The Direct Catalytic Asymmetric Three-Component Mannich Reaction

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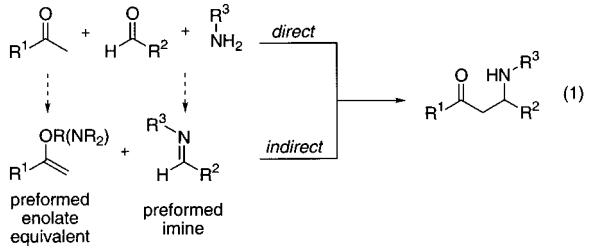
Received June 1, 2000

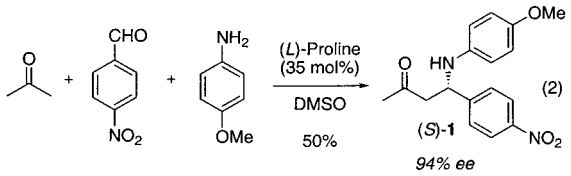
The Mannich reaction is enormously useful for the construction of nitrogenous molecules.[1] In this transformation, three components, a ketone, an aldehyde, and an amine, react to form a β-amino-ketone. The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen in drugs and natural products as well as by the potential of this multicomponent reaction to generate diversity. Both *direct* variants with unmodified ketone donors and *indirect* variants utilizing preformed enolate equivalents have been described.[1] In addition, the imine intermediate may be preformed or its amine and aldehyde precursors used directly (eq 1).



Only a handful of catalytic asymmetric Mannich reactions have been reported,[2] and all but one of these are indirect.[2f] Here we report direct proline-catalyzed highly enantioselective three-component Mannich reactions.

Few reports concerning asymmetric Mannich reactions exist.[3] Catalytic methods have been introduced only very recently by the groups of Tomioka, Kobayashi, Sodeoka, Lectka, and Shibasaki.[2] Noncatalytic enantioselective methods include the addition of chiral preformed enamines to imines.[3] Our interest in testing whether chiral amines or amino acids would also catalyze the Mannich reaction is based on these reports, Kobayashi's elegant work on three-component Mannich reactions,[4] the pioneering lessons we have learned from aldolase antibody 38C2,[5] and our own finding that proline catalyzes the direct asymmetric aldol reaction.[6] According to our mechanistic hypothesis, proline reacts with ketones to form a chiral enamine. We reasoned that (a) the nucleophilic addition of the proline enamine would be faster to an imine than to an aldehyde and (b) that imine formation with a primary amine would be faster than concurrent aldolization. Consequently, a Mannich reaction catalyzed by proline or another chiral amine can be performed as a three-component reaction utilizing an aldehyde, a ketone, and a primary amine.

We found that after stirring proline (35 mol %),[7] *p*-nitrobenzaldehyde (1 eq), and *p*-anisidine (1.1 eq) in acetone/DMSO (1:4) for 12h, the corresponding Mannich product **1** was formed in 50% yield and 94% ee (eq 2).



The aldol addition and condensation products were observed as side products in this reaction. Similarly, if 2-naphthaldehyde was used, β-amino ketone **2** was obtained in excellent enantioselectivity (96% ee), albeit in modest yield (35%) (Table 1, entry 2). Both α-substituted and α-unsubstituted aldehydes gave the corresponding β-amino ketones in good to excellent yields and with ee's of up to 93% (Table 1, entries 3−6).[8] Moreover, the reactions with α-unsubstituted aldehydes were performed in pure acetone, and after completion, proline could be recovered from the reaction mixture in almost quantitative yield by filtration. These reactions can also be performed in chloroform containing 20 vol % of acetone (Table 1, entry 3).

The PMP (*p*-methoxyphenyl) amine protecting group has been chosen because it can readily be removed under oxidative conditions (Scheme 1),[9] although other anilines can be used.[10] Furthermore, we found that ketones other than acetone furnish the desired Mannich products in excellent yields and enantioselectivities.[11,12] Most importantly, hydroxyacetone is an efficient and selective donor. For example, in the reaction with isobutyraldehyde, *syn*-amino alcohol **9** was formed within 12 h as the only detectable regioisomer in good ee (65%) and dr (17:1)

(1) Reviews: (a) Kleinnmann, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070.

