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Stereocontrolled Synthesis of Vicinal Diamines by Organocatalytic Asymmetric Mannich Reaction of *N*-Protected Aminoacetaldehydes: Formal Synthesis of (−)-Agelastatin A

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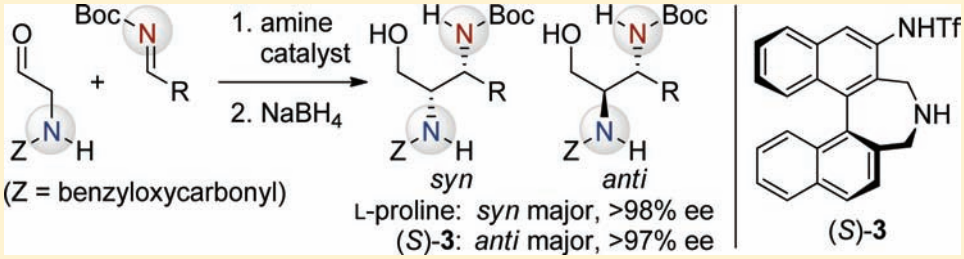
Supporting Information

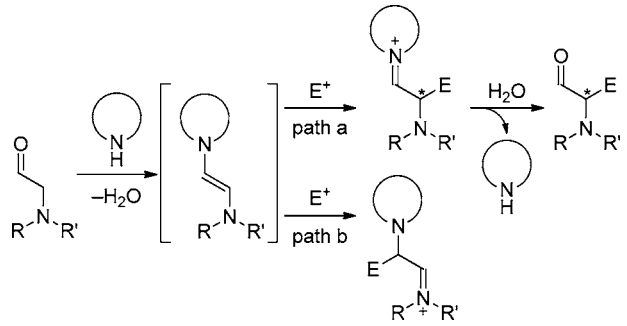


ABSTRACT: The 1,2-diamine (vicinal diamine) motif is present in a number of natural products with interesting biological activity and in many chiral molecular catalysts. The efficient and stereocontrolled synthesis of enantioenriched vicinal diamines is still a challenge to modern chemical methodology. We report here both *syn*- and *anti*-selective asymmetric direct Mannich reactions of *N*-protected aminoacetaldehydes with *N*-Boc-protected imines catalyzed by proline and the axially chiral amino sulfonamide (*S*)-**3**. This organocatalytic process represents the first example of a Mannich reaction using Z- or Boc-protected aminoacetaldehyde as a new entry of α-nitrogen functionalized aldehyde nucleophile in enamine catalysis. The obtained optically active vicinal diamines are useful chiral synthons as exemplified by the formal synthesis of (−)-agelastatin A.

INTRODUCTION

Chiral vicinal diamines constitute important structural motifs which are found in a broad variety of natural products, biologically active compounds, and chiral catalysts in various asymmetric reactions.[1] Despite their extensive utility, the development of new methods for the efficient preparation of vicinal diamines remains a significant and important challenge.[2,3] Various catalytic asymmetric Mannich-type reactions of carbonyl compounds having an α-nitrogen functional group have been employed for the synthesis of such chiral diamines;[4,5] however, the efficient method for the highly diastereoselective synthesis of both *syn*- and *anti*-diamines from the same set of reactants by simply replacing the catalyst has rarely been reported.[4f,k,l] In enamine catalysis, while both *syn*- and *anti*-selective asymmetric Mannich reactions of simple aliphatic aldehydes have been developed,[6] diastereo- and enantioselective synthesis of vicinal diamines by a Mannich approach using an α-nitrogen functionalized aldehyde as a nucleophile has not been reported to date. Here, an α-nitrogen functionality of aldehyde might promote the undesired side reaction through path b as shown in Scheme 1,[7] and to the best of our knowledge, use of aminoacetaldehyde **1** or **2** having a common and easily removable *N*-protecting group,[8] such as Z (benzyloxycarbonyl) and Boc (*t*-butoxycarbonyl), has not been reported so far in enamine catalysis. In this context, we have become interested in the possibility of asymmetric Mannich reaction of aminoacetaldehydes

Scheme 1. Amine-Catalyzed Reaction of Aminoacetaldehydes



1 and **2** as an efficient method for the stereocontrolled synthesis of vicinal diamines (Scheme 2). Here we report both *syn*- and *anti*-selective asymmetric Mannich reaction using Z- or Boc-protected aminoacetaldehyde as new entry of α-nitrogen functionalized aldehyde nucleophile in enamine catalysis.

