

syn-Selective Direct Catalytic Asymmetric Mannich-Type Reactions of Aromatic and Heteroaromatic Hydroxy Ketones Promoted by $Y[N(SiMe_3)_2]_3$/Linked-BINOL Complexes

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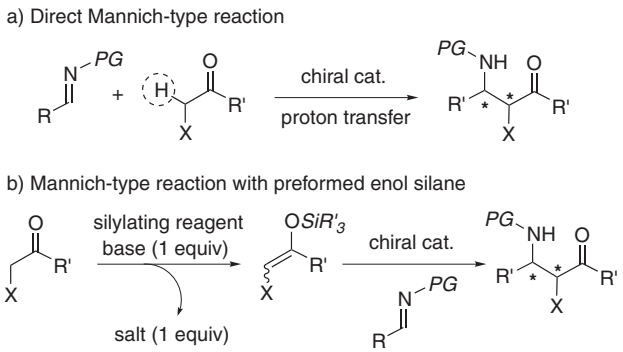
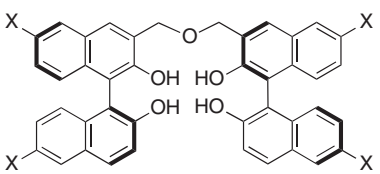
Full details of *syn*-selective catalytic asymmetric direct Mannich-type reactions of aromatic and heteroaromatic hydroxy ketones promoted by $Y[N(SiMe_3)_2]_3$/linked-BINOL complexes are described. From a screening of various rare-earth metals and linked-BINOL derivatives, a $Y[N(SiMe_3)_2]_3$/TMS-linked-BINOL (1.7/1) complex was determined to be the most effective. Mannich-type reactions of aromatic and heteroaromatic hydroxy ketones with aryl and alkenyl *N*-diphenylphosphinoylimines, catalyzed by 0.1 molar amount of $Y[N(SiMe_3)_2]_3$ and 0.059 molar amount of TMS-linked-BINOL, afforded *syn*-β-amino-α-hydroxy ketones in good yields (78–98%), high diastereoselectivity (*syn*/*anti* = 81/19–96/4), and high enantioselectivity (86–98% ee).

Chiral β-amino alcohol units are useful building blocks found in various natural products, compounds with pharmacologically important activity, chiral auxiliaries, and chiral ligands.[1] Various methods for enantioselective and diastereoselective preparation of β-amino alcohols have been developed over the last decade.[2] Among the methods available for their catalytic enantioselective syntheses,[3] catalytic asymmetric Mannich-type reactions[4] of α-alkoxy enolates are of particular interest because two adjacent stereocenters are constructed simultaneously with concomitant carbon–carbon bond formation.[5,6] To address this issue, direct catalytic asymmetric Mannich reactions[7,8] are ideal methods in terms of atom economy.[9] In the direct Mannich-type reactions, either a nucleophilic enolate or an enamine is generated in situ using catalytic amount of bifunctional metal complexes[10] or organocatalysts.[11] The reaction formally proceeds through simple proton transfer from a nucleophile to an electrophile. Therefore, the pre-activation of a nucleophile using stoichiometric amounts of a strong base and a silylating reagent is not required, enabling to avoid producing stoichiometric amount of salt waste. Difference between the direct Mannich-type reaction and the Mannich-type reactions with pre-formed enolates is summarized in Scheme 1.

During the last decade, several research groups including us realized the direct catalytic asymmetric Mannich-type reactions of α-oxy-donors, and they include the addition of unmodified α-hydroxy ketones,[12,13] α-oxyaldehydes,[14] and α-hydroxy-*N*-acylpyrrole as an ester surrogate[15,16] to imines.[17,18] Among the Mannich-type reactions of α-hydroxy ketones, we developed a Et_2Zn/linked-BINOL **1a** (Fig. 1)[19,20] complex, which efficiently catalyzed the Mannich-type reaction of 2-hydroxy-1-(2-methoxyphenyl)ethanone (**3a**).[13] By changing the imine protective groups, either *anti*- or *syn*-β-amino-α-hydroxy ketones were obtained (Scheme 2). A Mannich-type reaction using diphenylphosphinoylimine (Dpp-imine **2**)[21] afforded *anti*-products, whereas the use of a Boc-imine afforded *syn*-products. Although high catalyst turnover number and high ee were achieved, problems remained. 1) Modest *syn*-selectivity with Boc-imine; diastereoselectivity strongly depended on the imines used.[13b] Especially, α,β-unsaturated imines and heteroaromatic imines gave poor *syn*-selectivity. To the best of our knowledge, there are no reports of highly diastereo-



Scheme 1. a) Direct catalytic asymmetric Mannich-type reaction and b) Mannich-type reaction with preformed enol silane.



