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syn-Selective Direct Catalytic Asymmetric Mannich-Type Reactions of Hydroxyketones Using $Y\{N(SiMe_3)_2\}_3$/Linked-BINOL Complexes

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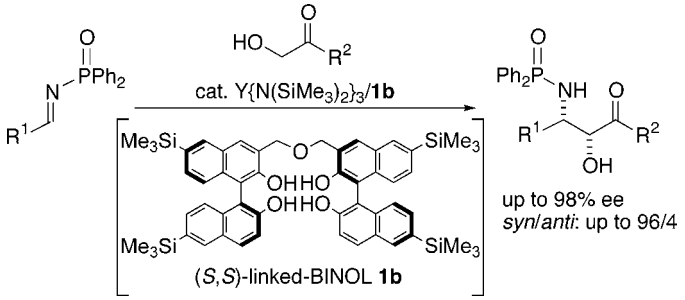
ABSTRACT



Chiral $Y\{N(SiMe_3)_2\}_3$/linked-BINOL catalyst generated Y-enolate in situ from various hydroxyketones (R^2 = aryl, heteroaryl). β-Amino-α-hydroxy ketones (R^1 = aryl, heteroaryl, alkenyl) were obtained *syn*-selectively (up to 96/4) in high ee (up to 98%) and good yield (up to 98% yield).

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.[1] Various methods for enantioselective and diastereoselective preparation of β-amino alcohols have been developed over the past decade.[2] Among the methods available for their catalytic enantioselective syntheses,[3] catalytic asymmetric Mannich-type reactions[4] of α-alkoxy enolate are of particular interest because two adjacent stereocenters are constructed simultaneously with a concomitant carbon−carbon bond formation. Toward this end, Kobayashi 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.[5,6] More atom-economical processes were recently reported:[7] the direct addition of unmodified α-hydroxyketones,[8,9] α-oxyaldehydes,[10] and α-hydroxy-*N*-acylpyrrole as an ester surrogate[11] to imines.[12,13] Among the Mannich-type reactions of α-hydroxyketones, a Et_2Zn/linked-BINOL (**1a**, Figure 1)[14,15] complex efficiently promoted the

(1) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Comprehensive Asymmetric Catalysis*, 1st ed.; Springer: Berlin, 1999.

(2) For reviews on asymmetric synthesis of vicinalamino alcohols, see: (a) Bergmeire, S. C. *Tetrahedron* **2000**, *56*, 2561. (b) Reetz, M. *Chem. Rev.* **1999**, *99*, 1121.

(3) Reviews: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 243.

(4) For a review on catalytic asymmetric Mannich-type reaction, see: Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2003; Supplement 1, Chapter 29.5, p 143.

(5) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.

(6) For another recent example using α-oxy ketene silyl acetal as nucleophile, see: Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.

(7) A review of direct Mannich reaction: Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.

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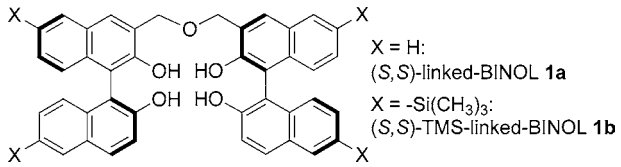
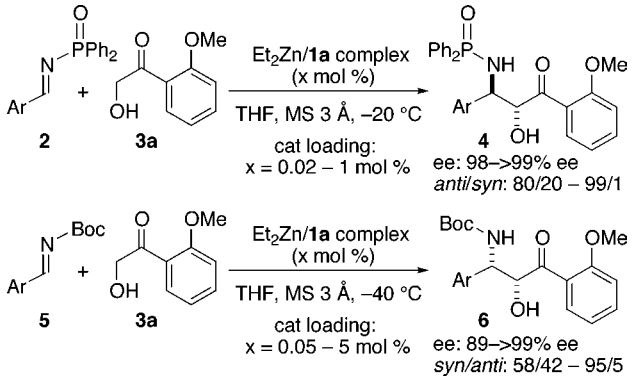


Figure 1. Structures of (*S*,*S*)-linked-BINOLs (**1a** and **1b**).

