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Stereoselective Organocatalytic One-Pot α,α-Bifunctionalization of Acetaldehyde by a Tandem Mannich Reaction/ Electrophilic Amination

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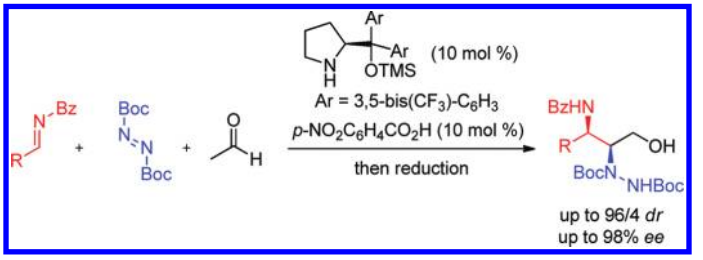
ABSTRACT



The first asymmetric organocatalyzed one-pot α,α-bifunctionalization of acetaldehyde with two different electrophiles is described. A diarylprolinol silyl ether-catalyzed reaction of acetaldehyde with an imine and di-*tert*-butyl azodicarboxylate affords *syn*-2,3-diaminoalcohols with excellent *ee* values of up to 98%. This methodology was successfully applied to the synthesis of a chiral α,β-diaminocarboxylic acid.

Asymmetric α-functionalization of aldehydes mediated by enamine catalysis has attracted considerable attention over the past decade.[1] Recent approaches in this field lie in the development of novel catalytic strategies aiming at higher-yielding, more selective and complex chemical transformations using simple substrates. Among carbonyl compounds, acetaldehyde is the simplest enolizable nucleophile but its use in organocatalysis has long been hampered by difficulties in controlling its reactivity.[2] In 2008, the research groups of List and Hayashi independently reported the first general enantioselective transformations of acetaldehyde under enamine catalysis.[3] Following these works, several research groups successfully developed organocatalytic transformations involving acetaldehyde as a substrate.[4] In 2009, List et al. reported a highly diastereo- and enantioselective proline-catalyzed double Mannich reaction of acetaldehyde with *N*-Boc imines.[4a]

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(2) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4632.

(3) (a) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453. (b) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082. (c) García-García, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 4719. (d) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722. (e) Hayashi, Y.; Okano, T.; Itoh, T.; Urushima, T.; Ishikawa, H.; Uchimaru, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9053. (f) Hayashi, Y.; Samanta, S.; Itoh, T.; Ishikawa, H. *Org. Lett.* **2008**, *10*, 5581.

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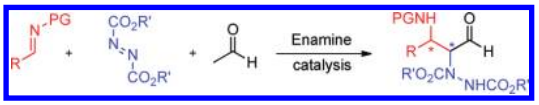
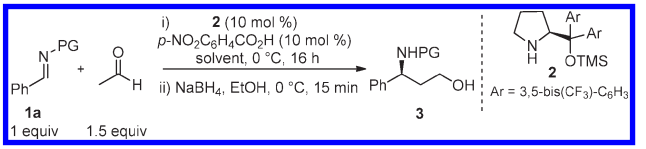
Despite this breakthrough, organocatalyzed α,α-bifunctionalization of acetaldehyde with two different electrophiles remains an untrodden process. As a part of our ongoing research into organocatalyzed C−N bond formation,[5] we report herein a stereoselective one-pot Mannich reaction/electrophilic amination of acetaldehyde through double enamine catalysis (Scheme 1). This would afford chiral α,*β*-diamino aldehydes which represent interesting building blocks for the synthesis of vicinal diamine-containing compounds.[6]

Scheme 1. One-Pot α,α-Bifunctionalization of Acetaldehyde



The successful implementation of a one-pot transformation in a sequential approach requires the optimization of the first step to make it compatible with the subsequent ones. With this aim in mind, the first step has to fulfill several criteria: (i) A quasi-equimolar ratio of reagents is required. An excess of one substrate might inhibit the subsequent reaction. (ii) The reaction has to proceed in high yield without the formation of any side products which could influence the following transformation. (iii) Reaction conditions must be compatible with each transformation. Based on the recent work of Hayashi et al.[3e] on the reaction of *N*-benzoyl-*N*-benzylideneamine (1 equiv) with acetaldehyde (5 equiv) catalyzed by the system diarylprolinol silyl ether **2**/*p*-nitrobenzoic acid, we first embarked upon optimization of the first step (Table 1). The reaction of acetaldehyde (1.5 equiv) with *N*-protected-*N*-benzylideneamine **1a** (1 equiv) was chosen as the model reaction. Under these conditions, *N*-Boc- and *N*-Cbz-*N*-benzylideneamines **1a** failed to react with acetaldehyde (entries 1 and 2). Reaction of acetaldehyde with *N*-Bz imine **1a** led to the desired alcohol **3** in 68% yield and 98% *ee* after in situ reduction (entry 3). It is worthwhile noting that decreasing the amount of acetaldehyde only slightly affects the yield while maintaining high enantioselectivity (entries 3 and 4). Dichloromethane and acetonitrile are good solvents for α-amination of aldehydes using catalyst **2**.[5a,7,8] These were tested in the Mannich reaction, and acetonitrile turned out to be the best solvent affording **3** in 84% yield and 98% *ee* (entries 5 and 6).

