JOC The Journal of Organic Chemistry

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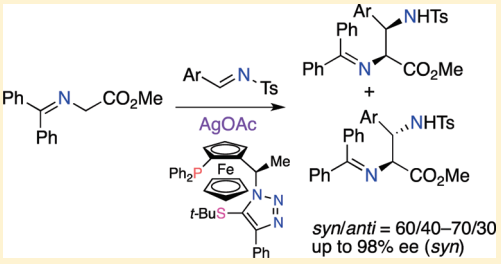
Ag/ThioClickFerrophos-Catalyzed Enantioselective Mannich Reaction and Amination of Glycine Schiff Base

Kazumi Imae, Kenta Shimizu, Kenichi Ogata, and Shin-ichi Fukuzawa*

Department of Applied Chemistry, Institute of Science and Engineering, Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan

Supporting Information

ABSTRACT: The AgOAc/ThioClickFerrophos complex catalyzed the asymmetric Mannich reaction of glycine Schiff base with *N*-tosylimines effectively to give a mixture of *syn* and *anti* adducts (*syn*/*anti* = 60/40−70/30) at high yields with high enantioselectivities (up to 98% ee). The complex also catalyzed the asymmetric amination of glycine Schiff base with di-*tert*-butyl azodicarboxylate with high enantioselectivity.



The asymmetric Mannich reaction of glycine Schiff base with imines is of current interest because it can provide an efficient route to the preparation of optically active α,β-diamino acids, which are versatile building blocks in organic synthesis and have medicinal and biological significance.[1] Therefore, chiral metal complex catalysts and organocatalysts have been developed[2] for the asymmetric Mannich reaction of glycine Schiff base since Jørgensen's group first reported the Cu(I)/phosphino-oxazoline complex-catalyzed reaction.[3] Wu and Hou's Cu(I)/ FcPHOX,[4] Wang's Cu(I)/TF-BiphamPhos,[5] Carretero's Cu(I)/Fesulphos,[6] and Feng's Cu(II)/*N*,*N*-dioxide[7] are representative, effective chiral metal catalysts for the reaction.

Recently, we reported that CuOAc/ClickFerrophos (**L2**) complexes exhibited highly *exo* stereoselectivity and excellent enantioselectivity in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with a vinyl sulfone.[8] We also succeeded in proceeding a highly *endo* and enantioselective reaction with α-enones and α,β-unsaturated esters by using AgOAc/ThioClickFerrophos complexes (**L6**).[9] Zhou et al. recently reported the first silver-catalyzed and highly enantioselective Mannich reaction of glycine Schiff base by using the AgOAc/FcPHOX complex.[10] Encouraged by Zhou's success with the silver-catalyzed reaction, we tried to create AgOAc/ClickFerrophos and ThioClickFerrophos-complex-catalyzed asymmetric Mannich reactions of glycine Schiff base with *N*-tosylimine **2**.

We initially focused on the exploration of appropriate ClickFerrophos and ThioClickFerrophos ligands and on an examination of reaction parameters such as silver salts and solvent. We chose **L2**−**L6** as ligands (Figure 1), which were revealed to be effective at producing high enantio- and diastereoselectivity in the asymmetric reductive aldol reaction,[11] allylic substitution,[12] and 1,3-dipolar reaction with azomethine ylides in our previous works.[8,9] Taniaphos ligand (**L1**),[13] which is structurally similar to

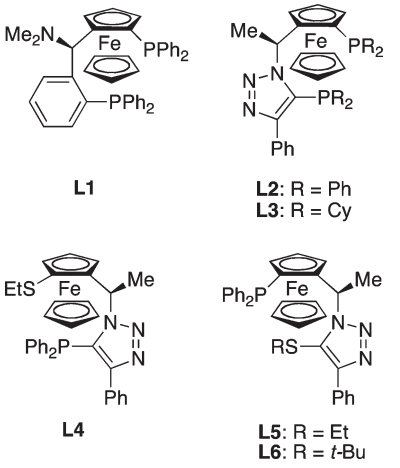
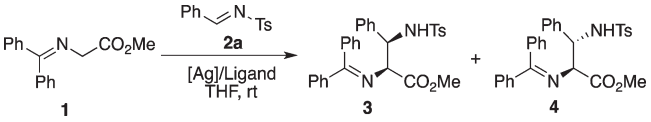


Figure 1. Diphosphines and P,S-ligands.

