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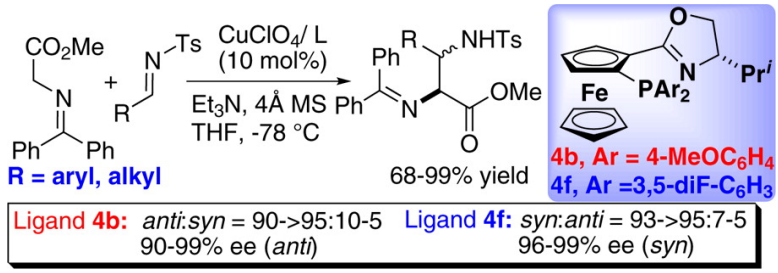

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Highly Diastereoselective Switchable Enantioselective Mannich Reaction of Glycine Derivatives with Imines

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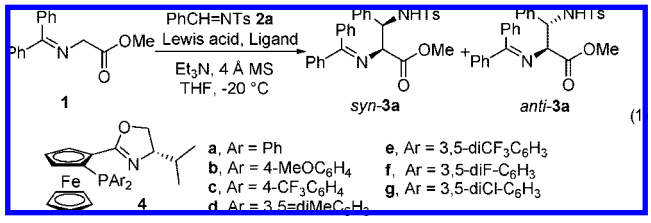
Chiral α,β-diamino acid derivatives are an important class of compounds because of their biological activities and their usefulness in organic synthesis.[1] Many synthetic approaches have been developed for them, as exemplified by an assemblage employing asymmetric Mannich type reaction of glycine derivatives with imines and nitro compounds under metallo-[2] and organocatalysis.[3] The chiral quarternary carbon center at the α-position was also established.[4] However, only a few reports realized both diastereo- and enantioselectivities and no paper dealt with the tuning of diastereoselectivity. In some cases the substrates were limited. Thus, challenges still remain regarding diastereo- and enantioselectivities and/or substrate scope for the reaction. On the other hand, tuning of diastereoselectivity by using different approaches have been well documented;[5,6] few reports accomplished it by changing the electronic factor of the ligand.[7,8] In the studies of chiral ligands in asymmetric catalysis,[9] we found a dramatic effect of the electronic property of ligands on the switch of regio- and diastereoselectivities in the Heck reaction and 1,3-dipolar cycloaddition.[10] Here we report our preliminary results showing that the same strategy can be applied to Lewis acid catalyzed Mannich reaction of glycine esters with both aromatic and aliphatic imines, achieving excellent diastereo- and enantioselectivities for both *syn* and *anti* products.

Initially, the reaction of glycine methyl ester **1** with *N*-tosyl imine **2a** was examined using different Lewis acids and ligand **4a**[11] (eq 1, Table 1). Reaction afforded α,β-diamino acid derivatives **3a** in favor of the *anti*-isomer in high yields using $CuClO_4$ (entry 1). Better diastereoselectivity was given using $Cu(OTf)_2$ than using AgOAc (entry 3 vs entry 2). Higher diastereo- and enantioselectivities were realized when the reaction proceeded at −78 °C (entry 4). THF was a better solvent over CH_2Cl_2, toluene, and Et_2O, leading to the best yield and diastereo- and enantioselectivities (not shown in Table 1).



In our previous work we have demonstrated that the diastereoselectivity is switchable via a change of the electronic factor of ligands **4b**−**e**.[10a] When they were tested for the current reaction, a dramatic change in diastereoselectivity was evident (Table 1). With ligand **4b** having an electron-donating methoxy group at the *para*-position of phenyl rings on the P atom, *anti*- and *syn*-**3a** in a ratio of 96:4 (99% ee for *anti*-**3a**) resulted (entry 5). A lower reaction temperature (−78 °C) favored the formation of the *anti*-product (entries 1 and 5 vs entries 4 and 6). On the other hand, a more *syn*-product was produced when ligand **4c** having an electron-withdrawing CF_3 group at the *para*-position of phenyl on the P atom was used (entry 7 vs entry 1). The amount of *syn*- and *anti*-products was almost equal when the ligand was **4d** with 3,5-diMeC_6H_3 on the P atom (entry 8). Finally, *syn*-**3a** in 99% ee became the major product (*syn*/*anti* ratio 91:9) in the reaction using ligand **4e** containing two strongly electron-withdrawing CF_3 groups at the 3,5-positions of phenyl rings (entry 9).

