

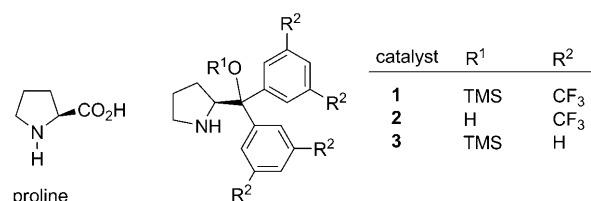
Direct Organocatalytic Mannich Reaction of Acetaldehyde: An Improved Catalyst and Mechanistic Insight from a Computational Study**

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The catalytic asymmetric Mannich reaction is one of the most powerful methods for the construction of chiral nitrogen-containing molecules.^[1] Since the discovery of the proline-mediated three-component direct Mannich reaction by List and co-workers in 2000,^[2] many asymmetric Mannich reactions involving organocatalysis have been developed.^[3] Recently, the proline-mediated Mannich reaction has been applied to *N*-Boc-imines by List and co-workers (Boc: *tert*-butoxycarbonyl); this has broadened the scope of the reaction.^[4]

On the other hand, control of the reaction of acetaldehyde has been considered difficult because of the compound's high reactivity, both as a nucleophile and as an electrophile. Moreover, the reaction products, α -unsubstituted aldehydes, are equally reactive for side reactions. Although a synthetic equivalent of acetaldehyde, namely siloxyethene, has been developed,^[5] it would be desirable to use acetaldehyde directly as a nucleophile.

Recently, our group^[6] and List and co-workers^[7] independently developed asymmetric reactions of acetaldehyde for the first time. We reported a cross-aldol reaction of acetaldehyde catalyzed by trifluoromethyl-substituted diaryl prolinol **2** (Scheme 1),^[6a] whereas List and co-workers reported the proline-catalyzed Mannich reaction of acetaldehyde and *N*-Boc-imine.^[7a] Just recently, both groups reported the Michael reaction of acetaldehyde and nitroalkene catalyzed by diphenylprolinol silyl ether **3** (Scheme 1).^[6b,7b] In our continued interest in the enantioselective Mannich reaction,^[8] we applied diaryl prolinol catalysts to the Mannich reaction of acetaldehyde. Optimization of the reaction led us to develop

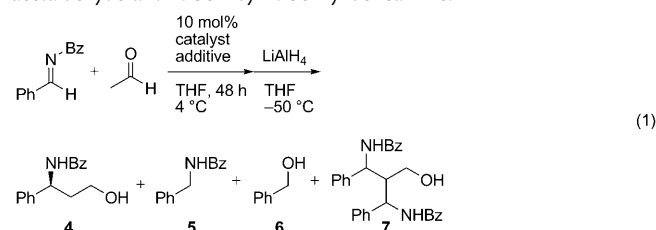


Scheme 1. Organocatalysts examined in this study. TMS: trimethylsilyl.

the high-yielding and highly enantioselective Mannich reaction described in this report.

The Mannich reaction of *N*-benzoyl-*N*-benzylideneamine and acetaldehyde was selected as a model, and the diaryl prolinol catalyst was investigated (Table 1). The generated β -amino aldehyde product was isolated after conversion into the corresponding alcohol by reduction with LiAlH₄. Scarcely

Table 1: The effect of catalyst and solvent on the Mannich reaction of acetaldehyde and *N*-benzoyl-*N*-benzylideneamine.^[a]



Entry	Catalyst	Additive	Yield [%] ^[b]				ee [%] ^[c]
			4	5	6	7	
1	proline ^[d]	–	51	9	23	7	92
2	1	–	< 5	90	5	< 5	–
3	2	–	< 5	90	6	< 5	–
4	3	–	< 5	82	13	< 5	–
5	1	PhCO ₂ H	60	6	10	14	98
6	1	<i>p</i> -NO ₂ PhCO ₂ H	83	9	6	2	98
7	1	<i>p</i> -TsOH	< 5	< 5	< 5	< 5	–
8	3	PhCO ₂ H	63	5	8	< 5	98
9	3	<i>p</i> -NO ₂ PhCO ₂ H	< 5	83	12	< 5	–
10	2	<i>p</i> -NO ₂ PhCO ₂ H	< 5	29	48	< 5	–

