectivity. We hypothesized that either *anti*- or *syn*-Mannich adducts would be selectively obtained by choosing the proper protective group of imines that favor the *Si*-face or *Re*-face approach toward the zinc-enolate, respectively (Fig. 3). Screening of various imines revealed that Dpp-imines **6** [8,25] afforded *anti*-β-amino alcohol, while Boc-imines **8** [8b] afforded *syn*-β-amino alcohol (Tables 1 and 2).

The present asymmetric zinc catalysis was applicable to various Dpp-imines **6** (Table 1). All reactions were performed with 1 mol% of **1a**, 4 mol% of Et_2Zn, and MS 3 Å. With imines derived from α-nonenolizable aldehydes, the enantiomeric excesses were uniformly high (98 → 99.5% ee). Imines from aromatic aldehydes with various substituents (**6a**–**6j**) afforded products with high *anti*-selectivity (dr: 94/6 → 98/2, entries 1–10). Imine **6k** from α,β-unsaturated aldehyde had less *anti*-selectivity. Imine **6l** also provided the Mannich adduct in high ee (99%) with modest *anti*-selectivity (entry 12).

Substrate scope and limitations of Mannich-type reactions using Boc-imines **8** are summarized in Table 2. *syn*-Adducts were obtained in good yield (entries 1–11: 80–100%), diastereomeric ratio (entries 1–11: *syn*/*anti* = 83/17–95/5), and ee (entries 1–11: 98 → 99.5% ee) using imines prepared from aromatic aldehydes. For selected examples, the reaction was also performed with 1 mol % catalyst, and still afforded a good yield, diastereomeric ratio, and ee (entries 2, 4, and 8). Heteroaromatic imines were also applicable (entries 12–14). Imines **8l**, **8m**, and **8n** from α,β-unsaturated aldehydes gave products in high ee, although the diastereoselectivity was poor to modest (entries 15–17). Trials of Mannich-type reactions with reduced amounts of catalyst are shown in Scheme 4. A 0.02 mol% catalyst loading for Dpp-imine **6b** (turnover number: TON = 4920) and 0.05 mol% catalyst loading for Boc-imine **8a** (TON = 1760) were realized, maintaining high enantio- and diastereoselectivity. A high catalyst TON without product inhibition suggests that the Et_2Zn/linked-BINOL **1a** complex is compatible with both *anti*- and *syn*-β-amino alcohols.

Facile deprotection of the *N*-Dpp and *N*-Boc groups, and transformation of the ketone to an ester makes the present Mannich-type reactions synthetically more useful. As shown in Scheme 5, *anti*-Mannich adduct **7ba** was readily converted to cyclic carbamate **10** after removal of the



Scheme 3. Direct catalytic asymmetric aldol reaction and Michael reaction catalyzed by Et_2Zn/(*S*,*S*)-linked-BINOL **1a** complex.

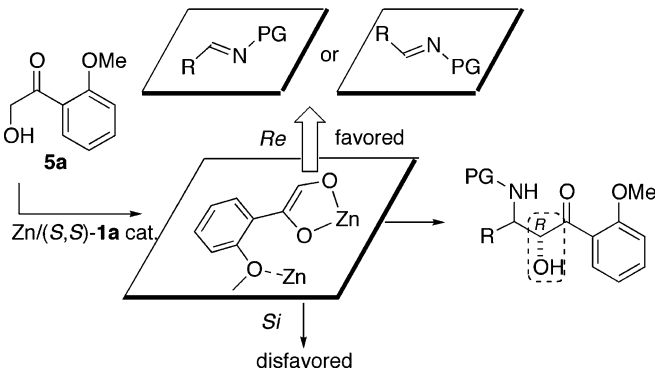
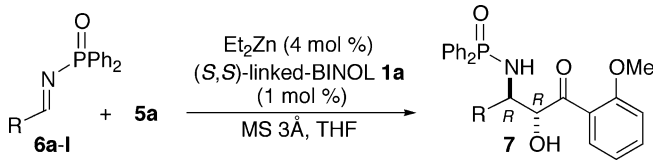


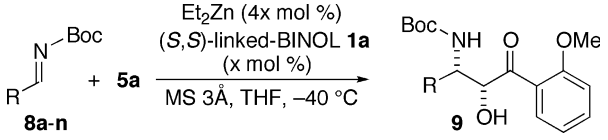
Fig. 3. Strategy to achieve enantio- and diastereoselective Mannich-type reaction.

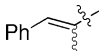
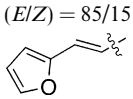
Table 1
anti-Selective direct catalytic asymmetric Mannich-type reaction with various *N*-Dpp-imines **6**



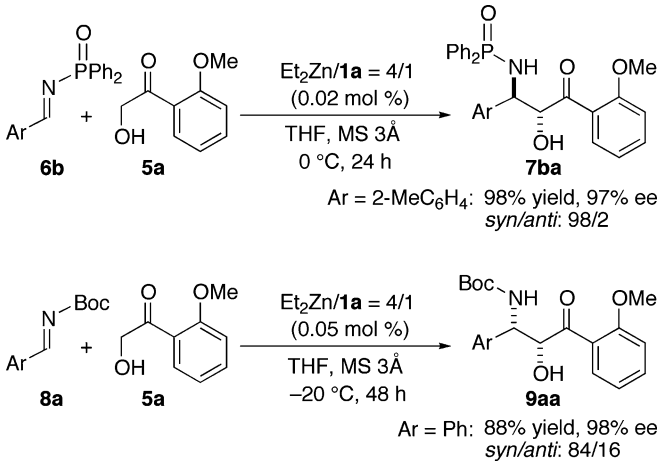
Entry	R		Product	Temp (°C)	Time (h)	Yield (%)	dr (*anti*/*syn*)	ee (%) (*anti*)
1	4-MeC_6H_4	**6a**	**7aa**	−20	9	98	96/4	98
2	2-MeC_6H_4	**6b**	**7ba**	−20	6	99	>98/2	99
3	C_6H_5	**6c**	**7ca**	−20	6	98	96/4	99
4	4-$MeOC_6H_4$	**6d**	**7da**	−20	6	97	95/5	99
5	4-$NO_2C_6H_4$	**6e**	**7ea**	−20	9	96	97/3	98
6	4-ClC_6H_4	**6f**	**7fa**	−20	4	97	97/3	98
7	4-BrC_6H_4	**6g**	**7ga**	−20	4	97	95/5	98
8	1-Naphthyl	**6h**	**7ha**	−20	6	97	98/2	>99.5
9	2-Naphthyl	**6i**	**7ia**	−20	7	95	94/6	99
10	2-Furyl	**6j**	**7ja**	−20	7	98	96/4	>99.5
11	(*E*)-Cinnam	**6k**	**7ka**	−30	7	97	81/19	>99.5
12	*cyclo*-Propyl	**6l**	**7la**	−30	5	98	80/20	99

