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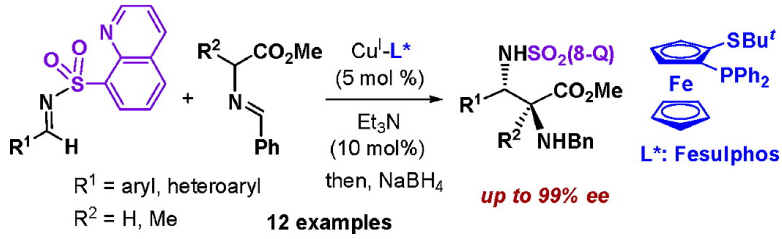
J. Am. Chem. Soc., **2008**, 130 (48), 16150-16151 • DOI: 10.1021/ja807583n • Publication Date (Web): 12 November 2008



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Direct Mannich Reaction of Glycinate Schiff Bases with *N*-(8-Quinolyl)sulfonyl Imines: A Catalytic Asymmetric Approach to *anti*-α,*β*-Diamino Esters

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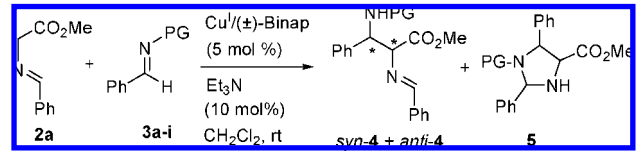
The wide-range significance of optically active α,*β*-diamino acids as key structural components in bioactive compounds, as well as valuable synthetic intermediates,[1] has prompted the need for new general and efficient procedures for the asymmetric synthesis of this simple, yet polyfunctional, motif. Despite the catalytic asymmetric direct Mannich-type reaction of glycinate Schiff bases with imines being one of the most convergent routes for accessing this type of nonproteinogenic aminoacid derivatives,[1a] only a handful of protocols have been so far described in the literature.[2] Although high levels of *syn*-diastereoselectivity and enantiocontrol were achieved, this strategy had not been applied to the preparation of α,*β*-diaminoester derivatives with *anti*-configuration[3] or those with an α-tetrasubstituted carbon stereocenter. To date, these limitations have been overcome with indirect approaches, mainly the catalytic asymmetric aza-Henry reaction, either between nitro compounds and α-iminoesters[4] or between α-nitro acetates and imines,[5,6] upon subsequent selective reduction of the nitro to amino group. Direct reaction of an α-isothiocyanate *N*-acyl oxazolidine with *N*-tosyl imines has also been reported to provide protected *anti*-α,*β*-diamino acids.[7] As a useful complementary method, herein we describe a catalytic asymmetric approach to orthogonally protected *anti*-α,*β*-diamino esters, including those with a tetrasubstituted carbon at C-α,[8] relying on the direct Mannich reaction of glycinate Schiff bases. The combined use of a Cu^{I} complex of the commercially available Fesulphos ligand (**1**)[9] as catalyst and readily available 8-quinolylsulfonyl-protected aldimines as substrates is key to attaining good reactivity, a broad scope, and high diastereo- and enantiocontrol.

Facing the challenge of achieving high diastereoselection, we first examined the influence of the protecting group at the iminic nitrogen in the Cu^{I}/(±)-Binap-catalyzed model reaction of *N*-benzylideneglycine methyl ester (**2a**) with different imines of benzaldehyde (**3a**−**i**) in the presence of Et$_3$N (10 mol%) as base (Table 1). Initial results were rather disappointing since the N-Boc-protected imine **3a**, as well as the *para*-substituted arylsulfonyl imines **3b**−**d** and the heteroarylsulfonyl[10] derivatives **3e**[9a,b,10b] and **3f**,[10a,c] led to mixtures of (*syn*+*anti*)-**4** with very poor diastereoselectivity (de = 0−20%, entries 1−6). The competitive formation of the 1,3-dipolar cycloaddition imidazolidine product **5** (as mixture of diastereomers) was also observed with the sulfonyl imines **3b**−**f**. However, the bulkier *o*-nosyl imine **3g** led cleanly to a mixture of **4g** with encouraging *anti*-diastereocontrol (*syn*/*anti* = 30:70, entry 7). Moreover, an excellent level of *anti*-diastereoselection was attained with the 8-quinolylsulfonyl-protected imine **3h**[10a,c] (8:92 mixture of *syn*/*anti*-**4h**, entry 8). Interestingly, the sterically similar 1-naphthylsulfonyl imine **3i** afforded a complex mixture of four products under identical conditions (entry 9), showing that the presence of the nitrogen of the 8-quinolyl moiety is crucial for good *anti*-diastereocontrol.