1,5-diphosphine to ClickFerrophos, was also examined for comparison. The glycine Schiff base **1** and phenyl tosylimine **2a** (1.2 equiv) were used as the model substrate. The reaction was carried out in THF at room temperature with a loading of 3 mol % of the silver complex derived from a silver salt and the ligand. The reaction proceeded to give a mixture of *syn* **3** and *anti* **4** diastereomers: the diastereomeric ratio and enantiomeric excess (% ee) of each isomer were determined by chiral HPLC. The results are summarized in Table 1. The use of Taniaphos **L1** gave a mixture of (2*S*,3*R*)-*syn*-**3** and (2*S*,3*S*)-*anti*-**4** in the ratio of 72/28 with low % ee values (entry 1). It took 16 h for the

Received: February 27, 2011
Published: March 16, 2011

Table 1. Optimization of the Mannich Reaction of Glycine Schiff Base[a]

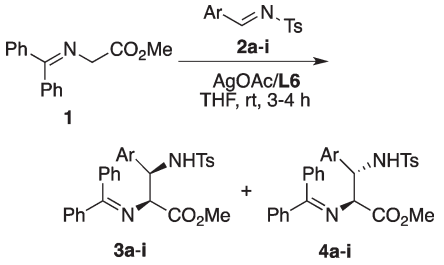


entry	[Ag]	ligand	time (h)	yield (%)[b]	*syn*/*anti*[c]	ee (%)[d] *syn*/*anti*
1	AgOAc	**L1**	8	99	72/28	58/36
2	AgOAc	**L2**	16	99	74/26	−87/−70
3	AgOAc	**L3**	16	98	67/33	−17/0
4	AgOAc	**L4**	3	99	63/37	−42/−44
5	AgOAc	**L5**	4	99	48/52	87/85
6	AgOAc	**L6**	3	99	60/40	98/98
7	AgOAc	*ent*-**L6**	3	99	60/40	−98/−98
8[e]	AgOAc	**L6**	5	99	66/34	97/95
9[f]	AgOAc	**L6**	19	94	69/31	97/95
10[g]	AgOAc	**L6**	20	88	67/33	93/98
11	AgOTf	**L6**	24	99	60/40	98/95
12	$AgBF_4$	**L6**	24	99	64/36	86/95
13	$AgPF_6$	**L6**	24	65	72/28	33/65
14[h]	$CuClO_4$	**L6**	18	99	46/54	96/96

[a] Glycine Schiff base (0.10 mmol), tosylimine (0.12 mmol), [Ag] (0.003 mmol, 3 mol %), ligand (0.0033 mmol, 3.3 mol %). [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC (Chiralpak AD-H). [e] The reaction was carried out in diethyl ether. [f] The reaction was carried out in toluene. [g] The reaction was carried out in CH_2Cl_2. [h] MS-4A and triethyl amine (4.5 mol %) were added.