Table 2
syn-Selective direct catalytic asymmetric Mannich-type reaction with various *N*-Boc-imines **8**

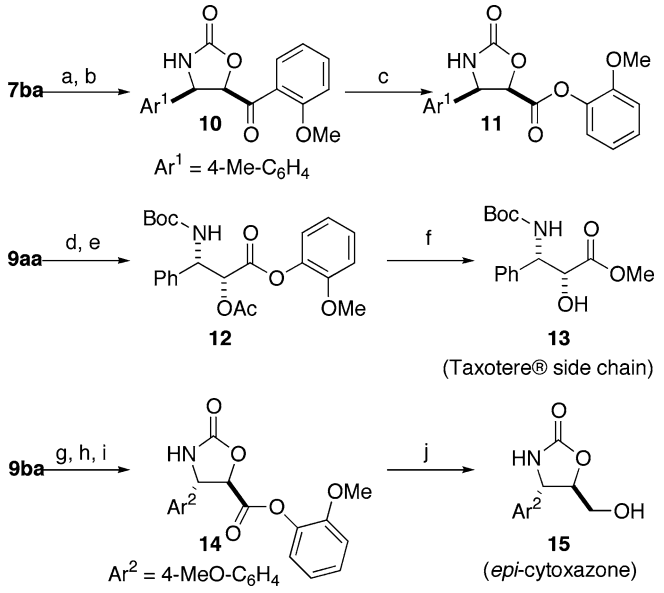


Entry	R		Product	Ligand 1 (*x* mol%)	Time (h)	Yield (%)	dr (*syn*/*anti*)	ee (%) (*syn*)
1	C_6H_5	**8a**	**9aa**	5	19	94	88/12	99
2	C_6H_5	**8a**	**9aa**	1	36	91	89/11	99
3	4-$MeOC_6H_4$	**8b**	**9ba**	5	25	>99	85/15	99
4	4-$MeOC_6H_4$	**8b**	**9ba**	1	51	91	85/15	99
5	4-MeC_6H_4	**8c**	**9ca**	5	20	>99	87/13	>99.5
6	3-MeC_6H_4	**8d**	**9da**	5	20	80	83/17	99
7	2-MeC_6H_4	**8e**	**9ea**	5	21	87	93/7	>99.5
8	2-MeC_6H_4	**8e**	**9ea**	1	35	89	94/6	99
9	4-ClC_6H_4	**8f**	**9fa**	5	27	82	83/17	98
10	1-Naphthyl	**8g**	**9ga**	5	27	85	95/5	99
11	2-Naphthyl	**8h**	**9ha**	5	26	80	85/15	99
12	2-Furyl	**8i**	**9ia**	5	26	>99	82/18	>99.5
13	2-Thiophenyl	**8j**	**9ja**	5	21	>99	86/14	99
14	3-Pyridyl	**8k**	**9ka**	5	21	67	72/28	89
15	(*E*)-cinnam	**8l**	**9la**	5	30	81	63/37	99
16		**8m**	**9ma**	5	26	95	80/20	>99.5
	(*E*/*Z*) = 85/15							
17		**8n**	**9na**	5	30	79	58/42	99

N-Dpp group under acidic conditions, followed by treatment with triphosgene. Baeyer-Villiger oxidation of **10** gave ester **11**. *syn*-Mannich adducts were also synthetically useful, because the Boc group is one of the most frequently utilized protective groups for amines. *syn*-Mannich adducts **9** were readily converted to a side chain of Taxotere **13** and *epi*-cytoxazone **15** through Baeyer-Villiger oxidation.



Scheme 4. Trials to reduce catalyst loading.



Scheme 5. Transformations of Mannich adducts to α-hydroxy-β-amino carboxylic acid derivative **11**, a side chain of Taxotere® **13**, and *epi*-cytoxazone **15**. Conditions: (a) *c*.HCl*aq*/THF, r.t., 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; (g) TFA, anisole, 25 °C, 2 h; (h) triphosgene, Py, CH_2Cl_2, −78 °C, 2 h, y. 92% (2 steps); (i) *m*CPBA, NaH_2PO_4, $Cl(CH_2)_2Cl$, 60 °C, 3 h, y. 63%; (j) $NaBH_4$, AcOH, THF, 25 °C, 2 h, y. 88%.

