First Example of Organocatalytic Asymmetric Mannich Reaction between Aldimines of Glycinates and Sulphonyl Imines

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Abstract: The catalytic enantioselective Mannich-type reaction between glycinates schiff base and imines have being one of the most efficient routes for accessing α, β-diamino acids. However, the Glycinates Schiff bases used in the references were almost ketimines. Only several examples of aldimines were used in the presence of metal catalyst. We developed the first example of asymmetric direct Mannich reaction using aldimines of glycinates instead of ketimines of glycinates. The reaction was well catalyzed by chiral guanidine with high yield (up to 92%) and moderate stereoselectivity (up to 65%).

Keywords: Organocatalyst, Aldimine, Glycinates, Sulphonyl imine, Chiral guanidine

Graphical Abstract

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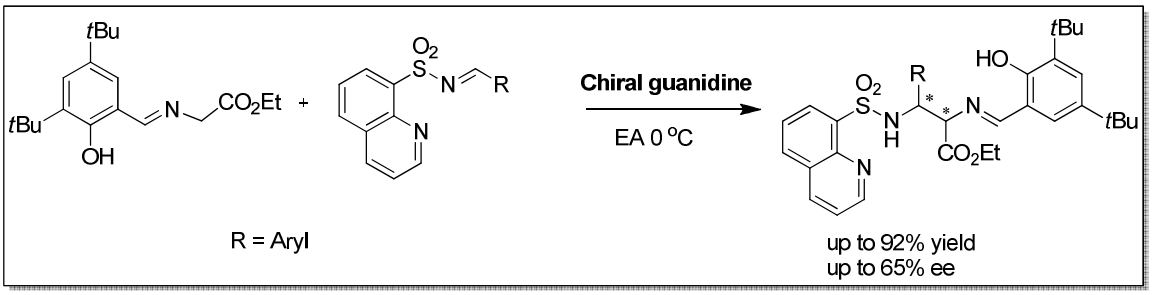

Introduction

The Optically active α,β-diamino acids and their derivatives[1] have attracted tremendous attention among organic chemists and biochemists through the years because of their wide-ranging significant bioactivity，as well as valuable synthetic applications.[2,3] As we know, catalytic asymmetric direct Mannich-type reaction of glycinates Schiff bases was one of the most efficient routes to optically active α, β-diamino acids (Scheme 1a).[4-9] However, to our knowledge, the glycinate Schiff bases used for Mannich-type reactions were synthesized from glycinates and special ketones [10-12] (Scheme 1b). Although the ketimines of glycinates Schiff base were efficiently applied in the literatures, [13-20] the corresponding Aldimines of glycinates Schiff base were difficult to be used in the Mannich reactions due to the following reasons: 1) the lower Pka of the α proton; 2) the competition of the two different types of imines as electrophiles may cause the reaction dirty. However, aldimines of glycinates were better choice considering the convenient transformation of the resulting products as well as atom economy, Scheme 1c. In fact, aldimines of glycinates were precursors of azomethine ylide, widely used in the asymmetric 1,3-dipolar cycloaddition with various dipoalrophiles.[21-25]

Scheme 1

More recently, Carretero and co-works have described the Fesulphos-Cu^{I} catalysed asymmetric direct Mannich reaction with aldimines of glycinates. [26] The obtained unstable Mannich products need in situ selective reduction of imines to amino group. However, to the best of our knowledge, metal free asymmetric direct Mannich-type reaction using aldimines of glycinates have never been reported. This might be ascribed to the unstable property of α anions of these aldimines donor compared with fluorenone or benzophenone imines which could be stabilized by resonance involving 1, 4 π-electrons of the aromatic ketone moiety.[10-12] Herein we report the first chiral guanidine catalyzed Mannich reaction using aldimine of glycinates.

Results and discussion

As we know, in the biological system, conversion of α-keto acid to α-amino acid in the presence of pyridoxal is a very important process.[27-29] The hydroxyl group of the aldimine is vital for the high reactivity and enantioselectivity.[30,31] Moreover, studies show that hydroxyl group could stabilize α anions in the presence of base (scheme 1). [32,33] Therefore, we initiated our studies with salicylic aldimine (**4a**) and *p*-Methyl arylsulfonyl imine (**5a**) in the presence of different catalysts in toluene at room temperature, Figure 1. As shown in (Table 1, entries 1-3), catalysts with tertiary amine, such as cinchonine, quinine or DABCO, couldn't catalyse this reaction smoothly. However, 1,1,3,3-tetramethylguanidine (TMG) (Table 1, entry 4) could efficiently catalyze the reaction with high yield.[34] Meanwhile, as we expected, the ordinary aldimine could not react under the same reaction conditions, (Table 1, entry 5).