[a] Bz: benzoyl; THF: tetrahydrofuran; Ts: toluene-4-sulfonyl. Unless otherwise shown, reactions were performed with *N*-benzoyl-*N*-benzylideneamine (0.3 mmol), acetaldehyde (1.5 mmol), catalyst (0.03 mmol), additive (0.03 mmol), and THF (0.6 mL) at 4 °C for 48 h. [b] Yield of isolated product. [c] Enantiomeric excess of Mannich adduct **4**, as determined by chiral HPLC analysis. [d] Proline (20 mol%) was employed in CH₃CN (2 mL) for 3 h.

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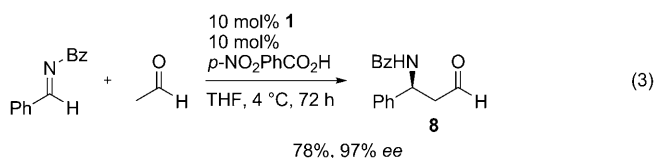
[**] This work was partially supported by the Toray Science Foundation, and a Grant-in-Aid for Scientific Research from MEXT. We thank Tsukuba Advanced Computing Center (TACC) for the provision of computational facilities.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200802073>.

any reaction occurred in the presence of trifluoromethyl-substituted diaryl prolinol **2** (Table 1, entry 3), which was a suitable catalyst in our cross-aldol reaction. Diaryl prolinol silyl ethers **1** and **3**,^[9–11] developed independently by our group^[9] and Jørgensen's group,^[10] were not effective unless an additive was used (Table 1, entries 2 and 4). The acidity of the additive dramatically affected the yield. The reaction with catalyst **1** achieved better yields and excellent enantioselectivities when *p*-nitrobenzoic acid was added (Table 1, entry 6). Only decomposition of the imine occurred, without formation of the Mannich adduct, in the presence of a stronger acid such as *p*-TsOH (Table 1, entry 7). Diphenylprolinol silyl ether **3** is a suitable catalyst with benzoic acid as the additive (Table 1, entry 8). The silyl ether functional group is essential, because diaryl prolinol **2** with *p*-nitrobenzoic acid did not promote the reaction (Table 1, entry 10). When proline was employed as a catalyst in CH₃CN under the conditions described by List and co-workers,^[7a] excellent enantioselectivity was obtained with moderate yield, because hydrolysis of the imine provided the benzyl alcohol **6** (23 %) and the double Mannich product **7** (7 %) as side-reaction products.

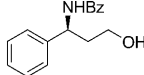
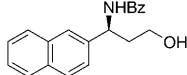
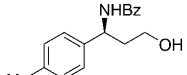
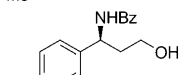
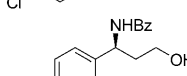
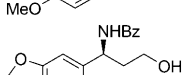
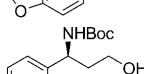
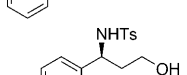
Excellent results were obtained for the model system, so the scope of the reaction was examined, with the results summarized in Table 2. The *N*-benzoylimines derived from 2-naphthalenecarbaldehyde and *p*-tolylcarbaldehyde gave excellent results (Table 2, entries 2 and 3). The reaction proceeds efficiently for *N*-benzoylimines derived from electron-deficient aryl aldehydes, such as *p*-chlorobenzaldehyde, and also electron-rich aldehydes, such as *p*-anisaldehyde and 3,4-methylenedioxybenzaldehyde, with good yields and excellent enantioselectivities (Table 2, entries 4–6). The *N*-benzoyl moiety is known to be removable under several conditions.^[12] Moreover, an *N*-Boc-imine was also a suitable substrate and provided the Mannich adduct in good yield and with excellent enantioselectivity (Table 2, entry 7). In addition, *N*-Ts-imines can be successfully employed to afford the desired products with good enantioselectivity (Table 2, entry 8).