3.2. Structure of Et_2Zn/linked-BINOL complex

The Zn/linked-BINOL **1a** catalyst affords the Mannich adducts **7ba** in high ee (99% ee) with a variable ratio of Et_2Zn/linked-BINOL **1a**, such as 1/1, 2/1, 3/1, and 4/1, suggesting that similar active species are generated. For the substrate scope and limitations, we used Et_2Zn/linked-BINOL **1a** = 4/1 ratio because the best reaction rate was observed with 4/1 ratio. For the analysis of the structure of Zn/linked-BINOL **1a** catalyst, we tried to obtain an X-ray grade single crystal from various Zn/**1a** ratio mixtures. After many trials, the structure of the Zn/**1a** = 3/2 pre-catalyst prepared from Et_2Zn/**1a** in a ratio of 2/1 was unequivocally determined (Fig. 4). The structure was supported by X-ray crystallography, NMR, and ESI-MS analysis. In the Zn/**1a** = 3/2 complex, each linked-BINOL had a non-C_2-symmetric environment, and one phenolic OH group remained unchanged, even in the presence of a slight excess of free Et_2Zn. CSI-MS analysis in the presence of hydroxyketone **5a** suggested that **5a** is incorporated into the Zn/**1a** complex to form an oligomeric Zn/**1a**/**5a** = 7/3/4 complex (Fig. 5). The proposed catalytic cycle of the Mannich-type reaction is shown in Fig. 6. The active species is postulated to be the Zn/linked-BINOL/ketone oligomeric complex [Ar*OZn, (I)]. Zinc-phenoxide would act as a Brønsted base to deprotonate the α-proton of the ketone, affording a zinc-enolate (II). Zinc would also function as a Lewis acid to activate imines (III), and then 1,2-addition would give (IV). Subsequent protonation and ligand exchange of (IV) with ketone **5a** regenerates (I). Initial rate

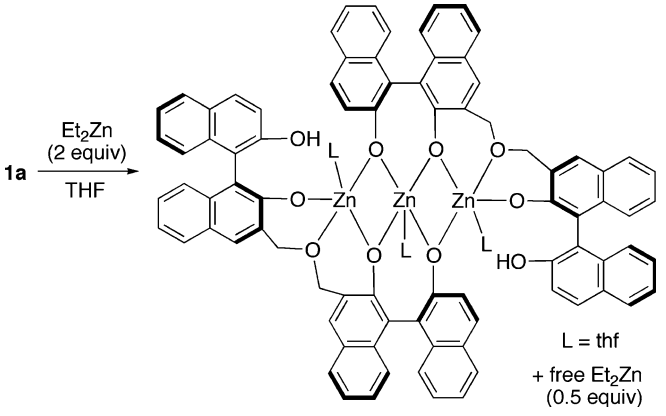


Fig. 4. Structure of Zn/**1a** = 3/2 complex determined by X-ray crystal analysis.

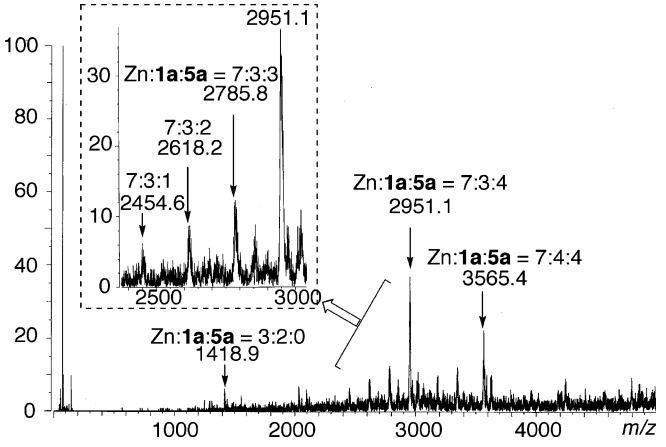


Fig. 5. CSI-MS analysis of Et_2Zn/linked-BINOL**1a**/ketone **5a** = 2/1/10 solution.

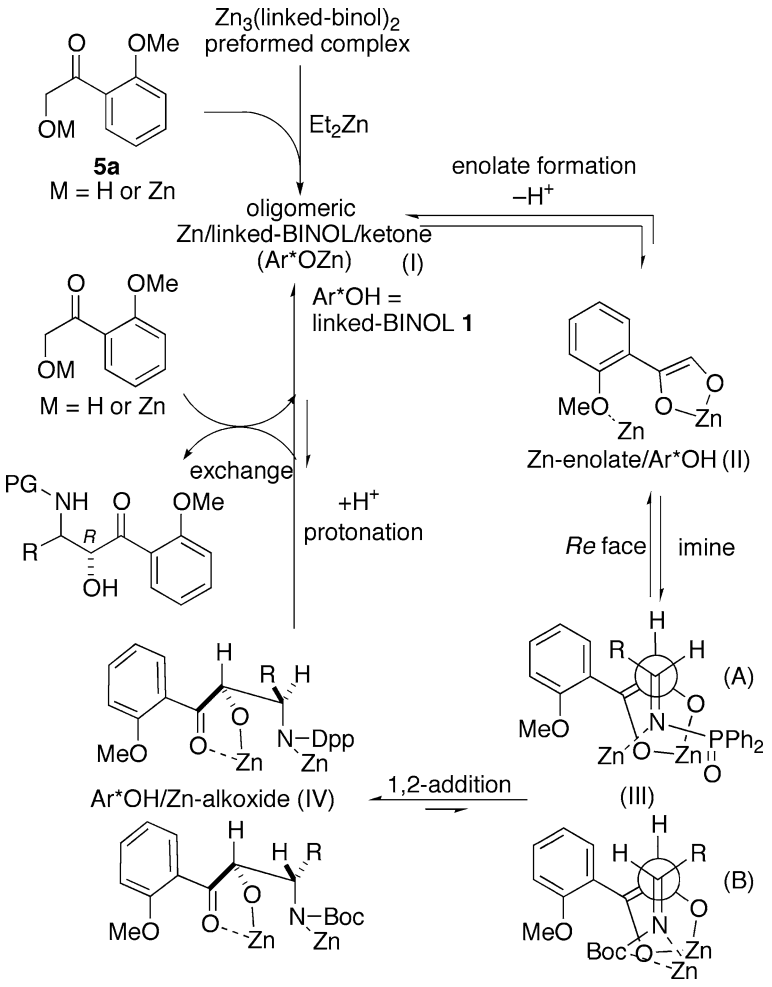


Fig. 6. Postulated catalytic cycle of Mannich-type reaction.

