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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 $\alpha_{,\beta}$ -diamino acid derivatives **3a** in favor of the anti-isomer in high yields using CuClO₄ (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 CH2Cl2, toluene, and Et2O, 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

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	Ndf
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	4 g	CuClO ₄	96	80:20	93/-

^a Molar ratio of 1/2a/ligand/Lewis acid/Et₃N = 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.

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 CF₃ group at the paraposition 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-diMeC₆H₃ 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 CF₃ groups at the 3,5-positions of phenyl rings (entry 9).

Although the syn-selectivity was realized using ligand 4e, the diastereoselectivity was moderate (syn/anti = 72:28) for electrondeficient 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) calculations¹³ 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 synselectivity 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 4)	ligand 4f		
entry	2 , R	yield% (<i>syn/anti</i>) ^{a,b}	ee% ^c	yield% (<i>syn/anti</i>) ^{a,b}	ee%c	
1	a, Ph	92 (4:96)	99	97 (>95: 5)	99	
2	b , <i>m</i> -MeO-C ₆ H ₄	92 (6:94)	96	98 (93:7)	99	
3	c , <i>o</i> -Br-C ₆ H ₄	96 (87:13)	93	94 (83:17)	91	
4	d , <i>m</i> -Cl-C ₆ H ₄	94 (5:>95)	99	92 (93:7)	98	
5	\mathbf{e} , <i>p</i> -Br-C ₆ H ₄	95 (9:91)	99	96 (95:5)	98	
6	$\mathbf{f}, p-NO_2-C_6H_4$	97 (7:93)	97	99 (93:7)	97	
7	g, 2-furan	99 (10:90)	94	98 (>95: 5)	96	
8	\mathbf{h} , \mathbf{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 ¹H 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 (2S,3R) and (2S,3S) by X-ray diffraction analysis. The same (2S) 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 (2S,3R) 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.

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