X = H: (*S*,*S*)-linked-BINOL **1a**
X = -Si(CH$_3$)$_3$: (*S*,*S*)-TMS-linked-BINOL **1b**
X = -Br: (*S*,*S*)-Br-linked-BINOL **1c**

Fig. 1. Structures of (*S*,*S*)-linked-BINOLs (**1a**, **1b**, and **1c**).

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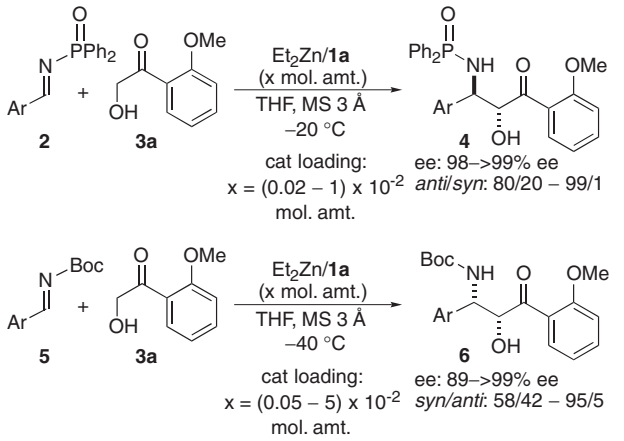


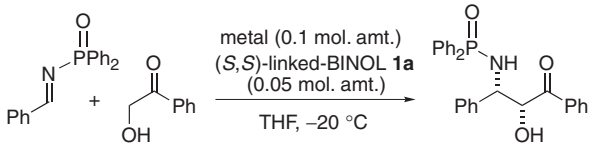
Scheme 2. Direct catalytic asymmetric Mannich-type reaction of hydroxy ketone **3a** promoted by a Et_2Zn/linked-BINOL **1a** complex.

and enantioselective (dr: >90/10, ee: >90% ee) direct catalytic asymmetric Mannich-type reactions of α,β-unsaturated imines using hydroxy ketones as donors.[22] 2) Nucleophile generality: Use of ketone **3a** was essential to achieve good selectivity. The methoxyphenyl group in the Mannich adducts is synthetically useful, because the methoxy group facilitates efficient conversion of the Mannich adducts in Scheme 2 into β-amino-α-hydroxycarboxylic esters through Baeyer–Villiger oxidation;[13a,13b] however, zinc catalysis is not suitable for the synthesis of various β-amino-α-hydroxy ketones. For example, when using 2-hydroxyphenylethanone (**3b**) and 1-(2-furyl)-2-hydroxyethanone (**3f**) without a methoxy group on the aromatic ring, Mannich adducts are obtained in only modest enantioselectivity.[23] To overcome the modest *syn*-selectivity and the lack of nucleophile generality of our zinc catalyzed Mannich-type reactions, we previously communicated new $Y[N(SiMe_3)_2]_3$/linked-BINOLs complexes (Fig. 1).[24] Herein, we describe full details of the yttrium-catalyzed direct enantioselective Mannich-type reactions. The $Y[N(SiMe_3)_2]_3$/TMS-linked-BINOL (**1b**) complex was applicable to various aromatic and heteroaromatic hydroxy ketones, to afford Mannich adducts *syn*-selectively in good yield (up to 98%), and high enantio- and diastereoselectivity (up to 98% ee, *syn*/*anti* = up to 96/4).

