

Enantioselective Organocatalytic Aminomethylation of Aldehydes: A Role for Ionic Interactions and Efficient Access to β^2 -Amino Acids

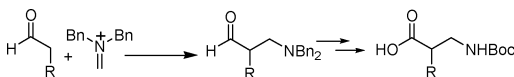
Yonggui Chi and Samuel H. Gellman*

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received March 13, 2006; E-mail: gellman@chem.wisc.edu

The Mannich reaction,¹ in which an enol or enolate attacks an imine or an iminium ion, is a powerful tool for introducing aminoalkyl fragments into organic molecules. Imines derived from aryl aldehydes have been common substrates in recent efforts to develop asymmetric organocatalytic versions of this reaction; these substrates necessarily provide Mannich adducts containing aryl substituents adjacent to nitrogen.² Our attention was drawn to formaldehyde-derived substrates because β^2 -amino aldehydes from such substrates can be used to generate β^2 -amino acids, which are valuable building blocks for β -peptide foldamers and other targets.³ Many routes to enantioenriched β^2 -amino acids have been described; most involve chiral auxiliaries, and few are amenable to large-scale synthesis.⁴ Here we report an enantioselective organocatalytic method for aminomethylation of aldehydes, which leads to a new and efficient synthesis of β^2 -amino acids (Scheme 1). Our observa-

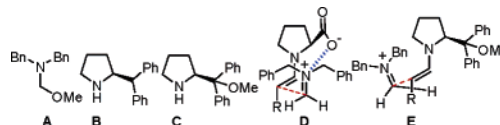
Scheme 1. Aminomethylation of Aldehydes and Its Application in β^2 -Amino Acid Synthesis



tions provide evidence that non-H-bonded ionic interactions at the Mannich reaction transition state can influence stereochemical outcome.

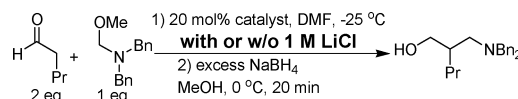
Formaldehyde does not form stable imines,⁵ so we examined formaldehyde derivatives, such as **A**, that can generate a methylene iminium species in situ.⁶ We examined L-proline and chiral pyrrolidines as catalysts for nucleophilic activation of aldehyde reactants. The Mannich reaction products, α -substituted β -amino aldehydes, were immediately reduced to the corresponding β -substituted γ -amino alcohols to avoid epimerization. Initial studies involving pentanal revealed modest enantioselectivity when the reaction was carried out with 20 mol % catalyst in DMF at -25°C for 24 h. The enantiomeric preference observed with L-proline was opposite that observed with 2-alkylpyrrolidines derived from L-proline, such as **B** or **C**⁷ (used with equimolar acetic acid). A comparable switch in product configuration for organocatalytic Mannich reactions involving aryl imines and for α -amination of aldehydes has been observed by Barbas, Jørgensen, List, Cordova, and others.^{2,11c} The commonly accepted rationale for this stereochemical preference switch involves hydrogen bonding:⁸ the carboxylic acid group of the L-proline-derived enamine is thought to H-bond to the electrophile at the transition state, while the substituent of a 2-alkylpyrrolidine sterically repels the electrophile, forcing it to approach the enamine from the opposite face. This hypothesis is reasonable but cannot explain our results with L-proline since our electrophile, an iminium ion, cannot accept a hydrogen bond. We propose instead that approach of the electrophile to the proline-derived enamine is controlled by an electrostatic attraction of iminium to carboxylate (**D**); the carboxylate is presumably generated by methoxide liberated upon iminium forma-

tion. We follow precedent in invoking steric repulsion to rationalize the results with 2-alkylpyrrolidines (**E**).



