Highly Enantio- and Diastereoselective Mannich Reactions of Glycine Schiff Bases with *in situ* Generated *N*-Boc-imines Catalyzed by a Cinchona Alkaloid Thiourea
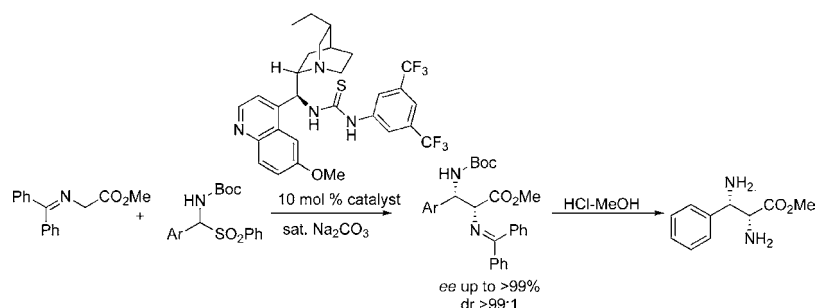
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ABSTRACT

Highly enantio- and diastereoselective organocatalytic Mannich reactions of glycine Schiff bases with *N*-Boc-protected imines are described. Imines were generated *in situ* from bench-stable α-amido sulfones. Catalysis mediated by a cinchona alkaloid thiourea provided optically active α,β-diamino acid derivatives with up to 99% ee and near-perfect diastereoselection.

Optically active α,β-diamino acids have biological significance as well as utility in organic synthesis.[1] Catalytic asymmetric synthesis of α,β-diamino acids through carbon−carbon bond-forming reactions is challenging because two vicinal stereocenters must be generated with complete diastereomeric and enantiomeric control. Among various synthetic approaches, direct catalytic asymmetric Mannich reactions[2]

are elegant and efficient solutions for the stereocontrolled assembly of both *syn*- and *anti*-α,β-diamino acid derivatives. Recently, advances in two complementary synthetic approaches have been reported: direct Mannich reactions of glycine Schiff bases with imines[3] and nitro-Mannich reactions of nitro compounds with imines facilitated by metal catalysis and organocatalysis.[4] Approaches based on glycine esters have the obvious synthetic advantage that glycinate

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(3) Direct Mannich reactions of glycine Schiff bases with imines: (a) Yan, X. X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X. L.; Wu, Y. D. *J. Am. Chem. Soc.* **2008**, *130*, 14362. (b) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J* **2007**, *2*, 794. (c) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564. (d) Ooi, T.; Kameda, M.; Fujii, J.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397. (e) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583.

esters are inexpensive and the commonly used benzophenone protecting/activating group is readily removed. Surprisingly, however, only a handful of efficient catalytic asymmetric reactions based on this strategy have been reported.

The use of glycine Schiff bases in asymmetric phase transfer catalysis (PTC) was pioneered by O'Donnell.[5] Recently, there have been advances in asymmetric Lewis acid and PTC catalyzed Mannich reactions of glycine Schiff bases. Copper salt catalyzed Mannich reactions of glycine Schiff bases with toluene-4-sulfonyl (Ts) imines suffer the drawbacks of an air-sensitive catalyst and the difficulties inherent with the Ts protecting group that is only removed under very harsh reaction conditions.[3a,e] Maruoka has reported a spiro quaternary ammonium salt based phase-transfer catalyst that works with a limited number of PMP-protected glyoxylate imine acceptors to provide Mannich products with moderate diastereomeric ratios and enantioselectivity.[3d] Other quaternary ammonium salts have been reported by Shibasaki as catalysts of the Mannich reaction of a glycine Schiff base with N-Boc-imines to provide α,β-diamino acids with moderate ee's.[3b,c] Finally, Liu et al. have reported Mannich reactions of preformed chiral Ni complexes of glycine with α-amido sulfones;[6] however, this methodology suffers with respect to efficiency and practicality. As an alternative to either of these approaches, we have previously explored organocatalytic direct asymmetric Mannich reactions[7] of azidoketones with imines. These reactions afforded α,β-diamino acids with excellent enantioselectivities.[8] In this approach, however, the diastereoselectivities were not satisfactory, and the use of azidoketones on a large scale might not be practical.