Figure 1

Table 1

Chiral guanidines have been shown to be efficient catalysts for asymmetric reaction due to the high pKa values [35-39] and hydrogen-bonding activity.[40,41] Therefore, chiral guanidine (**6a**) was synthesized and used as catalyst for this mannich type reaction. The result revealed that this catalyst could catalyze the reaction with high yield and poor stereoselectivity (Table 1, entry 6). Moreover, *o*-methyl arylsulfonyl imine (**5b**) instead of p-methyl arylsulfonyl imine (**5a**) led cleanly to a mixture of (**7b**) with improving diastereoselectivity (Table 1, entry 7).

Scheme 2

Further experiment for increasing the stereoselectivity, we screened the reaction conditions such as reaction temperature and solvent (Table S1, See supporting information). Under the optimal conditions, the yield as well as the stereoselectivity were slightly improved (Table 2, entry 1). Then we turned our attention to examine different salicylic aldimines. As a result, aldimines with electron donating group (**4b**, **4e**), electron withdrawn group (**4c**) as well as bulkier group (**4d**) were investigated. We found that sterically hindered aldimine (**4d**) offer higher enantioselectivity (Table 2, entry 2-5). Meanwhile, salicylic aldimine

(**4f**) bearing di-hydroxyl groups were synthesised and used as substrate. However, no product was obtained in our reaction (Table 2, entry 6).

Table 2

Next, we examined more chiral guanidines. As a result, a variety of chiral guanidines derived from L-proline, which was previously used as proper catalyst for Michael reaction of acylsilane and nitro olefin were prepared (Scheme 2). The results suggested that catalysts containing various electronic properties on the aromatic ring of the amide moiety appeared to have a very limited effect on the stereoselectivity (Table 3, entries 1-2). It was noteworthy that the bulkier group on the amide posed positive impact to enantioselectivity. Catalyst (**6d**) with diphenylmethylamine gave slightly higher ee value and similar dr value (Table 3, entry 3). However, the other guanidine catalyst bearing larger amide failed to afford good results (Table 3, entries 4-5). We also tried to promote the catalytic result through introducing more hydrogen bond donors into chiral guanidine catalyst (**6h**). Unfortunately, the desired result was not found (Table 3, entry 6).

Table 3

Next, we examined different sulfonyl imine and iminoester in the presence of **6d** under optimized condition. Fortunately, sterically hindered N-(8-quinolyl)sulfonyl aldimines **5d** afford higher enanotioselectivity (Table 4, entry 2). Meanwhile, ethyl esters moiety was suitable for higher enantioselectivity under identical conditions (Table 4, entries 2-4).

Table 4

After that, we examined the catalysts again with **4d** and **5d** as substrate. The results were summarized in Table 5. It was interesting that guanidine **6g** with bulky 2, 6-diisopropyl substituent achieved the best enantioselectivity (Table 5, entry 4).

Table 5

Finally, various sulfonyl imines were used to afford the corresponding products **7** with high yield (87%) and moderate enantioselectivity (Table 6). Moreover, substituents on the phenyl ring of the imine,

including electron-withdrawing (Table 6, entry 3), electron-donating (Table 6, entry 2), neutral (Table 7, entry 1, 4) or imine with condensed-ring (Table 6, entry 6) and hetero aromatic (Table 6, entry 5) furnished the desired products maintaining high yield and moderate stereoselectivity. The absolute configuration of **7** was determined by comparing NMR and chiral HPLC spectra of the derivative of **7** with literature, (see supporting information).[20]

Table 6

In summary, we have developed an organocatalytic asymmetric Mannich-type reaction of aldimines of glycine esters by screening a number of organocatalyst and substrate, thus creating the first example of organocatalytic Mannich reaction of aldimines of glycine esters with sulphonyl imine with excellent yields and middle stereoselectivity. Further investigations to understand the exact role of the salicylic aldimine are underway.