(2) (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060−2061. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153−7154. (c) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431−432. (d) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474−2475. (e) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549. (f) For the only method that utilizes unmodified ketones, see the following: Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307−310 and Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857−8867. This report describes asymmetric three-component Mannich reactions. However, yields (≤16%) and ee's (≤64%) were modest.

(3) For asymmetric Mannich reactions utilizing stoichiometric chiral controller, see, for example: (a) Kober, R.; Papadopoulus, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. *Tetrahedron* **1985**, *41*, 1693−1701 (b) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287−5290. (c) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520−10524. (d) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 981−984. (e) Zarghi, A.; Naimi-Jamal, M. R.; Webb, S. A.; Balalaie, S.; Saidi, M. R.; Ipaktschi, J. *Eur. J. Org. Chem.* **1998**, 197−200. For diastereoselective Mannich reactions, se, for example: (f) Seebach, D.; Betschart. C.; Schiess, M. *Helv. Chim. Acta* **1984**, *67*, 1593−1597. (g) Risch, N.; Arend, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2422−2423.

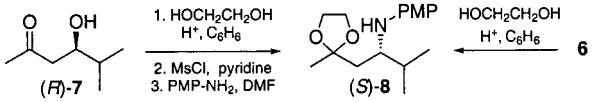
(4) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965−1967.

(5) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768−2779, and references therein.

(6) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386-7387. Our studies are based on the landmark contributions by Wiechert and Hajos and their collegues: Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

(7) We have screened various other catalytic proline derivatives. All of these gave lower yields and ee's. See Supporting Information.

(8) The absolute configuration of β-amino ketone **6** has been determined by correlation (chiral-phase HPLC) with aldol **7**:[6a]

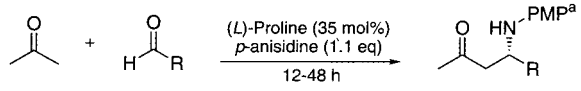


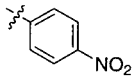
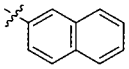
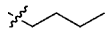
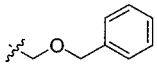
(9) For example, see: Bravo, P.; Guidetti, M.; Viani, F.; Zanda, M.; Markovsky, A. L.; Sorochinsky, A. E.; Soloshonok, I. V.; Soloshonok, V. A. *Tetrahedron* **1998**, *54*, 12789−12806.

(10) We investigated three different anilines in Mannich reactions with isovaleraldehyde in pure acetone: *p*-chloroaniline (56% yield, 84% ee), *o*-anisidine (43% yield, < 10% ee), and 2-aminophenol (51% yield, < 10% ee).

10.1021/ja001923x CCC: $19.00
Published on Web 09/07/2000

Table 1. Products from the Proline-Catalyzed Asymmetric Three-Component Mannich-Reaction



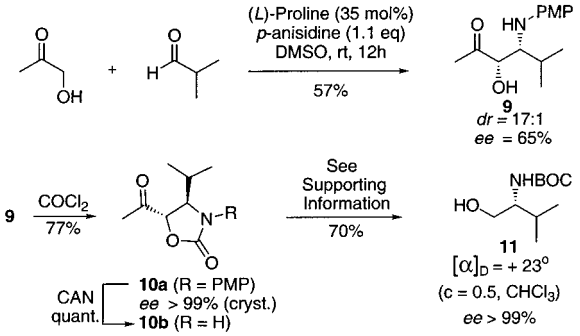
Entry	R =	Product	Yield	ee[b]
(1)		**1**[c]	50%	94%
(2)		**2**[c]	35%	96%
(3)		**3**[d]	90% (87%)[e]	93% (91%)[e]
(4)		**4**[d]	74%	73%
(5)		**5**[d]	82%	75%
(6)		**6**[c]	56%	70%

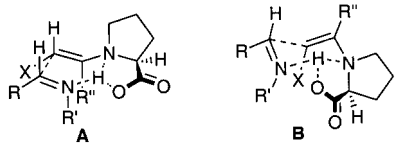
[a] PMP = *p*-methoxyphenyl. [b] The ee's of compounds **1**−**6** were determined by chiral-phase HPLC analysis using Chiralpak AD and AS columns (Daicel Chemical Industries, Ltd.) with hexane/2-propanol mixtures as eluents. [c] Reactions in DMSO/acetone 4:1. [d] Reactions in pure acetone. [e] Reaction in $CHCl_3$/acetone 4:1.

