DOI: 10.1002/chem.201002571

Guanidine Organocatalyst for the Asymmetric Mannich-Type Reaction between α-Isothiocyanato Imide and Sulfonyl Imines

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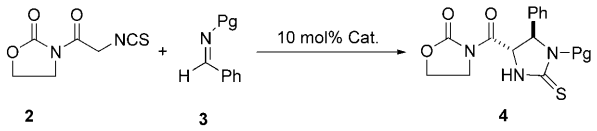
α,β-Diamino acids are key structural components in many molecules,[1] such as biologically active natural products and synthetic materials.[2] Various methods for the preparation of optically active α,β-diamino derivatives have been established.[3] Most of these approaches have focused on Mannich reactions of glycine imines or nitro esters with various imines, which provide a direct and favorable method for the construction of these compounds.[4–6] In recent years, α-isothiocyanato imides have been employed as glycine imine equivalents in Mannich reactions. Willis and co-workers reported the first example of a Mannich reaction of the α-isothiocyanato imide with imines using chiral magnesium complex derivatives from DBFox.[7a] Seidel's group and Zhong's group both found that quinidine-derived organocatalysts could catalyze the reaction with good diastereoselectivity and enantioselectivity.[7b,c] Despite these excellent results, the design of new catalyst systems remains a considerable challenge. The guanidine group plays important roles in molecular recognition and as a catalyst in biological systems owing to its characteristics, such as high pK_a value and dual hydrogen-bonding.[8] Over the past few years, chiral guanidines have become an attractive target in asymmetric organocatalysis and have been shown to be powerful reagents for enantioselective reactions.[9–10] Herein, we present a readily prepared chiral bisguanidine organocatalyst for the asymmetric Mannich-type reaction of α-isothiocyanato imide with *N*-Ts-protected imines, which provides excellent results under mild conditions.

Initially, monoguanidine **1a** was synthesized to catalyze the asymmetric Mannich-type reaction because it could serve as a bifunctional catalyst.[9f] Moderate results were obtained from α-isothiocyanato imide **2** and *N*-Ts-imine **3** derived from benzaldehyde (Table 1, entry 1). A series of bisguanidines with a chiral or achiral linkage were synthesized to improve the outcomes (Scheme 1). Chiral bisguanidine **1d** derived from benzene-1,3-diamine was superior to **1b** and **1c** derived from (1*S*,2*S*)-1,2-diphenylethylenediamine and (1*S*,2*S*)-cyclohexane-1,2-diamine, respectively, giving the desired product in 96% yield, >95:5 d.r. and 82% *ee* (Table 1, entry 4 vs. entries 2 and 3); the linkage was able to adjust the spatial arrangement of the two guanidine moieties to meet the proper asymmetric induction. A solvent survey revealed that adducts could be obtained with the best results, 94% yield, >95:5 d.r. and 89% *ee* using $CHCl_3$ as co-solvent (Table 1, entry 5, for details, see Supporting Infor-

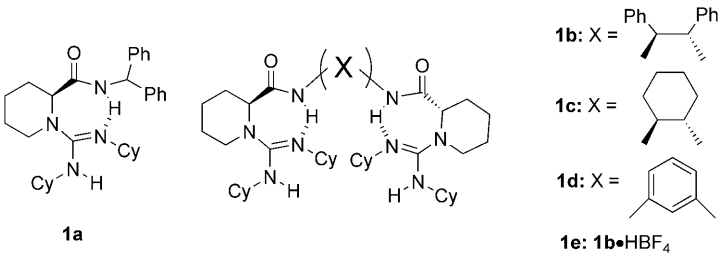
Table 1. Optimization of reaction conditions.