Table 1. Optimization of the Mannich Reaction[a]

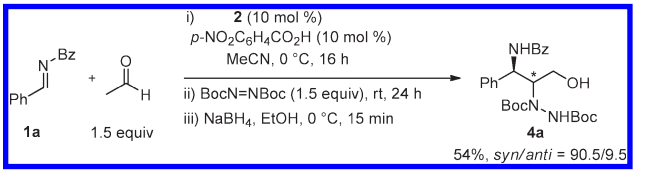


entry	PG	solvent	yield (%)[b]	*ee* (%)[c]
1	Boc	THF	n.r.	n.d.
2	Cbz	THF	n.r.	n.d.
3	Bz	THF	68	98
4[d]	Bz	THF	76	97
5	Bz	CH_2Cl_2	60	82
6	Bz	MeCN	84	98

[a] Unless otherwise noted, reactions were run with *N*-PG imine **1a** (0.3 mmol), acetaldehyde (0.45 mmol) in solvent at 0 °C for 16 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Reaction carried out with 5 equiv of acetaldehyde.

With the optimized conditions for the Mannich reaction in hand, we then turned our attention on the α-amination step as part of a one-pot procedure (Scheme 2).

Scheme 2. α,α-Bifunctionalization of Acetaldehyde by Sequential Addition of Reagents



The one-pot procedure consists of the reaction of acetaldehyde (1.5 equiv) with *N*-Bz imine **1a** (1 equiv) catalyzed by 10 mol % of **2**/*p*-$NO_2C_6H_4CO_2H$. The reaction was stirred at 0 °C for 16 h, at which point 1.5 equiv of di-*tert*-butylazodicarboxylate was added. Monitoring of the reaction showed that electrophilic amination did not occur at 0 °C under these conditions. Raising the temperature to room temperature and further stirring for 24 h led to the formation of **4a** in 54% yield as a separable mixture of two diastereoisomers (*syn*/*anti* = 90.5/9.5) after in situ reduction and purification on silica gel. The above results prompted us to investigate a procedure whereby all the reagents would be present at the beginning of the reaction and a simple change of temperature from 0 °C to room temperature would promote electrophilic amination. Under these conditions, reaction of **1a**, di-*tert*-butylazodicarboxylate, and acetaldehyde for 16 h at 0 °C followed by further stirring at room

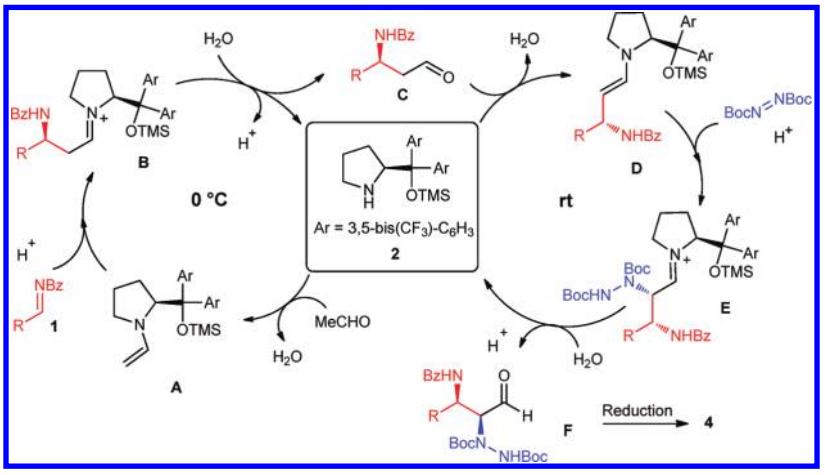
(5) For recent articles, see: (a) Ait-Youcef, R.; Sbargoud, K.; Moreau, X.; Greck, C. *Synlett* **2009**, 3007. (b) Kalch, D.; Ait-Youcef, R.; Moreau, X.; Thomassigny, C.; Greck, C. *Tetrahedron: Asymmetry* **2010**, *21*, 2302. (c) Ait-Youcef, R.; Moreau, X.; Greck, C. *J. Org. Chem.* **2010**, *75*, 5312. (d) Desmarchelier, A.; Marrot, J.; Moreau, X.; Greck, C. *Org. Biomol. Chem.* **2011**, *9*, 994. (e) Desmarchelier, A.; Yalgin, H.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron Lett.* **2011**, *52*, 4430.

