One-Pot Organocatalytic Direct Asymmetric Synthesis of γ-Amino Alcohol Derivatives

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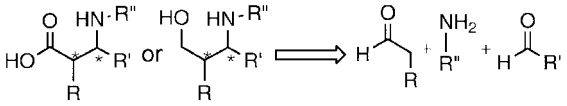
Received 21 May 2003

Abstract: This report describes the unprecedented use of unmodified aldehydes as donors in catalytic three component one-pot asymmetric Mannich reactions. The Mannich-type reactions were also readily performed for the first time with both in situ generated and preformed *N*-PMP protected aromatic aldimines. The proline-catalyzed reactions provided an efficient and very mild entry to either enantiomer of γ-amino alcohol derivatives in high yield and stereoselectivity.

Key words: asymmetric synthesis, asymmetric catalysis, Mannich reactions, aldehydes, imines

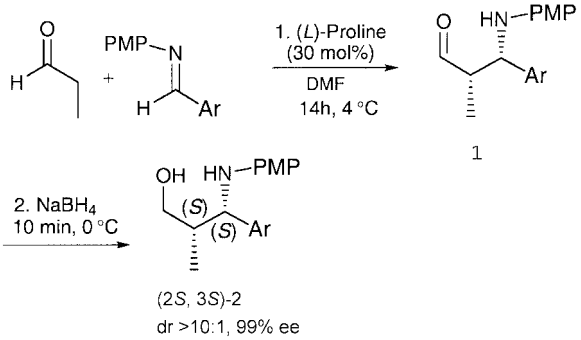
γ-Amino alcohols and β-amino acids are present in several molecules of pharmaceutical and biological interest.[2] Among the plethora of methods that exist for their construction,[3,4] the Mannich reaction is one of the most attractive carbon-carbon bond forming routes.[5] Retrosynthetic analysis suggests that the most efficient Mannich process would be a three component one-pot operation (Scheme 1). However, these transformations are very difficult to control and could result in unwanted side-reactions. Therefore, β-amino acid derivatives are synthesized via asymmetric Mannich-reactions involving carbon-carbon bond formation between preformed ester enolate equivalents and imines. Initially, chiral auxiliaries were used with the disadvantage that they have to be removed in additional steps.[6] Recent advances in catalytic asymmetric Mannich-type reactions have led to excellent protocols for the preparation of β-amino acid derivatives.[7] However, these catalytic systems are also indirect and require formation of the starting materials prior to the reaction.



Scheme 1 Retrosynthetic analysis of β-amino acid and γ-amino alcohol derivatives based on the one-pot three component Mannich reaction with unmodified aldehydes.

Based on our research program on amine-catalyzed asymmetric synthesis,[8] we demonstrated that L-proline[9] and its derivatives can catalyze Mannich-type reactions between unmodified aldehydes and *N*-PMP-protected α-imino ethyl glyoxylate affording α-amino and β-amino acid derivatives.[10] However, we were unable to use other preformed imines as electrophiles, which significantly limited the generality of the reaction. In this context, reactions with aromatic imines would have been highly attractive since they open a novel route for synthesis of γ-amino alcohol and β-amino acid derivatives that are used as chiral synthons for enzyme inhibitors and cancer drugs.[2a] Moreover, there is no report of a catalytic asymmetric three component Mannich reaction with unmodified aldehydes as donors.[11] We therefore embarked on the search for a catalytic asymmetric three-component one-pot Mannich process that would involve aldehydes for both nuchleophile and electrophile generation. Herein, we disclose the first direct three component one-pot asymmetric Mannich reactions with aldehydes that provide a new entry for the synthesis of either enantiomer of γ-amino alcohol derivatives with excellent enantioselectivities.

In initial experiments, propionaldehyde, *N*-PMP-protected α-imino *p*-nitrophenyl (0.1 M) and L-proline (30 mol%) were reacted under different conditions. After several attempts, we discovered that the corresponding Mannich adduct **1** could be obtained if the aldehyde was added in small portions to the reaction mixture. We decided to reduce 3-amino substituted propanal **1** with excess $NaBH_4$ to γ-amino alcohol **2** prior to isolation and ee determination, due to epimerization and racemization of **1** during work-up and purification.[12] We found that slow addition of the propionaldehyde (1 M) in DMF at 4 °C afforded the highest conversion providing γ-amino alcohol **2** in 81% yield and 99% ee as a predominant diastereomer (Scheme 2).[13,14]

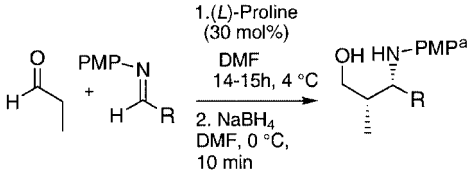


Scheme 2 One-pot direct asymmetric synthesis of 3-amino aldehyde **1** and alcohol **2**. Ar = *p*-$NO_2C_6H_4$, PMP = *p*-methoxyphenyl.