Results and Discussion

The rare-earth metal alkoxide/linked-BINOL **1a** complexes are useful in several asymmetric reactions,[25] therefore we screened various rare-earth metal/linked-BINOL **1a** complexes using Dpp-imine **2a** and 1.2 molar amount of hydroxyketone **3b** (Table 1). Using a 0.1 molar amount of a metal source and 0.05 molar amount of linked-BINOL **1a**, a Mannich-type reaction was performed in THF at −20 °C. In contrast to our initial assumption based on results obtained by the Et_2Zn/linked-BINOL **1a** complex (Scheme 1),[13a] the reaction proceeded *syn*-selectively with rare-earth metal complexes.[26] The use of rare-earth metal alkoxides of La, Gd, Y, and Yb afforded only modest enantioselectivity and reactivity (Entries 1–4, 20–65% ee).[27] Therefore, other rare-earth metal sources were screened, and rare-earth metal hexamethyldisilazide $[RE[N(SiMe_3)_2]_3]$[27] had much better reactivity and selectivity (Entries 5–8). Among $RE[N(SiMe_3)_2]_3$ sources, $Y[N(SiMe_3)_2]_3$ and $Yb[N(SiMe_3)_2]_3$ gave the best results (Entry 7, 89% yield, *syn*/*anti* = 88/12, 85% ee; Entry 8, 82% yield, *syn*/*anti* = 87/13, 89% ee). Because $Y[N(SiMe_3)_2]_3$ was superior to $Yb[N(SiMe_3)_2]_3$ in terms of reaction rate (48 h vs 60 h), further optimization was performed using $Y[N(SiMe_3)_2]_3$ as the metal source.

Table 1. Screening of Various Rare-Earth Metal/Linked-BINOL **1a** Complexes Using Hydroxy Ketone **3b** as a Donor

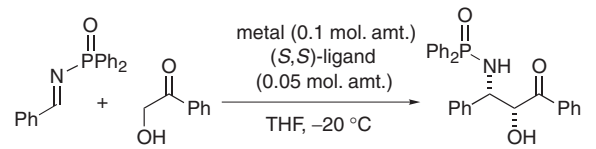


2a **3b** (1.2 mol. amt.) **7ab**

Entry	Metal source	Time /h	Yield[a] /%	dr[b] (*syn*/*anti*)	ee (%) (*syn*)
1	$La(O\text{-}iPr)_3$	60	78	60/40	20
2	$Gd(O\text{-}iPr)_3$	60	51	75/25	45
3	$Y(O\text{-}iPr)_3$	93	25	77/23	64
4	$Yb(O\text{-}iPr)_3$	60	50	72/28	65
5	$La[N(SiMe_3)_2]_3$	60	81	60/40	12
6	$Gd[N(SiMe_3)_2]_3$	60	78	84/16	66
7	$Y[N(SiMe_3)_2]_3$	48	89	88/12	85
8	$Yb[N(SiMe_3)_2]_3$	60	82	87/13	89

a) Isolated yield. b) Determined by ^{1}H NMR analysis.

Table 2. Effects of Chiral Ligands **1a–1i**



2a **3b** (1.2 mol. amt.) **7ab**

Entry	Ligand	Time /h	Yield[a] /%	dr[b] (*syn*/*anti*)	ee (%) (*syn*)
1	**1a**	48	89	88/12	85
2	**1b**	48	95	93/7	94
3	**1c**	88	54	64/36	38
4	**1d**	88	91	64/36	10
5	**1e**	87	18	53/47	14
6	**1f**	87	29	43/57	5
7	**1g**	88	91	59/41	14
8	**1h**	88	93	55/45	25
9	**1i**	88	84	57/43	13
10	**1j**	88	90	50/50	2
11	BINOL[c]	89	24	45/55	3

a) Isolated yield. b) Determined by ^{1}H NMR analysis. c) 0.1 mol amt. of BINOL was used.

Table 2 summarizes the results using different linked-BINOL derivatives. Although ligands **1d–1j** (Fig. 2), which have one chiral moiety, were effective in the Et_2Zn/linked-BINOL-catalyzed reaction,[13c] ligands **1d–1j** were unsatisfactory when used with $Y[N(SiMe_3)_2]_3$ (Table 2, Entries 4–10).