Asymmetric catalysis was then investigated by screening a number of well established chiral ligands (5 mol%) in the reaction of **2a** with imine **3h** under the previous conditions. For better chiral

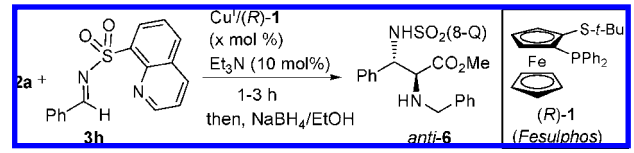
Table 1. Influence of Imine Protecting Group in the Cu^{I}-Catalyzed Mannich Reaction of Glycinate Schiff Base **2a** with Imines **3a**−**i**[a]



entry	PG (imine)	time (h)	*syn*-**4**/*anti*-**4**/**5**[b]
1	Boc (**3a**)	6	60:40:--[c]
2	Ts (**3b**)	3	43:52:5[c,d]
3	*p*-Nosyl (**3c**)	5	38:37:25[c,d]
4	4-OMe(C$_6$H$_4$)SO$_2$- (**3d**)	2	40:40:20[c,d]
5	(2-Thienyl)SO$_2$- (**3e**)	3	17:48:35[c,d,c]
6	(2-Pyridyl)SO$_2$- (**3f**)	2	35:35:30[c,d]
7	*o*-Nosyl (**3g**)	5	30:70:--
8	**(8-Quinolyl)SO$_2$- (3h)**	**2**	**8:92:--**
9	(1-Naphthyl)SO$_2$- (**3i**)	2	*complex mixture*

[a] Conditions: **2a** (1 equiv), **3** (1.1 equiv), Cu(CH$_3$CN)$_4$ClO$_4$ (5 mol%), (±)-Binap (5 mol%), Et$_3$N (10 mol%), CH$_2$Cl$_2$, rt. [b] By NMR from the crude reaction mixture. [c] *syn*/*anti* configuration not established. [d] Imidazolines **5** were obtained as diastereomeric mixtures.

Table 2. Cu^{I}/Fesulphos-Catalyzed Enantioselective Direct Mannich Reaction of Iminoester **2a** with Sulfonyl Imine **3h**



entry	Cu^{I} (x mol%)	solvent	*t* (°C)	*anti*/*syn*[a]	yield (%)[b]	ee (%)[c]
1	Cu(CH$_3$CN)$_4$ClO$_4$ (5)	CH$_2$Cl$_2$	rt	92:8	79	91
2	CuOTf (5)	CH$_2$Cl$_2$	rt	94:6	77	91
3	Cu(CH$_3$CN)$_4$PF$_6$ (5)	CH$_2$Cl$_2$	rt	93:7	85	92
4	Cu(CH$_3$CN)$_4$PF$_6$ (5)	CH$_3$CN	rt	91:9	62	90
5	Cu(CH$_3$CN)$_4$PF$_6$ (5)	toluene	rt	94:6	79	91
6	Cu(CH$_3$CN)$_4$PF$_6$ (5)	THF	rt	96:4	80	92
7	**Cu(CH$_3$CN)$_4$PF$_6$ (5)**	**THF**	**−40**	**99:1**	**74**	**96**
8	**Cu(CH$_3$CN)$_4$PF$_6$ (5)**	**THF**	**−78**	**99:1**	**73**	**96**
9	Cu(CH$_3$CN)$_4$PF$_6$ (3)	THF	−40	98:2	71	91
10[d]	Cu(CH$_3$CN)$_4$PF$_6$ (1)	THF	rt	91:9	35	--

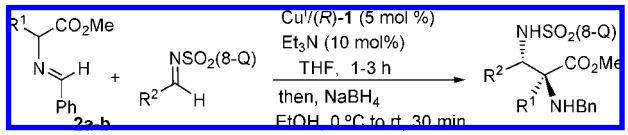
[a] By NMR and/or HPLC. [b] Isolated yield. [c] By chiral HPLC. [d] 12 h reaction time.

