

# ***syn*-Selective Direct Catalytic Asymmetric Mannich-Type Reactions of Aromatic and Heteroaromatic Hydroxy Ketones Promoted by Y[N(SiMe<sub>3</sub>)<sub>2</sub>]<sub>3</sub>/Linked-BINOL Complexes**

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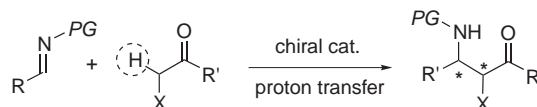
Received April 10, 2006; E-mail: mshibasa@mol.f.u-tokyo.ac.jp

Full details of *syn*-selective catalytic asymmetric direct Mannich-type reactions of aromatic and heteroaromatic hydroxy ketones promoted by Y[N(SiMe<sub>3</sub>)<sub>2</sub>]<sub>3</sub>/linked-BINOL complexes are described. From a screening of various rare-earth metals and linked-BINOL derivatives, a Y[N(SiMe<sub>3</sub>)<sub>2</sub>]<sub>3</sub>/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<sub>3</sub>)<sub>2</sub>]<sub>3</sub> and 0.059 molar amount of TMS-linked-BINOL, afforded *syn*- $\beta$ -amino- $\alpha$ -hydroxy ketones in good yields (78–98%), high diastereoselectivity (*syn/anti* = 81/19–96/4), and high enantioselectivity (86–98% ee).

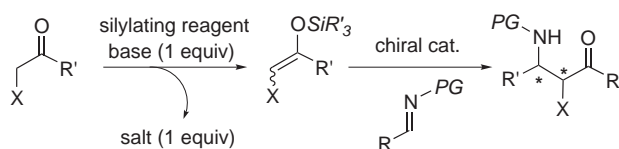
Chiral  $\beta$ -amino alcohol units are useful building blocks found in various natural products, compounds with pharmacologically important activity, chiral auxiliaries, and chiral ligands.<sup>1</sup> Various methods for enantioselective and diastereoselective preparation of  $\beta$ -amino alcohols have been developed over the last decade.<sup>2</sup> Among the methods available for their catalytic enantioselective syntheses,<sup>3</sup> catalytic asymmetric Mannich-type reactions<sup>4</sup> of  $\alpha$ -alkoxy enolates are of particular interest because two adjacent stereocenters are constructed simultaneously with concomitant carbon–carbon bond formation.<sup>5,6</sup> To address this issue, direct catalytic asymmetric Mannich reactions<sup>7,8</sup> are ideal methods in terms of atom economy.<sup>9</sup> In the direct Mannich-type reactions, either a nucleophilic enolate or an enamine is generated in situ using catalytic amount of bifunctional metal complexes<sup>10</sup> or organocatalysts.<sup>11</sup> 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  $\alpha$ -oxy-donors, and they include the addition of unmodified  $\alpha$ -hydroxy ketones,<sup>12,13</sup>  $\alpha$ -oxyaldehydes,<sup>14</sup> and  $\alpha$ -hydroxy-*N*-acylpyrrole as an ester surrogate<sup>15,16</sup> to imines.<sup>17,18</sup> Among the Mannich-type reactions of  $\alpha$ -hydroxy ketones, we developed a Et<sub>2</sub>Zn/linked-BINOL **1a** (Fig. 1)<sup>19,20</sup> complex, which efficiently catalyzed the Mannich-type reaction of 2-hydroxy-1-(2-methoxyphenyl)ethanone (**3a**).<sup>13</sup> By changing the imine protective groups, either *anti*- or *syn*- $\beta$ -amino- $\alpha$ -hydroxy ketones were obtained (Scheme 2). A Mannich-type reaction using diphenylphosphinoylimine (Dpp-imine **2**)<sup>21</sup> af-