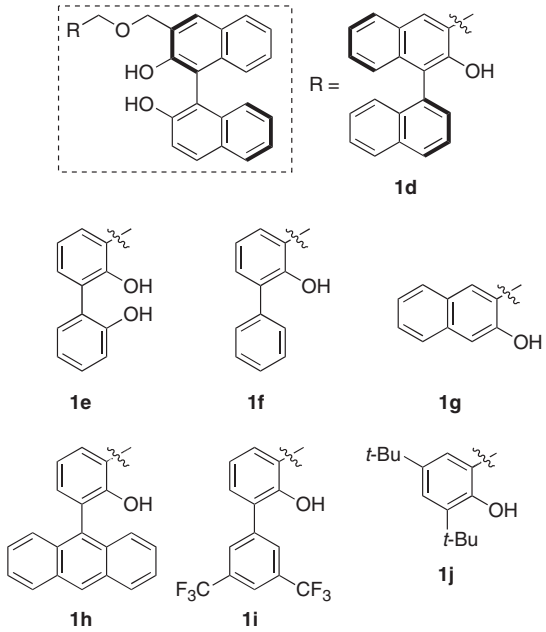
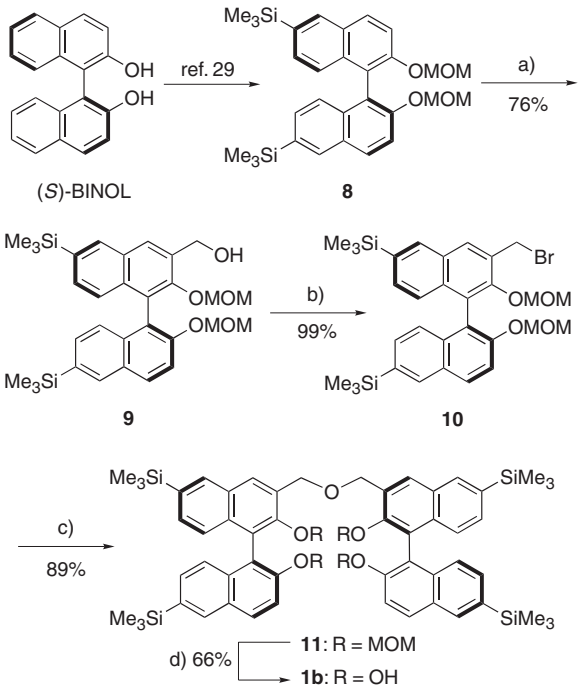


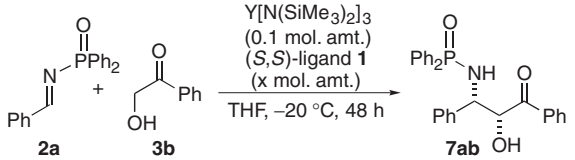
Fig. 2. Structures of linked-BINOL derivatives **1d–1j** for screening.

BINOL, itself, also afforded poor reactivity and selectivity (Entry 11, 24% yield, 3% ee). The present $Y[N(SiMe_3)_2]_3$ complex required two chiral BINOL units for high reactivity and enantioselectivity (Entry 1, 89% yield, 85% ee). Modification at the 6,6′,6″,6‴-positions of linked-BINOL **1** improved stereoselectivity. When TMS-linked-BINOL **1b** (Fig. 1) was used,[28] Mannich adduct **7ab** was obtained in 95% yield, 94% ee and *syn*/*anti* = 93/7 (Table 2, Entry 2). We speculate that the bulky trimethylsilyl group at the 6,6′-position of binaphthyl affects the dihedral angle of the ligand, thereby improving stereoselectivity. On the other hand, electron-withdrawing groups at 6,6′,6″,6‴-positions had adverse effects. The use of Br-linked-BINOL **1c** resulted in poor yield, diastereoselectivity and enantioselectivity (Entry 3). The synthetic procedure for TMS-linked-BINOL **1b** is summarized in Scheme 3. Intermediate **8** was synthesized following the reported procedure.[29] Compound **9** was obtained in 76% yield (2 steps) by formylation and reduction with $NaBH_4$. Compound **10** was obtained in 99% yield (2 steps from compound



