J|A|C|S
COMMUNICATIONS

Published on Web 12/13/2002

A Direct Catalytic Asymmetric Mannich-type Reaction to *syn*-Amino Alcohols

Barry M. Trost* and Lamont R. Terrell

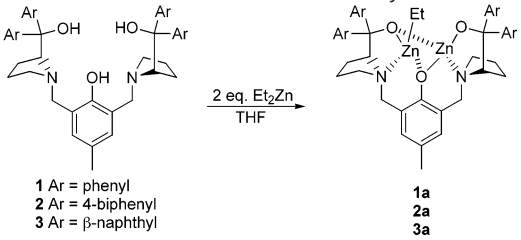
Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received October 2, 2002; E-mail: bmtrost@stanford.edu

The Mannich reaction is one of the most widely utilized chemical transformations for the construction of nitrogen-containing compounds.[1] By the sheer nature of this multicomponent reaction, considerable diversity with as many as two chiral centers could be generated. With the increasing occurrence of nitrogen in drugs and natural products, highly asymmetric variants of the Mannich reaction are desirable.[2] Moreover, a catalytic diastereo- and enantioselective reaction would be the most efficient means of constructing this class of compounds because the chirality controlling element is used in limited quantities. Although the Mannich reaction has gained increased popularity, only recently have asymmetric catalytic variants been realized.[3] Our interest in the development of a catalytic asymmetric Mannich-type reaction stems from our results with the analogous aldol reaction.[4] In this communication, we report the application of our dinuclear zinc catalyst to a highly asymmetric imine aldol (Mannich-type) reaction to generate syn 1,2-amino alcohols.

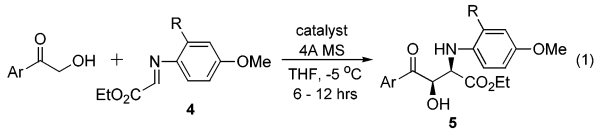
As previously reported,[4] the dinuclear zinc catalyst is generated by exposing ligands **1**−**3** to 2 equiv of diethylzinc in THF (Scheme 1). Subjection of glyoxalate imine **4a** (R = H) and hydroxy-

Scheme 1. Generation of Dinuclear Zinc Catalysts



acetophenone to the standard dinuclear zinc catalyst (10 mol %) gave a high yield of the desired amino alcohol adduct **5**[5] with good diastereoselectivity favoring the syn adduct (6.5:1) and excellent enantioselectivity (95%) (eq 1 and Table 1, entry 1).

Optimization of the reaction conditions as well as the substitution pattern of the nitrogen arene showed that the sterically more demanding 2-methyl-4-methoxy aniline derivatives gave better results (eq 1 and Table 1, entries 2−6). With hydroxyacetophenone



and imine **4b** (R = methyl) (entry 2a), an increase in both the diastereo- (8:1 vs 6.5:1) and the enantioselectivity (98% vs 95%) of the resultant amino alcohol was observed with a substantial lower catalyst load (2.5 mol % vs 10 mol %). The reaction also showed a dramatic ligand effect. With biphenyl ligand **2** (entry 2b), a further increase in the dr was observed (12:1 vs 8:1) accompanied by a yield increase. Thus, biphenyl ligand **2** was adopted as the standard ligand for the glyoxalate series.

Table 1. Additions to Glyoxalate Imines[a]

entry	ketone Ar =	imine **4** R =	cat.	yield **5**[b] (%)	dr[c] **5**	ee[d] **5** (%)
1[e]	C_6H_5	H	**1a**	76	6.5:1	95
2a[f]			**1a**	79	8:1	>98
b[f]	C_6H_5	CH_3	**2a**	92	12:1	>99
c[f,g]			**1a**	97	8.6:1	98
3	4-MeO-C_6H_4	CH_3	**1a**	75	2:1	94
4	3-MeO-C_6H_4	CH_3	**2a**	59	7:1	98
5	2-MeO-C_6H_4	CH_3	**2a**	81	>20:1	>99
6	2-furyl	CH_3	**2a**	81	8:1	>99

[a] All reactions are as in eq 1 using a 2:1 ratio of hydroxyketone to imine using 5 mol % catalyst unless noted otherwise. [b] See ref 5. [c] Determined by ^{1}H NMR spectroscopy on the crude mixture. [d] Determined by chiral HPLC on a Chiracel OD or AD column. [e] 10 mol % catalyst. [f] 2.5 mol % catalyst. [g] Hydroxyketone-to-imine ratio 1.1:1 in the presence of 3.7 mol % Ph_3PS.

