Asymmetric Catalysis

Non-C_2-Symmetric, Chirally Economical, and Readily Tunable Linked-binols: Design and Application in a Direct Catalytic Asymmetric Mannich-Type Reaction**

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Asymmetric catalysis employing chiral metal complexes is one of the most general and flexible methods in asymmetric synthesis.[1] In the development of asymmetric metal catalysts for highly enantioselective and reactive reactions, the design of chiral ligands for the metal center is of key importance: the activity and selectivity of the metal centers can be tuned by chiral ligands. A delicate balance between the steric and electronic properties of the catalyst determines the reaction efficiency. Thus, a chiral ligand with a readily tuneable framework is desirable.[2]

We recently reported the preparation of a series of chiral ligands termed "linked-binols" (**1a–c**; Scheme 1).[3,4] These linked-binols consist of two chiral 1,1′-bi-2-naphthol units connected at the 3 and 3″-positions by a flexible linker containing one heteroatom. Linked-binols often provide a better chiral environment than 1,1′-bi-2-naphthol (**2**;

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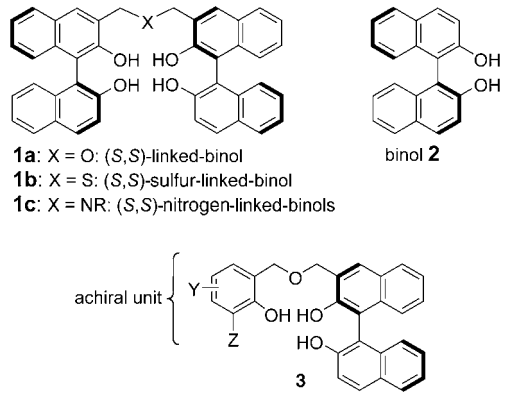
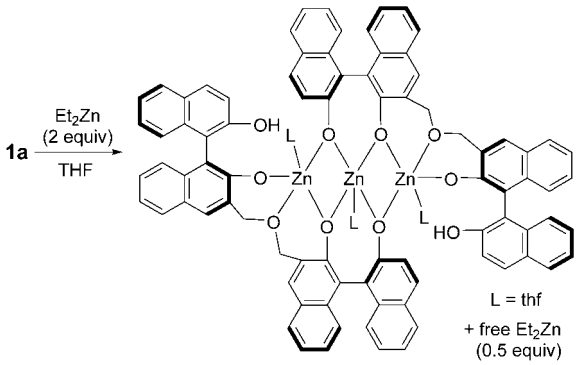
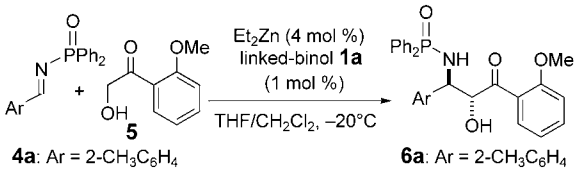


Scheme 1. Structures of (*S*,*S*)-linked-binols **1a–c**, 1,1′-bi-2-naphthol **2**, and new ligands **3**.



Scheme 2. Structure of a Zn/**1a** (3:2) complex.



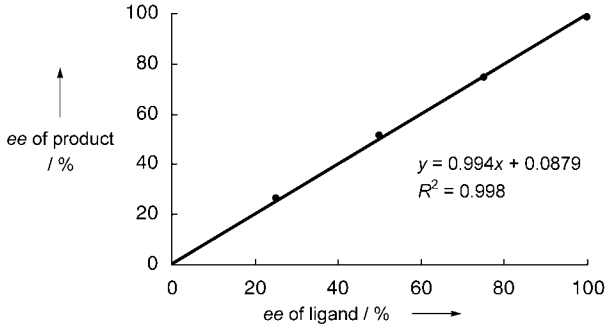
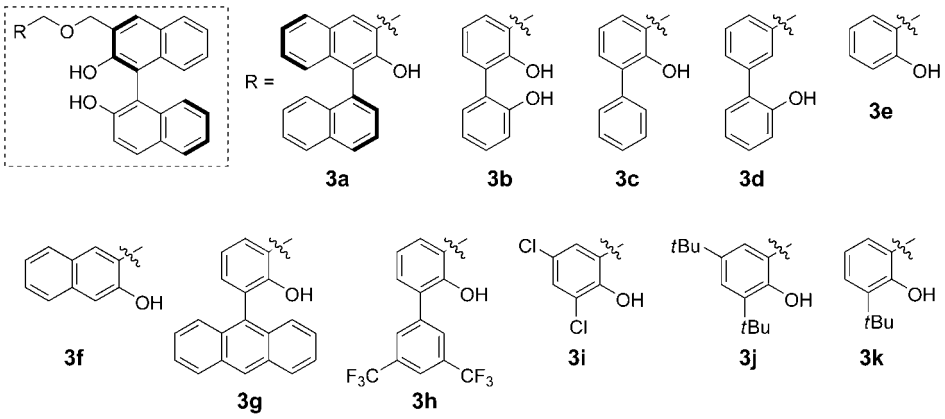