Table 1. Reaction of **1** with **2a** Using Different Ligands and Lewis Acids[a]

entry	ligand	Lewis acid	yield%[b]	*syn*/*anti*[c]	ee% (*syn*/*anti*)[d]
1	**4a**	$CuClO_4$	97	15:85	-/97
2	**4a**	AgOAc	93	47:53	Nd[f]
3	**4a**	$Cu(OTf)_2$	97	14:86	-/99
4[e]	**4a**	$CuClO_4$	93	8:92	-/99
5	**4b**	$CuClO_4$	96	12:88	-/99
6[e]	**4b**	$CuClO_4$	92	4:96	-/99
7	**4c**	$CuClO_4$	95	27:73	96/99
8	**4d**	$CuClO_4$	94	43:57	93/99
9	**4e**	$CuClO_4$	89	91:9	99/-
10[e]	**4e**	$CuClO_4$	19	94:6	98/-
11	**4f**	$CuClO_4$	96	91:9	96/-
12[e]	**4f**	$CuClO_4$	97	95:5	99/-
13	**4g**	$CuClO_4$	96	80:20	93/-

[a] Molar ratio of **1**/**2a**/ligand/Lewis acid/Et_3N = 1:1.2:11 mol%:10 mol%:10 mol%. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC. [e] Run at −78 °C. [f] Not determined.

Although the *syn*-selectivity was realized using ligand **4e**, the diastereoselectivity was moderate (*syn*/*anti* = 72:28) for electron-deficient aromatic imine **2f**. When the reaction proceeded at −78 °C the yields of **3f** decreased sharply (<20%). This was observed for several other substrates (see SI), indicating the reactivity of ligand **4e** was lower. To correlate the diastereoselectivity and to increase the catalytic activity, a computational study was performed with the density functional theory method B3LYP/6-31G*(Lanl2dz).[12] The complexes of **4**−Cu with the anion of iminoester **1** were fully optimized, and the structures adopt a distorted tetrahedral geometry (Figure 1B). As shown in Figure 1A, charge distribution analysis using electrostatic potential (ESP) calculations[13] indicated that the phenyl rings of the phosphine are more electron-deficient with 3,5-difluoro substitution in **4f** than 3,5-bis(trifluoromethy) substitution in **4e** and 3,5-dichloro substitution in **4g** (*a* in Figure 1A). Thus, ligand **4f** might lead to a better *syn*-selectivity than **4e** and **4g**. In addition, the calculated negative charge at the C_α (*b* in Figure 1A) of iminoester **1** is the least for the complex

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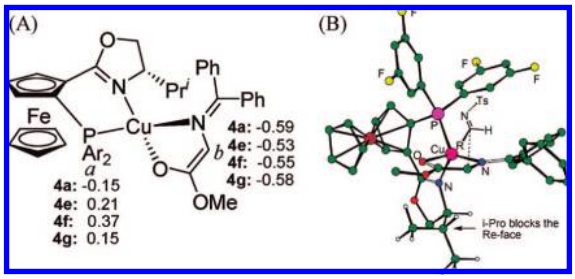


Figure 1. (A) ESP charge of different ligands: (a) total charge on the arene; (b) the charge on the iminoester anion. (B) Calculated structure of **4f**−Cu−**1** complex and the working model for the reaction with **2**.