kinetics studies suggested that the rate-determining step with Dpp-imines **6** was the product dissociation step [from (IV) to (I)], while the rate-determining step with Boc-imines **8** was the 1,2-addition step [from (III) to (IV)]. To avoid steric repulsion between the Dpp-group and zinc-enolate, the Mannich-type reaction would proceed via the transition state (A) in Fig. 6, preferentially affording *anti*-adducts. When using the less sterically demanding Boc-imine **8**, the facial selectivity of the imine would be the opposite. To avoid steric repulsion between a substituent (R) of imine and zinc-enolate, the Mannich-type reaction would proceed via the transition state (B) in Fig. 6, giving *syn*-adducts.

3.3. Non-C_2-symmetric linked-BINOLs [8c]

The results in Fig. 4 suggested that (1) C_2-symmetry of linked-BINOL **1a** is not important, and (2) one phenolic OH group would not be required. Mechanistic studies suggested that the active species of the Zn catalysis is an oligomeric species; however, there was a linear relationship between the enantiomeric excess of product **7ba** and chiral ligand **1a** used in the Mannich-type reaction of Dpp-imine **6b** and hydroxyketone **5a** (Fig. 7), suggesting that (3) a

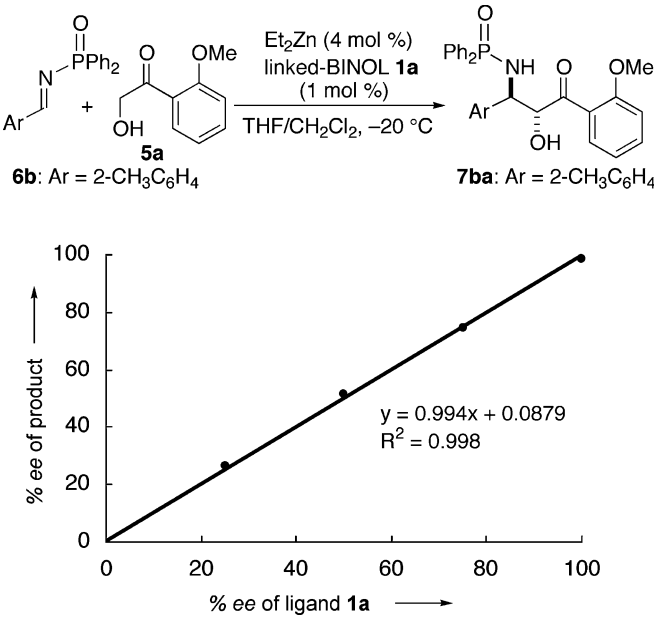


Fig. 7. Linear-relationship between Mannich-adduct **7ba** and (*S*,*S*)-linked-BINOL **1a** observed in direct Mannich-type reaction of **6b** with **5a**.

homo-chiral complex is more favorable than a hetero-chiral complex. We hypothesized that one of the chiral binaphthol units can be replaced with an achiral unit such as *atropisomeric*-biphenol or achiral phenol derivatives. Chirality would be transferred to the flexible achiral unit upon complexation with zinc metals and a similar chiral environment would be obtained with a chirally economical ligand [26].

The structures of the evaluated ligands (**16a**–**16k**) are summarized in Fig. 8. The potentials of the ligands were evaluated in a direct catalytic asymmetric Mannich-type reaction of imine **6b** and hydroxyketone **5a** using 5 mol% of ligand **16** and 20 mol% of Et_2Zn at −20 °C in THF/CH_2Cl_2 ([imine] = 150 mM, [ligand **16**] = 7.5 mM). With the original ligand **1a**, the reaction completed within 1 h, and Mannich-adduct **7ba** was obtained in 99% yield, *anti*/*syn* = 98/2, and >99% ee (Table 3, entry 1). A control experiment with 10 mol% of simple BINOL **2** had a much lower reaction rate and enantiomeric excess (entry 2, 68 h, 24% ee). Ligand **16a**, which lacks one phenolic OH group, gave results similar to those obtained with **1a** (entry 3). Ligand **16b** with an *atropisomeric*-biphenol unit was also efficient (entry 4), suggesting that the chirality of the biphenol unit was controlled by complexation with zinc metals. Even an achiral unit like **16c** gave excellent results (entry 5, 1 h, 99% yield, 99% ee), while ligand **16d**, which has a phenolic-OH group in the 2′-position, had a poor reaction rate and poor enantioselectivity (entry 6, 23 h, 74% yield, 9% ee). On the other hand, ligands **16e** and **16f** also produced an unsatisfactory reaction rate and only modest enantioselectivity (entries 7 and 8). The results in entries 5–8 implied that both the phenolic-OH group at the proper