Experimental

All reactions that required anhydrous conditions were carried by standard procedures under nitrogen atmosphere. Commercially available reagents from Alfa Aesar and Aldrich were used as received. The solvents were dried by distillation over the appropriate drying reagents. ^{1}H NMR spectra were recorded on commercial instruments (400 MHz). Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t =triplet, q = quartet, m = multiplet), coupling constants (Hz), integration and assignment. ^{13}C NMR spectra were collected on commercial instruments (101 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0). Mass spectra were recorded on ThermoQuest Finnigan LCQ^{DECA} system equipped with an ESI source.

Typical procedural for preparation of 7

To a 10 mL tube with a magnetic stirring bar were sequentially added the aldimines of glycine imine schiff base **4** (0.06 mmol, 1.0 equiv), sulfonyl imine **5** (0.066 mmol , 1.1 equiv), 40 mg 4A molecular sieve and 15 mol% of catalyst **6g** in 1.5 mL ice EA under dry nitrogen at 0°C for 12 h.. When the

reaction completed (monitored by TLC), the obtained mixture was purified directly by flash chromatography on silica gel to afford **7** for H-NMR (confirmed the dr). The ee of the major isomer was determined by chiral HPLC analysis. (**Note:** The dr of some **7** was determined by HPLC analysis.), characterizations and analysis of product could be found in the supporting information.

Acknowledgements

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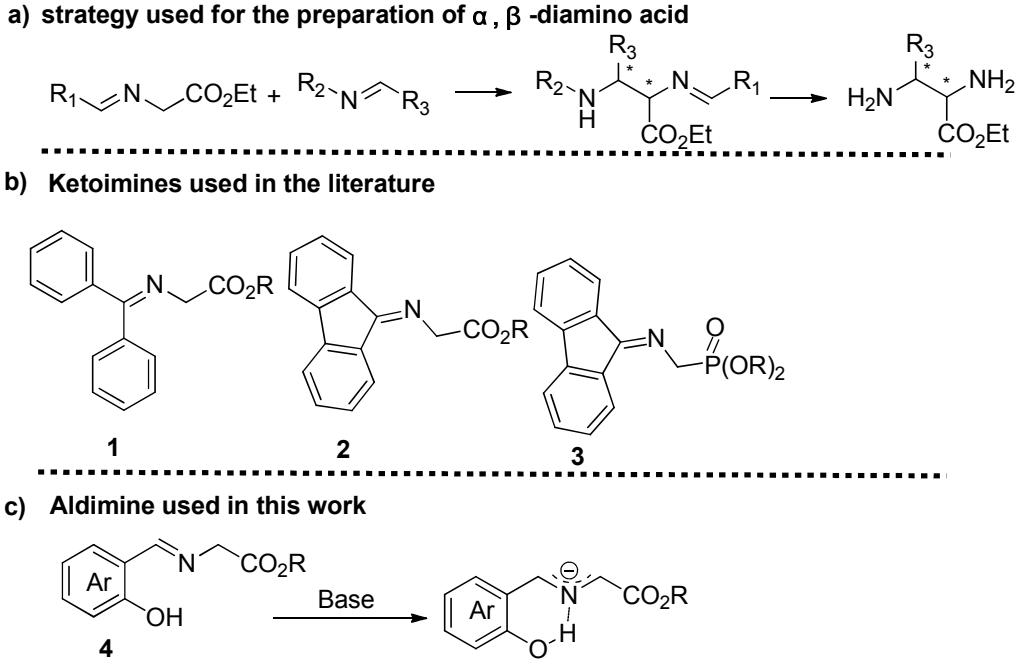
Scheme 1 strategy used for the preparation of α, β-diamino acid



Scheme 2 Chiral guanidines used in this study.

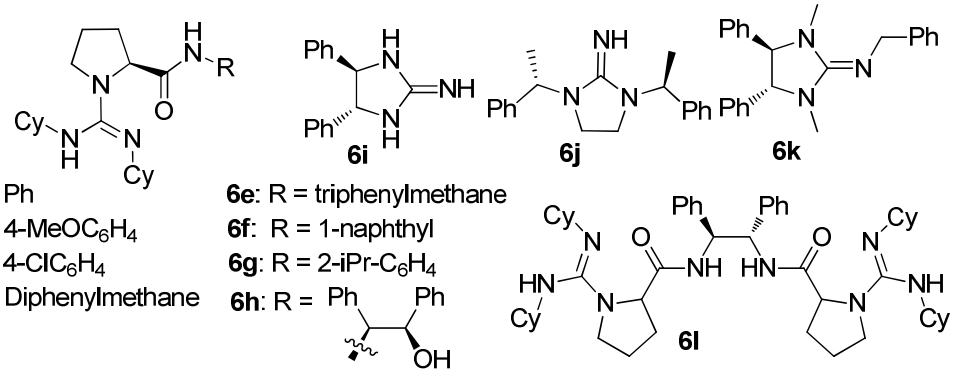
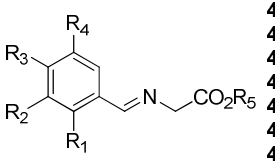
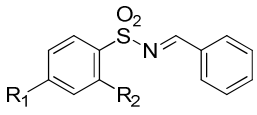