The Mannich adduct can also be isolated as its β-amino aldehyde derivative [Eq. (3)]. Rapid column chromatography produced the aldehyde **8** in 78 % yield and with excellent enantioselectivity. β-Amino aldehydes are synthetically important intermediates, which can be converted into natural products, pharmaceuticals, β-amino acids, and other building blocks, as already shown by List and co-workers.^[7a]



In the cross-aldol reaction of acetaldehyde catalyzed by diaryl prolinol, we proposed a transition state with a hydrogen-bonding interaction between the acidic proton of the hydroxy group in the catalyst and the lone pair of the formyl oxygen atom.^[6a] A similar hydrogen-bond interaction between the acidic proton of the carboxylic acid and the

Table 2: Catalytic asymmetric Mannich reaction of acetaldehyde with various imines.^[a]

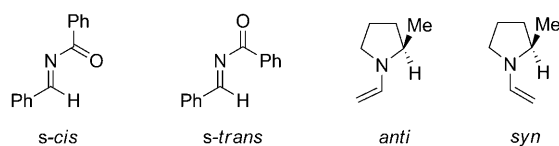
$ \begin{array}{c} \text{R}^1 \text{---} \text{N} \text{---} \text{R}^2 \\ \text{C} \text{=H} \end{array} + \text{HCHO} \xrightarrow[\text{THF, 4 °C}]{\begin{array}{c} 10 \text{ mol\% } \mathbf{1} \\ 10 \text{ mol\% } p\text{-NO}_2\text{PhCO}_2\text{H} \end{array}} \begin{array}{c} \text{R}^1 \text{---} \text{N} \text{---} \text{R}^2 \\ \text{CH} \text{---} \text{CH}_2 \text{---} \text{CHO} \end{array} \xrightarrow[\text{THF, -50 °C}]{\text{LiAlH}_4} \begin{array}{c} \text{R}^1 \text{---} \text{N} \text{---} \text{R}^2 \\ \text{CH} \text{---} \text{CH}_2 \text{---} \text{OH} \end{array} \quad (2) $				
Entry	Product	<i>t</i> [h]	Yield [%] ^[b]	ee [%] ^[c]
1		72	87	97
2		72	77	98
3		84	78	98
4		84	65	98
5		72	80	95
6		84	70	98
7		84	58	98
8 ^[d]		72	74	80

[a] Unless otherwise shown, the reaction was performed with imine (0.3 mmol), acetaldehyde (1.5 mmol), catalyst **1** (0.03 mmol), *p*-NO₂PhCO₂H (0.03 mmol), and THF (0.6 mL) at 4 °C. [b] Yield of isolated alcohol. [c] Optical purity was determined by chiral HPLC analysis; see the Supporting Information for details. [d] NaBH₄ was employed instead of LiAlH₄.

lone pair of the imine would be expected in the proline-mediated Mannich reaction.^[7a] That is, the intermolecular proton in the enamine activates the electrophile, in which a rigid transition state would be formed to generate the excellent enantioselectivity. In the present reaction, however, a similar transition state could not be expected because of the necessity for an additional acid, which is in marked contrast to the Michael reaction catalyzed by diphenylprolinol silyl ether **3** without an acid.^[6b,7b] To understand the reaction mechanism and the role of the acid, a quantum mechanical computational study was performed. 2-Methylpyrrolidine was selected as a model for the diaryl prolinol silyl ether, and the Mannich reaction with *N*-benzoyl-*N*-benzylideneamine was calculated by using restricted B3LYP (RB3LYP) calculations with the 6-31G(d) basis set.^[13]

The conformational behavior of the imine and enamine molecules was examined. For the imine molecule, the energy minima of the *trans* and *cis* geometries in relation to the C=N bond were located, and the *trans* energy minimum was calculated to be lower in energy than the *cis* energy minimum

by about 30 kcal mol⁻¹. Rotation of the N–C(O) bond in the imine molecule with *trans* geometry gives rise to two conformations, *s-cis* and *s-trans* (Scheme 2). The *s-cis* confor-



Scheme 2. Conformations of the imine and the enamine molecules.

mer was found to be an energy minimum, and the *s-trans* conformer corresponded to the transition state for N–C(O) bond rotation. For the enamine molecule, *syn* and *anti* geometries were located as energy minima. The *anti* structure of the enamine was slightly lower in energy than the *syn* conformer by circa 0.7 kcal mol⁻¹. Hereafter, we consider the *trans s-cis* conformation of the imine and the *anti* structure of the enamine.