Scheme 3. Synthetic scheme of (*S*,*S*)-TMS-linked-BINOL **1b**. Reagents and conditions: a) 1. BuLi (1.1 mol amt.), TMEDA (1.2 mol amt.), THF, 0 °C, 1 h; then DMF (1.05 mol amt.), −78 °C, 3 h; 2. $NaBH_4$ (1.0 mol amt.), THF/MeOH, 0 °C, 30 min, 76% (2 steps); b) Ms_2O (1.5 mol amt.), iPr_2NEt (1.6 mol amt.), 25 °C, 1 h; then LiBr (5 mol amt.), DMF, 0 °C, 10 h, 99%; c) **B** (1.0 mol amt.), NaH (1.2 mol amt.), 25 °C, 3.5 h, 89%; d) $pTsOH \cdot H_2O$ (0.2 mol amt.), CH_2Cl_2/MeOH, 35 °C, 14 h, 66%.

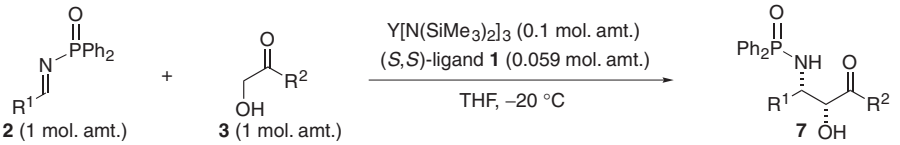
Table 3. Effects of $Y[N(SiMe_3)_2]_3$:Ligand Ratio, and Hydroxy Ketone **3b** Amount on Diastereoselectivity and Enantioselectivity



Entry	$Y[N(SiMe_3)_2]_3$:Ligand ratio	Ligand (*x* mol amt.)	**3b** (mol amt.)	Yield[a] /%	dr[b] (*syn*/*anti*)	ee (%) (*syn*)
1	2.0:1	**1a** (0.050)	1.2	89	88/12	85
2	1.7:1	**1a** (0.059)	1.2	97	90/10	91
3	1.5:1	**1a** (0.067)	1.2	94	84/16	86
4	1.3:1	**1a** (0.077)	1.2	95	76/24	63
5	1:1	**1a** (0.10)	1.2	92	68/32	26
6	1.7:1	**1b** (0.059)	1.2	98	94/6	95
7	1.7:1	**1a** (0.059)	3.0	98	83/17	82
8	1.7:1	**1a** (0.059)	1.0	90	95/5	95

a) Isolated yield. b) Determined by ^1H NMR analysis.

Table 4. Direct Catalytic Asymmetric Mannich-Type Reaction Using Hydroxy Ketones **3c–3g** and Imines **2b–2f**



