



AgOAc-catalyzed asymmetric amination of glycine Schiff bases with azodicarboxylates

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ABSTRACT

Asymmetric amination of glycine Schiff bases with azodicarboxylates has been developed with high yields and up to 98% ee using AgOAc/Taniaphos complex as the catalyst.

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The stereoselective construction of the C–N bonds is an important task in organic synthesis and catalysis. The direct catalytic enantioselective amination has attracted much attention in this rapidly growing area due to its simple experimental procedures and easily available starting materials.¹ In 1997, the first catalytic asymmetric α -amination of carbonyl compounds using azodicarboxylates as the nitrogen source was developed by Evans, who employed a chiral magnesium bis(sulfonamide) complex as the catalyst.² Subsequently, much progress has been achieved in the asymmetric α -amination of aldehydes,³ ketones,⁴ α -keto esters,⁵ β -keto esters,⁶ α -cyano esters,⁷ and other compounds.⁸ However, little attention has been paid to the enantioselective α -amination of glycine Schiff bases to provide optically active α,α -diamino carbonyl compounds and their derivatives, which are of great synthetic potential in the preparation of pharmaceuticals and agrochemicals.

Recently, we have developed efficient bifunctional AgOAc-catalyzed asymmetric cycloaddition and Mannich reaction with high activities and excellent stereoselectivities, in which reactions the enolization of carbonyl compound was promoted by acetate, and extra base was not necessary for achieving high yields or good stereoselectivities.^{9,10} In continuation of our research on bifunctional AgOAc-catalyzed asymmetric reactions, we envisioned the possibility of applying the same strategy to the electrophilic amination of carbonyl compounds using azodicarboxylates as the Michael acceptors. Herein, we described AgOAc-catalyzed asymmetric ami-

nation of glycine Schiff bases with azodicarboxylates achieving high yields and excellent enantioselectivities.

In our initial investigation, we found AgOAc/**L1** system could efficiently catalyze the amination of glycine Schiff base **2a** and azodicarboxylate **1a** with high activity and moderate enantioselectivity (50% ee) in THF (Table 1, entry 1). In order to obtain high selectivity of the product, the effect of ligands was evaluated (entries 1–10). Taniaphos (**L6**) emerged as the best ligand (92% ee, entry 6) for this asymmetric amination compared to other ferrocenyl-derived ligands (entries 1–5). Some commercially available ligands had also been explored in the enantioselective amination of **2a**. However, no satisfied results were obtained (entries 7–10). The influence of solvents was studied using **L6** as the ligand, a better enantioselectivity was obtained in toluene at 0 °C (entry 13). Decreasing the reaction temperature dramatically deteriorated the catalytic activity, but slightly improved the enantioselectivity (entry 14). Thus, the optimal conditions for this asymmetric amination reaction are AgOAc/**L6**/toluene/–25 °C.

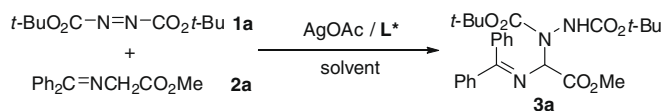
Having established the optimal conditions, the generality of the AgOAc-catalyzed asymmetric amination reaction was investigated (Table 2). This investigation revealed the enantioselectivity of this reaction strongly depended on the steric property of both substrates. The selectivity decreased (from 98% ee to 75% ee) with increasing the steric hindrance of the substituents in glycine Schiff bases **2** (entries 1–4). In contrast, increasing the steric bulkiness of the substituents in azodicarboxylates **1** was good for improving the enantioselectivity (entries 1, 5–7). The best stereoselectivities (98% ee) were obtained in the asymmetric amination reaction of di-*tert*-butyl azodicarboxylate **1a** with benzophenone imine glycine

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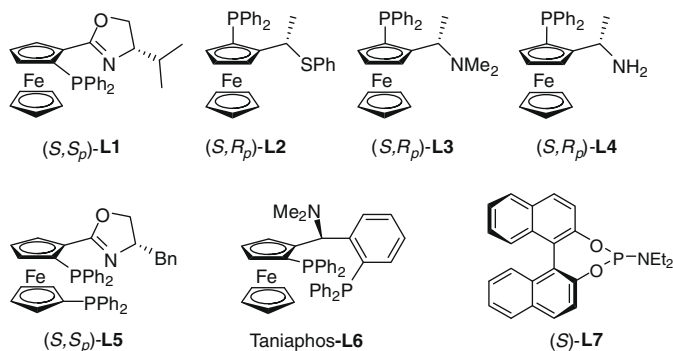
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Table 1

Optimization of the reaction conditions for AgOAc-catalyzed asymmetric amination of glycine Schiff bases with azodicarboxylates



Entry ^a	Ligand	Solvent	Time (h)	Yield ^b (%)	ee ^c (%)
1	L1	THF	1.5	95	50
2	L2	THF	1.5	99	58
3	L3	THF	1.5	99	14
4	L4	THF	1.5	98	69
5	L5	THF	1.5	95	7
6	L6	THF	4	98	92
7	L7	THF	1.5	98	41
8	(R)-SynPhos	THF	1.5	95	12
9	(R,R)-Me-DuPhos	THF	1.5	98	13
10	(S)-Mop	THF	1.5	94	20
11	L6	Et ₂ O	1.5	95	86
12	L6	CH ₂ Cl ₂	45	97	65
13	L6	Toluene	3.5	99	94
14 ^d	L6	Toluene	22	95	98



^a Conditions: **2a** (0.23 mmol), **1a** (1.2 equiv), AgOAc (3 mol %), ligand (3.3 mol %), concentration (0.12 M), 0 °C.