complex of AgOAc/(*S*,*Rp*)-**L2** to complete the reaction that produced a mixture of the opposite enantiomer of *syn*/*anti* adducts quantitatively, % ee of (2*R*,3*S*)-*syn* and (2*R*,3*R*)-*anti* adducts being 87% and 70%, respectively (entry 2). The cyclohexyl derivative **L3** also gave a mixture of **3** and **4** as adducts with poor enantioselectivities (17%, and 0% ee, respectively): *syn*/*anti* = 67/33 (entry 3). We found that derivative **L6** was the most appropriate ligand for the production of high % ee for both *syn* and *anti* adducts, although diastereoselectivity was low; (2*S*,3*R*)-**3** and (2*S*,3*S*)-**4** were both obtained at 98% ee (entry 6).[14] Additionally, the reaction could be completed in a much shorter time (3 h) than that with **L2**. Ligand **L4**, in which P- and S-donor atoms were opposite to those in **L5**, was not effective at producing the enantiomer of **3** and **4** at low enantioselectivities (entry 4). It must be noted that similarly configured *syn* (and *anti*) adduct(s) were obtained with the use of **L2** and **L6**, where central and planar chirality were opposite to each other; **L2** and **L6** are configured as (*S*,*Rp*) and (*R*,*Sp*), respectively. The use of the enantiomer of **L6** produced the enantiomer of **3** and **4**. Having established ThioClickFerrophos **L6** as the optimal ligand, we investigated the effects of the metal precursor and solvent in order to further optimize the reaction conditions. The use of other solvents such as diethyl ether, toluene, and CH_2Cl_2 required longer reaction time (5−20 h) to complete the reaction, and diastereo- and enantioselectivity was almost the same as THF (entries 8−10). Other silver salts such as AgOTf, $AgPF_6$, and $AgBF_4$ took longer reaction time to complete the reaction: $AgPF_6$ gave a low yield and enantioselectivity (entries 11−13). The copper complex as $CuClO_4$ was tested as a metal complex precursor combining **L6** in the presence of MS-4A and triethylamine: it yielded a 1:1 mixture of **3** and **4** with 96% ee values after an 18−h reaction. Thus, we concluded that the optimal catalyst and solvents were AgOAc/**L6** and THF, respectively, with the goal of completing the reaction in the shortest time (3 h) and obtaining the highest enantioselectivities for *syn* and *anti* adducts. However, the high diastereoselectivity could not be achieved by using the catalyst in the presence or absence of MS-4A.

Table 2. Scope of Mannich Reaction of Glycine Schiff Base with Respect to Tosylimines[a]



entry	imine (Ar)	yield (%)[b]	*syn*/*anti*[c]	ee (%)[c]
1	**2a** (Ph)	99	60/40	98/98
2	**2b** (*o*-FC_6H_4)	99	68/32	98/97
3	**2c** (*o*-ClC_6H_4)	99	71/29	98/97
4	**2d** (*o*-BrC_6H_4)	99	75/25	95/98
5	**2e** (*o*-MeC_6H_4)	99	58/42	95/98
6	**2f** (*p*-ClC_6H_4)	99	58/42	98/98
7	**2g** (*p*-$CF_3C_6H_4$)	99	56/44	97/96
8	**2h** (*p*-MeC_6H_4)	99	60/40	85/94
9	**2i** (*p*-$MeOC_6H_4$)	99	57/43	91/91

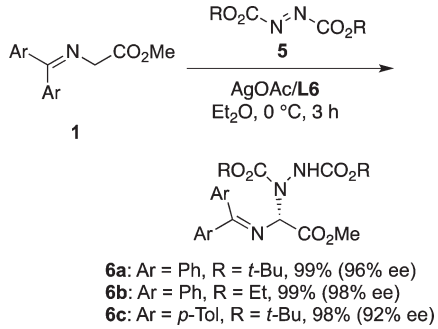
[a] Glycine Schiff base (0.10 mmol), tosylimine (0.12 mmol), AgOAc (0.003 mmol, 3 mol %), ligand (0.003 mmol, 3 mol %). [b] Isolated yield. [c] Determined by HPLC (AD-H, OD-H, IA, and IB).