2 3 4

Entry[a]	Cat	Pg	Yield [%][b]	*trans*:*cis*[c]	*ee* [%][d]
1	**1a**	tosyl	84	>95:5	68
2	**1b**	tosyl	96	90:10	46
3	**1c**	tosyl	93	88:12	61
4	**1d**	tosyl	96	>95:5	82
5[e]	**1d**	tosyl	94	>95:5	89
6[e,f]	**1d**	phenyl	87	82:18	0
7[e]	**1d**	2-hydroxyphenyl	N.R[g]	–	–
8[e]	**1d**	diphenylmethyl	N.R[g]	–	–
9[e,h]	**1d**	4-methoxyphenyl	74	56:44	25

[a] Unless otherwise noted, all reactions were carried out with **2** (0.1 mmol), **3** (0.2 mmol), 10 mol% catalyst in THF (1.0 mL) at −20°C for 6 h. [b] Isolated yield of combined diastereomers. [c] Determined by ^{1}H NMR analysis. [d] *ee* of the *trans* isomer, measured by chiral HPLC using Chiracel ADH column. [e] THF/$CHCl_3$ (v/v) = 1/1. [f] *ee* and *trans*:*cis* of the product, measured by chiral HPLC using Chiracel ADH column. [g] N.R. = no reaction. [h] *ee* and *trans*:*cis* of the product, measured by chiral HPLC using Chiracel IA column.



Scheme 1. Catalysts evaluated in this study.

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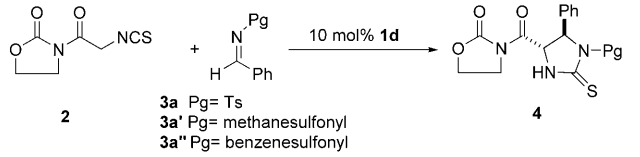
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002571.

mation). The influence of other protecting groups of imines were also investigated (Table 1, entries 6–9). On replacement of the tosyl group with the phenyl group, no *ee* value was obtained, although the yield was satisfactory, which implied that the interaction between the tosyl group and the catalyst was crucial for stereo-induction (Table 1, entry 6). On employing the 2-hydroxyphenyl and diphenylmethyl protecting groups, no reaction occurred (Table 1, entries 7 and 8). The Mannich-type reaction of 4-methoxyphenyl-protected imine also proceeded with low stereoselectivity (Table 1, entry 9).

To further improve the enantioselectivity of the reaction, some achiral additives were employed.[11] The Brønsted basicity of guanidine was crucial for the activation of the isothiocyanato imide, since no product was detected if guanidine salt **1e** with two BF_4^- counteranions was used. Interestingly, weak acids were found to have positive effect on the reaction. When *p*-$CNC_6H_4CO_2H$ (**5b**) was used as additive, the enantioselectivity was improved, but the yield was retained (94% yield, 97% *ee*, Table 2, entry 2). Compared

Table 2. Acidic additives screened in this reaction.



Entry[a]	Acid	pK_a[b]	Yield [%][c]	*trans: cis*[d]	*ee* [%][e]
1	$C_6H_5CO_2H$ (**5a**)	4.20	95 (**4a**)	>95:5	91
2	*p*-$CNC_6H_4CO_2H$ (**5b**)	3.55	94 (**4a**)	>95:5	97
3	*p*-$NO_2C_6H_4CO_2H$ (**5c**)	3.42	88 (**4a**)	>95:5	93
4	*p*-$MeC_6H_4CO_2H$ (**5d**)	4.38	96 (**4a**)	>95:5	90
5	*p*-$MeOC_6H_4CO_2H$ (**5e**)	4.47	90 (**4a**)	>95:5	92
6[f]	*p*-$CNC_6H_4CO_2H$ (**5b**)	3.55	92 (**4a**)	>95:5	93
7[g]	*p*-$CNC_6H_4CO_2H$ (**5b**)	3.55	86 (**4a**)	>95:5	95
8[h]	*p*-$CNC_6H_4CO_2H$ (**5b**)	3.55	92 (**4a**)	>95:5	96
9[h,i]	*p*-$CNC_6H_4CO_2H$ (**5b**)	3.55	85 (**4a′**)	>95:5	65
10[h,j]	*p*-$CNC_6H_4CO_2H$ (**5b**)	3.55	80 (**4a″**)	>95:5	92