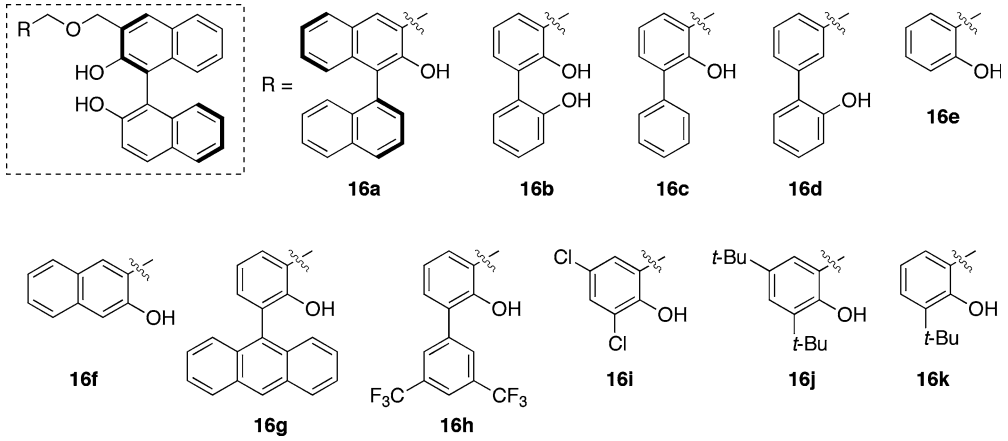
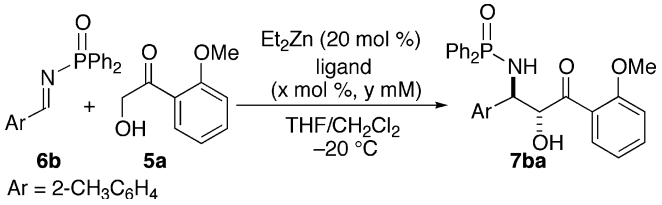


Fig. 8. Structures of non-C_2-symmetric (*S*)-linked-BINOL derivatives **16a**–**16k** consisted with one achiral unit and one chiral binaphthol unit.

Table 3
Catalytic asymmetric Mannich-type reaction using various chiral ligands (**la**, **2**, and **16a**–**16k**)



6b **5a** **7ba**

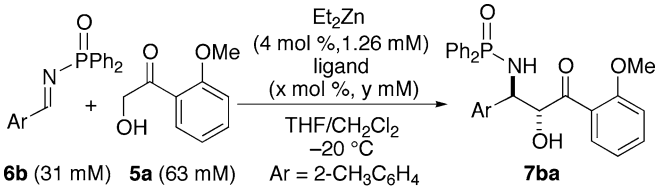
Ar = 2-$CH_3C_6H_4$

Entry	Ligand (*x* mol%)	[Ligand] (y mM)	Time (h)	Yield (%)	*anti*/*syn*	ee (%)
1	**1a** (5)	7.5	1	99	97/3	>99
2	**2** (10)	15	68	85	87/13	24
3	**16a** (5)	7.5	1	99	94/6	99
4	**16b** (5)	7.5	1	98	98/2	98
5	**16c** (5)	7.5	1	99	97/3	99
6	**16d** (5)	7.5	23	74	91/9	9
7	**16e** (5)	7.5	11	92	95/5	90
8	**16f** (5)	7.5	5	93	95/5	87
9	**16g** (5)	7.5	1	98	96/4	99
10	**16h** (5)	7.5	1	95	98/2	98
11	**16i** (5)	7.5	1	94	98/2	98
12	**16j** (5)	7.5	1	96	98/2	98
13	**16k** (5)	7.5	1	95	98/2	98

position and a substituent on the aromatic ring are required.

Although many of the ligands shown in Fig. 8 gave high enantioselectivity (Table 3), it was 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 turn over frequency (TOF) and 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 **16**] = 0.31 mM, 1 mol%), and ligands **16c**, **16j**, and **16k** had the best reaction rate among the ligands shown in Fig. 8. The reaction profiles with ligands **1a**, **2**, **16c**, **16j**, and **16k** are shown in Fig. 9. Ligands with achiral units had a better reaction rate than the original linked-BINOL **1a** with two chiral units.

The utility of ligand **16c** was further demonstrated as shown in Scheme 6. Catalyst loading was successfully reduced with **16c**. The Mannich-type reaction proceeded smoothly with as little as 0.01 mol% loading of **16c**, affording the product in good yield and selectivity (86%, 98% ee, TON = 8600) at 0 °C after 36 h. The reaction proceeded smoothly even with low ligand concentration ([ligand **16c**] = 0.095 mM). This is the best catalyst TON in the catalytic asymmetric Mannich-type reaction.



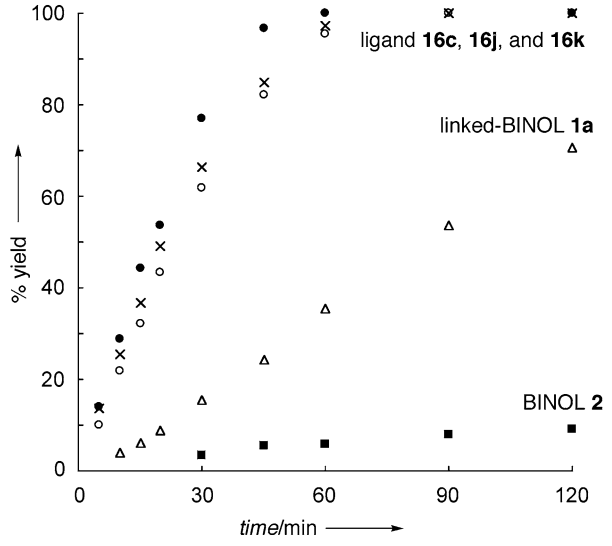
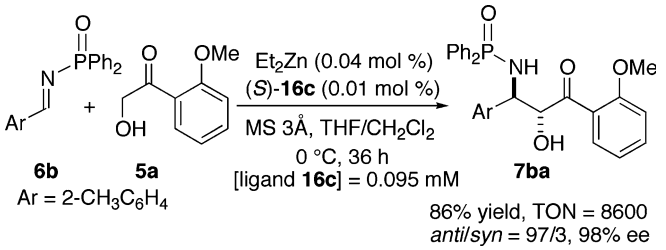


Fig. 9. Reaction profiles with chiral ligands **1a** (△, 0.31 mM, 1 mol%), **2** (■, 0.62 mM, 2 mol%), **16c** (○, 0.31 mM, 1 mol%), **16j** (×, 0.31 mM, 1 mol%), and **16k** (●, 0.31 mM, 1 mol%).