The scope of the Mannich reaction with glycine Schiff base was evaluated by using various aryl tosylimines (**2a**−**i**) by altering the nature of the substituents on the phenyl ring under the optimized conditions. The substitution pattern of the phenyl ring in the tosylimines had an effect on the transformation. The electron-withdrawing substituents in the *ortho* position tended to produce higher *syn* selectivity (*syn*/*anti* = 70/30) than those with unsubstituted tosylimine **2a** (Table 2, entries 2−4); however, the *o*-methyl group gave a similar ratio to **2a**. For these substrates, the % ee values of the adducts remained at as high a level as that of **2a**. *para*-Electron-donating substituents had a slight, negative effect on enantioselectivity (entries 8 and 9), whereas *para*-electron-withdrawing substituents had little effect on enantioselectivity; % ee was similar to that of unsubstituted **2a** (entries 6 and 7). In either substrate, the *syn*/*anti* ratio was moderate, at 60/40.

Next, we applied the AgOAc/**L6** complex to α-amination of the glycine Schiff base **1** with azodicarboxylate **5** (Scheme 1).[15] After optimization experiment with di-*tert*-butyl azodicarboxylate **5** (R = *t*-Bu), we could conclude that optimal conditions were that the reaction occurred at 0 °C for 3 h in diethyl ether. The optimal conditions would produce (−)-**6** at the highest enantioselectivity (96% ee). The same level of enantioselectivity was obtained at even lower temperature (−20 °C). Solvents such as THF, toluene, and CH_2Cl_2 could be used as a solvent, yielding enantioselectivities of 93%, 93%, and 96% ee, respectively. The

dx.doi.org/10.1021/jo2003727 |*J. Org. Chem.* 2011, 76, 3604–3608

Scheme 1. Asymmetric Amination of Glycine Schiff Base



6a: Ar = Ph, R = *t*-Bu, 99% (96% ee)
6b: Ar = Ph, R = Et, 99% (98% ee)
6c: Ar = *p*-Tol, R = *t*-Bu, 98% (92% ee)

use of other silver salts resulted in lower yield and enantioselectivity: $AgBF_4$, 93% (85% ee); AgOTf, 43% (78% ee); $AgPF_6$, 26% (84% ee). The ethyl and *tert*-butyl esters of azodicarboxylate **5** gave almost the same level of enantioselectivity and the reaction with *p*-methylbenzophenone imino ester (**1**: Ar = *p*-tolyl) gave lower %ee values.

In conclusion, AgOAc/ThioClickFerrophos **L6** complex catalyzed the asymmetric Mannich reaction of glycine Schiff base with tosylimines. The *syn* and *anti* adducts were obtained with high enantioselectivities (up to 98% ee) but with a low to moderate *syn* selectivity. The complex was also effective for the enantioselective α-amination of glycine Schiff base with azodicarboxylate.