Table 2. Additions to Aldimines[a]

entry	Ketone Ar =	Imine	cat.	yield **7**[b] (%)	dr[c] **7**	ee[d] **7** (%)
1a		**6a**	**1a**	61	1.7:1	99
b			**3a**	64	4.3:1	99
2a		**6b**	**1a**	66	>15:1	>99
b			**3a**	70	>15:1	99
3a[e,f]		**6c**	**1a**	90	>15:1	>99
b			**3a**	87	>15:1	>99
4		**6c**	**1a**	68	>15:1	>98
5		**6c**	**1a**	74	>15:1	99

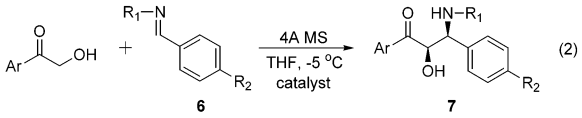
[a] All reactions are as in eq 1 using a 2:1 ratio of hydroxyketone to imine using 5 mol % catalyst unless noted otherwise. [b] See ref 5. [c] Determined by ^{1}H NMR spectroscopy on the crude mixture. [d] Determined by chiral HPLC on a Chiracel OD or AD column. [e] Hydroxyketone-to-imine ratio 1.1:1 in the presence of 7.5 mol % Ph_3AsO. [f] 5 mmol scale.

The use of more electron-rich aromatic hydroxy ketones required higher catalyst loads of 5 mol % (no reaction at the 2.5 mol % load) (entries 3−6). The electron-rich arenes should facilitate the subsequent Baeyer−Villiger oxidation. Surprisingly, the 4′-methoxy hydroxy ketone (entry 3) saw a dramatic drop in the diastereoselectivity. The syn-to-anti ratio was a mere 2:1. With the methoxy substituent in the meta-position (entry 4), the diastereoselectivity was regained (dr = 7:1, 98% ee) but with some loss of reactivity (59% yield). With the ortho-substituted methoxy hydroxy ketone (entry 5), complete diastereo- and enantioselectivity were observed (dr = >20:1, >99% ee). In addition, a "near" atom-economical reaction (1.1 equiv of ketone) is possible with the "zincaphilic" additive Ph_3PS (entry 2c) with no deleterious effect on conversion or stereocontrol (entry 2a vs 2c). Hetereoaromatic hydroxy ketones were also found to be applicable in our imine aldol reaction. 2-Hydroxyacetylfuran (entry 6) gave the desired 1,2-amino alcohol adduct with comparable selectivities as the parent acetophenone

10.1021/ja028782e CCC: $25.00

donor. Moreover, the furan moiety adds another element of diversity to the amino alcohol scaffold.

Another class of imines investigated was those derived from aromatic aldehydes. Table 2 and eq 2 summarize the results for a number of examples. The standard phenyl ligand **1** (5 mol %) with hydroxyacetophenone and imine **6a** (R_1 = 4-methoxyphenyl, R_2 = H) (entry 1a) only slightly favored the syn-isomer (1.7:1), but, encouragingly, both diastereomers had excellent enantioselectivity (99%). A strong ligand effect was also observed in this aromatic series. The β-naphthyl ligand **3** (entry 1b) more than doubled the diastereoselectivity (4.3:1).

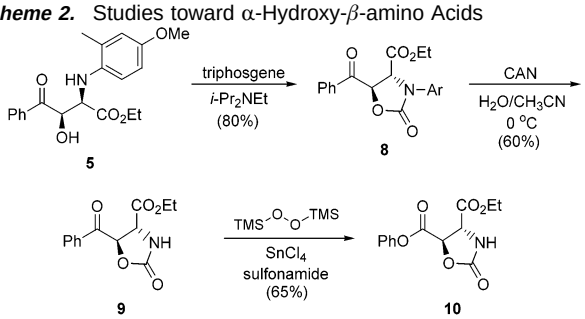


With imine **6b** (R_1 = 2-methoxyphenyl, R_2 = H) (entry 2a), a dramatic increase in diastereoselectivity (>15:1) was observed. The increased diastereoselectivity can be rationalized through a bidentate binding model with the ortho-substituted derivative. The two-point binding of the imine through the nitrogen and methoxy helps rigidify the dynamic nature of the imine-Lewis acid complex.[6] The increased rigidity should prevent the *E*/*Z* isomerization of the carbon−nitrogen double bond, which may account for the low dr in entry 1a.