Figure 1. Linear relationship between Mannich-adduct **6a** and (*S*,*S*)-linked-binol **1a** observed in a direct Mannich-type reaction of **4a** with **5**.

Scheme 1), as was demonstrated in various catalytic asymmetric reactions, such as epoxide openings,[3a] a direct aldol reaction,[5] Michael reactions,[6,7] and direct Mannich-type reactions.[8] Although they are conformationally rigid, two chiral binaphthyl units seem essential to provide an efficient chiral environment for high enantioselectivity; however, they also impose severe limitations on ligand design. So far, the properties of linked-binol complexes could only be tuned by changing the heteroatom of the linker (**1a–c**).[3] Electronic and steric modifications of the binaphthyl moiety is tedious and lengthy because of the presence of two chiral units. Thus, improving the performance of ligands with the original linked-binol framework in catalytic reactions is a formidable challenge. For example, many steps are required when modifying the electronic properties by preparing 6,6′,6″,6‴-tetrasubstituted C_2-symmetric linked-binols. A simple, more flexible strategy is required to overcome this intrinsic dilemma and tune the properties of linked-binols. Herein, we report a readily tuneable, non-C_2-symmetric linked-binol **3** with only one chiral 1,1′-bi-2-naphthol unit and one flexible achiral unit (Scheme 1).[9] On the basis of our mechanistic studies on the Et_2Zn/linked-binol **1a** catalytic system, new ligands were designed and evaluated in direct catalytic asymmetric Mannich-type reactions. The introduction of an achiral unit was not only economical in terms of chirality[10] but also afforded comparable enantioselectivity and a much higher reaction rate than the original linked-binol **1a** with two chiral 1,1′-bi-2-naphthol units.

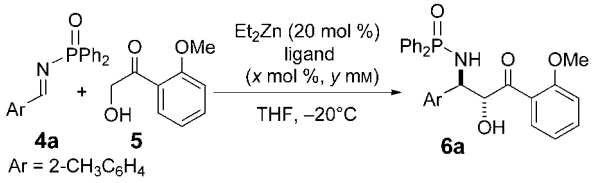
For the design and evaluation of the new linked-binols, a Et_2Zn/**1a** complex was used for reference because its structure and reactivity had been previously studied. The structure of the Zn/**1a** (3:2) precatalyst, prepared from Et_2Zn/**1a** (2:1; Scheme 2), was determined by X-ray crystallographic, NMR spectroscopic, and ESI mass-spectrometric analysis.[11] In the Zn/**1a** (3:2) complex, neither of the linked-binol units had a C_2-symmetric environment and one of the phenolic OH groups remained unchanged, even in the presence of a slight excess of Et_2Zn. On the other hand, there was a linear relationship between the enantiomeric excess of product **6a** and that of the chiral ligand **1a** used in the Mannich-type reaction of diphenylphosphanoylimine (**4a**) and hydroxyketone **5** (Figure 1).[12] The structure of the Zn/**1a** (3:2) complex (Scheme 2) and the results shown in Figure 1 suggested that 1) C_2 symmetry in linked-binol **1a** is not important, 2) one phenolic OH group is not required, and 3) a homochiral complex is more favorable than a heterochiral complex. We hypothesized that one of the chiral binaphthol units could be replaced with an achiral unit, such as an atropisomeric biphenol or an achiral phenol derivative. Chirality should be then transferred to the flexible achiral unit on complexation with a zinc center, and a similar chiral environment should be obtained with a ligand that was economical in terms of chirality.

The structures of ligands **3a–k** are shown in Scheme 3.[13] The catalytic potential of these ligands was evaluated in a direct asymmetric Mannich-type reaction of imine **4a** and hydroxyketone **5** using 5 mol% of ligand **3** and 20 mol% of Et_2Zn at −20°C in THF/CH_2Cl_2 ([imine] = 150 mM, [**3**] = 7.5 mM). When the original ligand **1a** was used, the reaction was completed within 1 h and the Mannich adduct **6a** was obtained in 99% yield with *anti*/*syn* selectivity of 98:2 in >99% *ee* (Table 1, entry 1). A control experiment with 10 mol% of binol **2** had a much lower reaction rate and



Scheme 3. Structures of non-C_2-symmetric (*S*)-linked-binol derivatives **3a–k** containing one achiral unit and one chiral binaphthol unit.