EXPERIMENTAL SECTION

Typical Experimental Procedure for the Mannich-Type Reaction of Glycine Schiff Base. All reactions were carried out under nitrogen atmosphere with oven-dried glassware. In a 20-mL Schlenk tube containing a stirring bar, ThioClickFerrophos **L6** (2.07 mg, 0.0033 mmol) and AgOAc (0.50 mg, 0.0030 mmol) were dissolved in THF (2.5 mL) and the mixture was stirred at room temperature for 30 min under nitrogen. Glycine Schiff base **1** (25.3 mg, 0.10 mmol) was added then followed by phenyl tosylimine **2a** (31.1 mg, 0.12 mmol). The resulting solution was stirred at the same temperature for 3 h and then filtered through Celite and concentrated. The ^{1}H NMR measurement of the crude product showed the presence of a diastereomeric mixture of adducts (*syn*/*anti* = 60/40). The residue was purified by preparative TLC (*n*-hexane/EtOAc = 4/1) to afford a mixture of *syn*-**3a** and *anti*-**4a** as a white solid, yield 51.0 mg (99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H, Me_{anti}), 2.34 (s, 3H, Me_{syn}), 3.49 (s, 3H, OMe_{anti}), 3.51 (s, 3H, OMe_{syn}), 4.14 (d, 1H$_{syn}$, J = 2.5 Hz), 4.36 (d, 1H$_{anti}$, J = 5.7 Hz), 4.71 (dd, 1H$_{anti}$, J = 5.8, 7.6 Hz), 5.17 (dd, 1H$_{syn}$, J = 2.4, 8.6 Hz), 5.80 (d, 1H, J = 7.5 Hz, NH_{anti}), 6.34 (d, 2H$_{syn}$, J = 6.7 Hz), 6.40 (d, 1H, J = 8.6 Hz, NH_{syn}), 6.85−7.83 (m, 17H$_{syn}$, 19H$_{anti}$). ^{13}C NMR ($CDCl_3$) δ 21.4 (Me), 52.1 (C_{anti}NH), 52.3 (C_{syn}NH), 59.4 (C_{syn}N═), 60.0 (C_{anti}N═), 69.4 (OMe_{anti}), 70.0 (OMe_{syn}), 126.5−142.9 (several Ar signals), 169.6$_{syn}$, 170.0$_{anti}$, 172.1$_{anti}$, 173.1$_{syn}$. The enantiomeric excess (98% and 98% ee values) and absolute configuration were determined by HPLC by reference to the literature.[3,4] HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 254 nm): t_R = 21.5 min (2*R*,3*S*)-isomer, 28.1 min (2*R*,3*R*)-isomer, 33.0 min (2*S*,3*S*)-isomer, 45.1 min (2*S*,3*R*)-isomer. HRMS calcd for $C_{30}H_{28}N_2O_4SNa$ $[M + Na]^+$ 535.1668, found 535.1664.

Methyl 2-[(diphenylmethylene)amino]-3-(*o*-fluorophenyl)-3-(tosylamino)propanoate *syn*-3b + *anti*-4b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H, Me_{anti}), 2.35 (s, 3H, Me_{syn}), 3.44 (s, 3H, OMe_{syn}), 3.52 (s, 3H, OMe_{anti}), 4.21 (d, 1H$_{syn}$, J = 2.4 Hz), 4.42 (d, 1H$_{anti}$, J = 6.5 Hz), 4.96 (dd, 1H$_{anti}$, J = 6.4, 7.7 Hz), 5.45 (dd, 1H$_{syn}$, J = 2.5, 8.6 Hz), 5.84 (d, 1H, J = 7.8 Hz, NH_{syn}), 6.39 (d, 2H$_{syn}$, J = 8.0 Hz), 6.40 (d, 1H, J = 7.5 Hz, NH_{anti}), 6.75−7.82 (m, 16H$_{syn}$, 18H$_{anti}$). ^{13}C NMR ($CDCl_3$) δ 21.38 (Me_{min}), 21.41 (Me_{maj}), 52.2 (C_{min}NH), 52.3 (C_{maj}NH), 53.7 (d, J = 2.4 Hz, C_{maj}N═), 55.2 (d, J = 1.1 Hz, C_{min}N═), 68.0 (OMe_{maj}), 68.3 (OMe_{min}), 115.0$_{maj}$ (d, J = 21.5 Hz), 115.1$_{min}$ (d, J = 21.9 Hz), 123.8$_{maj}$ (d, J = 3.6 Hz), 123.9$_{min}$ (d, J = 3.4 Hz), 126.2−138.7 (several Ar signals), 142.98$_{maj}$, 143.03$_{min}$, 159.0 (d, J = 246.1 Hz, C_{maj}F), 169.3$_{anti}$, 169.9$_{syn}$, 173.2$_{maj}$ (d, J = 43.4 Hz). ^{19}F NMR ($CDCl_3$) δ 119.3$_{syn}$, 120.5$_{anti}$. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 254 nm): t_R = 25.9 min (minor *syn*), 36.9 min (minor anti), 42.3 min (major *anti*), 47.8 min (major *syn*). HRMS calcd for $C_{30}H_{28}FN_2O_4S$ $[M + H]^+$ 531.1748, found 531.1766.