Synlett 2003, No. 11, Print: 02 09 2003. Web: 25 08 2003.
Art Id.1437-2096,E;2003,0,11,1651,1654,ftx,en;D11403ST.pdf.
DOI: 10.1055/s-2003-41423

To broaden the scope of this transformation, a set of different aromatic *N*-PMP-protected imines were reacted with propionaldehyde to afford aromatic γ-amino alcohol derivatives **2**–**7a** (Table 1). In most cases, the reaction proceeded smoothly with excellent enantioselectivities. In addition, Mannich reactions with other aldehydes besides propanal were also catalyzed by proline under the set reaction conditions. For example, heptanal reacted with *N*-PMP-protected α-imino *p*-nitrophenyl to provide the corresponding Mannich product in 60% yield and dr>19:1 and 90% ee.[15] The reactions were readily performed on 10 mmol scale with no detrimental effect on yield or enantioselectivity.

Table 1 Products from the Proline-Catalyzed Mannich-Reaction of Unmodified Aldehydes with *N*-PMP-Protected α-Imino Aryls[a]

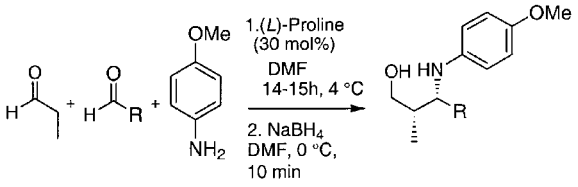


Entry	R	Yield[b]	dr[c]	ee[d]	Product
1	*p*-$NO_2C_6H_4$	81%	>10:1	99%	**2**
2	*p*-CNC_6H_4	72%	7:1	98%	**3**
3	*p*-BrC_6H_4	57%	6:1	95%	**4**
4	*p*-ClC_6H_4	81%	>10:1	93%	**5**
5	C_6H_5	81%	4:1	81%	**6**
6	*m*-BrC_6H_4	89%	3:1	96%	**7**
7	*p*-$MeOC_6H_4$	75%	2:1	55%	**7a**

[a] PMP = *p*-methoxyphenyl.
[b] Isolated yields of pure product after column chromatography.
[c] Dr = *syn*/*anti* as determined by NMR after column chromatography.
[d] The ee's of products **2**–**7a** were determined by chiral-phase HPLC analysis.

Thereafter, we addressed the more challenging task of performing the transformations as three component one-pot operations. We believed that we would be able to direct the role of the aldehyde components of the reaction by adding the donor slowly to the reaction mixture. Hence, slow addition of the propionaldehyde (1 M) to the reaction mixture containing *p*-methoxyaniline (0.1 M), *p*-nitrobenzaldehyde (0.1 M) and L-proline followed by in situ reduction with $NaBH_4$ afforded γ-amino alcohol **2** in 75% yield and 95% ee (Table 2, entry 1).[16] Furthermore, performing the one-pot procedure with other aromatic aldehydes as acceptors afforded β-amino alcohol derivatives **3**–**7** with excellent enantioselectivities. The reactions proceeded with superb chemo-selectivity with no formation of cross-aldol products or self-Mannich adducts. In fact, proline was able to catalyze the two-component direct asymmetric Mannich reaction between propionaldehyde and *p*-anisidine affording self-Mannich adduct **8** in 55% yield with dr of >10:1 and 81% ee (entry 7). As compared to the reactions with preformed imines the yields were slightly decreased. Nevertheless, the ee was not significantly affected. Furthermore, electron-deficient acceptor aldehydes were also efficiently converted with only 2 equivalents of propionaldehyde and 10 mol% proline.