It is apparent from both our own studies and the studies of others that significant improvements in this reaction are needed. Although organocatalytic phase-transfer reactions have shown promise, organocatalytic routes not based on PTC have not been explored. Finally, the protecting group employed on the imine is critical. N-Carbamoylimines are known to be sensitive and unstable, but recent advances allow for the in situ generation of N-carbamoylimines from bench-stable α-amido sulfones.[9,10] Herein, we describe our contributions to the development of practical and efficient syntheses of the α,β-diamino derivatives and report the first examples of bifunctional alkaloid thiourea catalysts for highly enantio- and diastereoselective organocatalytic direct Mannich reactions of a glycine Schiff base with *in situ* generated N-carbamoylimines.[11]

In order to address the stability issue of *tert*-butoxycarbonyl (N-Boc) imines while preserving the advantages of the N-Boc protecting group, we decided to base our approach on α-amido-sulfone precursors. As a model reaction we chose to study the reaction of glycine methyl ester **1**[12] with the bench-stable α-amido sulfone derived from benzaldehyde **2**. We focused our catalyst screening efforts on thiourea catalysts[13,14] and performed the reaction in the presence of a saturated solution of Na_2CO_3 to facilitate *in situ* generation of the N-Boc-imine of benzaldehyde (Scheme 1).

Gratifyingly, the desired product was obtained with good enantiomeric excess. The ee was 88% when a thiourea catalyst prepared from the cinchona alkaloid dihydroquinine (DHQ)[14] was used (**3a**). The reaction, however, did not go to completion.[15] Takemoto's catalyst **3b** gave the best conversion to the

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(9) For a comprehensive review of use of α-amido sulfones as stable precursors of N-acylimino derivatives, see: Petrini, M. *Chem. Rev.* **2005**, *105*, 3949.

(10) For examples of α-amido sulfones as imine precursors in Mannich-type reactions, see: (a) Song, J.; Shih, H. W.; Deng, L. *Org. Lett.* **2007**, *9*, 603. (b) Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622. (c) Lou, S.; Dai, P.; Schaus, S. E. *J. Org. Chem.* **2007**, *72*, 9998. (d) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975.

(11) For thiourea catalyzed 1,3-dipolar cycloaddition of azomethine ylides of glycine Schiff bases with nitroalkenes, see: Xue, M. X.; Zhang, X. M.; Gong, L. Z. *Synlett* **2008**, 691.

(12) When glycine *tert*-butyl ester was employed in the Mannich reaction with in situ generated N-carbamoylimines in the presence of thiourea catalyst and base under the same conditions, little of the desired product was obtained.

(13) Reviews on organocatalysts, including urea and thiourea catalysts: (a) Connon, S. J. *Synlett* **2009**, 354. (b) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

(14) For pioneering work on cinchona alkaloid-derived thiourea catalysts, see: (a) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (c) Wang, Y.-Q.; Song, J.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (d) Wang, J.; Li, H.; Zu, L. Z.; Xie, H. X.; Duan, W. H.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652. (e) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *127*, 11256. (f) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sagarzabu, V. *Tetrahedron* **2006**, *62*, 375. (g) Li, B.; Jiang, L.; Liu, M.; Chen, Y.; Ding, L.; Wu, Y. *Synlett* **2005**, *4*, 603. (h) Ye, J.; Dixon, D. J.; Hynes, P. *Chem. Commun.* **2005**, *35*, 4481.
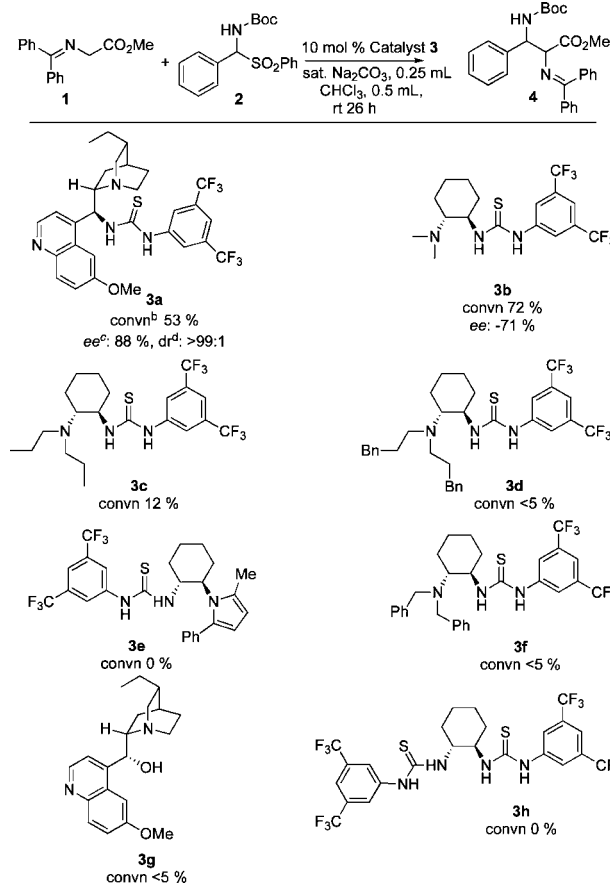
desired product; however, the ee was significantly lower than that provided by **3a**. Attempts to optimize this cyclohexane-derived catalyst through the preparation of derivatives **3c−f** failed.[16] Neither DHQ **3g** nor bisthiourea **3h** alone could efficiently catalyze this reaction, demonstrating that the bifunctional nature of **3a** is key. Presumably, the tertiary amine of this catalyst activates the glycine Schiff base as a nucleophile while the thiourea portion activates the *N*-Boc-imine as an electrophilic acceptor through H-bonding to the nitrogen of the imine. Having failed to find a catalyst more promising than **3a**, a solvent screen was performed.