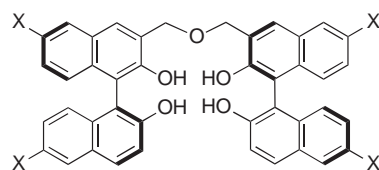
a) Direct Mannich-type reaction



b) Mannich-type reaction with preformed enol silane



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



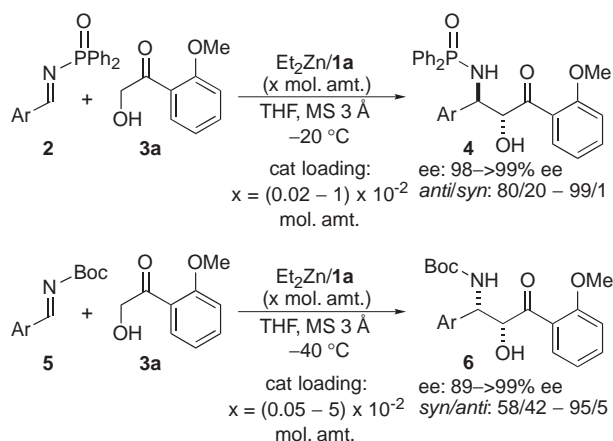
X = H: (S,S)-linked-BINOL **1a**

X = -Si(CH<sub>3</sub>)<sub>3</sub>: (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**).

fording *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.<sup>13b</sup> Especially,  $\alpha,\beta$ -unsaturated imines and heteroaromatic imines gave poor *syn*-selectivity. To the best of our knowledge, there are no reports of highly diastereo-



Scheme 2. Direct catalytic asymmetric Mannich-type reaction of hydroxy ketone **3a** promoted by a  $\text{Et}_2\text{Zn}$ /linked-BINOL **1a** complex.

and enantioselective (dr: >90/10, ee: >90% ee) direct catalytic asymmetric Mannich-type reactions of  $\alpha,\beta$ -unsaturated imines using hydroxy ketones as donors.<sup>22</sup> 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  $\beta$ -amino- $\alpha$ -hydroxycarboxylic esters through Baeyer–Villiger oxidation;<sup>13a,13b</sup> however, zinc catalysis is not suitable for the synthesis of various  $\beta$ -amino- $\alpha$ -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.<sup>23</sup> To overcome the modest *syn*-selectivity and the lack of nucleophile generality of our zinc catalyzed Mannich-type reactions, we previously communicated new  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$ /linked-BINOLs complexes (Fig. 1).<sup>24</sup> Herein, we describe full details of the yttrium-catalyzed direct enantioselective Mannich-type reactions. The  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$ /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,<sup>25</sup> 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  $-20^\circ\text{C}$ . In contrast to our initial assumption based on results obtained by the  $\text{Et}_2\text{Zn}$ /linked-BINOL **1a** complex (Scheme 1),<sup>13a</sup> the reaction proceeded *syn*-selectively with rare-earth metal complexes.<sup>26</sup> 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).<sup>27</sup> Therefore, other rare-earth metal sources were screened, and rare-earth metal hexamethyl-

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

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

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

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

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

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

disilazide  $[\text{RE}[\text{N}(\text{SiMe}_3)_2]_3]$ <sup>27</sup> had much better reactivity and selectivity (Entries 5–8). Among  $\text{RE}[\text{N}(\text{SiMe}_3)_2]_3$  sources,  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$  and  $\text{Yb}[\text{N}(\text{SiMe}_3)_2]_3$  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  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$  was superior to  $\text{Yb}[\text{N}(\text{SiMe}_3)_2]_3$  in terms of reaction rate (48 h vs 60 h), further optimization was performed using  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$  as the metal source.

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  $\text{Et}_2\text{Zn}$ /linked-BINOL-catalyzed reaction,<sup>13c</sup> ligands **1d–1j** were unsatisfactory when used with  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$  (Table 2, Entries 4–10).