2 (1 mol. amt.) **3** (1 mol. amt.) **7**

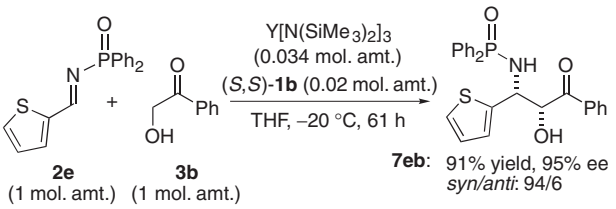
Entry	Imine: R^1	Ketone: R^2	Product	Ligand	Time /h	Yield[a] /%	dr[b] (*syn*/*anti*)	ee (%) (*syn*)
1	Ph- **2a**	4-MeO-C_6H_4- **3c**	**7ac**	**1a**	82	43	94/6	96
2	Ph- **2a**	4-MeO-C_6H_4- **3c**	**7ac**	**1b**	84	89	91/9	98
3	Ph- **2a**	4-Me-C_6H_4- **3d**	**7ad**	**1a**	65	84	91/9	92
4	Ph- **2a**	4-Me-C_6H_4- **3d**	**7ad**	**1b**	63	91	91/9	96
5	Ph- **2a**	4-Cl-C_6H_4- **3e**	**7ae**	**1a**	60	70	81/19	80
6	Ph- **2a**	4-ClC_6H_4- **3e**	**7ae**	**1b**	48	94	81/19	86
7	Ph- **2a**	2-Furyl **3f**	**7af**	**1a**	60	68	82/18	74
8	Ph- **2a**	2-Furyl **3f**	**7af**	**1b**	60	94	94/6	93
9	Ph- **2a**	2-Thienyl **3g**	**7ag**	**1a**	89	65	90/10	74
10	Ph- **2a**	2-Thienyl **3g**	**7ag**	**1b**	36	95	95/5	92
11	4-Cl-C_6H_4- **2b**	Ph- **3b**	**7bb**	**1a**	60	73	88/12	92
12	4-Cl-C_6H_4- **2b**	Ph- **3b**	**7bb**	**1b**	48	78	94/6	95
13	4-MeO-C_6H_4- **2c**	Ph- **3b**	**7cb**	**1a**	89	69	89/11	86
14	4-MeO-C_6H_4- **2c**	Ph- **3b**	**7cb**	**1b**	84	90	95/5	94
15	2-Furyl **2d**	Ph- **3b**	**7db**	**1a**	60	90	93/7	95
16	2-Furyl **2d**	Ph- **3b**	**7db**	**1b**	39	93	95/5	96
17	2-Thienyl **2e**	Ph- **3b**	**7eb**	**1a**	61	83	93/7	95
18	2-Thienyl **2e**	Ph- **3b**	**7eb**	**1b**	39	95	96/4	97
19	PhCH=CH- **2f**	Ph- **3b**	**7fb**	**1a**	66	86	96/4	96
20	PhCH=CH- **2f**	Ph- **3b**	**7fb**	**1b**	60	87	96/4	95
21	4-Cl-C_6H_4CH=CH- **2g**	Ph- **3b**	**7gb**	**1a**	65	93	96/4	94
22	4-Cl-C_6H_4-CH=CH- **2g**	Ph- **3b**	**7gb**	**1b**	42	94	95/5	93
23	4-Me-C_6H_4CH=CH- **2h**	Ph- **3b**	**7hb**	**1a**	40	94	92/8	92
24	4-Me-C_6H_4CH=CH- **2h**	Ph- **3b**	**7hb**	**1b**	60	92	93/7	91
25	2-FurylCH=CH- **2i**	Ph- **3b**	**7ib**	**1a**	65	87	96/4	94
26	2-FurylCH=CH- **2i**	Ph- **3b**	**7ib**	**1b**	42	89	96/4	94

a) Isolated yield. b) Determined by ^{1}H NMR analysis.

9) by mesylation of **9**, followed by treatment with LiBr. Coupling reaction of compounds **9** and **10** and removal of MOM group afforded linked-BINOL **1b**.

The ratio of $Y[N(SiMe_3)_2]_3$ and linked-BINOL **1a** affected both reactivity and stereoselectivity (Table 3, Entries 1–5). Using a 0.1 molar amount of $Y[N(SiMe_3)_2]_3$ and variable amounts of linked-BINOL **1a** (0.05–0.1 molar amount), the Mannich-type reaction of **2a** with 1.2 molar amount of **3b** was examined. The best diastereo- and enantioselectivity were obtained when the ratio of $Y[N(SiMe_3)_2]_3$/linked-BINOL **1a** was 1.7/1. With a catalyst prepared from $Y[N(SiMe_3)_2]_3$/**1a** = 1.7/1 ratio, Mannich adduct **7ab** was obtained in 97% yield, *syn*/*anti* = 90/10, and 91% ee (Entry 2). When TMS-linked-BINOL **1b** was used, Mannich adduct **7ab** was obtained in 98% yield, *syn*/*anti* = 94/6, and 95% ee (Entry 6). The amount of hydroxy ketone **3b** also affected stereoselectivity. Excess hydroxy ketone **3b** negatively affected enantio- and diastereoselectivity. When 3 molar amounts of hydroxy ketone **3b** was used, both diastereoselectivity and enantioselectivity decreased (Entry 7, *syn*/*anti* = 83/17, 82% ee). Whereas when using 1.0 molar amount of ketone **3b** was used, **7ab** was obtained in *syn*/*anti* = 95/5 and 95% ee using ligand **1a** as a ligand (Entry 8). It is noteworthy that the Mannich adduct was obtained in 90% yield, even with an equimolar amount of the nucleophile.