Methyl 3-(*o*-chlorophenyl)-2-[(diphenylmethylene)amino]-3-(tosylamino)propanoate *syn*-3c + *anti*-4c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H, Me_{anti}), 2.35 (s, 3H, Me_{syn}), 3.44 (s, 3H, OMe_{syn}), 3.48 (s, 3H, OMe_{anti}), 4.30 (d, 1H$_{syn}$, J = 2.0 Hz), 4.48 (d, 1H$_{anti}$, J = 5.8 Hz), 4.85 (dd, 1H$_{anti}$, J = 5.8, 6.5 Hz), 5.54 (dd, 1H$_{syn}$, J = 2.0, 8.1 Hz), 6.28 (d, 2H$_{syn}$, J = 6.5 Hz), 6.29 (d, 1H, J = 6.0 Hz, NH_{syn}), 6.47 (d, 1H, J = 7.5 Hz, NH_{anti}), 6.80−7.82 (m, 16H$_{syn}$, 18H$_{anti}$). ^{13}C NMR ($CDCl_3$) δ 21.40 (Me_{min}), 21.41 (Me_{maj}), 52.0 (C_{min}NH), 52.3 (C_{maj}NH), 56.2 (C_{maj}N═), 66.5 (OMe_{maj}), 66.6 (OMe_{min}), 126.5−143.5 (several Ar signals), 169.4$_{syn}$, 170.0$_{anti}$, 172.6$_{anti}$, 173.6$_{syn}$. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 254 nm): t_R = 9.8 min (minor *syn*), 10.2 min (minor *anti*)-isomer, 11.8 min (major *anti*), 18.4 min (major *syn*). HRMS calcd for $C_{30}H_{27}ClN_2O_4SNa$ $[M + Na]^+$ 569.1278, found 569.1295.

Methyl 3-(*o*-bromophenyl)-2-[(diphenylmethylene)amino]-3-(tosylamino)propanate *syn*-3d + *anti*-4d:[3,4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H, Me_{anti}), 2.36 (s, 3H, Me_{syn}), 3.45 (s, 3H, OMe_{anti}), 3.46 (s, 3H, OMe_{syn}), 4.33 (d, 1H$_{syn}$, J = 2.1 Hz), 4.50 (d, 1H$_{anti}$, J = 5.2 Hz), 4.80 (dd, 1H$_{anti}$, J = 6.3, 5.5 Hz), 5.50 (dd, 1H$_{syn}$, J = 2.2, 8.1 Hz), 6.26 (d, 2H$_{syn}$, J = 6.3 Hz), 6.40 (d, 1H, J = 4.2 Hz, NH_{anti}), 6.48 (d, 1H, J = 7.8 Hz, NH_{syn}), 6.81−7.83 (m, 16H$_{syn}$, 18H$_{anti}$). ^{13}C NMR ($CDCl_3$) δ 21.40 (Me_{anti}), 21.41 (Me_{syn}), 52.0 (C_{anti}NH), 52.3 (C_{syn}NH), 58.4 ($C_{syn+anti}$N═), 66.48 (OMe_{anti}), 66.51 (OMe_{syn}), 122.3−143.1 (several Ar signals), 169.4$_{syn}$, 169.8$_{anti}$, 172.5$_{anti}$, 173.6$_{syn}$. HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH 90/10, flow rate 0.8 mL/min, 254 nm): t_R = 11.4 min (2*R*,3*R*)-isomer, 12.7 min (2*R*,3*S*)-isomer, 17.2 min (2*S*,3*R*)-isomer, 27.4 min (2*S*,3*S*)-isomer. HRMS calcd for $C_{30}H_{27}BrN_2O_4SNa$ $[M + Na]^+$ 613.0773, found 613.0794.