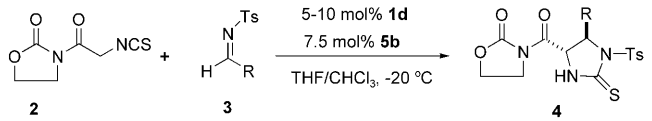
[a] Unless otherwise noted, all reactions were carried out with **2** (0.1 mmol), **3a** (0.2 mmol), 10 mol% additive, 10 mol% **1d** in THF/$CHCl_3$ (v/v, 1/1, 1.0 mL) at −20°C for 10 h. [b] Relative pK_a in water.[12] [c] Isolated yield of combined diastereomers. [d] Determined by ^1H NMR analysis. [e] *ee* of the *trans* isomer, measured by chiral HPLC using Chiracel ADH column. [f] 5 mol% catalyst loading, 5 mol% additive. [g] 5 mol% catalyst loading, 10 mol% additive. [h] 5 mol% catalyst loading, 7.5 mol% additive. [i] Mesyl group protected imine **3a′** was used. [j] Benzenesulfonyl-protected imine **3a″** was used.

with acid **5b**, the slightly less acidic $C_6H_5CO_2H$ (**5a**), *p*-$MeC_6H_4CO_2H$ (**5d**), and *p*-$MeOC_6H_4CO_2H$ (**5e**) led to less improvement of the *ee* values (Table 2, entries 1, 4, 5, vs. 2), whereas the more acidic *p*-$NO_2C_6H_4CO_2H$ (**5c**) exhibited lower reactivity and enantioselectivity (Table 2, entry 3 vs. 2). The influence of the protonic acid might by partly associated with the formation of a guanidinium salt, which could activate the imines through hydrogen bonding.[10] The carboxylate anion adhering nearby might fine tune the stereosurrounding to optimum. Moreover, when catalyst loading was decreased from 10 mol% to 5 mol%, the enantioselectivity of the reaction decreased slightly (Table 2, entry 6 vs. 2). Fortunately, when the dosage of additive **5b** was increased to 7.5 mol%, the results were generally maintained, while further increasing the amount of acid **5b** to 10 mol% resulted in loss of yield (Table 2, entry 8 vs. 6, 7). The influence of the sulfonyl group of the imine was tested. Use of the benzenesulfonyl group protected imine gave 92% *ee*, whereas the sterically smaller mesyl group protected imine afforded the product with greatly reduced enantioselectivity (65% *ee*) and comparative yield (entry 9 vs. entries 8 and 10), which might result from the more flexible conformation of the imine with a methanesulfonyl group. The poor results of other imines without sulfonyl substituents (Table 1, entries 6–9) clearly illustrated the important role of the sulfonyl group on the stereoselectivity. Screening of other reaction conditions identified that the optimal conditions were 5 mol% bisguanidine **1d**, 7.5 mol% additive **5b**, 0.1 mmol α-isothiocyanato imide **2**, and 0.2 mmol *N*-Ts-protected imine **3a** in 1.0 mL THF/$CHCl_3$ (v/v, 1/1) at −20°C (Table 2, entry 8). In addition, the configuration of the product **4a** was assigned to be (4*S*, 5*R*) by comparison of the optical rotation to the reported value of the corresponding enantiomer.[7c]

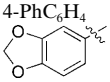
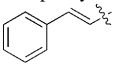
A series of representative *N*-Ts-protected imines were investigated under the optimized conditions (Table 3). A variety of aldimine substrates provided the corresponding products in good to excellent yields, with high diastereoselectivity (up to >95:5 d.r.) and excellent *ee* values (up to 99%). The aromatic imines underwent the Mannich-type reactions to yield the optically active adducts in excellent yields and 90–>99% *ee*. It is noteworthy that not only the electronic properties of the substitutions at the aromatic ring, but also the steric hindrance, had no obvious effect on the diastereoselectivity and enantioselectivity (Table 3, entries 1–17). While the condensed-ring imines reacted smoothly with α-isothiocyanato imide, giving the products with 96% *ee* and 93% *ee* (Table 3, entries 18 and 19), the α,β-unsaturated imines showed a slightly reduced reactivity and diastereoselectivity (Table 3, entry 20). Heteroaromatic substituted variants delivered the Mannich-type adduct with a high selectivity of 95–98% *ee* (Table 3, entries 21 and 22). Both acyclic and cyclic aliphatic imines could also be converted to the corresponding adducts with excellent results (Table 3, entries 23 and 24). Other substrates such as *N*-Ts-protected ketoimine also were explored, but the adducts were not detected.[13]