The Mannich reaction proceeds in the presence of a Brønsted acid, and, hence, we examined protonation sites in the imine and enamine molecules. The imine molecule has three possible sites for protonation (Scheme 2): 1) the nitrogen atom on the imine, 2) the oxygen atom on the carbonyl group *syn* with respect to the nitrogen atom of the imine, and 3) the oxygen atom on the carbonyl group *anti* with respect to the nitrogen atom of the imine. Not only in the gas phase but also in the THF-solution phase (the polarized continuum model^[14]), B3LYP calculations indicated that the most favorable protonation site on the imine was the nitrogen atom (Table 3). Protonation also possibly occurs on the nitrogen atom of the enamine molecule. We compared the energy of the N-protonated imine and neutral enamine with

that of the neutral imine and protonated enamine. Gas-phase B3LYP calculations indicated that protonation of the imine was energetically more favorable by 6.29 kcal mol⁻¹ (including the zero-point energies) than protonation of the enamine. Conversely, calculations on the THF-solution phase indicated that protonation of the enamine was more favorable by 1.67 kcal mol⁻¹ (including the zero-point energies).

The chirality of the reaction products indicates that attack of the enamine predominantly occurs on the *si* face of the imine. The enamine intermediates generated from diaryl prolinols **1–3** possess bulky substituents on the carbon atom neighboring the proline nitrogen atom, and thus, the face of the enamine opposite the bulky substituent will approach the *si* face of the imine in the most energetically favorable reaction path to yield the Mannich adduct. We thus consider that the C–C bond forms between the *si* face of the N-protonated imine and the face of the enamine opposite the methyl group in our model calculation. Postulating such a reaction path, we explored the potential energy surface along the reaction coordinate for C–C bond formation in the Mannich reaction. C–C bond formation was found to be unlikely to occur between neutral imine and protonated enamine molecules. On the other hand, the protonated imine and neutral enamine were found to form a C–C bond between them to yield the Mannich products. The imine molecule has three possible sites for protonation (Table 3), and we also calculated the Mannich products protonated by three different modes that correspond with the protonation of the imine. The Mannich product protonated on the nitrogen atom of its imine moiety was found to be more stable by about 20 kcal mol⁻¹ than the O-protonated Mannich products (Figure 1).

The reaction of the N-protonated imine and neutral enamine resulting in the N-protonated Mannich product was found to be highly exothermic with a large negative reaction energy: the exothermicities calculated by using the B3LYP level were –38.82 and –31.12 kcal mol⁻¹ in the gas phase and in the THF-solution phase, respectively (including the zero-point energies). By starting from the N-protonated Mannich product (Figure 1 a), we explored the reaction coordinate for the C–C bond formation, and we found that the energy of the adduct of the N-protonated imine and neutral enamine simply increased as the C–C bond was lengthened (Figure 2). In addition, we optimized the structure of the adduct of the N-protonated imine and neutral enamine with the length of the newly formed C–C bond fixed at 3.0 Å. In Figure 3, the energy of the model system is plotted against the dihedral angle of the newly formed C–C bond. This energy profile indicates three energy-minimum structures, **A–C**, for the model system. According to B3LYP energy evaluations, the energy differences between these 3 rotamers were calculated to be less than 2 kcal mol⁻¹, with rotamer **A** being the most energetically preferable.

Even after taking the basis-set superposition error (BSSE)^[15,16] into account, the energy profile in Figure 2 did not suggest a distinct transition state along the reaction coordinate for this C–C bond-formation process. Accordingly, B3LYP calculations suggested that the reaction of the N-protonated imine and neutral enamine should occur readily

Table 3: Structures and relative energies (in kcal mol⁻¹) of protonated imine.^[a]

Gas-phase structures

	Protonation site		
	N	O (<i>syn</i>)	O (<i>anti</i>)
gas phase	0.00	8.02	9.56
	(0.00)	(7.78)	(9.07)
solution phase (THF) ^[b]	0.00	7.50	10.69
	(0.00)	(6.50)	(9.69)

[a] The gas-phase structures are shown. Values in parentheses include zero-point energies. [b] Calculated with the polarized continuum model. The solution-phase structures optimized with the polarized continuum model (solvent=THF) did not differ significantly from the gas-phase structures (see the Supporting Information).