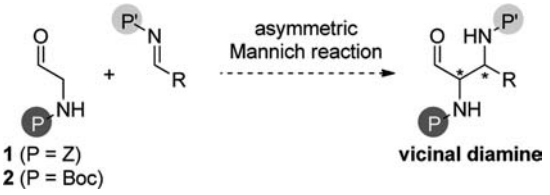
RESULTS AND DISCUSSION

We first examined the Mannich reaction between *N*-Z-protected aminoacetaldehyde **1**[9] and *N*-Boc-protected imine

Received: February 3, 2012
Published: April 9, 2012

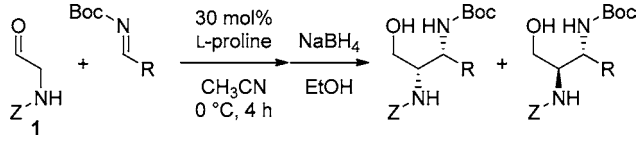
   dx.doi.org/10.1021/ja301120z | *J. Am. Chem. Soc.* 2012, 134, 7516−7520

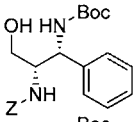
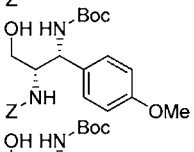
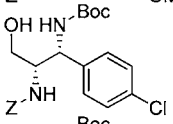
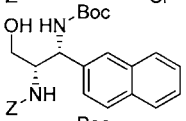
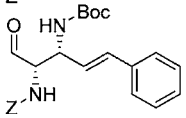
Scheme 2. Diastereo- and Enantioselective Synthesis of Vicinal Diamines



derived from benzaldehyde in the presence of 30 mol % of L-proline in acetonitrile at 0 °C.[6k] Fortunately, the reaction proceeded smoothly to give the desired *syn*-Mannich product, which was a *syn*-vicinal diamine protected by Z and Boc groups, in virtually perfect enantioselectivity without forming by-products (Table 1, entry 1).[10] This result suggested that the Z group was sufficient to suppress undesired side reactions (path b in Scheme 1) caused by the nucleophilic character of the α-nitrogen. With several other *N*-Boc imines, almost optically pure *syn*-Mannich products were obtained in moderate to good yield (entries 2−5). The reactive imine derived from 4-chlorobenzaldehyde was added slowly using a syringe pump to prevent catalyst deactivation by the undesired addition of proline to the imine (entry 3).

Table 1. *syn*-Selective Mannich Reaction between *N*-Z-Aminoacetaldehyde 1 and *N*-Boc Imines Catalyzed by L-Proline[a]

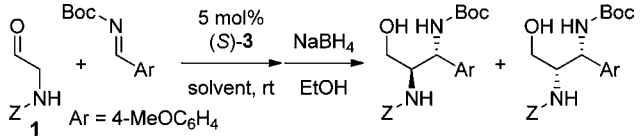


entry	product	yield (%)[b]	syn/anti[c]	ee (%)[d]
1		63	4.7/1	99
2		83	9.0/1	99
3[e]		67	6.7/1	99
4		74	3.5/1	99
5[f]		69	6.4/1	98

[a]The reaction of 1 (0.375 mmol) with an *N*-Boc imine (0.125 mmol) was carried out in the presence of L-proline (0.0375 mmol) in CH_3CN (1.0 mL) at 0 °C for 4 h. [b]Isolated yield of diastereomeric mixture. [c]Determined by ^1H NMR. [d]The ee of *syn*-product was determined by HPLC using chiral column. [e]The *N*-Boc imine was added using a syringe pump over 4 h. Stirring was then continued for 3 h. [f]The Mannich adduct was isolated before reduction with $NaBH_4$.