The initial solvent screen was performed at 4 °C. At this temperature the reaction was very slow. We then evaluated various solvents in reactions initiated at 4 °C and then continued at room temperature for 26 h (Table 1). Under these conditions, toluene provided a product with higher ee than CH₂Cl₂ or CHCl₃. Among the solvents screened, PhCF₃ gave the best results with respect to both ee and conversion. Attempts to further optimize the reaction by the combining CHCl₃ and PhCF₃ were not successful; under these condi-

Table 1. Solvent Screen: Mannich Reaction of Glycine Schiff base with *in situ* Generated *N*-Boc-phenylimine[a]

entry	solvent	convn[b] (%)	dr[c]	ee[d] (%)
1	CHCl₃	50	>99:1	91
2	CH₂Cl₂	45	>99:1	92
3	toluene	59	>99:1	96
4	PhCF₃	77	>99:1	99
5	*m*-xylene	63	>99:1	96
6	PhCF₃+ CHCl₃	63	>99:1	92
7	THF	14		
8	cyclohexane	48	>99:1	95

[a] Typical reaction conditions: To a mixture of α-amido sulfone (0.15 mmol, 1.5 equiv) and glycine Schiff Base (0.1 mmol, 1.0 equiv) in the indicated solvent (0.5 mL) was added catalyst (0.01 mmol, 0.01 equiv, 10 mol % to the glycine Schiff base) followed by aqueous base (0.25 mL). The mixture was stirred at room temperature. [b] The conversion was determined by HNMR of the crude product. [c] The dr was determined by HPLC. [d] The ee was determined by chiral-phase HPLC analysis.

tions, the ee and the reactivity of the catalyst decreased. Significantly, each solvent system provided products with near perfect diastereoselection.

In order to further optimize the reaction, other parameters were varied (Table 2). When the reaction was both initiated

Table 2. Optimization of Conditions: Mannich Reaction of Glycine Schiff Base with *in situ* Generated *N*-Boc-phenylimine[a]

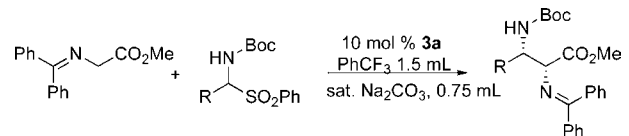| entry	base	temp (°C)	time (h)	convn (%)[b]	ee (%)[c]
1	Na₂CO₃ (sat aq)	4 to rt	36, then 26	77	99
2	Na₂CO₃ (sat aq)	rt	26	77	97
3	Na₂CO₃ (satd aq)	rt	60	81	96
4	Na₂CO₃ (satd aq)	4 to rt	14, then 48	80	99
5	Na₂CO₃ (S, 10 equiv)	rt	24	58	96
6	Na₂CO₃(satd aq)	45	24	82	92
7	Na₂CO₃ (S, 10 equiv)	45	24	66	92
8	K₂CO₃ (satd aq)	rt	26	69	
9	K₂CO₃ (satd aq)	rt	60	77	
10	K₂CO₃ (S, 10 equiv)	rt	24	100	45
11	CS₂CO₃ (satd aq)	rt	26	62	
12	CS₂CO₃ (satd aq)	rt	60	62	

[a] Typical reaction conditions: To a mixture of α-amido sulfone (0.15 mmol, 1.5 equiv) and glycine Schiff base (0.1 mmol, 1.0 equiv) in PhCF₃ (0.5 mL) was added catalyst (0.01 mmol, 0.01 equiv, 10 mol % to the glycine Schiff base) followed by the addition of the base (0.25 mL of aqueous base or 10 equiv of solid base, indicated by S). The mixture was stirred at room temperature. [b] The conversion was determined by HNMR of the crude product. [c] The ee was determined by chiral-phase HPLC analysis.

and run at room temperature a small decrease in ee was noted compared to the reaction initiated at 4 °C (entry 1 versus

entry 2). Increasing the reaction time only slightly increased the reaction conversion (entry 2 versus entry 3). Use of solid Na_2CO_3 (no water) decreased the conversion to the desired product (entry 5). Increasing the reaction temperature improved the reaction conversion but decreased the ee (entry 2 versus entry 6, entry 5 versus entry 7). Stronger aqueous bases K_2CO_3 or Cs_2CO_3 did not increase the conversion to the desired product (entries 8, 9, 11, and 12). Complete conversion was observed when solid K_2CO_3 (no water) was used; however, the ee was decreased (entry 10).