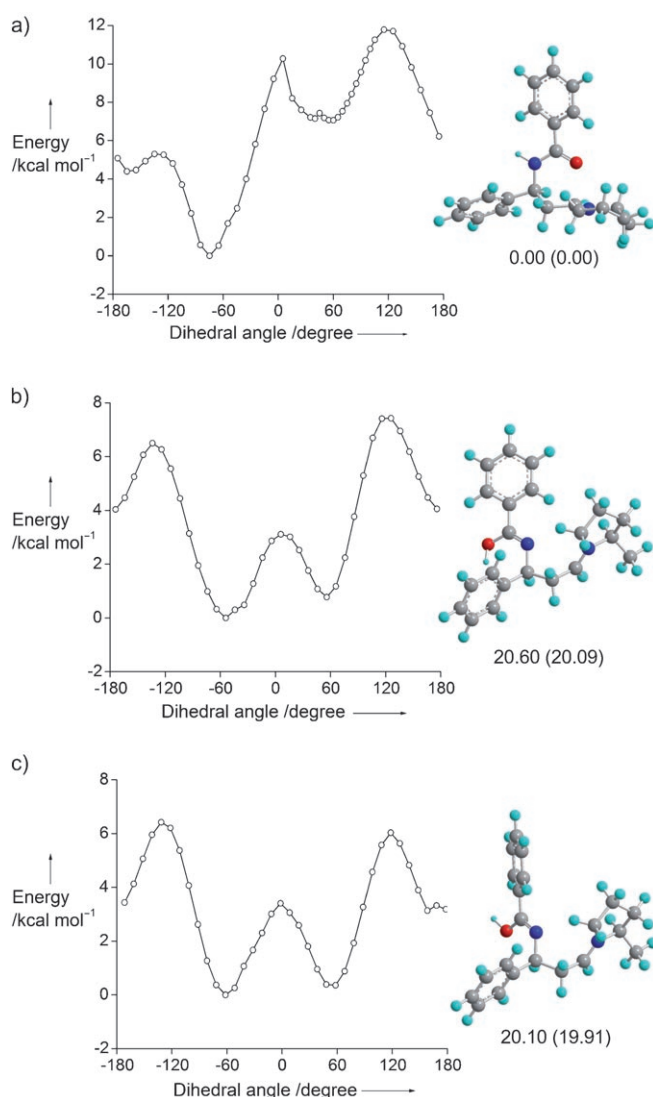


Figure 1. The Mannich products formed from the protonated imine and neutral enamine. The imine moiety has three possible sites for protonation: a) the nitrogen atom of the imine, b) the oxygen atom on the carbonyl moiety *syn* with respect to the nitrogen atom of the imine, and c) the oxygen atom on the carbonyl group *anti* with respect to the nitrogen atom of the imine. The energy profiles for the rotation of the newly formed C–C bond and the most energetically favorable structures are shown for the three protonation states (a–c) of the Mannich product. Energies relative to that of N-protonated Mannich product in a) are given below the structures. (Values in parentheses include the zero-point energies.)

to yield the Mannich product. These results indicate that C–C bond formation takes place with almost no activation barrier between the N-protonated imine and neutral enamine molecules. In the aldol reaction of acetaldehyde and *N,N*-dimethylvinylamine, a similar conclusion was obtained. That is, the C–C bond-forming step has no activation barrier, and the rate-limiting step is the generation of the enamine.^[17]

These results suggest that C–C bond formation in the present Mannich reaction should proceed extremely quickly in the presence of a Brønsted acid. Formation of the enamine from acetaldehyde and diaryl prolinol silyl ether **1** involves