HPLC separation of products, in this study the resulting α-imino ester **4h** was reduced to its α-benzylamino derivative *anti*-**6** upon addition of NaBH$_4$ (1.2 equiv)/EtOH to the crude reaction mixture. Among 12 tested ligands,[11] only Fesulphos (**1**)[9,12] led to a high *anti*-diastereo- (*anti*/*syn* = 92:8) and enantioselectivity (91% ee, Table 2, entry 1). Further refinement of reaction conditions by exploring other solvents and copper salts led to improved catalyst performance (entries 2−8). The highest diastereo- (*anti*/*syn* = 99:1) and enantiocontrol (96% ee) were attained in THF at −40 or −78 °C with Cu(CH$_3$CN)$_4$PF$_6$/(*R*)-**1** (5 mol%, entries 7 and 8).

10.1021/ja807583n CCC: $40.75

Catalyst loading could be reduced to 3 mol% while maintaining high reactivity and stereocontrol (91% ee, entry 9). Further decrease to 1 mol% led to a dramatic drop of reactivity (entry 10).

Table 3. Structural Variations at the α-iminoester and Sulfonyl Imine[a]

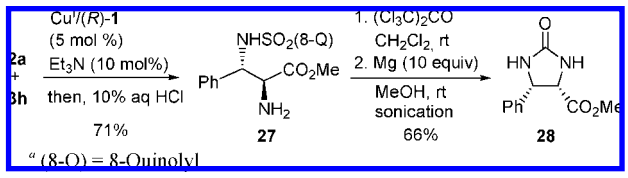


entry	R^1	R^2 (sulfonyl imine)	product	*anti*/*syn*[b]	yield (%)[c]	ee (%)[d]
1[e]	H	4-OMeC$_6$H$_4$ (**7h**)	**16**	98:2	72	95
2[e]	H	4-ClC$_6$H$_4$ (**8h**)	**17**	98:2	92	93
3[f]	H	2-MeC$_6$H$_4$ (**9h**)	**18**	98:2	80	99
4[e]	H	2-Naph (**10h**)	**19**	97:3	75	94
5[e]	H	2-Furyl (**11h**)	**20**	95:5	71	85
6[e]	H	3-Pyridyl (**12h**)	**21**	98:2	72	90
7[e]	H	Cinnamyl (**13h**)	**22**	85:15	64	25
8[e]	Me	Ph (**3h**)	**23**	90:10	55	89
9[e]	Me	4-ClC$_6$H$_4$ (**8h**)	**24**	97:3	65	87
10[e]	Me	2-thienyl (**14h**)	**25**	94:6	52	96
11[e]	Me	2-BrC$_6$H$_4$ (**15h**)	**26**	89:11	61	92

[a] (8-Q) = 8-Quinolyl; Cu^I = $Cu(CH_3CN)_4PF_6$. [b] By NMR and/or HPLC. [c] Isolated yield. [d] By chiral HPLC. [e] Reaction at −78 °C. [f] Reaction at −40 °C.

Table 3 summarizes the evaluation of the scope under the optimized conditions. A survey of electronically and sterically varied aryl and heteroaryl *N*-(8-quinolyl)sulfonyl aldimines[13] revealed a high degree of stereochemical fidelity in their reaction with glycinate **2a**, showing excellent diastereoselectivity (95:5−98:2) and ≥90% ee in most cases[14] (entries 1−6, products **16**−**21**). The α,β-unsaturated imine **13h**, from cinnamaldeyde, was the only exception to this trend, providing moderate diastereocontrol and very low asymmetric induction (25% ee, entry 7). Pleasingly, the reaction was equally successful with the α-substituted imino ester derived from L-alanine **2b**, a kind of nucleophile not yet reported in this reaction even though it generates α,β-diaminoacid derivatives tetrasubstituted at C-α. In the four tested reactions (entries 8−11), **2b** provided the corresponding Mannich product (**23**−**26**) with similar diastereo- and enantioselectivity (87−96% ee) to that observed from **2a**, albeit the chemical yields were somewhat lower (52−65%). The relative and absolute configuration of the Mannich products was established by X-ray diffraction analysis of a crystal of pure *anti*-**6**[15] (>99% ee) obtained by recrystallization (from CH_2Cl_2−hexane) of a 98:2 *anti*/*syn* mixture formed in the reaction of **2a** with imine **3h** (2 mmol scale) using 3 mol% of Cu^I−Fesulphos.