Mannich-type reaction of 2-hydroxy-2′-methoxyacetophenone **3a**.[9] By changing the imine protective groups, either *anti*- or *syn*-*β*-amino-α-hydroxy ketones were obtained (Scheme 1). A Mannich-type reaction using diphenylphosphinoyl imine (Dpp-imine **2**)[16] afforded *anti*-products, whereas the use of 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.[9b] 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- and enantioselective (dr >90/10, ee >90%) direct catalytic asymmetric Mannich-type reactions of α,*β*-unsaturated imines using hydroxyketones as donors.[17] (2) Nucleophile generality. Use of 2-hydroxy-2′-methoxyacetophenone **3a** 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 in Scheme 1 into *β*-amino-α-hydroxy esters through Baeyer−Villiger oxidation;[9a,b] however, zinc catalysis is not suitable for the synthesis of various *β*-amino-α-hydroxy ketones. For example, when using 2-hydroxyacetophenone **3b** and 2-hydroxyacetylfuran **3f** without a methoxy group on the aromatic ring, Mannich adducts are obtained in only modest enantioselectivity.[18] Herein, we report our efforts to overcome the modest *syn*-selectivity and the limitation in the nucleophile generality of previous zinc-catalyzed Mannich-type reactions. A new Y{N(SiMe$_3$)$_2$}$_3$/TMS-linked-BINOL (Figure 1, **1b**) complex is applicable to various aromatic and heteroaromatic hydroxyketones, affording Mannich adducts *syn*-selectively in good yield and high enantio- and diastereoselectivity.

Scheme 1. Direct Catalytic Asymmetric Mannich-Type Reaction of Hydroxyketone **3a** Using a Et$_2$Zn/**1a** Complex



The rare earth metal alkoxide/linked-BINOL **1a** complexes are useful in other asymmetric reactions,[19] therefore we screened various rare earth metal (10 mol %)/linked-BINOL

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(12) For selected other examples of direct Mannich-type reactions using metal catalysts, see the following. Ketones as donors: (a) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307. (b) Juhl, K.; Gathergood, K. N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. Malonates and ketoesters as donors: (c) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359. (d) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525.

(13) For selected other examples of direct Mannich reactions using unmodified ketone and/or aldehyde as donors with organocatalysts, see: (a) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (b) Córdova, A.; Watanabe, S.-i.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (c) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624. (d) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677. (e) Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987 and references therein. (f) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476. (g) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (h) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528. (i) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.

(14) For other applications of the Et$_2$Zn/linked-BINOL **1a** complex, see the following. Aldol reaction: (a) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169. (b) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539. (c) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. Michael reaction: (d) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251. (e) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582. (f) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559.

(15) Synthesis of linked-BINOL **1a**: Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252.

(16) Use of diphenylphosphinoyl imine is favorable because removal of the protective group is relatively easy. For a review for the use of diphenylphosphinoyl imines **2** in organic synthesis, see: Weinreb, S. M.; Orr, R. K. *Synthesis* **2005**, 1205.

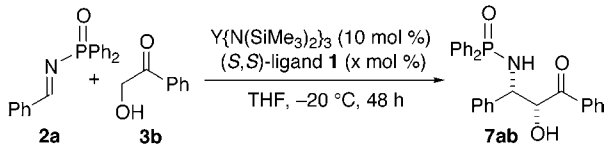
(17) For highly enantioselective catalytic Mannich-type reactions using alkenyl imines, see the following. With enol silane and ketene silyl acetal as donors: (a) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734. (b) Josephsohn, N. S.; Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Org. Lett.* **2005**, *7*, 2711 and references therein. For direct Mannich-type reaction of alkenyl imines with 2-hydroxy-*N*-acylpyrrole as a donor, see ref 11.

(18) When using the Et$_2$Zn/linked-BINOL **1a** complex (5 mol % of **1a**), Mannich adducts were obtained in 58% ee with 2-hydroxyacetophenone **3b** and in 36% ee with 2-hydroxyacetylfuran **3f**. See ref 9b.

(19) (a) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (b) Majima, K.; Takita, R.; Okada, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837.

