Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Organocatalytic, Asymmetric, One-Pot, Three-Component Mannich Reaction of Hydroxyacetone

Qing Gu [a] , Ling-Xia Jiang [a] , Kui Yuan [a] , Lei Zhang [a] & Xin-Yan Wu [a]

[a] Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology , Shanghai, China

Published online: 31 Oct 2008.

To cite this article: Qing Gu , Ling-Xia Jiang , Kui Yuan , Lei Zhang & Xin-Yan Wu (2008) Organocatalytic, Asymmetric, One-Pot, Three-Component Mannich Reaction of Hydroxyacetone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:23, 4198-4206, DOI: 10.1080/00397910802323098

To link to this article: http://dx.doi.org/10.1080/00397910802323098

Synthetic Communications®, 38: 4198–4206, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802323098

Taylor & Francis
Taylor & Francis Group

Organocatalytic, Asymmetric, One-Pot, Three-Component Mannich Reaction of Hydroxyacetone

Qing Gu, Ling-Xia Jiang, Kui Yuan, Lei Zhang, and Xin-Yan Wu
Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Shanghai, China

Abstract: The direct three-component asymmetric Mannich reactions of hydroxyacetone with anilines and aromatic aldehydes in the presence of (2*S*,5*S*)-5-(methoxycarbonyl)pyrrolidine-2-carboxylic acid afforded *syn*-1,2-amino alcohols in good-to-excellent yields (55∼91%) and up to 98% ee.

Keywords: Amino alcohol, asymmetric Mannich reaction, enantioselectivity, hydroxyacetone, organocatalysis

INTRODUCTION

The asymmetric Mannich reaction is one of the most powerful carbon–carbon bond-forming reactions for the construction of optically enriched nitrogen-containing compounds.[1] The ideal Mannich reaction would involve a catalytic process employing directly the unmodified carbonyl donor, amine, and acceptor aldehyde in one pot.[2] The first example of direct enantioselective Mannich-type reactions was reported Yamasaki and co-workers using heterodimetallic complexes as catalysts.[3] Recently asymmetric reactions catalyzed by metal-free organic molecules have become increasingly popular. The direct organocatalytic three-component Mannich reaction was reported first

Received February 27, 2008.
Address correspondence to Xin-Yan Wu, Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Shanghai 200237, China. E-mail: xinyanwu@ecust.edu.cn

by List[4] and was followed by the excellent work of several groups.[5–12] L-Proline,[4–9] proline-derived tetrazole,[10] acylic amino acids and their derivatives,[11] and chiral phosphoric acids[12] were developed as enantioselective catalysts for the direct, one-pot, three-component Mannich reactions. Although 1,2-amino alcohol can be constructed via Mannich reaction of hydroxyacetone to imines, hydroxyacetone was seldom used as donor in the asymmetric, catalyzed, direct Mannich reactions.[4b,11b,13]

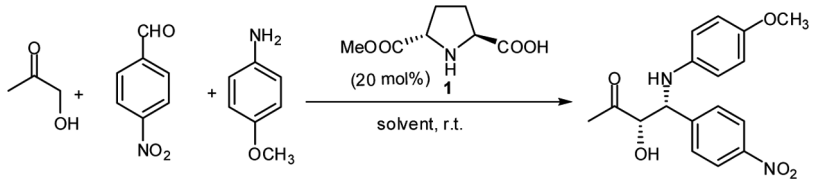
To the best of our knowledge, most of the reported proline-based organocatalysts were designed by changing the carboxylic acid function of proline, and less attention has been paid to the modification on five-membered ring of proline.[14–17] The steric features of a substituent at the 5-position of the pyrrolidine can be used to fix the conformation of the enamine intermediate for Mannich reaction.[16] Thus we designed (2*S*,5*S*)-5-(methoxycarbonyl)pyrrolidine-2-carboxylic acid (**1**) as organocatalyst for the direct, one-pot, three-component Mannich reaction with hydroxyacetone as donor to furnish chiral 1,2-amino alcohols.

RESULTS AND DISCUSSION

Initially a three-component Mannich reaction of 4-nitrobenzaldehyde, *para*-methoxyaniline, and hydroxyacetone was carried out at room temperature with 20 mol% of **1** in dimethyl sulfoxide (DMSO). The Mannich adducts were obtained in 74% yields with 85/15 *dr* (*syn*/*anti*) and 60% ee for the *syn*-isomer (Table 1, entry 1). Similar to L-proline, organocatalyst **1** provided *syn*-Mannich product in the reactions of hydroxyketone as donor. It was reported that (3*R*,5*R*)-5-methyl-β-proline was ineffective in the Mannich-type reactions of ketones originated from relatively slow formation of the enamine intermediates, due to the steric hindrance of the 5-methyl group.[18] Our result suggested that the carboxyl group at the 5-position of proline in *trans* configuration would not block the formation of (*E*)-enamine intermediate or inflect the *syn*-selectivity.