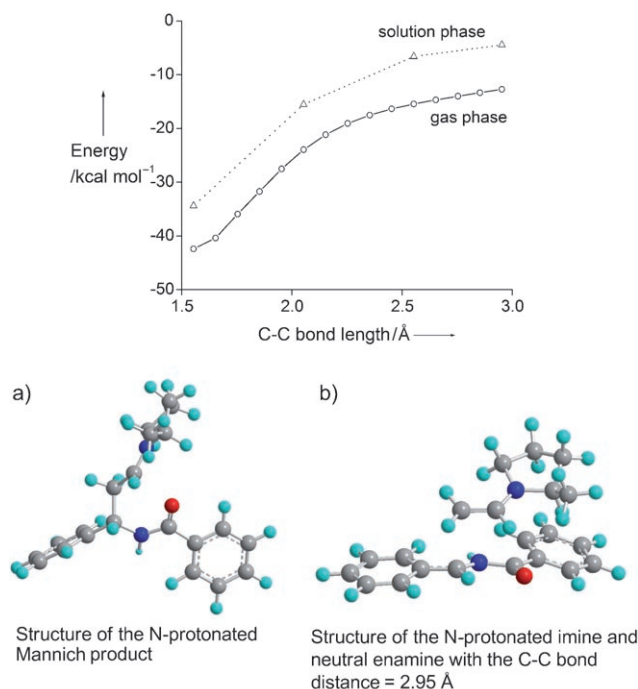


Figure 2. By starting from the N-protonated Mannich product, the reaction coordinate for the C–C bond formation was explored. The change in potential energy is plotted against the C–C bond length. The energy of the reactants, the N-protonated imine and neutral enamine, is set to zero. The structures of a) the final Mannich product of the N-protonated imine and the neutral enamine and b) the N-protonated imine and the neutral enamine with a C–C bond length of 2.95 Å are shown below the energy profile. In the structure shown in b) the geometries of the N-protonated imine and neutral enamine moieties are quite close to those in the isolated states. The counterpoise calculations suggested a basis-set superposition error (BSSE) of 7.60 and 3.10 kcal mol⁻¹ for the structures in a) and b), respectively.

several reaction steps, namely attack of the nitrogen atom of catalyst **1** at the carbonyl carbon atom of acetaldehyde, proton transfer, and dehydration. Enamine formation must be a relatively slow process. A rapid protonation and deprotonation process between the imine and the enamine molecules would occur. Once a proton is transferred from the enamine to the imine, C–C bond formation will be fast. Consequently, the concentration of enamine must be kept low during the reaction: once the enamine is formed, it will react immediately with the imine by rapid protonation and deprotonation processes under acidic conditions, followed by C–C bond formation, to yield the Mannich adduct.

In general, it is quite difficult to control the high reactivity of acetaldehyde. An acid activates the imine selectively rather than the aldehyde^[8c] and promotes the Mannich reaction efficiently, whereas the reactivity of the enamine is reduced with suppression of the generation of an enamine from the product, which reduces the overall reactions, because of the bulkiness of catalyst **1**. The Mannich reaction catalyzed by bulky organocatalyst **1**, combined with acid additives, distinguishes it from the proline-mediated reaction.^[7a]

In summary, we have developed a highly enantioselective Mannich reaction of acetaldehyde and *N*-benzoyl-, *N*-Boc-, and *N*-Ts-imines catalyzed by a combination of a diaryl