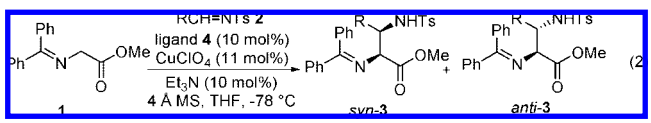
Table 2. Diastereoselectivity Switch of Mannich Reaction of Glycine Ester **1** with Imines **2**

		ligand **4b**		ligand **4f**	
entry	**2**, R	yield% (*syn*/*anti*)[a,b]	ee%[c]	yield% (*syn*/*anti*)[a,b]	ee%[c]
1	**a**, Ph	92 (4:96)	99	97 (>95: 5)	99
2	**b**, *m*-MeO-C_6H_4	92 (6:94)	96	98 (93:7)	99
3	**c**, *o*-Br-C_6H_4	96 (87:13)	93	94 (83:17)	91
4	**d**, *m*-Cl-C_6H_4	94 (5:>95)	99	92 (93:7)	98
5	**e**, *p*-Br-C_6H_4	95 (9:91)	99	96 (95:5)	98
6	**f**, *p*-NO_2-C_6H_4	97 (7:93)	97	99 (93:7)	97
7	**g**, 2-furan	99 (10:90)	94	98 (>95: 5)	96
8	**h**, Pr^i	76 (5:>95)	99	72 (>95: 5)	99
9	**i**, Cy	89 (5:>95)	97	87 (>95: 5)	99
10	**j**, Bu^n	70 (5:>95)	90	68 (>95: 5)	99

[a] Isolated yield. [b] The number in parentheses is the ratio of *syn*/*anti*, determined by ^{1}H NMR. [c] For major stereoisomer, determined by chiral HPLC.

of **4e**−Cu, indicating that **4f**−Cu and **4g**−Cu might be more reactive than **4e**−Cu. From such hints ligands **4f** and **4g** were synthesized and used in the reaction. Indeed, when **4f** was used, excellent yield and *syn*-selectivity were obtained for the reaction of glycine ester **1** and imine **2a** at −20 °C, giving *syn*-**3a** and *anti*-**3a** in a ratio of 91:9 (96% ee for *syn*-**3a**) (Table 1, entry 11). While **4g** was a ligand, a reduced *syn*-selectivity (*syn*/*anti* = 80:20, 93% ee for *syn*-**3a**) resulted (entry 13). When the reaction proceeded at −78 °C excellent yield and an increased *syn*-selectivity (*syn*/*anti* = 95:5) were observed (entry 12). Thus, ligand **4f** appeared to give both high *syn*-selectivity and high reactivity.

Using **4b** and **4f** as ligands, the Mannich reaction of glycine ester **1** with a wide range of imines **2b**−**j** was studied (eq 2, Table 2). Not only aromatic imines (entries 1−7) but also aliphatic imines (entries 8−10) were suitable for this reaction, generating α,*β*-diamino acid derivatives **3** in high yields, high diastereoselectivity, and excellent enantioselectivity. More importantly, a switching of diastereoselectivity was realized: Ligand **4b** gave high *anti*-selectivity while ligand **4f** gave excellent *syn*-selectivity for all substrates except for *ortho*-bromobenzalidene imine **2c**, for which the same diastereo- and enantioselectivities were obtained with both ligands **4b** and **4f** (entry 3). A detailed understanding of this special ortho-group effect is lacking.



The absolute configurations of the *syn*-**3e** and *anti*-**3e** were assigned as (2*S*,3*R*) and (2*S*,3*S*) by X-ray diffraction analysis. The same (2*S*) configuration for the two products indicates that the addition of *N*-Ts imine is on the *Si*-face of the Cu-bound iminoester anion with both **4b** and **4f** ligands. This can be understood based on the fact that the *Re*-face is blocked by the iso-propyl group of the ligand (Figure 1B). A working model is proposed to correlate the observed stereochemistry. Imine approaches the C_α anion center in a staggered conformation with the N atom pointing to Cu. The Ts group occupies the valley formed by the two arene groups if the two rings are electron-deficient in ligand **4f**, giving a (2*S*,3*R*) product (*Si*-face for imine). The imine attacks the C_α with its *Re*-face when the arene rings are electron-rich in ligand **4b**.