Table 1: Catalytic asymmetric Mannich-type reaction using various chiral ligands (**1a**, **2**, and **3a–k**).



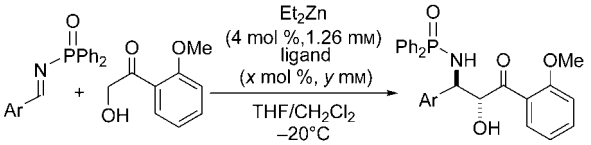
4a Ar = 2-$CH_3C_6H_4$ **5** **6a**

Entry	Ligand (mol%)	[Ligand] [mM]	*t* [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	**3a** (5)	7.5	1	99	94:6	99
4	**3b** (5)	7.5	1	98	98:2	98
5	**3c** (5)	7.5	1	99	97:3	99
6	**3d** (5)	7.5	23	74	91:9	9
7	**3e** (5)	7.5	11	92	95:5	90
8	**3f** (5)	7.5	5	93	95:5	87
9	**3g** (5)	7.5	1	98	96:4	99
10	**3h** (5)	7.5	1	95	98:2	98
11	**3i** (5)	7.5	1	94	98:2	98
12	**3j** (5)	7.5	1	96	98:2	98
13	**3k** (5)	7.5	1	95	98:2	98

ee value (68 h, 24% *ee*; entry 2). Ligand **3a**, which lacks one phenolic OH group, gave results similar to those obtained with **1a** (entry 3). Ligand **3b** with an atropisomeric biphenol unit was also efficient (entry 4), thus suggesting that the chirality of the biphenol unit was controlled by complexation with the zinc center.[14] Even an achiral unit, such as **3c**, gave excellent results (1 h, 99% yield, 99% *ee*; entry 5), whereas ligand **3d**, which has a phenolic OH group in the 2′-position, had a low reaction rate and poor enantioselectivity (23 h, 74% yield, 9% *ee*; entry 6). Ligands **3e** and **3f** also produced unsatisfactory yields and modest enantioselectivities (entries 7 and 8). The results shown in entries 5–8 imply that both the phenolic OH group at the proper position and a substituent on the aromatic ring are required. To evaluate the effects of substituents on the phenol ring, ligands **3g–k** were used, and all of them showed a high reactivity and enantioselectivity (entries 9–15). The achiral units in ligands **3i–k** were readily accessible from commercially available salicylic aldehyde derivatives.[15]

Although many ligands in Scheme 3 gave high enantioselectivities (Table 1), it was difficult to compare their performance precisely in terms of reaction rate. Generally, catalyst concentration becomes rather low when catalyst loading is reduced to <0.1 mol% because of substrate-solubility limitations. Thus, high turnover frequencies (TOF) and turnover numbers (TON) under dilute conditions are required to lower the catalyst loading. To evaluate the ligands quantitatively, the reaction for each ligand was monitored under dilute conditions ([imine] = 31 mM, [**3**] = 0.31 mM, 1 mol%; Table 2 and Figure 2). The initial rate of the reaction with each ligand (**1a**, **2**, and **3a–k**) is summarized in Table 2, and the profiles of the reactions with ligands **1a**, **2**, **3c**, **3j**, and **3k** are shown in Figure 2.[16] It is of note that many ligands with achiral units (shown in Scheme 3) gave a better reaction rate than the original linked-binol **1a** that contained two chiral units (initial

Table 2: Initial reaction rate with various chiral ligands (**1a**, **2**, and **3a–k**) under dilute conditions.



4a (31 mM) **5** (63 mM) **6a**

Entry	Ligand (mol%)	[Ligand] [mM]	Initial rate [mM min^{-1}]
1	**1a** (1)	0.31	0.199
2	**2** (2)	0.62	0.015
3	**3a** (1)	0.31	0.333
4	**3b** (1)	0.31	0.354
5	**3c** (1)	0.31	0.696
6	**3d** (1)	0.31	0.019
7	**3e** (1)	0.31	0.096
8	**3f** (1)	0.31	0.135
9	**3g** (1)	0.31	0.375
10	**3h** (1)	0.31	0.455
11	**3i** (1)	0.31	0.435
12	**3j** (1)	0.31	0.742
13	**3k** (1)	0.31	0.848