Methyl 2-[(diphenylmethylene)amino]-3-(*o*-methylphenyl)-3-(tosylamino)propanoate *syn*-3e + *anti*-4e:[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (s, 3H, Me_{anti}), 2.04 (s, 3H, Me_{syn}), 2.26 (s, 3H, Me_{anti}), 2.33 (s, 3H, Me_{syn}), 3.51 (s, 3H, OMe_{syn}), 3.53 (s, 3H, OMe_{anti}), 4.06 (d, 1H$_{syn}$, J = 2.0 Hz), 4.31 (d, 1H$_{anti}$, J = 6.6 Hz), 4.86 (dd, 1H$_{anti}$, J = 6.3 Hz), 5.40 (dd, 1H$_{syn}$, J = 2.1, 8.4 Hz), 6.00 (d, 1H, J = 6.3 Hz, NH_{anti}), 6.20 (d, 2H$_{syn}$, J = 4.6 Hz), 6.41 (d, 1H, J = 7.7 Hz, NH_{syn}), 6.79−7.82 (m, 16H$_{syn}$, 18H$_{anti}$). ^{13}C NMR ($CDCl_3$) δ 18.5 (Me_{syn}), 18.9 (Me_{anti}), 21.4 ($Me_{syn+anti}$), 52.1 (C_{anti}NH), 52.4 (C_{syn}NH), 55.96 (C_{syn}N═), 55.97 (C_{anti}N═), 67.4 (OMe_{syn}), 68.4 (OMe_{anti}), 122.2−138.6 (several Ar signals), 142.8$_{syn}$, 142.9$_{anti}$, 169.8$_{syn}$, 170.3$_{anti}$, 172.3$_{syn}$, 173.2$_{anti}$. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH 85:15, flow rate 1.0 mL/min, 254 nm): t_R = 10.4 min (2*R*,3*S*)-isomer, 15.4 min (2*R*,3*R*)-isomer, 16.6 min (2*S*,3*S*)-isomer, 24.0 min (2*S*,3*R*)-isomer. HRMS calcd for $C_{31}H_{31}N_2O_4S$ $[M + H]^+$ 527.2000, found 527.2003.

Methyl 3-(*p*-chlorophenyl)-2-[(diphenylmethylene)amino]-3-(tosylamino)propanate *syn*-3f + *anti*-4f:[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H, Me_{anti}), 2.37 (s, 3H, Me_{syn}), 3.50 (s, 3H + 3H, $OMe_{syn+anti}$), 4.13 (d, 1H$_{syn}$, J = 2.2 Hz), 4.35 (d, 1H$_{anti}$, J = 5.7 Hz), 4.69 (dd, 1H$_{anti}$, J = 5.7, 7.3 Hz), 5.11 (dd, 1H$_{syn}$, J = 2.1, 8.3 Hz), 5.75 (d, 1H, J = 7.4 Hz, NH_{anti}), 6.38 (d, 1H, J = 8.0 Hz, NH_{syn}), 6.45 (d, 2H$_{syn}$, J = 7.1 Hz), 6.79−7.82 (m, 16H$_{syn}$, 18H$_{anti}$). ^{13}C NMR ($CDCl_3$) δ 21.4 (Me), 52.2 (C_{anti}NH), 52.4 (C_{syn}NH), 58.9 (C_{syn}N═), 59.3 (C_{anti}N═), 69.0

dx.doi.org/10.1021/jo2003727 |*J. Org. Chem.* 2011, 76, 3604–3608

(OMe_{syn}), 69.6 (OMe_{anti}), 126.5−138.6 (several Ar signals), 143.1$_{syn}$, 143.2$_{anti}$, 169.4$_{syn}$, 169.7$_{anti}$, 173.4$_{syn}$, 173.5$_{anti}$. HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH 85:15, flow rate 0.6 mL/min, 254 nm): t_R = 10.9 min (2*R*,3*R*)-isomer, 12.3 min (2*R*,3*S*)-isomer, 13.4 min (2*S*,3*S*)-isomer, 22.7 min (2*S*,3*R*)-isomer. HRMS calcd for $C_{30}H_{27}ClN_2O_4SNa$ $[M + Na]^+$ 569.1278, found 569.1281.