(Scheme 1). The relative and absolute configuration was determined from the X-ray structure of cyclic derivative **10a** and via conversion to enantiomerically pure *N*-(BOC)-D-valinol (**11**), respectively. The Mannich reactions with hydroxyacetone complement the Sharpless asymmetric aminohydroxylation (AA)[13] for the construction of chiral nonracemic *vic*-amino alcohols.[14]

Currently we speculate that this reaction follows an enamine mechanism and involves either a boatlike transition state **A** or chairlike transition state **B**. Both transition states include a (*Z*)-imine, which has been implicated earlier in related reactions with boron enolates.[3b] The geometry of the enamines from substituted ketones (X ≠ H) is (*E*) in **A** and (*Z*) in **B**. These transition states readily explain the observed *si*-facial enantioselectivity. The opposite selectivity (*re*) has previously been observed in proline-catalyzed *aldol* reactions.[6] The additional nitrogen substituent of the imine may destabilize the corresponding chairlike transition state of the aldol reaction.

Scheme 1. Three-Component Mannich Reaction with Hydroxyacetone





In summary, we have shown the first examples of the proline-catalyzed asymmetric three-component Mannich reaction. Important features of this new transformation are the following: (1) The reactions typically display high enantioselectivity (up to 99% ee)[11] and yield. (2) The inexpensive catalyst proline is available in both enantiomeric forms and can be recovered from the reaction mixture via filtration. (3) The PMP group can be readily removed after further transformations. (4) Aliphatic unbranched aldehydes can be utilized in this process. (5) The reactions do not require preformed enolate equivalents or preformed imine equivalents.

Future studies will aim to shed light on the mechanism and scope of this reaction and on further applications of proline and other chiral amines in important carbon−carbon bond-forming reactions.[15]

Acknowledgment. Generous support by Richard A. Lerner and The Scripps Research Institute is most gratefully acknowledged. We thank Reza M. Ghadiri for critical review of the manuscript and Raj K. Chadha for the X-ray structural analysis of **10a**.

Supporting Information Available: Experimental procedures, characterization of new compounds, determination of absolute configurations, and X-ray structural analysis of oxazolidine **10a** (print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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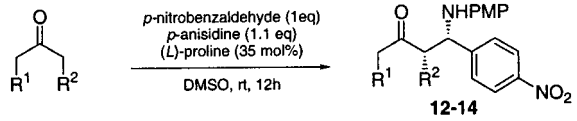
(11) The following products were obtained via the reaction:



12a (R^1 = H, R^2 = Me), dr > 20:1, ee = 99% and **12b** (R^1 = Me, R^2 = H), ee = 94%, 96% combined yield from 2-butanone. **13** (R^1 = H, R^2 = OMe), dr > 20:1, ee = 98%, 93% yield from methoxyacetone. **14** (R^1 = R^2 = CH_2-CH_2CH_2), dr = 2:1, ee = 84% (major diastereomer), ee = 23% (minor diastereomer), 50% combined yield from cyclohexanone. 3-Pentanone and 3-methyl-butan-2-one did not react under these conditions.

(12) In all these reactions, we used the ketone component in excess. However, Mannich reactions in which all three components are used stoichiometrically have been reported. See ref 4.

(13) Review: O'Brien, P. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 326−329.

(14) Review: Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561−2576.

(15) For amine-catalyzed asymmetric Diels−Alder reactions, see: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243−4244. (b) Serebryakov, E. P.; Nigmatov, A. G.; Shcherbakov, M. A.; Struchkova, M. I. *Russ. Chem. Bull.* **1998**, *47*, 82−90.