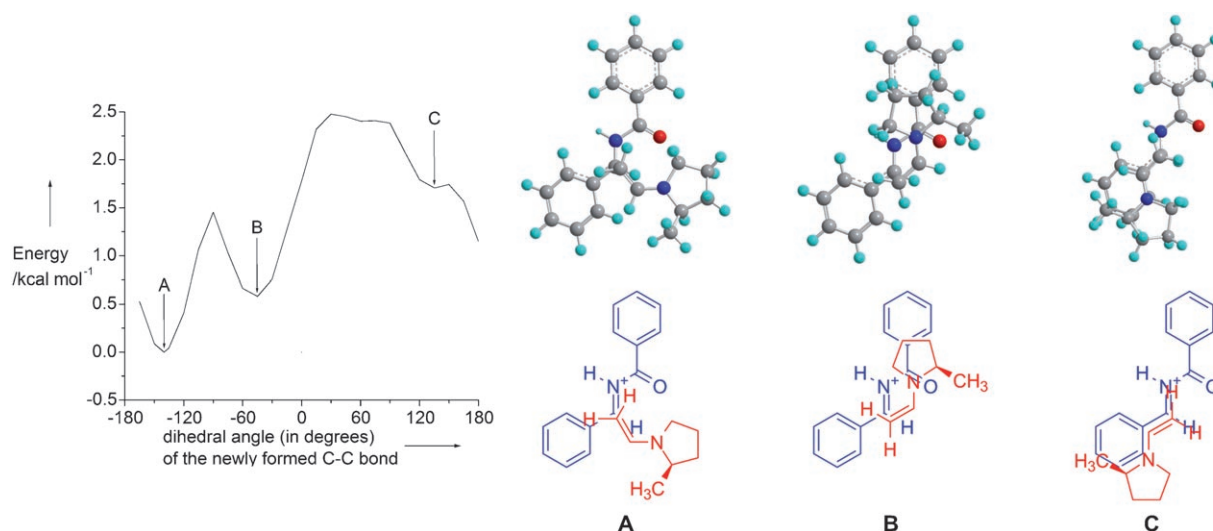


Figure 3. Energy profile of the system of the N-protonated imine and neutral enamine plotted against the dihedral angle with regard to the newly formed C–C bond (the angle between the C=N bond in the imine and the C=C bond in the enamine). In addition, the structures corresponding to the energy minima A–C are shown below the energy profile.

prolinol silyl ether and *p*-nitrobenzoic acid. The Mannich products are synthetically important chiral building blocks, as already shown by List and co-workers.^[7a] The present method has several useful features: 1) the catalyst loading (10 mol %) is less than that of the proline-catalyzed version, 2) suppression of imine decomposition and the double Mannich reaction gives improved yields, and 3) B3LYP calculations show that the formation of the enamine is the rate-determining step and that once the enamine forms, it reacts with the protonated imine with no activation barrier.

Experimental Section

Typical procedure for the asymmetric Mannich reaction of acetaldehyde: Acetaldehyde (84 μ L, 1.5 mmol) was added to a mixture of (*S*)-2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsilyloxymethyl]pyrrolidine (**1**; 17.9 mg, 0.03 mmol), *p*-nitrobenzoic acid (5.0 mg, 0.03 mmol), and *N*-benzoyl-*N*-benzylideneamine (62.6 mg, 0.3 mmol) in anhydrous THF (0.6 mL) in a sealed tube (Ace Glass, product no. 5027-05) at 4 °C. After the reaction mixture was stirred for 48 h, THF (0.6 mL) and LiAlH₄ (22.7 mg, 0.6 mmol) were added at –50 °C. The resulting mixture was stirred for an additional 1 h at –50 °C, before the reaction was quenched with phosphate buffer solution (pH 7.0). The organic materials were extracted with chloroform three times. The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated in vacuo after filtration. Purification by preparative thin layer chromatography (ethyl acetate/hexane 2:1) gave (*S*)-3-benzoylamino-3-phenylpropanol (63.2 mg, 0.25 mmol) in 83 % yield. The *ee* value was 98 %.

Received: May 2, 2008

Revised: August 28, 2008

Published online: October 16, 2008

Keywords: acetaldehyde · asymmetric catalysis · imines · Mannich reactions · organocatalysis