1a (5 mol %) complexes using Dpp-imine **2a** and 1.2 equiv of hydroxyketone **3b**. In contrast to our initial assumption based on results obtained by the Et_2Zn/linked-BINOL **1a** complex, the reaction proceeded *syn*-selectively with rare earth metal complexes,[20] and $Y\{N(SiMe_3)_2\}_3$ gave the best result (Table 1, entry 1, **7ab**, 89% yield, *syn*/*anti* = 88/12, 85% ee).[21] The ratio of $Y\{N(SiMe_3)_2\}_3$ and linked-BINOL **1a** affected both reactivity and stereoselectivity (Table 1, entries 1−5). The best diastereo- and enantioselectivity were obtained with $Y\{N(SiMe_3)_2\}_3$/linked-BINOL **1a** = 1.7/1 ratio, giving **7ab** in 97% yield, *syn*/*anti* = 90/10, 91% ee (entry 2). Modification at the 6,6′,6″,6‴-positions of linked-BINOL further improved stereoselectivity. When using TMS-linked-BINOL **1b** (Figure 1),[22] **7ab** was obtained in 98% yield, *syn*/*anti* = 94/6, 95% ee (entry 6). Although the precise reason for the positive effects of ligand **1b** is not yet clear, bulky substituents at 6,6′-position of binaphthyl might slightly affect the dihedral angle of the ligand, thereby improving stereoselectivity. The amount of hydroxyketone **3b** also affected stereoselectivity. When using 1 equiv of **3b**, **7ab** was obtained in *syn*/*anti* = 95/5 and 95% ee using **1a** (entry 7). It is noteworthy that the Mannich adduct was obtained in 90% yield, even with an equimolar amount of the nucleophile. Although the structure of the catalyst is not determined yet,[23] we believe the yttrium complex would function as a Lewis acid/Brønsted base bifunctional catalyst in a similar manner as reported for metal-catalyzed direct Mannich-type reactions.[8d,9,11] 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.

Table 1. Optimization of Reaction Conditions



entry	$Y\{N(SiMe_3)_2\}_3$: ligand ratio	ligand (mol %)	**3b** (equiv)	yield[a] (%)	dr[b] (*syn*/*anti*)	ee (%) (*syn*)
1	2.0:1	**1a** (5.0)	1.2	89	88/12	85
2	1.7:1	**1a** (5.9)	1.2	97	90/10	91
3	1.5:1	**1a** (6.7)	1.2	94	84/16	86
4	1.3:1	**1a** (7.7)	1.2	95	76/24	63
5	1:1	**1a** (10)	1.2	92	68/32	26
6	1.7:1	**1b** (5.9)	1.2	98	94/6	95
7	1.7:1	**1a** (5.9)	1.0	90	95/5	95

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

In the direct Mannich-type reaction of Dpp-imines **2**, the $Y\{N(SiMe_3)_2\}_3$/linked-BINOL complex gave *syn*-adducts, whereas the Et_2Zn/linked-BINOL complex gave *anti*-adducts. We assume that the coordination mode of Dpp-imine **2** on Lewis acidic metal is different. With a more oxophilic rare earth metal, Dpp-imine **2** would coordinate to yttrium through the oxygen atom of the diphenylphosphinoyl group. 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, affording the *syn*-product (Figure 2).

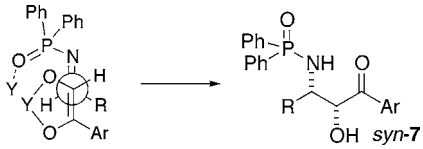
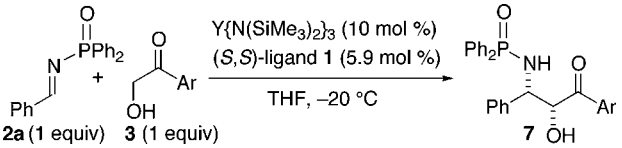


Figure 2. Postulated acyclic *anti*-periplanar transition state model to give *syn*-Mannich adduct.