We have previously designed the axially chiral amino sulfonamide catalyst (*S*)-**3**,[11,12] which has the advantage of giving mainly *anti*-products in the direct asymmetric Mannich reaction, while proline and the related catalysts show the opposite *syn*-selectivity.[6k,12] To develop an efficient method for the preparation of *anti*-vicinal diamines, we then examined (*S*)-**3** as catalyst in the reaction between *N*-Z-protected aminoacetaldehyde **1** and *N*-Boc-protected imine derived from 4-methoxybenzaldehyde (Table 2). When the reaction was performed in acetonitrile, the desired *anti*-Mannich product was obtained in moderate yield, albeit with low diastereoselectivity (entry 1). After screening a variety of solvents, DMSO was found to be the among best in terms of both yield and stereoselectivity (entry 9).

Table 2. *anti*-Selective Mannich Reaction between *N*-Z-Aminoacetaldehyde 1 and a *N*-Boc Imine Catalyzed by (*S*)-3[a]



entry	solvent	yield (%)[b]	anti/syn[c]	ee (%)[d]
1	CH_3CN	65	2.0/1	94
2	THF	81	1.8/1	99
3	dioxane	41	1.9/1	97
4	CH_2Cl_2	63	2.4/1	91
5	DMF	76	4.5/1	92
6	NMP	76	5.3/1	98
7[e]	NMP	0	–	–
8	HMPA	75	4.7/1	81
9[f]	DMSO	90	5.4/1	97

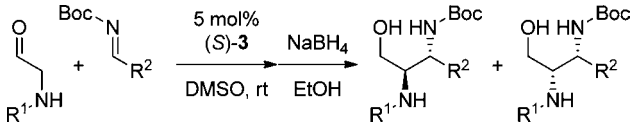
[a]The reaction of **1** (0.375 mmol) with an *N*-Boc imine (0.125 mmol) was carried out in the presence of (*S*)-**3** (0.0063 mmol) in a solvent (250 μL) at room temperature. The *N*-Boc imine was added using a syringe pump over 4 h. Stirring was then continued for 3 h. [b]Isolated yield of diastereomeric mixture. [c]Determined by ^1H NMR. [d]The ee of *anti*-product was determined by HPLC using chiral column. [e]The reaction was performed at 0 °C. [f]Use of 375 μL of DMSO.

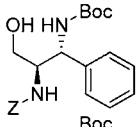
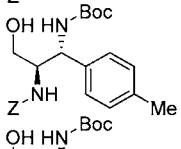
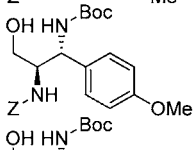
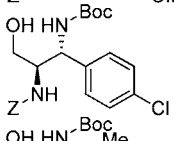
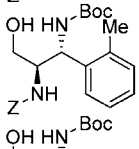
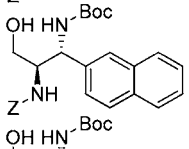
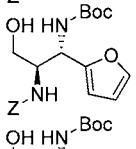
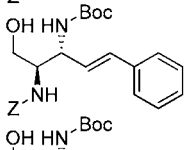
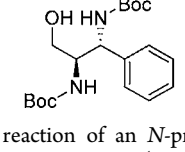
With the optimal reaction conditions, the *anti*-selective and enantioselective direct Mannich reaction of *N*-Z-protected aminoacetaldehyde **1** with several other *N*-Boc imines was examined, and the results are summarized in Table 3. All reactions examined proceeded to give *anti*-Mannich products with excellent enantioselectivity (entries 1−8). The *N*-Boc-protected aminoacetaldehyde **2**[13] was also applicable to the present Mannich reaction, thus giving the *N*,*N*′-di-Boc protected *anti*-vicinal diamine (entry 9).