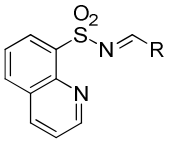
Figure 1 Substrates and products structures



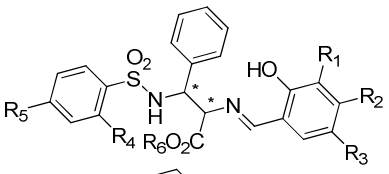
	R_1	R_2	R_3	R_4	R_5
4a	OH	H	H	H	Et
4a'	H	H	H	H	Et
4b	OH	H	OCH_3	H	Et
4c	OH	Br	H	Br	Et
4d	OH	t-Bu	H	t-Bu	Et
4e	OH	H	$N(Et)_2$	H	Et
4f	OH	H	OH	H	Et
4g	OH	t-Bu	H	t-Bu	Me
4h	OH	t-Bu	H	t-Bu	t-Bu



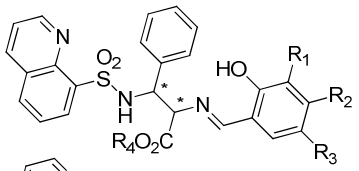
	R_1	R_2
5a	Me	H
5b	H	Me
5c	OCH_3	H



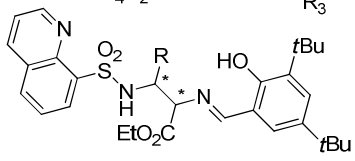
	R
5d	Phenyl
5e	4-methyl phenyl
5f	4-methoxy phenyl
5g	4-chloro phenyl
5h	2-methyl phenyl
5i	thiophen-2-yl
5j	naphthalen-1-yl



	R_1	R_2	R_3	R_4	R_5	R_6
7a	H	H	H	H	Me	Et
7b	H	H	H	Me	H	Et
7c	H	OCH_3	H	Me	H	Et
7d	Br	H	Br	Me	H	Et
7e	t-Bu	H	t-Bu	Me	H	Et
7f	t-Bu	H	t-Bu	H	OCH_3	Et



	R_1	R_2	R_3	R_4
7g	t-Bu	H	t-Bu	Et
7h	t-Bu	H	t-Bu	Me
7i	t-Bu	H	t-Bu	t-Bu



	R
7j	4-methyl phenyl
7k	4-methoxy phenyl
7l	4-chloro phenyl
7m	2-methyl phenyl
7n	thiophen-2-yl
7o	naphthalen-1-yl

Table 1 Initial screening of Mannich reaction[a].

Entry	Substrate	Cat.	Yield[%][b]	Anti/syn[c]	ee[%][d]
1	**4a**,**5a**	DABCO	**7a**: 30	-	-
2	**4a**,**5a**	Quinine	**7a**: 24	13:1	15/4
3	**4a**,**5a**	Cinchonine	**7a**: 17	11:1	26/6
4	**4a**,**5a**	TMG	**7a**: 91	-	-
5	**4a'**,**5b**	TMG	n.d	-	-
6	**4a**,**5a**	**6a**	**7a**: 85	1.2:1	3/0
7	**4a**,**5b**	**6a**	**7b**: 84	1.8:1	5/7

[a] Unless otherwise noted, the reaction was carried out with 0.06 mmol **1a** or **4a**, 0.066 mmol **5a** or **5b**, Molecular sieves 4 Å (40 mg) and 20 mol% catalyst in toluene (1.0 mL) at 25 ℃ for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Corresponding ee of anti/syn.