(6) For reviews, see: (a) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) Saibabu Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101. (c) Kizirian, J. C. *Chem. Rev.* **2008**, *108*, 140.

(7) For seminal reports on organocatalyzed α-amination of aldehydes, see: (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (b) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790.

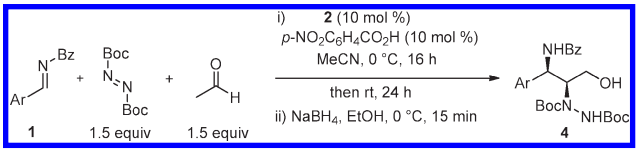
(8) For relevant reviews on organocatalyzed α-amination, see: (a) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377. (b) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292. (c) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465. (d) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917.

Scheme 3. Proposed Catalytic Cycle for the Temperature-Controlled Tandem Mannich Reaction/Electrophilic Amination



temperature for 24 h gave rise to **4a** after careful purifications on silica gel in 50% yield with excellent stereoselectivities (Table 2, entry 1).[9] Decreasing the amount of di-*tert*-butylazodicarboxylate (1 equiv) led to **4a** in lower yield (36%) and diastereoselectivity (*syn*/*anti* = 88/12) while maintaining high enantioselectivity (*ee* for **4**-*syn* = 96%).

Table 2. One-Pot α,α-Bifunctionalization of Acetaldehyde with Various Imines[a]



entry	Ar	4	*syn*/*anti*[b]	yield 4-*syn*(%)	*ee* (%)[c]
1	C_6H_5	**4a**	94/6	50	96
2	4-ClC_6H_4	**4b**	92/8	45	98
3	3-ClC_6H_4	**4c**	90.5/8.5	32	98
4	4-MeC_6H_4	**4d**	93.5/6.5	41	90
5	4-FC_6H_4	**4e**	88/12	40	97
6	2-naphthyl	**4f**	88/12	51	96
7	3-$MeOC_6H_4$	**4g**	91/9	35	96
8	2-$MeOC_6H_4$	**4h**	96/4	23	88

[a] Reactions were run with *N*-Bz imine **1** (0.3 mmol), di-*tert*-butylazodicarboxylate (0.45 mmol), and acetaldehyde (0.45 mmol) in MeCN at 0 °C for 16 h and then stirred at room temperature for 24 h. [b] Determined by UHPLC-ESI of the crude product after workup. [c] Determined by chiral HPLC analysis for the major *syn*-diastereoisomer.

The one-pot procedure was then extended to a focus selection of imines with the results summarized in Table 2. Regardless of the substitution on the aromatic ring, high levels of diastereo- and enantioselectivities were obtained (entries 2−8). With respect to aryl substitution, *para*- and *meta*-substituents were well tolerated leading to **4b**−**g** in 32−51% yields and high enantioselectivities (entries 2−7). A lower yield was obtained when an *ortho*-substituted imine was employed as a substrate (entry 8). The proposed catalytic cycle depicted above is suggested to explain the selective formation of **4** through a temperature-controlled tandem Mannich reaction/electrophilic amination (Scheme 3). The reaction starts with the condensation of **2** with acetaldehyde to form the enamine **A**. Under acidic conditions, **A** reacts with *N*-Bz imine **1** to furnish the iminum **B**. Hydrolysis of this intermediate leads to the β-amino aldehyde **C** and direct elimination of the catalyst **2**. Reaction of **2** with **C** allows the formation of the enamine **D**. It should be noted that formation of **D** from **B** cannot be ruled out at this stage. Electrophilic amination of **D** by di-*tert*-butylazodicarboxylate furnishes the iminium **E** with a *syn* geometry as the major intermediate. This could be explained by electrophilic attack from the *Si*-face of the most stable *anti*-(*E*)-enamine **D**.[10] Hydrolysis of **E** and subsequent reduction of **F** afford **4** with *syn*-configuration as the major diastereoisomer. Starting from *N*-Bz imine **1b** (R = 4-ClC_6H_4), ESI-MS analyses were carried out to characterize the intermediates and to support the proposed catalytic cycle.[11]

We then focused our attention on the application of this tandem reaction to the synthesis of enantioenriched α,β-diaminocarboxylic acids. These constitute an important class of compounds found in a multitude of biologically active synthetic and natural molecules.[12] To assign the absolute configuration of the obtained *syn*-diaminoalcohol **4**, the developed methodology was successfully applied