Our hypothesis is consistent with computational results of Houk et al. for Mannich reaction of imines, in which an ionic attraction between protonated imine and carboxylate was proposed.⁹ We tested our hypothesis by conducting the L-proline-catalyzed reaction in the presence of LiCl. If the putative iminium/carboxylate attraction determines the direction of iminium approach to the enamine, then the ionic additive should diminish enantioselectivity because the lithium cation will compete with the iminium for ion pairing, and chloride will compete with the carboxylate. Indeed, the L-proline-catalyzed Mannich reaction showed little or no enantioselectivity in the presence of 1 M LiCl (Table 1), which supports transition

Table 1. Salt Effect



entry ^a	catalyst	salt	time	ee ^b	favored enantiomer ^c
1	L-proline		24 h	49	S
2	L-proline	LiCl	24 h	<5	
3	C-HOAc		2 h	67	R
4	C-HOAc	LiCl	2 h	80	R

^a Yield of all reactions was $>80\%$ as measured by ^1H NMR of the crude reaction mixture before reduction; the reduction is quantitative. ^b Determined by chiral phase HPLC. ^c See Supporting Information for stereochemistry determination.

state model **D**. However, 1 M LiCl leads to a moderate but reproducible enantioselectivity *enhancement* for the reaction catalyzed by 2-alkylpyrrolidine **C**; a similar result was observed for **B**.¹⁰ The origin of this enhancement is unclear.

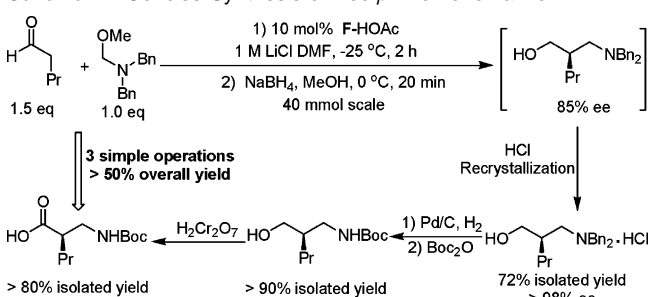
In our initial studies, the reaction catalyzed by **C** gave better enantioselectivity than did **B**. We attribute the improved enantioselectivity of catalyst **C** relative to **B** to the increased steric bulk of the 2-substituent in **C**. Jørgensen et al., Hayashi et al., and Cordova et al. have recently reported nucleophilic activation of aldehydes by **F**,¹¹ in which the trimethylsilyl group provides a further increase in steric bulk relative to the methyl group in **C**. We found that **F** leads to an improvement in enantioselectivity relative to **C**.¹⁰ Table 2 shows that Mannich reactions of five aldehydes proceeded with $\geq 90\%$ ee when catalyzed by 20 mol % of **F** (with 20 mol % of acetic acid) in DMF containing 1 M LiCl.

Table 2. Enantioselective Aminomethylation of Aldehydes

entry	R	isolated yield (%) ^a	ee (%) ^b
1	Et	84	90
2	Pr	87	92
3	<i>i</i> -Pr	86	91
4	Bn	81	92
5	MeO ₂ CCH ₂	65	90

^a After column chromatography on silica gel. ^b Determined by chiral phase HPLC.

The β -substituted γ -amino alcohols generated via the Mannich/reduction sequence could be converted in a straightforward manner to appropriately protected β^2 -amino acids, as illustrated in Scheme 2. Starting with 5.3 g of pentanal, 9.7 g of **A**, and 10 mol % of

Scheme 2. Concise Synthesis of Boc- β^2 -Homonorvaline

catalyst **F** and recrystallizing the HCl salt of the γ -amino alcohol gave a 72% yield of material with >98% ee. The benzyl groups were removed and replaced by Boc in an efficient one-pot operation. Jones oxidation¹² then provided desired β^2 -amino acid product after simple extraction, with >50% overall yield from **A**. The route is short, and purifications are simple; therefore, this protocol is amenable to large-scale synthesis.