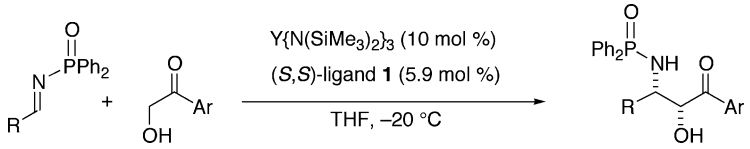
Scheme 6. Catalytic asymmetric Mannich-type reaction using 0.01 mol% of **16c**.

4. Y{N(SiMe$_3$)$_2$}$_3$/linked-BINOL complex [9]

Although high catalyst TON and high ee were achieved using the Et$_2$Zn/linked-BINOLs **1** and **16** complexes, problems remained: (1) Modest *syn*-selectivity with Boc-imine; diastereoselectivity strongly depended on the imines used. In particular, α,β-unsaturated imines and heteroaromatic imines gave poor *syn*-selectivity. (2) Nucleophile generality; use of 2-hydroxy-2′-methoxyacetophenone **5a** was essential to achieve good selectivity. The methoxy phenyl group in the Mannich adducts is synthetically useful, because the methoxy group facilitates efficient conversion of the Mannich adducts into β-amino-α-hydroxy esters through Baeyer-Villiger oxidation (Scheme 5); however, zinc catalysis is not suitable for the synthesis of various β-amino-α-hydroxyketones. For example, when using 2-hydroxyacetophenone **5b** and 2-hydroxyacetylfuran **5f** without a methoxy group on the aromatic ring, Mannich adducts are obtained in only modest enantioselectivity.

To overcome the modest *syn*-selectivity and the limitation in the nucleophile generality of the zinc catalyzed Mannich-type reactions, various rare earth metal/linked-BINOL complexes were screened. After intensive optimization, the best diastereo- and enantioselectivity were obtained with Y{N(SiMe$_3$)$_2$}$_3$/linked-BINOL **1a** = 1.7/1 ratio (Table 4, entry 1). Modification at the 6,6′,6″, 6‴-positions of the linked-BINOL further improved stereoselectivity. When using TMS-linked-BINOL **1b** (Fig. 1), Mannich adduct **7cb** was obtained in 98% yield, *syn*/*anti* = 94/6, 95% ee (entry 2). Although the precise reason for the positive effects of ligand **1b** 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. The Mannich adduct was obtained in 90% yield, even with an equimolar amount of the nucleophile (entry 3). The Y{N(SiMe$_3$)$_2$}$_3$/**1a** or **1b** = 1.7/1 complex was applicable to various aromatic and heteroaromatic hydroxyketones **5b**–**5g** (Table 4, entries 1–8). TMS-linked-BINOL **1b** gave better chemical yield, diastereoselectivity, and ee than linked-BINOL **1a** in all hydroxyketones. Entries 9–14 illustrate the imine substrate scope. The high diastereoselectivity obtained with α,β-unsaturated imines **6k** and

Table 4
syn-Selective direct catalytic asymmetric Mannich-type reaction of Dpp-imine 6 using various hydroxyketones **5b–5g**



6 **5** **7**

Entry	Imine	R	KetoneAr (equiv)		Product	Ligand	Time (h)	Yield (%)	dr (*syn*/*anti*)	ee (%) (*syn*)
1	Ph	**6c**	Ph	**5b** (1.2)	**7cb**	**1a**	48	90	90/10	91
2	Ph	**6c**	Ph	**5b** (1.2)	**7cb**	**1b**	48	98	94/6	95
3	Ph	**6c**	Ph	**5b** (1.0)	**7cb**	**1a**	48	90	95/5	95
4	Ph	**6c**	4-MeO–C_6H_4	**5c** (1.0)	**7cc**	**1b**	84	89	91/9	98
5	Ph	**6c**	4-Me–C_6H_4	**5d** (1.0)	**7cd**	**1b**	63	91	91/9	96
6	Ph	**6c**	4-Cl–C_6H_4	**5e** (1.0)	**7ce**	**1b**	48	94	81/19	86
7	Ph	**6c**	2-Furyl	**5f** (1.0)	**7cf**	**1b**	60	94	94/6	93
8	Ph	**6c**	2-Thienyl	**5g** (1.0)	**7cg**	**1b**	36	95	95/5	92
9	4-Cl–C_6H_4	**6f**	Ph	**5b** (1.0)	**7fb**	**1b**	48	78	94/6	95
10	4-MeO–C_6H_4	**6d**	Ph	**5b** (1.0)	**7db**	**1b**	84	90	95/5	94
11	2-Furyl	**6j**	Ph	**5b** (1.0)	**7jb**	**1b**	39	93	95/5	96
12	2-Thienyl	**6m**	Ph	**5b** (1.0)	**7mb**	**1b**	39	95	96/4	97
13[a]	2-Thienyl	**6m**	Ph	**5b** (1.0)	**7mb**	**1b**	61	91	94/6	95
14	PhCH=CH–	**6k**	Ph	**5b** (1.0)	**7kb**	**1b**	60	87	96/4	95
15[b]	Ar^1CH=CH–	**6n**	Ph	**5b** (1.0)	**7nb**	**1b**	42	94	95/5	93
16[b]	Ar^2CH=CH–	**6o**	Ph	**5b** (1.0)	**7ob**	**1b**	60	92	93/7	91
17[b]	Ar^3CH=CH–	**6p**	Ph	**5b** (1.0)	**7pb**	**1b**	42	89	96/4	94

[a] 2 mol% of ligand **1b** and 3.4 mol% of $Y\{N(SiMe_3)_2\}_3$ was used.
[b] Ar^1 = 4-Cl–C_6H_4–; Ar^2 = 4-Me–C_6H_4–; Ar^3 = 2-furyl.