The absolute configuration of both *syn*- and *anti*-Mannich products was determined by conversion to the known cyclic ureas[14] and comparison of the optical rotations (see Supporting Information). The L-proline-catalyzed Mannich reaction of **1** was found to give a *syn*-vicinal diamine having (1*R*,2*S*) configuration. On the other hand, the absolute configuration of an *anti*-vicinal diamine obtained in the reaction catalyzed by (*S*)-**3** was determined to be (1*R*,2*R*). Based on the observed stereochemistry, transition-state models can be proposed as shown in Figure 1. In the case of the L-proline-catalyzed reaction, the *si* face of *N*-Boc-protected imine approaches the *Si* face of the dominant *E*-s-*trans*-enamine (**TS1**) over the sterically congested *E*-s-*cis*-enamine (**TS2**). While both *E*-s-*trans*- and *E*-s-*cis*-enamine

dx.doi.org/10.1021/ja301120z | J. Am. Chem. Soc. 2012, 134, 7516−7520

Table 3. *anti*-Selective Mannich Reaction between *N*-Protected Aminoacetaldehydes and *N*-Boc Imines Catalyzed by (*S*)-3[a]



entry	product	yield (%)[b]	anti/syn[c]	ee (%)[d]
1		96	6.7/1	99
2		79	6.0/1	99
3[e]		90	5.4/1	97
4		61	4.9/1	99
5		74	7.8/1	97
6		76	5.2/1	99
7		97	3.7/1	97
8		51	5.7/1	99
9[f]		71	4.5/1	99

[a]The reaction of an *N*-protected aminoacetaldehyde (0.375 mmol) with an *N*-Boc imine (0.125 mmol) was carried out in the presence of (*S*)-**3** (0.0063 mmol) in DMSO (250 μL) at room temperature. The *N*-Boc imine was added using a syringe pump over 4 h. Stirring was then continued for 3 h. [b]Isolated yield of diastereomeric mixture. [c]Determined by ^{1}H NMR. [d]The ee of *anti*-product was determined by HPLC using chiral column. [e]Use of 375 μL of DMSO. [f]The reaction was performed at 50 °C.

might be formed in the reaction catalyzed by (*S*)-**3**, the reaction of *E*-s-*cis*-enamine with the activated *N*-Boc-protected imine at the appropriate position (**TS4**) is faster than that of *E*-s-*trans*-enamine with *N*-Boc-protected imine (**TS3**), giving the *anti*-vicinal diamine predominantly.[11,12]

DFT calculations at the B3LYP/6-31G* level were also done to address the observed stereoselectivities.[15] The most favorable transition state is in accord with our previously mentioned transition-state model **TS4** for the Mannich reaction of **1** catalyzed by (*S*)-**3** (Figure 2).[16]

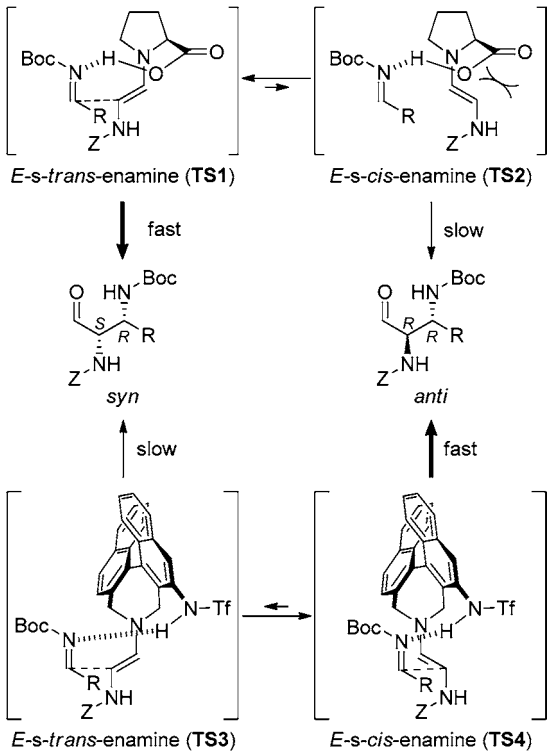


Figure 1. Transition-state models for the asymmetric Mannich reaction catalyzed by L-proline and (*S*)-**3**.