The enantioselectivity of the *syn*-isomer increased to 76% ee when 4 Å molecular sieves were added (entry 2). It should be noted that the molecular sieves play a special role in the transition state other than desiccants (entry 3 vs. 4). The reaction temperature had effect on the enantioselectivity. Decreasing the reaction temperature to 10 °C, the corresponding *syn*-amino alcohol was afforded in 86% ee (entry 3). Among the solvents screened, N,N-dimethylformamide (DMF) provided good enantioselectivity (entry 5). Other solvents, including MeOH, CH_3CN,

Table 1. Optimization of reaction conditions



Entry	Solvent	Time (h)	Yield (%)[a]	*dr* (*syn*/*anti*)[b]	Ee (%)[c]
1	DMSO	36	74	85/15	60
2[d]	DMSO	36	73	84/16	76
3[d,e]	DMSO	36	72	82/18	86
4[e,f]	DMSO	36	70	84/16	69
5	DMF	48	59	72/28	71
6	CH_3OH	30	48	78/22	6
7	CH_3CN	30	48	64/36	24
8	CH_2Cl_2	30	60	47/53	9
9	Toluene	30	43	61/39	31

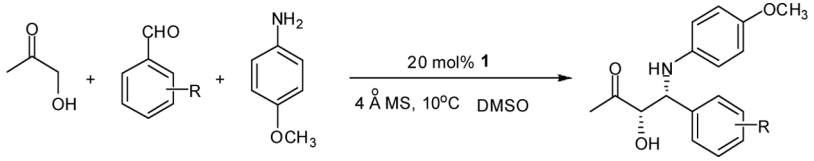
[a]Isolated yield after silica-gel column chromatography.
[b]Determined by HPLC analysis.
[c]Ee values of *syn*-isomer, determined by HPLC using chiralpak AD-H column.
[d]4 Å Molecular sieves were added.
[e]The reaction was carried out at 10 °C.
[f]Performed imine was used.

CH_2Cl_2 and toluene, were found to be less satisfactory in terms of the yield and the enantioselectivity (entries 6–9 vs. 1).

Under the optimized reaction conditions, a variety of aromatic aldehydes were reacted with *para*-methoxyaniline and hydroxyacetone (Table 2). The Mannich products were obtained in moderate to good yields with up to 95% ee and diasteromer ratio (*dr*) ranging from 78/22 to 94/6. The stereochemical outcome depends significantly on the electronic properties of the substituent on benzaldehyde. Electron-withdrawing groups had a positive effect on the enantioselectivities (entries 1–9 vs. 10 and 11).

Also, several different phenylamine components were investigated. As shown in Table 3, the Mannich products were achieved in good to excellent yields with up to 98% ee. The structure of the amine component has a considerable effect on the Mannich reaction. Compared to *para*-methoxyphenylamine, other anilines studied provided better diastero- and enantioselectivities.

Table 2. Three-component direct asymmetric Mannich reactions of different aromatic aldehydes



Entry	R	Time (h)	Yield (%)[a]	*dr* (*syn*/*anti*)[b]	Ee (%)[c]
1	4-NO_2	36	72	82/18	86
2	3-NO_2	48	66	88/12	91
3	2-NO_2	60	76	94/6	95
4	4-CN	60	70	90/10	85
5	3-CN	48	60	94/6	77
6	4-F	48	75	84/16	72
7	4-Cl	60	71	82/18	65
8	2-Cl	48	57	80/20	67
9	4-Br	60	62	89/11	64
10	H	72	70	80/20	33
11	4-Me	72	55	78/22	26

[a]Isolated yield after column chromatography.
[b]Determined by HPLC analysis.
[c]Enantiomeric excess of *syn*-product was determined by HPLC using Chiralcel OD-H or Chiralpak AD-H column.

CONCLUSION

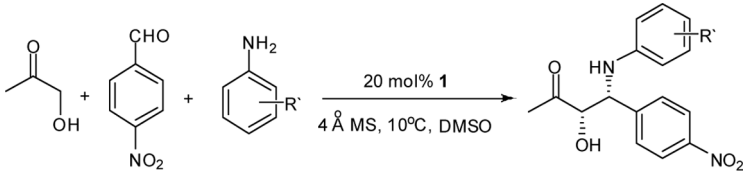
Organocatalyst **1** was efficient for three-component, direct, asymmetric Mannich reactions of hydroxyacetone, the Mannich products were achieved in good yields with up to 94/6 *dr* and 98% ee.