6n–6p is noteworthy, because the Et_2Zn/linked-BINOL **1a** complex gave only modest diastereoselectivity using α,β-unsatu- rated imines, even when using hydroxyketone **5a**. The Mannich adduct from α,β-unsaturated imine is synthetically useful, because the Mannich adduct can be a precursor for the β-alkyl-β-amino-α-hydroxy carbonyl compound. Catalyst loading was successfully reduced (entry 13). With 2 mol% of **1b** and 3.4 mol% of $Y\{N(SiMe_3)_2\}_3$, a Mannich-type reaction of imine **6m** and hydroxyketone **5b** gave **7mb** in 91% yield and 95% ee after 61 h.

Although the structure of the catalyst is not clarified yet, we believe that the yttrium complex would function as a Lewis acid-Brønsted base bifunctional catalyst in a similar manner as zinc-catalyzed direct Mannich-type reactions. The Y-OAr (Ar = linked-BINOL) moiety would function as a Brønsted base to generate Y-enolate from hydroxyketones, and the Y center would function as Lewis acid to activate imines. In the direct Mannich-type reaction of Dpp-imines **6**, the $Y\{N(SiMe_3)_2\}_3$/linked-BINOL complex gave *syn*-adducts, while the Et_2Zn/linked-BINOL complex gave *anti*-adducts. We assume that the coordination mode of Dpp-imine **6** on Lewis acidic metal is different. With more oxophilic rare earth metals, Dpp-imine **6** would coordinate to yttrium through the oxygen atom. The reaction would proceed via the acyclic *anti*-periplanar transition state to minimize gauche interactions between imine **6** and Y-enolate (Fig. 10), affording the *syn*-product.

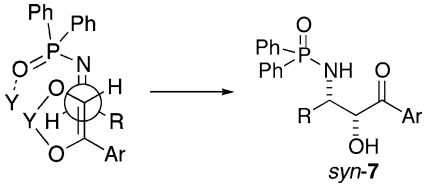


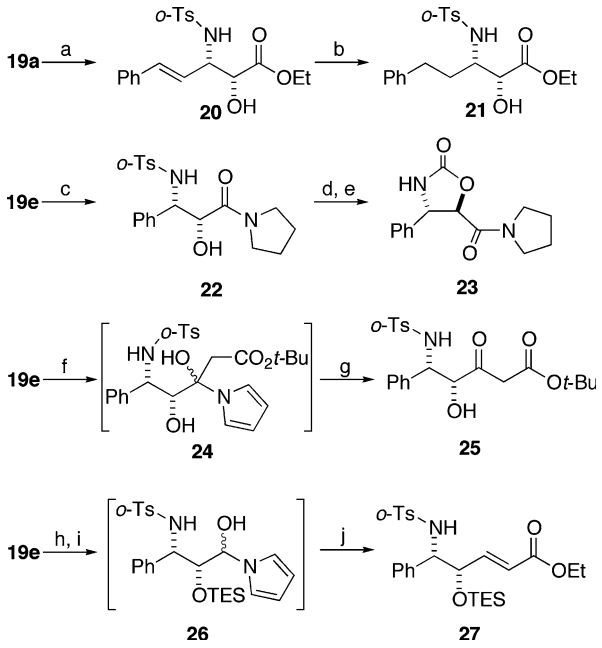
Fig. 10. Postulated acyclic *anti*-periplanar transition state model with oxophilic yttrium catalyst to give *syn*-Mannich adducts.

5. In(O-*i*Pr)$_3$/linked-BINOL complex [10]

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 ketones 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 than in ketones. Catalytic in situ generation of enolate from carboxylic acid derivatives is much more difficult than that from ketones. The development of a suitably activated ester equivalent donor and/or a new asymmetric catalyst are required to realize direct carbon–carbon bond forming reactions using ester equivalent donors [27,28]. As a donor substrate for investigation, we selected *N*-acylpyrrole as an achiral template for the following reasons. Evans reported the unique properties of *N*-acylpyrrole [29]. We subsequently demonstrated the utility

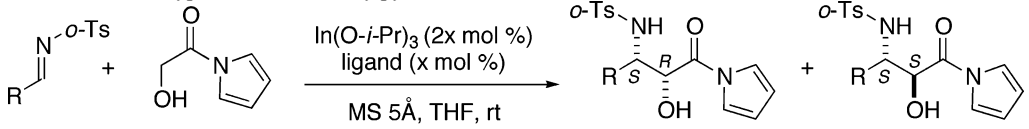
of the *N*-acylpyrrole moiety as an ester surrogate in catalytic asymmetric conjugate additions, where α,β-unsaturated *N*-acylpyrrole substrate was used as an activated, monodentate electrophile [30]. Because the lone pair on the nitrogen in the pyrrole ring is delocalized in an aromatic system, the properties of the carbonyl group are similar to those of a phenyl ketone. We supposed that *N*-acylpyrrole would also be useful as an ester equivalent donor because the aromaticity would assist enolate formation. Because the coordination mode of the *N*-acylpyrrole donor is similar to that of an aromatic ketone, the chiral environment optimized for ketone donors would be applicable for *N*-acylpyrrole.