The $Y[N(SiMe_3)_2]_3$/ligand **1a** or **1b** (1.7/1) complex was useful with various aromatic and heteroaromatic hydroxy ketones **3b–3g** (Table 4). TMS-linked-BINOL **1b** gave better chemical yield, diastereoselectivity, and ee than linked-BINOL **1a** in most entries. For hydroxy ketones **3c**, linked-BINOL **1a** gave Mannich adduct **7ac** in only 43% yield (Entry 1), while linked-BINOL **1b** gave **7ac** in 89% yield (98% ee, Entry 2). On the other hand, TMS-linked-BINOL **1b** was required to achieve good ee for hydroxy ketone **3e** with an electron-withdrawing group (Entry 5 vs 6). 1-(2-Furyl)-2-hydroxyethanone (**3f**), which affords versatile chiral building blocks,[30] was also a suitable nucleophile. Mannich adduct **7af** was obtained in 94% yield, *syn*/*anti* = 94/6, 93% ee using linked-BINOL **1b** (Entry 8), although only modest yield and ee were achieved with linked-BINOL **1a** (Entry 7, 74% ee). 2-Hydroxy-1-(2-thienyl)ethanone (**3g**) also required TMS-linked-BINOL **1b** to achieve high yield and ee (Entry 10, 95% yield, 92% ee). On the other hand, the present system is not applicable to aliphatic ketones such as hydroxyacetone. No reaction proceeded with hydroxy acetone, probably due to slightly lower acidity of α-proton in hydroxyacetone than in aromatic hydroxy ketones



Scheme 4. Mannich-type reaction with reduced catalyst loading.

3b–3g. Entries 11–26 illustrate the scope of useable imine substrates. Aromatic imines with an electron-withdrawing group **2b** and an electron-donating group **2c** were useable (Entries 11–14). Heteroaromatic imines **2d** and **2e** also afforded Mannich adducts **7db** and **7eb** in high stereoselectivity (Entries 15–18, 95–97% ee). α,β-Unsaturated imines **2f–2i** gave Mannich adducts in good yield and high diastereo- and enantioselectivity (Entries 19–26: 86–94% yield, 91–96% ee, *syn*/*anti* = 92/8–96/4). The high diastereoselectivity (Entries 19–26: 92/8–96/4) is noteworthy, because the Et_2Zn/linked-BINOL **1a** complex gave only modest diastereoselectivity using α,β-unsaturated imines, even when using hydroxy ketone **3a**.[31] The Mannich adducts from α,β-unsaturated imines are synthetically useful, because they are precursors for the β-alkyl-β-amino-α-hydroxycarbonyl compounds. The use of enolizable aliphatic imines was not successful in the present yttrium catalysis.[32] Catalyst loading was successfully reduced as shown in Scheme 4. Using 0.02 molar amount of linked-BINOL **1b** and 0.034 molar amount of $Y[N(SiMe_3)_2]_3$, the Mannich-type reaction with imine **2e** and hydroxy ketone **3b** gave **7eb** in 91% yield and 95% ee after 61 h.