We then studied the scope of this Mannich reaction using a variety of aromatic and heteroaromatic imines generated in situ. As summarized in Table 3, all of the reactions

Table 3. Reaction Scope: Mannich Reaction of Glycine Schiff Base with *in situ* Generated *N*-Boc-alkylimines[a]

entry	R	product	convn[b] (%)	yield[c] (%)	ee[d] (%)
1	C_6H_5	**4**	80	73	99
2[e]	C_6H_5	**4**	81	76	99
3	4-MeO-C_6H_5	**5**	68	62	98
4	4-NO_2-C_6H_5	**6**	100	86	94
5	4-Cl-C_6H_5	**7**	100	87	>99
6	4-Br-C_6H_5	**8**	100	90	>99
7	2-furyl	**9**	82	74	>99
8	α-naphthyl	**10**	97	80	98
9	4-CF_3-C_6H_5	**11**	100	98	>97
10	4-Me-C_6H_5	**12**	93	89	>95

[a] Typical reaction conditions: To a mixture of α-amido sulfone (0.6 mmol, 2.0 equiv or 0.45 mmol, 1.5 equiv) and glycine Schiff base (0.3 mmol, 1.0 equiv) in solvent (1.5 mL) was added catalyst (0.03 mmol, 0.03 equiv, 10 mol % to the glycine Schiff base) followed by the addition of the base. The mixture was stirred at 4 °C for 14 h and then incubated at room temperature for 28−48 h. [b] The conversion was determined by ^{1}H NMR of the crude product. [c] Isolated yield. [d] The ee was determined by chiral-phase HPLC analysis. [e] α-Amido sulfone (3 mmol, 1.5 equiv) and glycine Schiff base (2 mmol, 1.0 equiv).

afforded product with excellent ee and dr. The electronic character of substrate dramatically affected the rate of the Mannich transformation. Electron-rich substrates such as

o-tolyl imines had reduced reaction conversions (entries 3) compared to substrates with electron-withdrawing groups (entries 4−6). The reaction was also readily scaled without significant changes in yield or enantioselectivity (entry 2). Regardless of electronic and structural differences in the imines, all products were prepared as virtually single diastereomers.[17]

To confirm the stereochemistry of the Mannich adducts, imidazolidinone **14** was synthesized from **4** as shown in Scheme 2. The relative and absolute configuration of **14** was

Scheme 2. Efficient Synthesis of *cis*-Imidazolidinone **14**
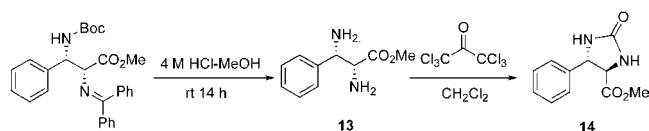
then determined by comparison with data reported in the literature and the configuration of all other products were assigned by analogy with this product.[18]

In summary, we have developed a highly efficient and practical strategy for the synthesis of chiral α,β-diamino acid derivatives with remarkable levels of diastereo- and enantiocontrol (up to >99% ee, dr > 99:1). We employed direct organocatalytic Mannich reactions of a glycine Schiff base with *N*-Boc-imines generated *in situ*. This is the first characterization of highly enantioselective direct Mannich reactions of a glycine Schiff base promoted by a DHQ-derived thiourea catalyst and not based on PTC. We believe that the tertiary amine thiourea catalyst activates the glycine Schiff base as a nucleophile through general base catalysis while simultanously activating the imine as an electrophile through H-bonding to the nitrogen of the imine. Further investigations of the scope and application of this strategy are in progress.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) The glycine Schiff base is quite stable in basic aqueous conditions. The reaction conversion was judged by the ratio of desired product to the remaining glycine Schiff base. ^{1}H NMR was used to monitor Boc-imine consumption and decomposition to benzaldehyde.

(16) By ^{1}H NMR of the crude reaction mixture, *N*-Boc-phenylimine was formed and little desired product was observed.

(17) Diastereomers were resolved by HPLC. See the Supporting Information.

(18) Lee, S.-H.; Yoon, J.; Chung, S.-H.; Lee, Y.-S. *Tetrahedron* **2001**, *57*, 2139.