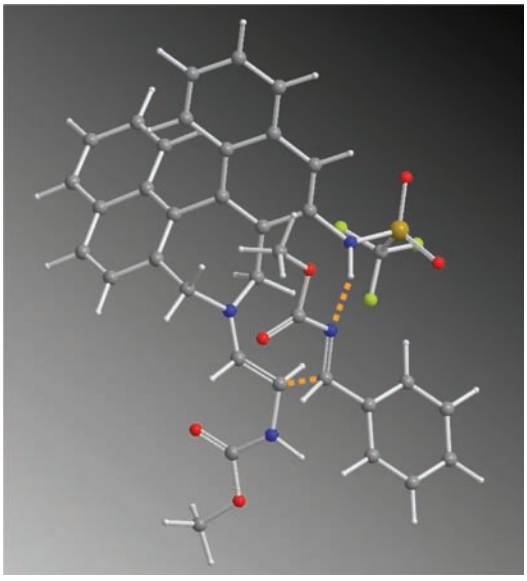


Figure 2. B3LYP/6-31G* optimized transition-state structure of the reaction.

To demonstrate the synthetic utility of this asymmetric transformation, the optically enriched *anti*-Mannich product was converted to the corresponding *α*,*β*-diamino ester and *β*-lactam, which are key structural motifs in many biologically active compounds (Scheme 3).[1b] Thus, the *anti*-Mannich product, which was obtained from the reaction between **1** and *N*-Boc-protected imine derived from benzaldehyde, was converted to the protected *anti*-*α*,*β*-diamino ester **4** by oxidation with $NaClO_2$ followed by esterification with $TMSCHN_2$ (60% yield over three steps). Subsequent *N*-Boc deprotection and treatment of the resulting *β*-amino ester **5** with TMSCl, triethylamine, and then

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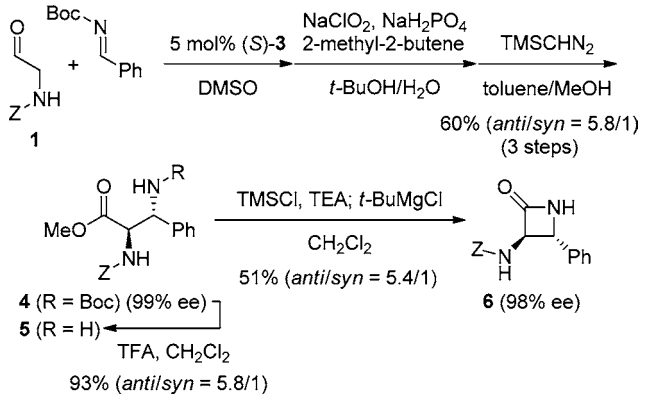
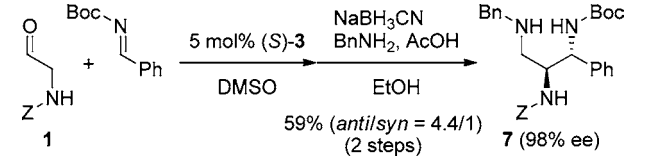
Scheme 3. Synthesis of α,β-Diamino Ester 4 and β-Lactam 6