The $Y\{N(SiMe_3)_2\}_3$/**1a** or **1b** = 1.7/1 complex was applicable to various aromatic and heteroaromatic hydroxyketones **3c**−**3g** (Table 2). TMS-linked-BINOL **1b** gave better chemical yield, diastereoselectivity, and ee than linked-BINOL **1a** in most entries. For hydroxyketones **3c**, linked-BINOL **1a** gave Mannich adduct **7ac** in only 43% yield (entry 1), whereas **1b** gave **7ac** in 89% yield (98% ee, entry

Table 2. Direct Catalytic Asymmetric Mannich-*type* Reaction Using Various Hydroxyketones **3c**−**3g**



entry	ketone: Ar		product	ligand	time (h)	yield[a] (%)	dr[b] (*syn*/*anti*)	ee (%) (*syn*)
1	4-MeO-C_6H_4	**3c**	**7ac**	**1a**	82	43	94/6	96
2	4-MeO-C_6H_4	**3c**	**7ac**	**1b**	84	89	91/9	98
3	4-Me-C_6H_4	**3d**	**7ad**	**1a**	65	84	91/9	92
4	4-Me-C_6H_4	**3d**	**7ad**	**1b**	63	91	91/9	96
5	4-Cl-C_6H_4	**3e**	**7ae**	**1a**	60	70	81/19	80
6	4-ClC_6H_4	**3e**	**7ae**	**1b**	48	94	81/19	86
7	2-furyl	**3f**	**7af**	**1a**	60	68	82/18	74
8	2-furyl	**3f**	**7af**	**1b**	60	94	94/6	93
9	2-thienyl	**3g**	**7ag**	**1a**	89	65	90/10	74
10	2-thienyl	**3g**	**7ag**	**1b**	36	95	95/5	92

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

(20) For the determination of the relative and absolute configuration of Mannich adducts, see Supporting Information.

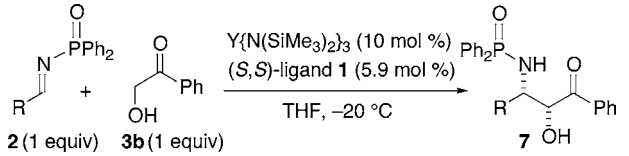
(21) Other rare earth metal souces such as La(O-*i*-Pr)$_3$ (20% ee), Gd(O-*i*-Pr)$_3$ (45% ee), Y(O-*i*-Pr)$_3$ (64% ee), Yb(O-*i*-Pr)$_3$ (65% ee), La$\{N(SiMe_3)_2\}_3$ (12% ee), and Gd$\{N(SiMe_3)_2\}_3$ (66% ee) gave less satisfactroy results. Yb$\{N(SiMe_3)_2\}_3$ gave similar results as $Y\{N(SiMe_3)_2\}_3$, although the reaction rate slightly decreased. RE$\{N(SiMe_3)_2\}_3$ compounds were purchased from Aldrich.

(22) Slightly positive effects of TMS-linked-BINOL **1b** over linked-BINOL **1a** was previously reported in In(O-*i*Pr)$_3$/linked-BINOL **1** complexes; see ref 11. Synthetic procedure of TMS-linked-BINOL **1b** is also reported in ref 11.

(23) Preliminary NMR analysis and ESI-MS analysis of the $Y\{N(SiMe_3)_2\}_3$/linked-BINOL **1a** complexes with variable Y/**1a** ratio failed. ^{1}H NMR of $Y\{N(SiMe_3)_2\}_3$/linked-BINOL **1a** complexes showed only very broad peaks, suggesting complicated mixtures of oligomeric species. ESI-MS analysis also gave no useful information.

2). On the other hand, TMS-linked-BINOL **1b** was required to achieve good ee for hydroxyketone **3e** with an electron-withdrawing group (entry 5 vs 6). 2-Hydroxyacetylfuran **3f**, which affords versatile chiral building blocks,[24] was also a suitable nucleophile. Mannich adduct **7af** was obtained in 94% yield, *syn*/*anti* = 94/6, 93% ee using **1b** (entry 8), although only modest yield and ee were achieved with linked-BINOL **1a** (entry 7, 74% ee). Hydroxyacetylthiophene **3g** also required TMS-linked-BINOL **1b** to achieve high yield and ee (entry 10, 95% yield, 92% ee). Table 3 illustrates