EXPERIMENTAL

General Considerations

DMSO and DMF were dried over CaH_2 and distilled under reduced pressure. Toluene and THF were distilled from sodium-benzophenone. Dichloromethane and acetonitrile were distilled from CaH_2. NMR spectra were recorded with a Bruker spectrometer at 500 MHz, and chemical

Table 3. Three-component direct asymmetric Mannich reactions of different amine components



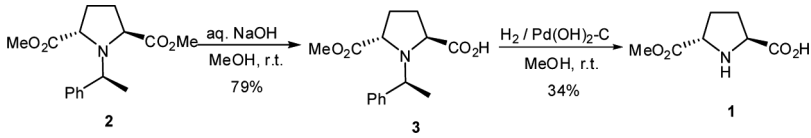
Entry	R′	Time (h)	Yield (%)[a]	*dr* (*syn*/*anti*)[b]	Ee (%)[c]
1	4-MeO	36	72	82/18	86
2	3-MeO	36	88	90/10	98
3	4-Me	36	81	85/15	87
4	2,4-Me_2	48	77	85/15	87
5	H	48	71	88/12	93
6	4-Cl	48	91	85/15	93

[a]Isolated yield after silica-gel column chromatography.
[b]Determined by HPLC analysis.
[c]Ee values of *syn*-isomer, determined by HPLC using Chiralpak AD-H column.

shifts were reported in parts per million (δ) relative to the internal standard Me_4Si (0 ppm). IR spectra were recorded on Nicolet Magna-I 550 spectrometer. Mass spectra were recorded on Micromass LCT spectrometer with EI resource. High-performance liquid chromatography (HPLC) analysis was performed on a Waters 510 with 2487 detector using Daicel Chiralcel OD-H or Chiralpak AD-H column.

Materials

All starting materials were obtained commercially and used directly.



Scheme 1. Synthesis of organocatalyst **1**.

General Procedure for Synthesis of 1 (Scheme 1)

Aqueous NaOH (1.0 M, 11.6 mL) was added dropwise to a solution of compound **2**[19] (2.02 g, 6.94 mmol) in methanol (16 mL) was added and stirred at room temperature for 3 days. The resulting mixture was concentrated, and the residue was dissolved in water (10 mL). The aqueous solution was washed with EtOAc and acidified to pH 2 by diluted hydrochloride (1.0 M). After saturating with NaCl, the aqueous solution was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel (3:1 PE/EA + 1% HOAc) to afford **3** as a white solid. Yield: 79% (1.51 g). Mp: 99–101 °C. $[\alpha]_D^{14} - 83.0$ (c 1.38, $CHCl_3$). ^1H NMR (D_2O, δ ppm) 7.30–7.25 (m, 2 H), 7.25–7.15 (m, 1 H), 7.20–7.15 (m, 2 H), 4.15 (q, $J = 6.7$ Hz, Hz, 1 H), 3.85 (dd, $J = 9.7$, 1.2 Hz, 1 H), 3.60 (d, $J = 7.6$ Hz, 1 H), 3.50 (s, 3 H), 2.55–2.45 (m, 1 H), 2.05–1.95 (m, 2 H), 1.80–1.75 (m, 1 H), 1.30 (s, 3 H). IR (film, cm^{-1}) 3059m, 3027m, 2952m, 2874m, 1732s, 1622w, 1492w, 1454m, 1373m, 1310m, 1206s, 1165s, 1092w, 1060w, 993w, 767s, 704s. MS (ESI) m/z (rel intensity): 278 ($[M + 1]^+$, 100), 279 ($[M + 2]^+$, 14). HRMS: calcd. for $C_{15}H_{20}NO_4(M + H)$: 278.1392; found: 278.1354.