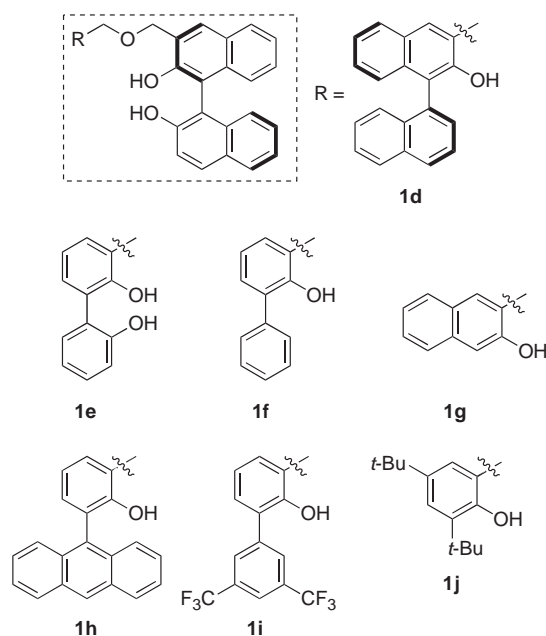
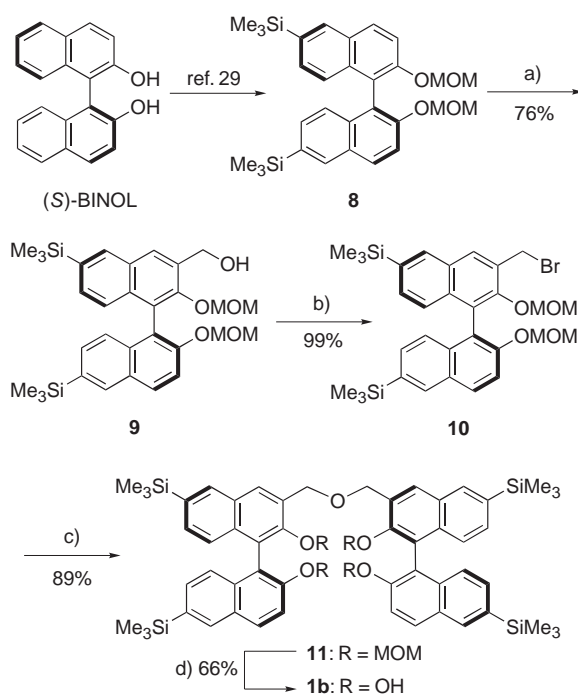


Fig. 2. Structures of linked-BINOL derivatives **1d–1j** for screening.

BINOL, itself, also afforded poor reactivity and selectivity (Entry 11, 24% yield, 3% ee). The present  $Y[N(\text{SiMe}_3)_2]_3$  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,<sup>28</sup> 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 syn-



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<sub>4</sub> (1.0 mol amt.), THF/MeOH, 0 °C, 30 min, 76% (2 steps); b) Ms<sub>2</sub>O (1.5 mol amt.), *i*Pr<sub>2</sub>NEt (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) *p*TsOH·H<sub>2</sub>O (0.2 mol amt.), CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 35 °C, 14 h, 66%.

thetic procedure for TMS-linked-BINOL **1b** is summarized in Scheme 3. Intermediate **8** was synthesized following the reported procedure.<sup>29</sup> Compound **9** was obtained in 76% yield (2 steps) by formylation and reduction with NaBH<sub>4</sub>. Compound **10** was obtained in 99% yield (2 steps from compound

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

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

a) Isolated yield. b) Determined by <sup>1</sup>H NMR analysis.

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

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

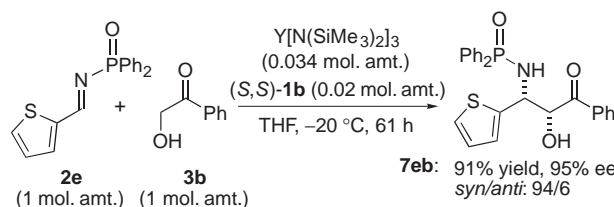
a) Isolated yield. b) Determined by <sup>1</sup>H NMR analysis.