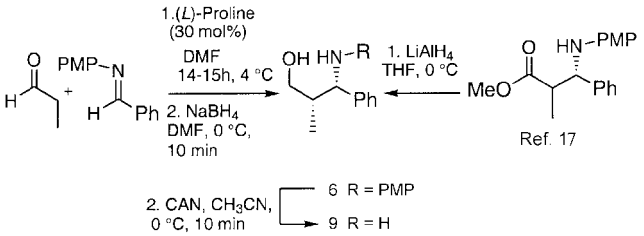
Table 2 One-Pot Direct Three Component Asymmetric Proline-Catalyzed Mannich Reactions with Unmodified Aldehydes



Entry	R	Yield[a]	dr[b]	ee[c]	Product
1	*p*-$NO_2C_6H_4$	75%	>10:1	99%	**2**
2	*p*-CNC_6H_4	65%	5:1	93%	**3**
3	*p*-BrC_6H_4	81%	10:1	91%	**4**
4	*p*-ClC_6H_4	65%	6:1	93%	**5**
5	C_6H_5	62%	4:1	75%	**6**
6	*m*-BrC_6H_4	77%	4:1	97%	**7**
7	Et	55%	>10:1	81	**8**

[a] Isolated yields of pure product after column chromatography.
[b] Dr = *syn*/*anti* as determined by NMR after column chromatography.
[c] The ee's of products **2**–**8** were determined by chiral-phase HPLC analysis.

The stereochemistry of the reaction was determined by synthesis and determined to be (2*S*,3*S*) based on NMR analysis and chiral-phase HPLC analysis of γ-amino alcohols **6** and **9** (Scheme 3).[17,18] Hence, L-proline provides *syn* β-amino aldehyde derivatives with *S* absolute stereochemistry. The stereochemical outcome is explained by L-proline directing a *si*-facial attack of the imines by the *si*-face of the enamine intermediates (Figure 1).



Scheme 3 Determination of absolute configuration of amino alcohol product **6** and its deprotection.[17]

In conclusion, for the first time unmodified aldehydes were successfully used in catalytic three component one-pot asymmetric Mannich reactions. We demonstrated that proline-catalyzed reactions provide a highly enantioselective multigram entry to either enantiomer of amino alco-

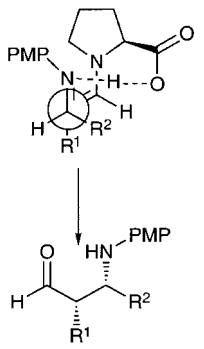


Figure 1 Potential transition state.

hol derivatives and the corresponding products **2**–**8** were obtained in high yields and excellent enantioselectivities. Moreover, our methodology starts with achiral, readily available and inexpensive materials and was performed under operationally simple conditions. Further research addressing the scope and applicability of this methodology is currently under investigation.

Acknowledgment

This study was supported in part by the Wennergren Foundation. The author would like to thank Prof. Kim D. Janda for valuable discussions.

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(12) We observed that Mannich product **1** was unstable and racemized if stored at room temperature or subjected to silica gel column chromatography. In addition, **1** is prone to epimerization that decreases the diastereomeric ratio.

(13) The reaction proceeded in other solvents as well at 23 °C: Dioxane: 65% yield, dr>10:1, 99% ee; THF: 51% yield, dr>10:1, 99% ee; Et_2O: 40% yield, dr>10:1, 99% ee; and at 4 °C: THF: 36% yield, dr>10:1, >99% ee; dioxane: 62% yield, dr>10:1, 99% ee.

(14) Anhydrous DMF (3 mL) was added to a vial containing the aldimine (0.5 mmol) and proline (30 mol%) and placed in a 4 °C cold room. The reaction was initiated by slow addition (0.2 mL/min) of a pree-cooled mixture of propionaldehyde (5.0 mmol) in anhyd DMF (2 mL) with syringe pump at 4 °C. After 15 h the reaction mixture was diluted with anhyd Et_2O (2 mL) and the temperature decreased to at 0 °C followed by reduction with $NaBH_4$ (400 mg) for 10 min. Next, the reaction mixture was poured into a vigorously stirred bi-phaseic solution of Et_2O and 1 M aq HCl. The organic layer was separated and the aq phase was extracted thoroughly with EtOAc. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column

chromatography (silica gel, mixtures of hexanes/EtOAc) to afford **2**. **(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-nitrophenyl)-propan-1-ol** (**2**): ^{1}H NMR ($CDCl_3$): δ = 0.91 (d, 3 H, *J* = 7.0 Hz), 2.21 (m, 1 H), 3.64 (m, 2 H), 3.67 (s, 3 H, OMe), 4.65 (d, 1 H, *J* = 4.0 Hz), 6.42 (d, 2 H, *J* = 8.8 Hz), 6.68 (d, 2 H, *J* = 8.8 Hz), 7.51 (d, 2 H, *J* = 8.8 Hz), 8.17 (d, 2 H, *J* = 8.8 Hz). ^{13}C NMR: δ = 11.9, 41.6, 56.0, 60.8, 66.0; 115.0, 115.1, 123.9, 128.3, 141.0, 147.3, 150.6, 152.6. HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): major isomer: t_R = 36.10 min; minor isomer: t_R = 21.49 min; $[\alpha]_D$ = –65.2 (*c* 0.2, MeOH). HRMS: 317.1496; $C_{17}H_{20}N_2O_4$ [(M + H$^+$): calcd 317.1496]; $C_{17}H_{20}N_2O_4$ (316.1423).