Table 3. Direct Catalytic Asymmetric Mannich-type Reaction Using Various Imines **2b**−**2f**



entry	imine: R		product	ligand	time (h)	yield[a] (%)	dr[b] (*syn*/*anti*)	ee (%) (*syn*)
1	4-Cl-C_6H_4	**2b**	**7bb**	**1a**	60	73	88/12	92
2	4-Cl-C_6H_4	**2b**	**7bb**	**1b**	48	78	94/6	95
3	4-MeO-C_6H_4	**2c**	**7cb**	**1a**	89	69	89/11	86
4	4-MeO-C_6H_4	**2c**	**7cb**	**1b**	84	90	95/5	94
5	2-furyl	**2d**	**7db**	**1a**	60	90	93/7	95
6	2-furyl	**2d**	**7db**	**1b**	39	93	95/5	96
7	2-thienyl	**2e**	**7eb**	**1a**	61	83	93/7	95
8	2-thienyl	**2e**	**7eb**	**1b**	39	95	96/4	97
9	PhCH=CH	**2f**	**7fb**	**1a**	66	86	96/4	96
10	PhCH=CH	**2f**	**7fb**	**1b**	60	87	96/4	95
11[c]	Ar^1CH=CH	**2g**	**7gb**	**1a**	65	93	96/4	94
12[c]	Ar^1CH=CH	**2g**	**7gb**	**1b**	42	94	95/5	93
13[c]	Ar^2CH=CH	**2h**	**7hb**	**1a**	40	94	92/8	92
14[c]	Ar^2CH=CH	**2h**	**7hb**	**1b**	60	92	93/7	91
15[c]	Ar^3CH=CH	**2i**	**7ib**	**1a**	65	87	96/4	94
16[c]	Ar^3CH=CH	**2i**	**7ib**	**1b**	42	89	96/4	94
17[d]	2-thienyl	**2e**	**7eb**	**1b**	61	91	94/6	95

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis. [c] Ar^1 = 4-Cl-C_6H_4; Ar^2 = 4-Me-C_6H_4; Ar^3 = 2-furyl. [d] 2 mol % of **1b** and 3.4 mol % of $Y\{N(SiMe_3)_2\}_3$ were used.

the imine substrate scope. Aromatic imines with electron-withdrawing group **2b** and electron-donating group **2c** were applicable (entries 1−4). Heteroaromatic imines **2d** and **2e** also afforded Mannich adducts **7db** and **7eb** in high stereoselectivity (entries 5−8, 95−97% ee). α,β-Unsaturated imines **2f**−**2i** gave Mannich adducts in good yield and high diastereo- and enantioselectivity (entries 9−16; 86−94% yield, 91−96% ee, *syn*/*anti* = 92/8−96/4). The high diastereoselectivity (96/4) obtained with α,β-unsaturated imine **2f** is noteworthy, because the Et_2Zn/linked-BINOL **1a** complex gave only modest diastereoselectivity using α,β-unsaturated imines, even when using hydroxyketone **3a**.[25] 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.[1] Catalyst loading was successfully reduced as shown in entry 17. With 2 mol % of **1b** and 3.4 mol % of $Y\{N(SiMe_3)_2\}_3$, a Mannich-type reaction of imine **2e** and hydroxyketone **3b** gave **7eb** in 91% yield and 95% ee after 61 h (entry 17).

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 hydroxyketones. Mannich adducts were obtained *syn*-selectively in good dr (81/19−96/4) and 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 hydroxyketones as donors is also complimentary to the Mannich reactions using organocatalyst[8] in terms of nucleophile scope. Further applications of the new yttrium catalysis in other asymmetric reactions as well as mechanistic studies are ongoing.

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Supporting Information Available: Detailed experimental procedure, spectroscopic data, and relative and absolute configuration of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) For use of 2-furyl group as a 4-oxygenated-2-enoic acid synthon using mild oxidation conditions (NBS, pyridine), see: (a) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505. For use of 2-furyl group as an ester synthon, see also: (b) Dondoni, A.; Franco, S.; Junquera, F.; Merchán, F. L.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5497. (c) Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513 and references therein.

(25) For the results using Et_2Zn/linked-BINOL **1a**, α,β-unsaturated imine, and hydroxyketone **3a** (with dpp-imine **2f**, *syn*/*anti* = 19/81, 99% ee; with Boc-imine derived from cinnam aldehyde, *syn*/*anti* = 63/37, 99% ee): see ref 9b. Although ee was excellent, diastereoselectivity was only modest.