Scheme 1. Orthogonal Deprotection of the Amino Groups and Chemical Correlation[a]



Scheme 1 exemplifies the sequential amino deprotection of the α,β-diaminoester adducts under mild conditions. The optically active amino ester **27** was obtained in one pot from the reaction of **2a** with **3h** upon smooth acid hydrolysis of the crude resulting imino ester (2*S*,3*S*)-*anti*-**4h**. The transformation of **27** into the known enantiopure urea **28**,[16] confirming otherwise the stereochemical assignment established by X-ray diffraction analysis,[15] was achieved in good yield by treatment with triphosgene (CH_2Cl_2, 0 °C to rt, 2 h) followed by easy cleavage of the 8-quinolylsulfonyl group with an excess of Mg turnings in MeOH, this latter step being accelerated under sonication.

In summary, we have developed a route to protected *anti*-α,β-diamino esters compatible with the generation of a tetrasubstituted carbon at C-α. The choice of Fesulphos−Cu^I as catalyst and *N*-(8-quinolyl)sulfonyl as protecting group at the imine substrate are the key elements for achieving efficient control of both diastereo- and enantioselectivity (typically ≥90% ee). Further investigations to understand the exact role of the 8-quinolyl group are underway.

Acknowledgment. This work was supported by the Ministerio de Ciencia e Innovación (MICINN, CTQ2006-01121) and UAM/Consejería de Educación de la Comunidad Autónoma de Madrid (CCG07-UAM/PPQ-1799). J.H.T. thanks the MICINN for a predoctoral fellowship.

Supporting Information Available: Experimental procedures and characterization data of new compounds, copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a review on synthesis and biological significance of α,β-diamino acids, see: (a) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167. Review on vicinal diamines: (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

(2) (a) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583. (b) Ooi, T.; Kameda, M.; Fujii, J.-i.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397. (c) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564. (d) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 794. (e) Kobayashi, S.; Yazaki, R.; Seki, K.; Yamashita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 5613.

(3) During the reviewing process of this paper, a *syn*/*anti* diastereoselective switchable asymmetric Mannich reaction of glycinate derivatives with imines was reported: Yan, X.-X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X.-L.; Wu, Y.-D. *J. Am. Chem. Soc.* **2008**, *130*, 14362.

(4) (a) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (b) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731.

(5) (a) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466. (b) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (c) Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 10878. (d) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866. (e) Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 8094.

(6) For the aza-Henry reaction between α-nitro acetates and α-imino esters, see: Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.

(7) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Köhn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632.

(8) For reviews on the importance of α,α-disubstituted α-aminoacids, see: (a) Cativiela, C.; Díaz de Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (b) Ohfune, Y.; Shinada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115.

(9) For recent applications of Fesulphos in asymmetric catalysis, see: (a) Salvador González, A.; Gómez Arrayás, R.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 2977. (b) García Mancheño, O.; Gómez Arrayás, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 10294. (c) Salvador González, A.; Rogríguez Rivero, M.; Gómez Arrayás, R.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335. (d) López-Perez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084.

(10) For some recent examples on the use of heteroarylsulfonyl imines in asymmetric catalysis, see: (a) Esquivias, J.; Goméz-Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 1480. (b) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 9588. (c) Nakamura, S.; Nakashima, H.; Sugimoto, H.; Sano, H.; Hattori, M.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2008**, *14*, 2145. (d) Nakamura, S.; Nakashima, H.; Yamamura, A.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1209. and refs 9a−c.

(11) See Supporting Information for the results with other chiral ligands.

(12) For 1,3-dipolar cycloaddition of azomethine ylides catalyzed by Fesulphos complexes, see: (a) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (b) Cabrera, S.; Gómez Arrayás, R.; Martín-Matute, B.; Cossío, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587, and ref 9d.

(13) Aliphatic imines were not explored since we have not succeeded so far in developing a method for the isolation of this more labile type of imines.

(14) See Supporting Information for a tentative stereochemical model accounting for the observed enantioselectivity and *anti*-diastereocontrol.

(15) See Supporting Information for X-ray diffraction data of *anti*-**6**.

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

JA807583N