In summary, we have achieved the tuning of diastereoselectivity in the Mannich reaction of glycine ester with *N*-tosyl imines through electronic adjustment of the ligand. Either *syn*- or *anti*-diamino acid derivatives can be obtained in excellent diastereo- and enantioselectivities by ligand modification. Further investigations on the applications of the electronic factor in asymmetric catalysis are in progress.

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Supporting Information Available: Procedure for the synthesis of **4f**, general procedure for Cu-catalyzed Mannich reaction, NMR spectra and HPLC data for **3**, cif files of X-ray analysis of *syn*-**3e** and *anti*-**3e**. The coordinates of calculated structures. Complete ref 12. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews: Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.
(2) (a) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992. (b) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583. (c) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Köhn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632. (d) See also: Salter, M. M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 3533.
(3) (a) Ooi, T.; Kameda, M.; Fujii, J.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397. (b) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564. (c) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 794. (d) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466.
(4) (a) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (b) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866.
(5) For review: Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719.
(6) Examples of tuning diastereoselectivities in catalytic asymmetric reactions: (a) Liao, W.-W.; Li, K.; Tang, Y. *J. Am. Soc. Chem.* **2003**, *125*, 13030. (b) Tang, Y.; Huang, Y.-Z.; Dai, L.-X.; Chi, Z.-F.; Shi, L.-P. *J. Org. Chem.* **1996**, *61*, 5762. (c) Ye, S.; Yuan, L.; Huang, Z.-Z.; Tang, Y.; Dai, L.-X. *J. Org. Chem.* **2006**, *65*, 6257. (d) Evans, D. A.; MacMillan, D. W. C.; Campos, D. K. R. *J. Am. Soc. Chem.* **1997**, *119*, 10859. (e) Williams, J. T.; Bahia, P. S.; Snaith, J. S. *Org. Lett.* **2002**, *4*, 3727. (f) Weatherwax, A.; Abraham, C. J.; Lectka, T. *Org. Lett.* **2005**, *7*, 3461. (g) Lu, B. Z.; Senanayake, C.; Li, N.; Han, Z.; Bakale, R. P.; Wald, S. A. *Org. Lett.* **2005**, *7*, 2599. (h) Barluenga, J.; Alonso, J.; Fananas, F. J. *J. Am. Chem. Soc.* **2003**, *125*, 2610. (i) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (j) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979. (k) Huang, Z.-Z.; Kang, Y.-B.; Zhou, J.; Ye, M.-C.; Tang, Y. *Org. Lett.* **2004**, *6*, 1677.
(7) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064.
(8) For review: Flanagan, S. P.; Guiry, P. J. *J. Organomet. Chem.* **2006**, *691*, 2125.
(9) (a) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659. (b) Hou, X. L.; Wu, X. W.; Dai, L. X.; Cao, B. X.; Sun, J. *Chem. Commun.* **2000**, 1195. (c) Yan, X. X.; Liang, C. G.; Zhang, Y.; Hong, W.; Cao, B. X.; Dai, L. X.; Hou, X. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6544. (d) Zhang, K.; Peng, Q.; Hou, X. L.; Wu, Y. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1741. (e) Wu, W. Q.; Peng, Q.; Dong, D. X.; Hou, X. L.; Wu, Y. D. *J. Am. Chem. Soc.* **2008**, *130*, 9717.
(10) (a) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979. (b) Tu, T.; Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-C. *Chem.—Eur. J.* **2003**, *9*, 3073.
(11) Sammakia, T.; Stangeland, E. L. *J. Org. Chem.* **1997**, *62*, 6104.
(12) The calculations were performed with Gaussian 03 program: Frisch, M. J.; et al. *Gaussian 03*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2004.
(13) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.

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