**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<sub>3</sub>)<sub>2</sub>]<sub>3</sub> and linked-BINOL **1a** affected both reactivity and stereoselectivity (Table 3, Entries 1–5). Using a 0.1 molar amount of Y[N(SiMe<sub>3</sub>)<sub>2</sub>]<sub>3</sub> 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<sub>3</sub>)<sub>2</sub>]<sub>3</sub>/linked-BINOL **1a** was 1.7/1. With a catalyst prepared from Y[N(SiMe<sub>3</sub>)<sub>2</sub>]<sub>3</sub>/ **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<sub>3</sub>)<sub>2</sub>]<sub>3</sub>/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,<sup>30</sup> 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

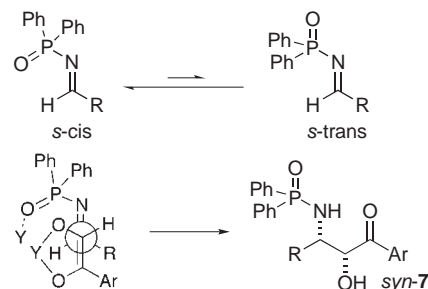


Scheme 4. Mannich-type reaction with reduced catalyst loading.

**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).  $\alpha,\beta$ -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  $\text{Et}_2\text{Zn}$ /linked-BINOL **1a** complex gave only modest diastereoselectivity using  $\alpha,\beta$ -unsaturated imines, even when using hydroxy ketone **3a**.<sup>31</sup> The Mannich adducts from  $\alpha,\beta$ -unsaturated imines are synthetically useful, because they are precursors for the  $\beta$ -alkyl- $\beta$ -amino- $\alpha$ -hydroxycarbonyl compounds. The use of enolizable aliphatic imines was not successful in the present yttrium catalysis.<sup>32</sup> 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  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$ , 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.<sup>12d,13,15</sup>  $\text{Y-OAr}^*$  ( $\text{Ar}^*\text{OH}$  = 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  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$ /linked-BINOL complex failed. NMR analysis and ESI-MS analysis of the  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$ /linked-BINOL **1a** complex with variable Y/**1a** ratio failed.  $^1\text{H}$ NMR of  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$ /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,<sup>25b</sup> more than two yttrium metals are probably involved in the active species. In the direct Mannich-type reaction of Dpp-imines **2**, the  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$ /linked-BINOL complex gave *syn*-adducts, while the  $\text{Et}_2\text{Zn}$ /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,<sup>33</sup> 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  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3/\text{TMS-}$

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

linked-BINOL **1b** complex for direct catalytic asymmetric Mannich-type reactions of various aromatic and heteroaromatic hydroxy ketones. Using the  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3/\mathbf{1b}$  (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  $\text{Et}_2\text{Zn}$ /linked-BINOL catalysis for *syn*-amino alcohol synthesis in terms of nucleophile generality and diastereoselectivity with  $\alpha,\beta$ -unsaturated imine and heteroaromatic imines. Use of various aromatic and heteroaromatic hydroxy ketones as donors is also complimentary to the Mannich reactions using organocatalyst<sup>11</sup> in terms of the scope of useable nucleophiles. Further applications of the new yttrium catalysis in other asymmetric reactions are ongoing.

## Experimental

**General Procedure for Direct Mannich-Type Reaction.** To a stirred solution of linked-BINOL **1a** or **1b** (8.8  $\mu\text{mol}$ ,  $5.86 \times 10^{-2}$  molar amount) in THF (0.5 mL) at room temperature was added  $\text{Y}[\text{N}(\text{SiMe}_3)_2]_3$  (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  $\text{HN}(\text{SiMe}_3)_2$ . THF (0.4 mL) was added, and the mixture was cooled to  $-20^\circ\text{C}$ . To the mixture solution at  $-20^\circ\text{C}$  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  $-20^\circ\text{C}$  for indicated time in Tables and quenched with aq 1 M (1 mol  $\text{dm}^{-3}$ ) HCl. The mixture was extracted with ethyl acetate ( $\times 3$ ). The combined organic layers were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . 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  $^1\text{H}$ NMR analysis of the crude mixture before purification. Ee of *syn*-isomer was determined by chiral HPLC analysis.

This work was supported by Grant-in-Aid for Specially Promoted Research and Grant-in-Aid for Encouragements for Young Scientists (B) (for SM) from JSPS and MEXT. We thank Mr. T. Yoshida for his generous support in synthesis of ligands **1d–1j**.

## 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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