In a flame-dried flask, a solution of compound **3** (1.50 g, 5.4 mmol) in anhydrous MeOH (20 mL) was hydrogenated over 26% $Pd(OH)_2/C$ (0.25 g, 17% wt) for 15 h. The catalyst was removed by filtering through a Celite® pad. The solvents were removed in vacuo to give a solid, then washed successively with CH_2Cl_2 and MeOH to afford pure **1** as a white solid. Yield: 34% (270 mg). Mp 184–186 °C. $[\alpha]_D^{14} - 87.8$ (c 0.88, CH_3OH). ^1H NMR (D_2O, δ ppm) 4.56 (dd, $J = 7.8$, 7.4 Hz, 1 H), 4.23 (t, $J = 7.50$ Hz, 1 H), 3.80 (s, 3 H), 2.44–2.35 (m, 2 H), 2.20–2.00 (m, 2 H). IR (film, cm^{-1}) 3421s, 3006s, 2991s, 2958s, 2935s, 2782m, 1743s, 1623s, 1563s, 1460m, 1440m, 1408s, 1389s, 1364m, 1295m, 1227s, 1155m, 1105w, 1072m, 1018s. MS (EI) m/z (rel intensity): 128 ($[M\text{-}COOH]^+$, 20), 114 ($[M\text{-}COOCH_3]^+$, 61), 68 ($[M\text{-}COOH\text{-}COOCH_3]^+$, 100). HRMS: calcd. for $C_7H_{11}NO_4(M)$: 173.0688; found: 173.0699.

General Procedure for Mannich Reaction

The solution of organocatalyst **1** (0.05 mmol), 4 Å molecule seives (12 mg), and hydroxyacetone (0.2 mL) in anhydrous DMSO (2 mL) was stirred for 5 min, then the aniline (0.25 mmol) and aromatic aldehyde (0.25 mmol) were added, and the reaction mixture was stirred at 10 °C

(monitored by thin-layer chromatography, TLC). The reaction mixture was treated with saturated ammonium chloride solution (2 mL) and extracted with ethyl acetate (3×5 mL). The combined organic phases were washed with brine (2×5 mL) and dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel to afford the desired product. The ratio of diasteroisomers and the enantiomeric excesses were determined by chiral HPLC.

ACKNOWLEDGMENT

We thank the National Natural Science Foundation of China (20402004) and the Science Foundation of Shanghai Municipality (06ZR14028) for financial support.

REFERENCES

1. (a) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*: E. N. Jacobsen, A. Pfaltz, and H. Yamamoto (Eds.): Springer-Verlag: Heidelberg, 1999: pp 923–961. (b) Kobayashi, S.; Ishitani, H. Catalytic enantioselective addition to imines. *Chem. Rev.* **1999**, *99*, 1069–1094; (c) Arend, M.; Westermann, B.; Risch, N. Modern variants of the Mannich reaction. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070.
2. For a recent overview on multicomponent reactions, see (a) Ramón, D. J.; Yus, M. Asymmetric multicomponent reactions (AMCRs): the new frontier. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; (b) Guillena, G.; Ramon, D. J.; Yus, M. Organocatalytic enantioselective multicomponent reactions (OEMCRs). *Tetrahedron: Asymmetry* **2007**, *18*, 693–700.
3. (a) Yamasaki, S.; Iida, T.; Shibasaki, M. Direct catalytic asymmetric Mannich-type reaction of unmodified ketones utilizing the cooperation of an AlLibis (binaphthoxide) complex and $La(OTf)_3 \cdot nH_2O$. *Tetrahedron Lett.* **1999**, *40*, 307–310: (b) Yamasaki, S.; Iida, T.; Shibasaki, M. Direct catalytic asymmetric Mannich reaction of unmodified ketones: Cooperative catalysis of an AlLi-bis(binaphthoxide) complex and $La(OTf)_3 \cdot nH_2O$. *Tetrahedron* **1999**, *55*, 8857–8867.
4. (a) List, B. The direct catalytic asymmetric three-component Mannich reaction. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. The proline-catalyzed direct asymmetric three-component Mannich reaction: Scope, optimization, and application to the highly enantioselective synthesis of 1,2-amino alcohols. *J. Am. Chem. Soc.* **2002**, *124*, 827–833.
5. Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas III, C. F. The scope of the direct proline-catalyzed asymmetric addition of ketones to imines. *Adv. Synth. Catal.* **2004**, *346*, 1131–1140.

6. Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. The direct and enantioselective, one-pot, three-component, cross-Mannich reaction of aldehydes. *Angew. Chem. Int. Ed.* **2003**, *42*, 3677–3680; (b) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. Application of high pressure induced by water-freezing to the direct catalytic asymmetric three-component List-Barbas-Mannich reaction. *J. Am. Chem. Soc.* **2003**, *125*, 11208–11209; (c) Hayashi, Y.; Urushima, T.; Shoji, M.; Uchimary, T.; Shiina, I. The direct, enantioselective, one-pot, three-component, cross-Mannich reaction of aldehydes: The reason for the higher reactivity of aldimine versus aldehyde in proline-mediated Mannich and aldol reactions. *Adv. Synth. Catal.* **2005**, *347*, 1595–1604.
7. (a) Ibrahem, I.; Casas, J.; Córdova, A. Direct catalytic enantioselective α-aminomethylation of ketones. *Angew. Chem. Int. Ed.* **2004**, *43*, 6528–6531; (b) Córdova, A. The direct catalytic asymmetric cross-Mannich reaction: A highly enantioselective route to 3-amino alcohols and α-amino acid derivatives. *Chem. Eur. J.* **2004**, *10*, 1987–1997; (c) Córdova, A. The direct catalytic asymmetric Mannich reaction. *Acc. Chem. Res.* **2004**, *37*, 102–112; (d) Ibrahem, I.; Córdova, A. Amino acid-catalyzed direct enantioselective synthesis of β-amino-α-oxyaldehydes. *Tetrahedron Lett.* **2005**, *46*, 2839–2843; (e) Ibrahem, I.; Coórdova, A. Amino acid catalyzed direct enantioselective formation of carbohydrates: One-step de novo synthesis of ketoses. *Tetrahedron Lett.* **2005**, *46*, 3363–3367; (f) Liao, W.-W.; Ibrahem, I.; Córdova, A. A concise enantioselective synthesis of iminosugar derivatives. *Chem. Commun.* **2006**, 674–676; (g) Ibrahem, I.; Zou, W.; Casas, J.; Sundén, H.; Córdova, A. Direct organocatalytic enantioselective α-aminomethylation of ketones. *Tetrahedron* **2006**, *62*, 357–364.
8. Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. Asymmetric synthesis of selectively protected amino sugars and derivatives by a direct organocatalytic Mannich reaction. *Angew. Chem. Int. Ed.* **2005**, *44*, 4079–4083.
9. Rodriguez, B.; Bolm, C. Thermal effects in the organocatalytic asymmetric Mannich reaction. *J. Org. Chem.* **2006**, *71*, 2888–2891.
10. Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas III, C. F. Expedient synthesis of chiral 1,2- and 1,4-diamines: Protecting group dependent regioselectivity in direct organocatalytic asymmetric Mannich reactions. *Org. Lett.* **2006**, *8*, 2839–2842.
11. (a) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y. Acyclic chiral amines and amino acids as inexpensive and readily tunable catalysts for the direct asymmetric three-component Mannich reaction. *Chem. Eur. J.* **2005**, *11*, 7024–7029; (b) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas III, C. F. Direct catalytic asymmetric synthesis of *anti*-1,2-amino alcohols and *syn*-1,2-diols through organocatalytic *anti*-Mannich and *syn*-aldol reactions. *J. Am. Chem. Soc.* **2007**, *129*, 288–289; (c) Cheng, L.; Wu, X.; Lu, Y. Direct asymmetric three-component organocatalytic *anti*-selective Mannich reactions in a purely aqueous system. *Org. Biomol. Chem.* **2007**, *5*, 1018–1020.

12. Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. Chiral Brønsted acid–catalyzed direct asymmetric Mannich reaction. *J. Am. Chem. Soc.* **2007**, *129*, 3790–3791.
13. Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentanob, G. Poly(ethylene glycol)-supported proline: A versatile catalyst for the enantioselective aldol and iminoaldol reactions. *Adv. Synth. Catal.* **2002**, *344*, 533–542.
14. Hanessian, S.; Shao, Z.; Warrier, J. S. Optimization of the catalytic asymmetric addition of nitroalkanes to cyclic enones with trans-4,5-methano-L-proline. *Org. Lett.* **2006**, *8*, 4787–4790.
15. Gu, L.; Yu, M.; Wu, X.; Zhang, Y.; Zhao, G. 4,4′-Disubstituted L-prolines as highly enantioselective catalysts for direct aldol reactions. *Adv. Synth. Catal.* **2006**, *348*, 2223–2228.
16. Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F. III. Direct asymmetric *anti*-Mannich-type reactions catalyzed by a designed amino acid. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041.
17. Diez, D.; Gil, M. J.; Moro, R. F.; Marcos, I. S.; Garc, P.; Basabe, P.; Garrido, N. M.; Broughton, H. B.; Urones, G. J. A new class of chiral pyrrolidine for asymmetric Michael addition reactions: New mechanism via simple 4 + 2 type attack of the enamine on the trans-nitrostyrene. *Tetrahedron* **2007**, *63*, 740–747.
18. Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas III, C. F. 3-Pyrrolidinecarboxylic acid for direct catalytic asymmetric *anti*-Mannich-type reactions of unmodified ketones. *J. Am. Chem. Soc.* **2006**, *128*, 9630–9631.
19. Yamamoto, Y.; Hoshin, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. A convenient synthesis of enantiomeric pairs of 2,5-disubstituted pyrrolidines of C_2-symmetry. *Synthesis* **1993**, 298–302.