Table 2 Catalytic Mannich-type reactions of **5b**[a]

Entry	Substrate	Cat.	Yield[%][b]	Anti/syn[c]	ee[%][d]
1	**4a**,**5b**	**6a**	**7a**: 87	1.7:1	11/5
2	**4b**,**5b**	**6a**	**7c**: 90	5.5:1	7/2
3	**4c**,**5b**	**6a**	**7d**: 78	5:1	8/0
4	**4d**,**5b**	**6a**	**7e**: 87	2.6:1	16/4
5	**4e**,**5b**	**6a**	n.d		
6	**4f**,**5b**	**6a**	n.d		

[a] Unless otherwise noted, the reaction was carried out with 0.06 mmol **4**, 0.066 mmol **5b**, molecular sieves 4 Å (40 mg) and 15 mol% catalyst in EA (1.0 mL) at 0℃ for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Corresponding ee of anti/syn.

Table 3 Catalytic Mannich-type template reactions [a]

Entry	Substrate	Cat.	Yield[%][b]	Anti/syn[c]	ee[%][d]
1	**4d**,**5b**	**6b**	**7e**: 82	1.8:1	10/12
2	**4d**,**5b**	**6c**	**7e**: 50	1.3:1	14/16
3	**4d**,**5b**	**6d**	**7e**: 79	1.2:1	22/14
4	**4d**,**5b**	**6e**	**7e**: 76	5:1	0/0
5	**4d**,**5b**	**6f**	**7e**: 76	2.6:1	16/10
6	**4d**,**5b**	**6h**	**7e**: 81	2.8:1	13/17

[a] Unless otherwise noted, the reaction was carried out with 0.06 mmol **4d**, 0.066 mmol **5b**，molecular sieves 4 Å (40 mg) and 15 mol% catalyst in EA (1.0 mL) at 0℃ for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Corresponding ee of anti/syn.

Table 4 Influence of imine protecting group and imine ester[a]

Entry	Substrate	Cat.	Yield[%][b]	Anti/syn[c]	ee[%][d]
1	**4d**,**5c**	**6d**	**7f**: 90	2:1	14/20
2	**4d**,**5d**	**6d**	**7g**: 78	1.6:1	51/47
3	**4g**,**5d**	**6d**	**7h**: 87	1.5:1	46/44
4	**4h**,**5b**	**6d**	**7i**: 76	1.5:1	42/26

[a] Unless otherwise noted, the reaction was carried out with 0.06 mmol **4**, 0.066 mmol **5**，molecular sieves 4 Å (40 mg) and 15 mol% **6d** in EA (1.0 mL) at 0 ℃ for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Corresponding ee of anti/syn.

Table 5 Optimization of the reaction catalyst [a]

Entry	Substrate	Cat.	Yield[%][b]	Anti/syn[c]	ee[%][d]
1	**4d**,**5d**	**6b**	**7g**: 92	1.8:1	44/28
2	**4d**,**5d**	**6d**	**7g**: 84	1.7:1	51/47
3	**4d**,**5d**	**6e**	**7g**: 82	1.2:1	37/46
4	**4d**,**5d**	**6g**	**7g**: 88	1.8:1	54/47
5	**4d**,**5d**	**6i**	**7g**: 50	1.9:1	9/0
6	**4d**,**5d**	**6j**	**7g**: 52	1.1:1	-6/4
7	**4d**,**5d**	**6k**	**7g**: 45	1.3:1	5/2
8	**4d**,**5d**	**6l**	**7g**: 71	3:1	10/0

[a] Unless otherwise noted, the reaction was carried out with 0.06 mmol **4d**, 0.066 mmol **5d**，molecular sieves 4 Å (40 mg) and 15 mol% catalyst in EA (1.0 mL) at 25 ℃ for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Corresponding ee of anti/syn.

Table 6 Generality of the reaction with various sulfonyl imines[a]

Entry	Substrate	Cat.	Yield[%][b]	Anti/syn[c]	ee[%][d]
1	**4d**,**5e**	**6d**	**7j**: 88	1.8:1	55/39
2	**4d**,**5f**	**6d**	**7k**: 83	1.9:1	55/44
3	**4d**,**5g**	**6d**	**7l**: 91	1.7:1	46/47
4	**4d**,**5h**	**6d**	**7m**: 87	2.1:1	65/60
5	**4d**,**5i**	**6d**	**7n**: 90	1.7:1	61/24
6	**4d**,**5j**	**6d**	**7o**: 82	2.0:1	58/44

[a] Unless otherwise noted, the reaction was carried out with 0.06 mmol **4d**, 0.066 mmol **5**，molecular sieves 4 Å (40 mg) and 15 mol% **6d** in EA (1.0 mL) at 0℃ for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Corresponding ee of anti/syn.