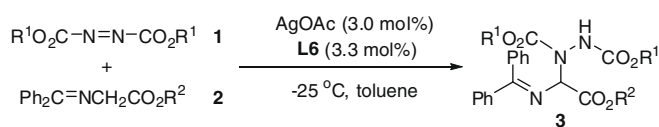
^b Isolated yields based on **2a**.

^c Determined by HPLC.

^d At -25 °C.

Table 2

AgOAc-catalyzed asymmetric amination of glycine Schiff bases with azodicarboxylates^{11,12}

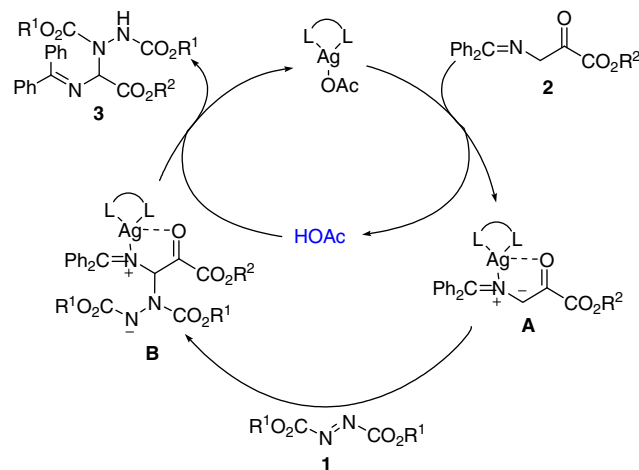


Entry ^a	R ¹ /R ² in 1 and 2	Time (h)	Yield ^b (%)	ee ^c (%)
1	<i>t</i> -Bu/Me	22	95 (3a)	98
2	<i>t</i> -Bu/Et	21	98 (3b)	98
3	<i>t</i> -Bu/4-BrC ₆ H ₄ CH ₂	6	95 (3c)	96
4	<i>t</i> -Bu/ <i>t</i> -Bu	51	93 (3d)	75
5	<i>i</i> -Pr/Me	16	98 (3e)	92
6	Bn/Me	16	98 (3f)	76
7	Et/Me	21	98 (3g)	75

^a Conditions: **2** (0.23 mmol), **1** (1.2 equiv), AgOAc (3 mol %), ligand (3.3 mol %), toluene (2 mL), -25 °C.

^b Isolated yields based on **2**.

^c Determined by HPLC.

**Scheme 1.** Proposed mechanism for AgOAc-catalyzed asymmetric amination.

methyl ester or benzophenone imine glycine ethyl ester (entries 1 and 2).

A possible mechanism on AgOAc-catalyzed asymmetric amination is proposed. The first step in the asymmetric amination is the deprotonation of glycine Schiff bases **2** promoted by acetate to form reactive metal-bound azomethine ylide dipole **A** and acetic acid (Scheme 1). Subsequently **A** undergoes enantioselective addition to azodicarboxylates **1** to produce intermediate **B**, which reacts with the above acetate acid to obtain the amination products **3** and to regenerate the catalyst.

In conclusion, we have demonstrated an effective AgOAc-catalyzed asymmetric amination of glycine Schiff bases with azodicarboxylates with high yields and with up to 98% ee, which provided an easy access to optically active α,α -diamino carbonyl compounds from simple and easily available starting materials.

Further investigations on the assignment of the absolute configuration of the products and AgOAc-catalyzed other asymmetric amination reactions are currently in progress, and related results will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.124.

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11. General procedure for the AgOAc-catalyzed asymmetric amination reactions (Table 2, entry 1): Ligand (0.0075 mmol) and AgOAc (1.2 mg, 0.007 mmol) were placed in a dried Schlenk tube under a nitrogen atmosphere and toluene (2.0 mL) was added. The mixture was stirred at room temperature for about 0.5 h. After it was cooled to the indicated temperature, benzophenone imine glycine methyl ester (0.23 mmol) was added followed by diethyl azodicarboxylate (0.276 mmol). Progress of the Ag-catalyzed amination reaction was typically monitored by TLC analysis. Upon consumption of the limiting reagent, the pure adducts were purified by column chromatography on silica gel.
12. Selected physical and spectral data for **3a**: Colorless oil, 98% ee, $[\alpha]_D^{28}$ –68.7 (c 1.92, CH₂Cl₂); *R*_f 0.32 (hexane/EtOAc, 5/1); HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90/10, 1.0 mL/min, detector: 254 nm, 30 °C) *t*_R = 10.1 (major) and 11.0 min (minor); ¹H NMR (400 MHz, DMSO-*d*₆, 60 °C): δ 8.89 (br s, 1H), 7.62–7.60 (m, 2H), 7.52–7.44 (m, 4H), 7.39–7.35 (m, 2H), 7.17 (br s, 2H), 5.71 (br s, 1H), 3.61 (s, 3H), 1.38 (s, 9H), 1.33 (s, 9H); ¹³C NMR (100 MHz, DMSO-*d*₆, 60 °C): δ 170.9, 167.9, 154.8, 153.5, 138.7, 135.3, 130.8, 129.0, 128.7, 128.6, 127.9, 127.3, 80.7, 79.1, 74.2, 52.1, 27.9, 27.7; HRMS calculated for C₂₆H₃₃N₃O₆ 484.2448, found 484.2455.