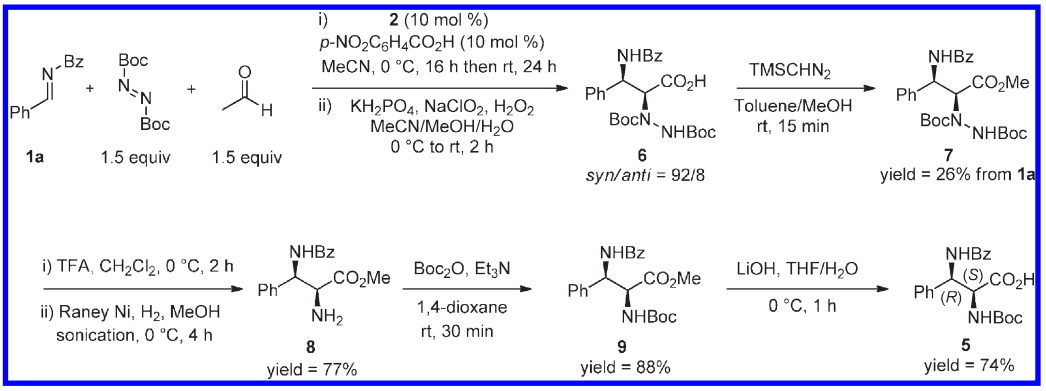
(9) Under these conditions, reaction of imine *N*-Bz **1a** with acetaldehyde and dibenzylazodicarboxylate afforded the desired compound along with side products as an inseparable mixture.

(10) For mechanistic discussions, see: (a) Grošelj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K.; Krossing, I.; Klose, P.; Hayashi, Y.; Uchimaru, T. *Helv. Chim. Acta* **2009**, *92*, 1225. (b) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632.

(11) See Supporting Information for further details.

(12) (a) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167. (b) Viso, A.; Fernández de la Pradilla, R.; Tortosa, M.; García, A.; Flores, A. *Chem. Rev.* **2011**, *111*, PR1.

Scheme 4. Synthesis of α,β-Diaminocarboxylic Acid **5** from Acetaldehyde



to the synthesis of the α,β-diaminocarboxylic acid **5**, an aminated analog of the taxol side chain (Scheme 4).[13] The synthetic sequence started with α,α-bifunctionalization of acetaldehyde and imine **1a** followed by in situ oxidation to afford **6** with a diastereoselectivity similar to that previously observed for **4a** (*syn*/*anti* = 92/8). Esterification of **6** led to **7** as a pure diastereoisomer in an overall yield of 26% from **1a**. Cleavage of the hydrazine was carried out through a two-step procedure: acidic cleavage of the carbamates and hydrogenolysis of the hydrazine in the presence of Raney Ni under sonication led to **8** in 77% yield.[14] Subsequent protection of the amine produced the carbamate **9** in 88% yield. Hydrolysis of the ester group yielded the *N*,*N*′-diprotected α,β-diaminocarboxylic acid **5** in 74% yield. By comparison of the optical rotation of **5** with the literature value,[13] the absolute configuration was confirmed to be (2*S*,3*R*).

In summary, we have disclosed the first asymmetric organocatalyzed α,α-bifunctionalization of acetaldehyde with two different electrophiles. The organocatalytic transformations were successfully optimized by lowering the amout of acetaldehyde to 1.5 equiv while a large amount of acetaldehyde (5−10 equiv) was generally used in similar processes.[4] Reaction of acetaldehyde with *N*-benzoyl imines **1** and di-*tert*-butylazodicarboxylate enabled the one-pot synthesis of the diamino compounds **4** with high levels of diastereo- and enantioselectivity. From these results, a catalytic cycle has been suggested to account for the selective formation of **4**. Furthermore, this methodology has been successfully exploited for the stereoselective synthesis of the α,β-diaminocarboxylic acid **5**. We anticipate that this transformation will find many applications in stereoselective synthesis and will spur further progress in the use of acetaldehyde in organocatalysis.

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Supporting Information Available. Experimental procedures and compound characterization data including NMR spectra, UHPLC-ESI data, and relevant HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Rossi, F. M.; Powers, E. T.; Yoon, R.; Rosenberg, L.; Meinwald, J. *Tetrahedron* **1996**, *52*, 10279–10286.

(14) It is important to note that reductive cleavage of the hydrazine carried out at room temperature for 24 h without sonication led to **8** in 33% yield as an inseparable mixture of diastereoisomers (*syn*/*anti*: 87/13).