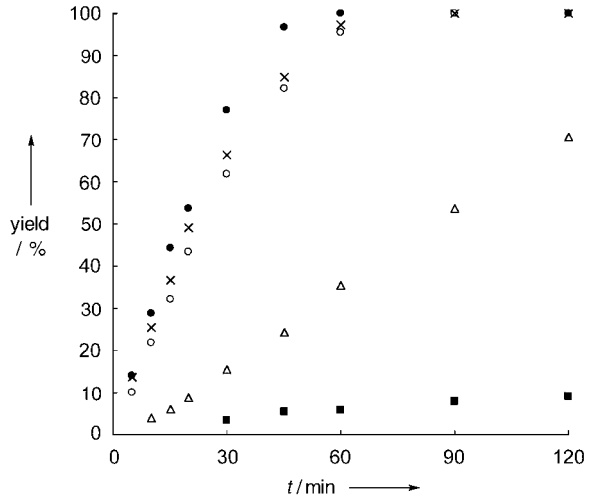
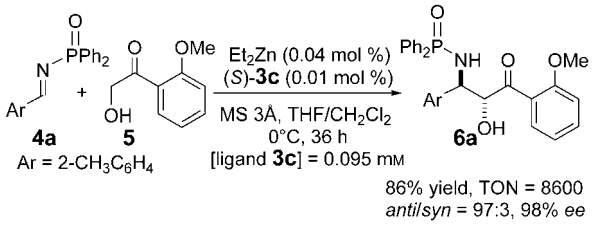


Figure 2. Reaction profiles with chiral ligands: **1a** (△ = 0.31 mM), **2** (■ = 0.62 mM), **3c** (○ = 0.31 mM), **3j** (× = 0.31 mM), and **3k** (● = 0.31 mM).

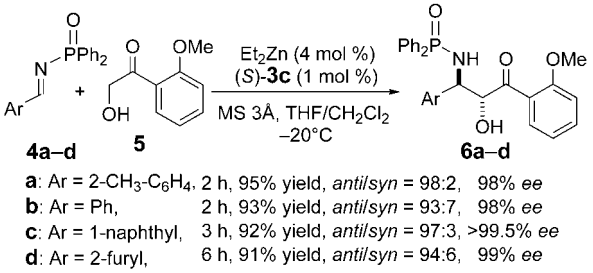
rate = 0.199 mM min^{-1}). Ligands **3j** and **3k** with electron-donating *t*Bu groups gave the highest reaction rates (**3j** = 0.742 mM min^{-1}, **3k** = 0.848 mM min^{-1}), and ligand **3c** also produced a comparable reaction rate (**3c** = 0.696 mM min^{-1}). Ligand **3g**, with a bulky aromatic substituent, had lower reactivity than **3c** but higher reactivity than **1a**. An electron-withdrawing group also had a lower reaction rate (**3h** and **3i**). These results suggested that an appropriate group at the *ortho* position of the phenolic OH group and a relatively less acidic phenolic OH group were suitable substituents on the ligands for the present Mannich-type reaction. These results demonstrated the usefulness of the present strategy to sterically and electronically fine-tune complexes of metal and linked-binols.

The utility of ligand **3c** was further demonstrated, as shown in Schemes 4 and 5. The catalyst loading for **3c** was successfully lowered: the Mannich-type reaction proceeded smoothly with as little as 0.01 mol% of **3c**, with the product being afforded in good yield and selectivity at 0 °C after 36 h (86%, 98% *ee*, TON = 8600; this is the highest TON value achieved in the catalytic asymmetric Mannich-type reaction so far.[17,18]) The reaction proceeded smoothly even with low concentrations of the ligand ([**3c**] = 0.095 mM). The broad substrate range of ligand **3c** is also summarized in Scheme 5.

Although a Et_2Zn/ligand stoichiometry of 4:1 was used for the Mannich-type reaction, characterization of the reaction



Scheme 4. Catalytic asymmetric Mannich-type reaction using 0.01 mol% of **3c**. MS 3 Å = molecular sieves (3 Å).