(15) **(1*S*,2*S*)-1-(4-Methoxyphenylamino)-1-(4-nitrophenyl)-2-hydroxymethylheptane:** ^{1}H NMR (CD_3OD): δ = 0.83 (t, 3 H, *J* = 7.0 Hz), 1.22–1.55 (m, 8 H), 2.08 (m, 1 H), 3.54 (d, 1 H, *J* = 3.3 Hz), 3.68 (s, 3 H, OMe), 3.73 (d, *J* = 3.3 Hz), 4.71 (d, *J* = 3.3 Hz), 6.48 (d, 2 H, *J* = 8.8 Hz), 6.68 (d, 2 H, *J* = 8.8 Hz). ^{13}C NMR: δ = 14.4, 22.9, 27.8, 29.7, 46.4, 56.1, 63.9, 96.6, 115.3, 124.1, 128.7, 147.5. HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm): major isomer: t_R = 17.79 min; minor isomer: t_R = 7.43 min; $[\alpha]_D$ = –24.7 (*c* 0.2, MeOH). HRMS: 373.2120; $C_{21}H_{28}N_2O_4$ [(M + H$^+$): calcd 373.2122); $C_{21}H_{28}N_2O_4$ (372.2048968).

(16) Anhydrous DMF (3 mL) was added to a vial containing *p*-nitrobenzaldehyde (0.5 mmol), *p*-anisidine (0.5 mmol) and proline (30 mol%) and placed in a 4 °C cold room. The reaction was initiated by slow addition (0.2 mL/min) of a pree-cooled mixture of propionaldehyde (5.0 mmol) in anhyd DMF (2 mL) with syringe pump at 4 °C. After 16 h of total reaction time the temperature was decreased to 0 °C followed by dilution with anhyd Et_2O (2 mL) and reduction with $NaBH_4$ (400 mg) for 10 min. Next, the reaction mixture was poured into a vigorously stirred bi-phaseic solution of Et_2O and 1 M aq HCl. The organic layer was separated and the aqueous phase was extracted thoroughly with EtOAc. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/EtOAc) to afford **2**.

(17) (a) NMR-data of the major diastereomer of PMP-deprotected **6** was identical to the previously reported *syn*-diastereomer, see: Jaeger, V.; Buss, V.; Schwab, W. *Liebigs Ann. Chem.* **1980**, 122. (b) **(2*S*,3*S*)-3-Amino-2-methyl-3-phenylpropan-1-ol** (**9**): ^{1}H NMR (CD_3OD): δ = 1.10 (d, 3 H, *J* = 4.4 Hz), 2.35 (m, 1 H), 3.44 (d, 1 H, *J* = 5.14 Hz), 3.48 (d, 1 H, *J* = 6.6 Hz), 4.35 (d, 1 H, *J* = 6.6 Hz), 7.54 (m, 5 H). ^{13}C NMR: δ = 12.0, 40.9, 59.1, 66.2, 126.9, 127.1, 128.2, 143.9. (c) L-Proline derived **6** had the same retention time as (2*S*,3*S*)-**6** that had been synthesized via known procedures, see: Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030. (d) See also: Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2001**, *3*, 773; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 14.02 min.

(18) **(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-phenylpropan-1-ol** (**6**): ^{1}H NMR (CD_3OD): δ = 0.95 (d, 3 H, *J* = 7.0 Hz), 2.05 (m, 1 H), 3.38 (dd, 1 H), 3.56 (dd, 1 H), 3.62 (s, 3 H, OMe), 4.43 (d, 1 H, *J* = 4.0 Hz), 6.38 (d, 2 H, *J* = 8.8 Hz), 6.50 (d, 2 H, *J* = 8.8 Hz), 7.12 (m, 1 H), 7.24 (m, 2 H); 7.31 (d, 2 H, *J* = 7.7 Hz). ^{13}C NMR: δ = 12.8, 43.7, 56.3, 61.4, 66.0, 115.7, 116.0, 127.7, 128.6, 129.3, 143.9, 144.6, 151.9, 153.1, 157.7. HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): major isomer: t_R = 14.02 min; minor isomer: t_R = 12.18; $[\alpha]_D$ = –6.2. (*c* 1, MeOH). HRMS: 272.1647; $C_{17}H_{21}NO_2$ [(M + H$^+$): calcd 272.1645); $C_{17}H_{21}NO_2$ (271.172206).