We have described catalytic asymmetric Mannich reactions involving a formaldehyde-derived iminium electrophile. Mechanistic analysis of the proline-catalyzed versions suggests that non-H-bonded ionic interactions can be used as a stereochemistry-determining feature in organocatalytic reactions, although, in our case, a more conventional steric repulsion strategy proved to be more effective for achieving the desired goal. The new organocatalytic process constitutes the key step in an efficient synthesis of β^2 -amino acids. This contribution is significant because β^2 -amino acid residues are essential for the formation of certain β -peptide secondary structures (12/10-helix, β^3/β^2 reverse turn).¹³ β -Peptides containing β^2 -residues display useful biological activities, such as mimicry of somatostatin signaling¹⁴ and inhibition of viral infection.¹⁵ To date, utilization β^2 -amino acid building blocks has been limited by the cumbersome routes that are generally required to prepare them.⁴ Few β^2 -amino acids are commercially available. In contrast, many β^3 -amino acids (side chain adjacent to nitrogen) are

commercially available, and such building blocks are readily prepared from the analogous α -amino acids.¹⁶ Our catalytic route offers large-scale access to β^2 -amino acids, as well as to other chiral molecules (α -substituted β -amino aldehydes, β -substituted γ -amino alcohols) of potential value.

Acknowledgment. This research was supported by NIH Grant GM56414 and NSF Grant CHE-0551920. NMR equipment purchase was supported in part by grants from NIH and NSF, and X-ray equipment by NSF. We thank Dr. Iliia Guzei for X-ray structure analysis.

Supporting Information Available: Experimental procedures and compound characterizations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Review: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.
- (2) Reviews: (a) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (c) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. Early studies: (d) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (e) List, B.; Porjalev, P.; Biller, W. T.; Martin, H. *J. Am. Chem. Soc.* **2002**, *124*, 827. (f) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (g) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. Recent examples: (h) Mitsumori, S.; Zhang, H.; Ha-Yeon Cheong, P.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040. (i) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700. (j) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M. Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896. (k) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256.
- (3) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219.
- (4) Reviews: (a) Lelais, G.; Seebach, D. *Biopolymers* **2004**, *76*, 206. (b) *Enantioselective Synthesis of β -Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V., Eds.; Wiley-VCH: New York, 2005.
- (5) Cordova et al. reported formaldehyde-derived imine generated in situ with aniline derivatives for aminomethylation of ketones catalyzed by proline, but such a strategy is not applicable to aminomethylation of aldehydes. See: (a) Ibrahim, I.; Casas, J.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528. (b) Ibrahim, I.; Zou, W.; Casas, J.; Sundén, H.; Cordova, A. *Tetrahedron* **2006**, *62*, 357. (c) Ibrahim, I.; Zou, W.; Engqvist, M.; Xu, Y.; Cordova, A. *Chem.—Eur. J.* **2005**, *11*, 7024.
- (6) Examples of using iminium precursors: (a) Hosomi, A.; Iijima, S.; Sakurai, H. *Tetrahedron Lett.* **1982**, *23*, 547. (b) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 981. (c) Rehn, S.; Ofial, A. R.; Mayr, H. *Synthesis* **2003**, 1790.
- (7) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253.
- (8) Hydrogen bonding catalysis: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (c) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (d) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (e) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (f) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (g) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101.
- (9) Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249 and ref 2b.
- (10) See Supporting Information for details.
- (11) (a) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (c) Ibrahim, I.; Cordova, A. *Chem. Commun.* **2006**, 1760.
- (12) Oxidation of chiral α -substituted aldehydes and alcohols without epimerization: Rangaishenvi, M. V.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 3286; and ref 7.
- (13) (a) Hintermann, T.; Seebach, D. *Synlett* **1997**, 437. (b) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1595. (c) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1595.
- (14) Gademann, K.; Kimmerlin, T.; Hoyer, D.; Seebach, D. *J. Med. Chem.* **2001**, *44*, 2460.
- (15) (a) English, E. P.; Chumanov, R. S.; Gellman, S. H.; Compton, T. J. *Biol. Chem.* **2006**, *281*, 2661. (b) Also see: Stephens, O. M.; Kim, S.; Welch, B. D.; Hodsdon, M. E.; Kay, M. S.; Schepartz, A. *J. Am. Chem. Soc.* **2005**, *127*, 13126.
- (16) Guichard, G.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 187.

JA061731N