The low catalyst loading, mild reaction conditions, and the inexpensive starting materials and available catalyst for this Mannich-type reaction offered a practical way to scale-up production. In the presence of 5 mol% of bisguanidine **1d**, 7.5 mol% of *p*-$CNC_6H_4CO_2H$ (**5b**), 10 mmol of α-isothiocyanato imide **2** reacted with 2.0 equivalents of *N*-Ts-protected imine **3a** to provide the desired product **4a** in 82% yield without any loss in the enantioselectivity and diastereoselectivity (Scheme 2).

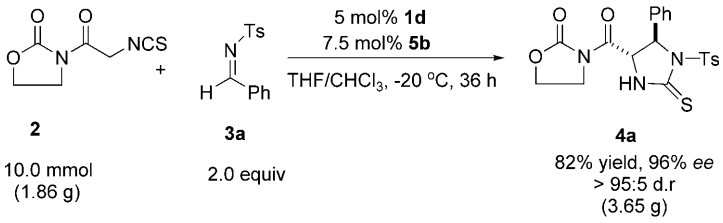
Table 3. Substrate scope for the catalytic asymmetric Mannich-type reaction.



2 3 4

Entry[a]	R	Product	Yield [%][b]	*trans*:*cis*[c]	*ee* [%][d]
1	3-BrC_6H_4	**4b**	90	92:8	94
2	4-BrC_6H_4	**4c**	94	92:8	93
3[e]	4-FC_6H_4	**4d**	96	>95:5	90
4	3-ClC_6H_4	**4e**	88	90:10	>99
5[e]	4-ClC_6H_4	**4f**	90	>95:5	90
6	2-$MeOC_6H_4$	**4g**	85	95:5	93
7	4-$MeOC_6H_4$	**4h**	89	>95:5	>99
8[e]	2-MeC_6H_4	**4i**	80	>95:5	93
9[e]	3-MeC_6H_4	**4j**	83	94:6	92
10[e]	4-MeC_6H_4	**4k**	90	>95:5	90
11	3-$PhOC_6H_4$	**4l**	93	>95:5	97
12[e]	3-$NO_2C_6H_4$	**4m**	91	>95:5	91
13	4-$NO_2C_6H_4$	**4n**	90	>95:5	91
14[e]	4-$CF_3C_6H_4$	**4o**	89	90:10	90
15	4-CNC_6H_4	**4p**	94	95:5	98
16	4-PhC_6H_4	**4q**	99	>95:5	96
17		**4r**	92	92:8	96
18	2-naphthyl	**4s**	90	93:7	96
19	1-naphthyl	**4t**	94	>95:5	93
20[e]		**4u**	86	80:20	93
21	2-thienyl	**4v**	90	>95:5	95
22	3-furyl	**4w**	86	>95:5	98
23	n-pentyl	**4x**	82	85:15	98
24	cyclohexyl	**4y**	90	85:15	95

[a] Unless otherwise noted, all reactions were carried out with **2** (0.1 mmol), **3** (0.2 mmol), 5 mol% catalyst **1d**, 7.5 mol% additive **5b** in $THF/CHCl_3$ (v/v, 1/1, 1.0 mL) at −20 °C for 8–24 h. [b] Isolated yield of combined diastereomers. [c] Determined by ^1H NMR analysis. [d] *ee* of the *trans* isomer, measured by chiral HPLC using Chiracel ADH column. [e] 10 mol% catalyst loading, 10 mol% additive.