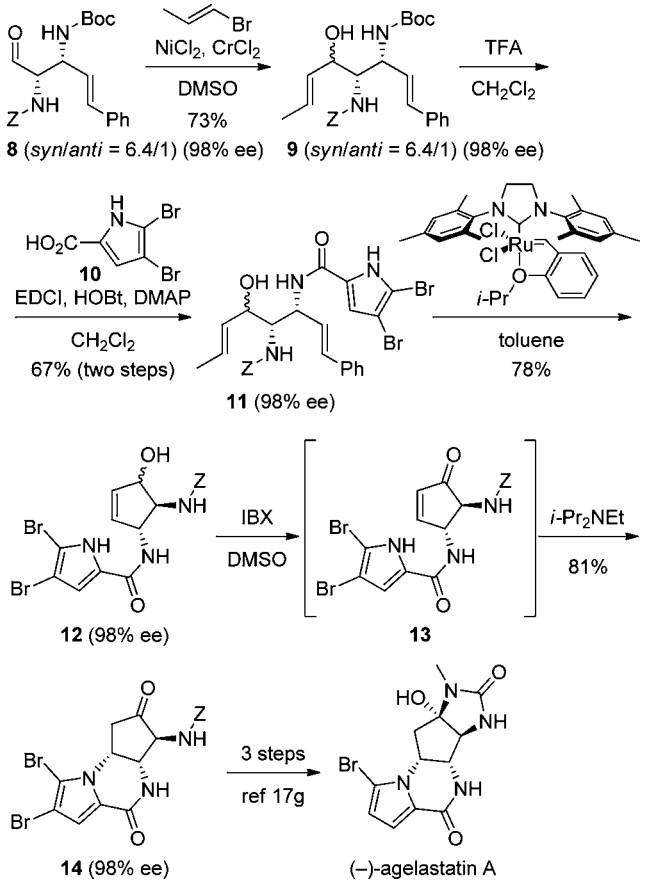


t-BuMgCl gave β-lactam **6** (51% yield over two steps).[17] In addition, the *anti*-Mannich product was readily converted to α,β,γ-triamine **7** with three different protecting groups by reductive amination (Scheme 4).

Scheme 4. Synthesis of α,β,γ-Triamine 7



Scheme 5. Formal Total Synthesis of (−)-Agelastatin A



Further synthetic utility of the present Mannich reaction was successfully demonstrated in the formal synthesis of a marine alkaloid, (−)-agelastatin A,[18] which has a potent antitumor activity, as shown in Scheme 5. Mannich product **8** was converted to diene **9** by Nozaki−Hiyama−Takai−Kishi coupling with (*E*)-1-bromoprop-1-ene.[19] After deprotection of the Boc group of **9**, amide **11** was formed under standard coupling conditions. Treatment of **11** with Hoveyda−Grubbs second-generation catalyst[20] cleanly afforded cyclopentene **12**,[21] which was converted in one pot to cyclopentanone **14** by 2-iodoxybenzoic acid (IBX) oxidation and the subsequent intramolecular conjugate addition of the pyrrole moiety.[18g] Since **14** was an intermediate in previous total synthesis of (−)-agelastatin A by Ichikawa's group,[18g] this work contributes to its formal synthesis.

In summary, we have developed a diastereo- and enantioselective direct Mannich reaction of *N*-protected aminoacetaldehydes with *N*-Boc-protected imines catalyzed by proline and the axially chiral amino sulfonamide (*S*)-**3**. This organocatalytic process represents the first example of Mannich reaction using Z or Boc-protected aminoacetaldehyde as new entry of α-nitrogen functionalized aldehyde nucleophile in enamine catalysis. The obtained optically active vicinal diamines are useful chiral synthons as exemplified by the formal synthesis of (−)-agelastatin A. Further investigations to expand the scope of this and related reactions are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure and spectral data for all new compounds and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research from MEXT, Japan. R.S. thanks the Japan Society for the Promotion of Science for Young Scientists for Research Fellowships. We thank the Research Center for Computational Science, Okazaki (Japan) for the use of their facility in our computational studies.

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(2) For reviews on catalytic asymmetric diamination of aklenes, see: (a) Muñiz, K. *New J. Chem.* **2005**, *29*, 1371. (b) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269. (c) de Figueiredo, R. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1190.

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