The yttrium complex should function as a Lewis acid–Brønsted base bifunctional catalyst similar to other metal-catalyzed direct Mannich-type reactions.[12d,13,15] Y-OAr* (Ar*OH = linked-BINOL **1a** or **1b**) moiety would function as a Brønsted base to generate Y-enolate from hydroxy ketones, and the Y center would function as a Lewis acid to activate imines. Unfortunately, trials to elucidate the structure of the $Y[N(SiMe_3)_2]_3$/linked-BINOL complex failed. NMR analysis and ESI-MS analysis of the $Y[N(SiMe_3)_2]_3$/linked-BINOL **1a** complex with variable Y/**1a** ratio failed. ^{1}H NMR of $Y[N(SiMe_3)_2]_3$/linked-BINOL **1a** complex showed only very broad peaks, suggesting complicated mixtures of oligomeric species. On the basis of previous mechanistic studies involving rare-earth metal/linked-BINOL complexes,[25b] more than two yttrium metals are probably involved in the active species. In the direct Mannich-type reaction of Dpp-imines **2**, the $Y[N(SiMe_3)_2]_3$/linked-BINOL complex gave *syn*-adducts, while the Et_2Zn/linked-BINOL complex gave *anti*-adducts. Because the structure of the present yttrium complex is unclear, it is difficult to discuss precisely the difference between Zn and Y complexes. We assume that the coordination mode of Dpp-imine **2** on a Lewis acidic metal is different. With more oxophilic rare-earth metals,[33] Dpp-imine **2** would coordinate to yttrium through oxygen atom as shown in Fig. 3. Dpp-imine **2** favors *s*-cis conformation to avoid steric repulsion, and the reaction would proceed via the acyclic *anti*-periplanar transition state to minimize gauche interactions between imine **2** and Y-enolate complex, affording the *syn*-product.

In summary, we developed a new $Y[N(SiMe_3)_2]_3$/TMS-linked-BINOL **1b** complex for direct catalytic asymmetric Mannich-type reactions of various aromatic and heteroaromatic hydroxy ketones. Using the $Y[N(SiMe_3)_2]_3$/**1b** (1.7/1) complex, Mannich adducts were obtained *syn*-selectively in good diastereomeric ratio (81/19–96/4), good yield (78–98%), and high ee (86–98%). The present yttrium catalysis compensates for the drawbacks of the previously reported Et_2Zn/linked-BINOL catalysis for *syn*-amino alcohol synthesis in terms of nucleophile generality and diastereoselectivity with α,β-unsaturated imine and heteroaromatic imines. Use of various aromatic and heteroaromatic hydroxy ketones as donors is also complimentary to the Mannich reactions using organocatalyst[11] in terms of the scope of useable nucleophiles. Further applications of the new yttrium catalysis in other asymmetric reactions are ongoing.

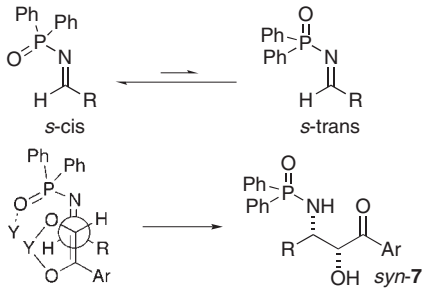


Fig. 3. Proposed acyclic *anti*-periplanar transition state model to give *syn*-Mannich adduct.

Experimental

General Procedure for Direct Mannich-Type Reaction. To a stirred solution of linked-BINOL **1a** or **1b** (8.8 μmol, 5.86×10^{-2} molar amount) in THF (0.5 mL) at room temperature was added $Y[N(SiMe_3)_2]_3$ (8.55 mg, 0.015 mmol, 0.1 molar amount) in THF (1.0 mL). The mixture was stirred at room temperature for 10 min, then THF was removed in vacuo to remove $HN(SiMe_3)_2$. THF (0.4 mL) was added, and the mixture was cooled to −20 °C. To the mixture solution at −20 °C were added imine **2** (0.15 mmol) and hydroxy ketone **3** (0.15 mmol) in THF (1.2 mL). The resulting mixture was stirred at −20 °C for indicated time in Tables and quenched with aq 1 M (1 mol dm^{-3}) HCl. The mixture was extracted with ethyl acetate (×3). The combined organic layers were washed with brine and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by flash silica-gel column chromatography to afford Mannich adducts **7**. Diastereomeric ratio of Mannich adducts was determined by ^{1}H NMR analysis of the crude mixture before purification. Ee of *syn*-isomer was determined by chiral HPLC analysis.

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Supporting Information

Detailed experimental procedures including Mannich-type reaction and synthesis of ligand **1b**, and spectroscopic data for new compounds; these materials are available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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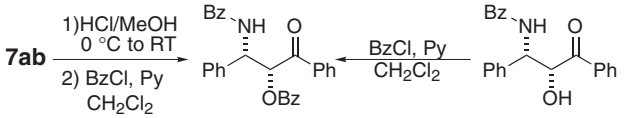

12ab **13**

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