2 10.0 mmol (1.86 g)

3a 2.0 equiv

4a 82% yield, 96% *ee* > 95:5 d.r (3.65 g)

Scheme 2. Scaled-up version of the Mannich-type reaction of α-isothiocyanato imide with *N*-Ts-protected imine **3a**.

The important evidence of the influence of additives demonstrated that hydrogen as well as the guanidine moiety both played crucial roles in the reactivity and asymmetric inductivity. Based on the experimental results and our previous work,[9f,i] we proposed the possible transition state of the reaction. As shown in Figure 1, one of the guanidine moieties is protonated by the weakly acidic additive **5b** to form a guanidinium salt, which activates the *N*-Ts-protected imine

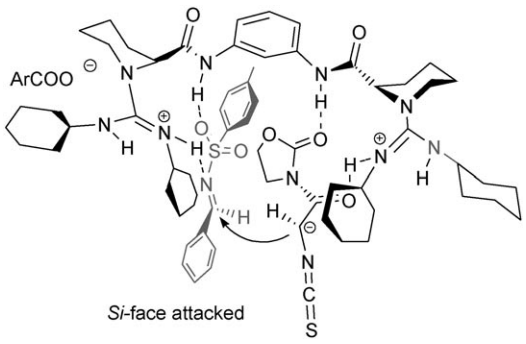


Figure 1. The proposed transition state mode of Mannich-type reaction of α-isothiocyanato imide with *N*-Ts-protected imine **3a**.

via hydrogen bonding to the nitrogen of the imine associated with the hydrogen bonding between the amide and tosyl group. On the other hand, the other guanidine moiety deprotonates the active hydrogen atom from α-isothiocyanato imide, which then stabilizes the α-isothiocyanato imide by an intermolecular hydrogen bond. Meanwhile, the N–H moiety of the amide on the same side of the guanidine might act as a Brønsted acid to locate the imide. In this transition state, the activated α-isothiocyanato imide was much more accessible to attack the *Si*-face of the activated *N*-Ts-protected imine to form the major (4*S*,5*R*) product, in accordance with the experimental results.

In summary, we have developed a highly efficient bisguanidine organocatalyst for the Mannich-type reaction of α-isothiocyanato imide with *N*-Ts-protected imines. Significant progress has been made with an extremely broad substrate scope, giving optically active α,β-diamino acid derivatives in excellent yields with high diastereoselectivities (up to >95:5 d.r.) and excellent enantioselectivities (up to 99% *ee*) under mild conditions. The possible transition state of the reaction was proposed. Further studies on the reaction mechanism and the application of this catalyst to other reactions are underway.

Experimental Section

Typical experimental procedure: A mixture of **1d** (3.7 mg, 0.005 mmol), α-isothiocyanato imide (18.6 mg, 0.1 mmol), and *p*-$CNC_6H_4CO_2H$ (**5b**; 1.1 mg, 0.0075 mmol) in $THF/CHCl_3$ (v/v, 1/1, 1.0 mL) was stirred in an open vessel at ambient temperature for 10 min. The temperature was then lowered to −20 °C and after 15 min, *N*-benzylidene-4-methylbenzenesulfonamide (51.8 mg, 0.2 mmol) was added, and the mixture was stirred for a further 6 h at −20 °C. The mixture of *trans* and *cis* products was isolated by column chromatography on silica gel (CH_2Cl_2/EtOAc: 9:1) to provide **4a** as colorless crystal.

Acknowledgements

We appreciate the National Natural Science Foundation of China (Nos. 20732003, 21021001, and 21072133), and the National Basic Research Program of China (973 Program: No. 2010CB833300) for financial sup-

port. We also thank the Sichuan University Analytical & Testing Center for NMR analysis and the State Key Laboratory of Biotherapy for HRMS analysis.

Keywords: amino acids · asymmetric catalysis · guanidine · Mannich-type reactions · organocatalysis

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Received: September 4, 2010
Published online: January 26, 2011