Screening of metal sources revealed that In(O-*i*Pr)$_3$ was the most effective. When using an In(O-*i*Pr)$_3$/linked-BINOL **1a** = 2/1 complex, the reaction of *N*-acylpyrrole **17** and **18a** in THF proceeded at room temperature to give the Mannich adduct **19a** in 94% yield, *syn*/*anti* = 91/9, and 96% ee (*syn*) (Table 5, entry 1). The substrate scope of the present catalysis is summarized in Table 5. The diastereomeric ratio depended on the imines used. Alkenyl imines **18a**–**18d** afforded *syn*-adducts with good diastereoselectivity (88/12-91/9) and high ee (*syn*: 93–97%, entries 1–4). *syn*-Selectivity of imines **18e**–**18f** with *para*-substituted or non-substituted aromatic ring was only modest (entries 5 and 6). On the other hand, imines **18g**–**18k** with *ortho*-substituted aromatic rings and cyclopropyl imine **18l** gave products *anti*-selectively in high ee (92–98% ee, *anti*; entries 7–12). Use of a modified linked-BINOL ligand **1b** gave slightly better stereoselectivity in some cases. In all entries in Table 5, both *syn*- and *anti*-adducts were obtained with the same absolute configuration at the β-position (*S*), implying that enantioface selection of the imines is identical. For the precise understanding of diastereoselectivity in Table 5 and the effects of the modified ligand **1b**, further mechanistic studies including clarification of the structure of the In(O-*i*Pr)$_3$/(*S*,*S*)-linked-BINOL **1** complex are required. In this reaction, we assumed that either In-alkoxide or In-phenoxide functions as a Brønsted base to deprotonate the α-proton of **17** to form In-enolate in situ. Although there are many reports on the Lewis acidic



Scheme 7. Transformations of *N*-acylpyrrole units. Conditions: (a) NaOEt, EtOH, 0 °C to room temperature, 5 min, y. quant.; (b) Pd/C, H_2, MeOH, room temperature, 30 min, y. 92%; (c) pyrrolidine, DBU, THF, 40 °C, 1 h, y. quant.; (d) triphosgene, Py, CH_2Cl_2, −78 °C to room temperature, 1 h, y. 94%; (e) Mg powder, MeOH, room temperature, 20 min, y. 81%; (f) LDA, *t*-Bu-acetate, THF, −78 °C, 10 min; (g) DBU, CH_2Cl_2, room temperature, 5 min, y. 62% (2 steps); (h) TESCl, imidazole, DMF, 0 °C, 30 min, y. 87%; (i) $LiBH_4$, THF, room temperature, 30 min; (j) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, CH_3CN, room temperature, 7 h, y. 67% (2 steps).

Table 5
Direct catalytic asymmetric Mannich-type reaction of *N*-acylpyrrole 17



Entry	Imine (R)		Ligand (*x* mol%)	Product	Time (h)	Yield (%)	dr (*syn*/*anti*)	ee (%) (*syn*/*anti*)
1	(*E*)-PhCH=CH–	**18a**	**1a** (10)	**19a**	96	94	91/9	96/83
2	(*E*)-*p*-tol–CH=CH–	**18b**	**1a** (10)	**19b**	97	86	89/11	95/76
3	(*E*)-*p*-ClC_6H_4–CH=CH–	**18c**	**1a** (10)	**19c**	97	79	88/12	93/71
4	(*E*)-2-furyl–CH=CH–	**18d**	**1a** (10)	**19d**	99	80	90/10	97/81
5	Ph	**18e**	**1a** (10)	**19e**	111	98	61/39	91/91
6	*p*-Cl–C_6H_4	**18f**	**1a** (10)	**19f**	89	97	59/41	96/94
7	1-Naphthyl	**18g**	**1b** (15)	**19g**	99	87	23/77	89/94
8	*o*-Cl–C_6H_4	**18h**	**1a** (10)	**19h**	76	87	17/83	81/93
9	*o*-Br–C_6H_4	**18i**	**1a** (10)	**19i**	89	68	14/86	90/95
10	*o*-Me–C_6H_4	**18j**	**1a** (15)	**19j**	92	76	24/76	85/93
11	*o*-MeO–C_6H_4	**18k**	**1b** (15)	**19k**	93	74	23/77	86/92
12	Cyclopropyl	**18l**	**1b** (10)	**19l**	65	86	25/75	90/98

Indium catalysis ($In(OTf)_3$, $InCl_3$, $InBr_3$, etc.) [31], the Brønsted basic property of Indium chiral catalysis was utilized for the first time in organic synthesis.

The utility of the *N*-acylpyrrole unit as an ester surrogate was demonstrated through several transformations of Mannich adducts, as shown in Scheme 7. The *N*-acylpyrrole unit of **19a** was readily transformed into an ethyl ester and an amide in quantitative yield. In addition to the substitution reaction with alcohol and amine, reaction with lithium enolate followed by treatment with DBU provided ketoester **25**. Protection with a TES group followed by reduction with $LiBH_4$ afforded pyrrole carbinol **26** as a stable intermediate. Under Masamune-Roush conditions [32], an aldehyde moiety was generated in situ from crude pyrrole carbinol **26**, and α,β-unsaturated ester **27** was obtained.

6. Summary

Direct catalytic asymmetric Mannich-type reactions catalyzed by metal/linked-BINOL complexes are summarized. Et_2Zn, $Y\{N(SiMe_3)_2\}_3$, and In(O-*i*Pr)$_3$/linked-BINOL complexes were suitable for the reactions. It is noteworthy that three kinds of metals with a different ionic radius were applicable to the same chiral ligand, suggesting the flexibility of linked-BINOL **1a**. Furthermore, simple BINOL **2** itself does not afford good selectivity and reactivity in many cases. The ether linker of linked-BINOL has a key role in providing flexible and suitable chiral environment for various metals as suggested by the crystal structure of the Zn_3/(linked-BINOL)$_2$ pre-catalyst. Concerning the direct Mannich-type reactions, use of ester equivalent donors remains problematic. Further investigations to enhance the reaction rate and to improve stereoselectivity and catalyst TON with ester equivalent donors are ongoing.

Acknowledgments

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