With imines **6b** and **6c**, the ligand effect was negligible (entry 2a vs 2b and entry 3a vs 3b). However, the reaction showed a significant electronic effect. With *para*-chlorine imine **6c** (R_1 = 2-methoxyphenyl, R_2 = Cl) (entry 3a), the reaction saw a dramatic rate increase with no adverse effect on stereocontrol. Similar to the glyoxalate series, a near "atom-economical" protocol (1.1 equiv of ketone) (entry 3a) is realized with the "zincaphilic" additive Ph_3AsO (7.5 mol %) with no change in chemoselectivity. The reaction at the 5 mmol scale (entry 3a) saw no change in conversion or stereocontrol. The electron-rich aromatic ketones (entries 4 and 5) showed excellent diastereo- and enantioselectivity with imine **6c**, although longer reaction times were needed due to a decrease in the reaction rate.

The imine aldol adducts are valuable synthetic intermediates. Baeyer−Villiger oxidation and oxidative dearylation should give α-hydroxy-β-amino acids, an increasingly important biological class of compounds. As such (Scheme 2), subjection of amino alcohol **5** to triphosgene in the presence of *i*-Pr_2EtN gave oxazolidinone **8**. At this point, the relative stereochemistry was established through nOe studies.[7] The absolute stereochemistry was determined by converting the amino alcohols into their O-methyl mandelate amides.[8] It is noteworthy that the absolute configuration in these reactions is opposite that observed in the aldol reaction − a result that may derive from the fact that lone pair coordination in the case of aldehydes occurs anti to the bulky group but syn in the case of imines. CAN-promoted oxidative dearylation gave oxazolidinone **9**. Regioselective Baeyer−Villiger oxidation with bis(trimethylsilyl) peroxide[9] as the oxidant gave phenyl ester **10** and "proof of principle" that the amino alcohols can be utilized as a synthetic scaffold for the synthesis of α-hydroxy-β-amino acids.

Scheme 2. Studies toward α-Hydroxy-β-amino Acids



In summary, we have demonstrated the application of our dinuclear zinc catalyst in the catalytic asymmetric Mannich-type reaction. Typically, the diastereoselectivity of the reaction was at least 8:1 with most substrates in the >15:1 range. In all cases, the enantiomeric excess of the reaction was typically >98%.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. L.R.T. thanks Pfizer, Inc., for support of his postdoctoral studies. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California−San Francisco supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reviews: (a) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; pp 923−961. (b) Kleinmann, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070.

(2) See: (a) Kober, R.; Papadopoulus, K.; Miltz, W.; Enders, D.; Steglich W.; Reuter, H.; Puff, H. *Tetrahedron* **1985**, *41*, 1693. (b) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287. (c) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. (d) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 981. (e) Vinkovic, V.; Sunjic, V. *Tetrahedron* **1997**, *53*, 689. (f) Zarghi, A.; Naimi-Jamal, M. R.; Webb, S. A.; Balalaie, S.; Saidi, M. R.; Ipaktschi, J. *Eur. J. Org. Chem.* **1998**, *197*, 7. (g) Palomo, C.; Oiarbide, M.; Gonzalez-Rego, M. C.; Sharma, A. K.; Garcia, J. M.; Gonzalez, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063.

(3) (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (c) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (d) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (e) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. For methods that utilize unmodified ketones, see the following: (f) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307. (g) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857. (h) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (i) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (j) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1843.

(4) Leading reference: Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

(5) This compound has been satisfactorily characterized spectroscopically, and its elemental composition has been established.

(6) (a) McCarty, C. G. In *The Chemistry of the Carbon−Nitrogen Double Bond*; Patai, S., Ed.; John Wiley & Sons: New York, 1970; Chapter 9. (b) Bjørgo, J.; Boyd, D. R.; Watson, C. G.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 2* **1974**, 757.

(7) In support of our assignment, the relative stereochemistry of oxazolidinones can also be determined by examination of the J_{4-5} coupling constants: Murakami, M.; Ito, H.; Ito, Y. *J. Org. Chem.* **1993**, *58*, 6766.

(8) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202.

(9) Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971.

JA028782E