- [1] For reviews, see: a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, 99, 1069; b) S. E. Denmark, O. J.-C. Nicaise in *Comprehensive Asymmetric Catalysis* (Ed.: E. N. Jacobsen), Springer, Berlin, **1999**, p. 923; c) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, 110, 1096; *Angew. Chem. Int. Ed.* **1998**, 37, 1044; d) E. F. Kleinman in *Comprehensive Organic Synthesis*, Vol. 2 (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, p. 893.
- [2] a) B. List, *J. Am. Chem. Soc.* **2000**, 122, 9336; b) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, 124, 827.
- [3] For reviews on the Mannich reaction, see: a) A. Cordova, *Acc. Chem. Res.* **2004**, 37, 102; b) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, 37, 580; c) M. M. B. Marques, *Angew. Chem.* **2006**, 118, 356; *Angew. Chem. Int. Ed.* **2006**, 45, 348; d) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797; e) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, 107, 5471. For reviews on organocatalysis, see: f) *Asymmetric Organocatalysis* (Eds.: A. Berkessel, H. Grogger), Wiley-VCH, Weinheim, **2005**; g) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, 116, 5248; *Angew. Chem. Int. Ed.* **2004**, 43, 5138; h) Y. Hayashi, *J. Syn. Org. Chem. Jpn.* **2005**, 63, 464; i) B. List, *Chem. Commun.* **2006**, 819; j) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001; k) M. J. Gaunt, C. C. C. Johnsson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, 12, 8; l) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**.
- [4] J. W. Yang, M. Stadler, B. List, *Angew. Chem.* **2007**, 119, 615; *Angew. Chem. Int. Ed.* **2007**, 46, 609.
- [5] a) S. E. Denmark, T. Bui, *J. Org. Chem.* **2005**, 70, 10190; b) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, 128, 48; c) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, 129, 2762.
- [6] a) Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, *Angew. Chem.* **2008**, 120, 2112; *Angew. Chem. Int. Ed.* **2008**, 47, 2082; b) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, 120, 4800; *Angew. Chem. Int. Ed.* **2008**, 47, 4722.
- [7] a) J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, 452, 453; b) P. García-García, A. Ladepeche, R. Halder, B. List, *Angew. Chem.* **2008**, 120, 4797; *Angew. Chem. Int. Ed.* **2008**, 47, 4719.
- [8] a) Y. Hayashi, W. Tsuboi, M. Shoji, N. Suzuki, *J. Am. Chem. Soc.* **2003**, 125, 11208; b) Y. Hayashi, W. Tsuboi, I. Ashimine, T.

- Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677; c) Y. Hayashi, T. Urushima, M. Shoji, T. Uchimaru, I. Shiina, *Adv. Synth. Catal.* **2005**, *347*, 1595; d) Y. Hayashi, T. Urushima, M. Shin, M. Shoji, *Tetrahedron* **2005**, *61*, 11393; e) Y. Hayashi, T. Urushima, W. Tsuboi, M. Shoji, *Nat. Protocols* **2007**, *2*, 113; f) Y. Hayashi, T. Urushima, S. Aratake, T. Okano, K. Obi, *Org. Lett.* **2008**, *10*, 21.
- [9] a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; b) H. Gotoh, R. Masui, H. Ogino, M. Shoji, Y. Hayashi, *Angew. Chem.* **2006**, *118*, 7007; *Angew. Chem. Int. Ed.* **2006**, *45*, 6853; c) H. Gotoh, Y. Hayashi, *Org. Lett.* **2007**, *9*, 2859; d) Y. Hayashi, T. Okano, S. Aratake, D. Hazeldard, *Angew. Chem.* **2007**, *119*, 5010; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922; e) H. Gotoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2007**, *9*, 5307.
- [10] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) M. Marigo, D. Fielenbach, A. Braunton, A. Kjasgaard, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 3769; *Angew. Chem. Int. Ed.* **2005**, *44*, 3703. For a recent report, see: c) P. T. Franke, R. L. Johansen, S. Bertelsen, K. A. Jørgensen, *Chem. Asian J.* **2008**, *3*, 216.
- [11] For selected examples of the application of diarylprolinol ether by other groups, see: a) D. Enders, M. R. M. Huttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861; b) J. Vesely, I. Ibrahim, G.-L. Zhao, R. Rios, A. Cordova, *Angew. Chem.* **2007**, *119*, 792; *Angew. Chem. Int. Ed.* **2007**, *46*, 778; c) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886; d) N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404. For a review, see: e) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876.
- [12] P. G. M. Wuts, T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, 4th ed., Wiley, Hoboken, **2007**.
- [13] Gaussian 03, Revision B.05, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **2003**.
- [14] a) M. T. Cancès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032; b) B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *106*, 5151; c) M. Cossi, V. Barone, B. Mennucci, J. Tomasi, *Chem. Phys. Lett.* **1998**, *286*, 253.
- [15] B. J. Ransil, *J. Chem. Phys.* **1961**, *34*, 2109.
- [16] S. F. Boys, F. Bernardi, *Mol. Phys.* **1970**, *19*, 553.
- [17] a) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 11273; b) C. Allemann, R. Gordillo, F. R. Clemente, P. H. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558.