Scheme 5. Catalytic asymmetric Mannich-type reaction of imines **4a–d** using **3c**.

mixture was difficult for both **1a** and **3c**. Thus, we investigated the structures of precatalysts of a Et_2Zn/ligand mixture in a 2:1 ratio for a preliminary evaluation of the properties of **3c** relative to **1a**.[19] The complex formed in the Et_2Zn/**3c** (2:1) mixture was confirmed to be similar to that in the Et_2Zn/**1a** (2:1) mixture (Zn/**1a** = 3:2; Scheme 2) by ESI mass-spectrometric analysis. The ESIMS spectrum of the Et_2Zn/**3c** (2:1) mixture showed major peaks at *m*/*z* 1183–1194,[20] which correspond to a Zn/**3c** (3:2) complex. The ^{1}H and ^{13}C NMR spectroscopic analysis of the Et_2Zn/**3c** (2:1) mixture indicated eight different benzylic protons and four benzylic carbon atoms,[20] thus suggesting that the Zn/**3c** (3:2) complex does not have C_2 symmetry, and that two molecules of **3c** were differentially involved, possibly in a head-to-tail fashion. Further investigations to determine the structure of the Zn/**3c** complex unequivocally are ongoing. Although the structure of the actual active species formed under the reaction conditions is not clear at the moment, we speculate that the coordination site at the zinc center would be sterically less crowded in the Zn/**3c** complex than in the Zn/**1a** complex, thus accelerating the rate-limiting exchange step[21] between the product and ketone **5** to regenerate the Zn/ligand/ketone complex. Further mechanistic studies are in progress.

In summary, we have developed readily tuneable, economical in terms of chirality, non-C_2-symmetric linked-binol derivatives. The new design overcomes the drawbacks inherent in the original C_2-symmetric ligand **1a** with two chiral binaphthol units. The present strategy has been useful to fine-tune metal/linked-binol complexes in a direct catalytic asymmetric Mannich-type reaction. Further application of these new sterically and electronically tuneable ligands to other asymmetric reactions, in which the original linked-binol **1a** produced unsatisfactory results, is currently ongoing.

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Keywords: amino alcohols · asymmetric catalysis · chiral ligands · Mannich reaction · zinc

[1] For general reviews, see: a) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, and **2003**; b) *Catalytic Asymmetric Synthesis*, *2nd ed.* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**.

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[13] For the synthesis and spectra of ligands **3a–k**, see the Supporting Information.

[14] The initial reaction rate of the Mannich-type reaction with a *meso*-linked-binol derivative prepared from (*S*)-binol and (*R*)-binol units was estimated relative to that of (*S*,*S*)-linked-binol **1a**. A similar initial reaction rate was observed for **1a** and the *meso*-linked-binol. The chirality of ligand **3b** should be controlled by (*S*)-biphenol-(*S*)-binol on complexation with the zinc center because the pseudo-*meso*-(*R*)-biphenol-(*S*)-binol-type complex would afford products in low enantiomeric excess.

[15] In terms of cost efficiency, **3b** and **3c** are also superior to **1a**: 2,2′-biphenol (500 g; Aldrich) and 2-phenylphenol (500 g; Aldrich).

[16] The reaction profiles with other ligands are summarized in the Supporting Information.

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[18] The best TON was achieved using 0.02 mol% of **1a** ([ligand **1a**] = 0.21 mM, TON = 4900)[8b]; however, the concentration of **1a** had to be > 0.2 mM to promote the reaction efficiently. Under similar conditions given in Scheme 2 ([ligand **1a**] = 0.1 mM, 0.01 mol%), TON < 4000.

[19] In the present Mannich-type reaction, the ratio of Et_2Zn/ligand (**1a** or **3c**) did not affect enantioselectivity. Et_2Zn/**1a** (2 mol% of **1a**): 2:1 (> 99% *ee*, d.r. 98:2, 2 h, > 95% yield), 3:1 (> 99% *ee*, d.r. 98:2, 1 h, > 95% yield), 4:1 (> 99% *ee*, d.r. 98:2, 1 h, > 95% yield); Et_2Zn/**3c** (2 mol% of **3c**): 2:1 (99% *ee*, d.r. 99:1, 1 h, > 95% yield), 3:1 (98% *ee*, d.r. 98:2, 1 h, > 95% yield), 4:1 (98% *ee*, d.r. 98:2, 1 h, > 95% yield); thus, we assumed that a similar active species formed under these reaction conditions, and that the structural information obtained with Et_2Zn/ligand (2:1) would give some insight into the properties of **3c**.

[20] ESI mass spectra as well as the ^1H NMR and ^{13}C NMR spectra of Et_2Zn/**3c** (2:1) are given in the Supporting Information. The ESI mass-spectrometric analysis showed several signals that correspond to the Zn/**3c** (3:2) trinuclear complex, depending on the natural-isotope distribution pattern of zinc.

[21] The rate-limiting step of the Mannich-type reaction of **4a** with **5** was determined to be a catalyst-turnover step by kinetic studies on the initial rate; see Ref. [8b]