Methyl 2-[(diphenylmethylene)amino]-3-(tosylamino)-3-(*p*-trifluoromethylphenyl)propanoate *syn*-3g + *anti*-4g:[7] ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H, Me_{anti}), 2.34 (s, 3H, Me_{syn}), 3.50 (s, 3H, OMe_{anti}), 3.52 (s, 3H, OMe_{syn}), 4.16 (d, 1H$_{syn}$, J = 2.1 Hz), 4.40 (d, 1H$_{anti}$, J = 5.5 Hz), 4.79 (dd, 1H$_{anti}$, J = 5.7, 7.5 Hz), 5.19 (dd, 1H$_{syn}$, J = 1.9, 8.2 Hz), 5.81 (d, 1H, J = 7.6 Hz, NH_{anti}), 6.38 (d, 2H$_{syn}$, J = 7.2 Hz), 6.46 (d, 1H, J = 8.0 Hz, NH_{syn}), 6.88−7.82 (m, 16H$_{syn}$, 18H$_{anti}$). ^{13}C NMR ($CDCl_3$) δ 21.29 (Me_{anti}), 21.32 (Me_{syn}), 52.2 (C_{anti}NH), 52.5 (C_{syn}NH), 59.1 (C_{syn}N═), 59.4 (C_{anti}N═), 68.9 (OMe_{anti}), 69.4 (OMe_{syn}), 124.9−143.3 (several Ar signals), 169.3$_{syn}$, 169.5$_{anti}$, 173.7$_{syn}$ (d, J = 24.0 Hz). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, 254 nm): t_R = 26.0 min (2*R*,3*S*)-isomer, 36.3 min (2*R*,3*R*)-isomer, 66.8 min (2*S*,3*R*)-isomer, 75.0 min (2*S*,3*S*)-isomer. HRMS calcd for $C_{31}H_{27}F_3N_2O_4SNa$ $[M + Na]^+$ 603.1542, found 603.1547.

Methyl 2-[(diphenylmethylene)amino]-3-(*p*-methylphenyl)-3-(tosylamino)propanoate *syn*-3h + *anti*-4h:[5] ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H, Me_{anti}), 2.26 (s, 3H, Me_{syn}), 2.28 (s, 3H, Me_{anti}), 2.35 (s, 3H, Me_{syn}), 3.48 (s, 3H, OMe_{syn}), 3.49 (s, 3H, OMe_{anti}), 4.14 (d, 1H$_{syn}$, J = 2.3 Hz), 4.35 (d, 1H$_{anti}$, J = 5.7 Hz), 4.66 (dd, 1H$_{anti}$, J = 5.7, 7.5 Hz), 5.10 (dd, 1H$_{syn}$, J = 2.0, 8.5 Hz), 5.74 (d, 1H, J = 7.5 Hz, NH_{anti}), 6.34 (d, 1H, J = 8.2 Hz, NH_{syn}), 6.40 (d, 2H$_{syn}$, J = 6.9 Hz), 6.86−7.82 (m, 16H$_{syn}$, 18H$_{anti}$). ^{13}C NMR ($CDCl_3$) δ 20.98 (Me_{syn}), 21.04 (Me_{anti}), 21.4 (Me_{anti}), 29.7 (Me_{syn}), 52.1 (C_{anti}NH), 52.3 (C_{syn}NH), 59.3 (C_{syn}N═), 59.8 (C_{anti}N═), 69.4 (OMe_{anti}), 70.0 (OMe_{syn}), 126.4−142.9 (several Ar signals), 169.7$_{syn}$, 170.1$_{anti}$, 172.96$_{syn}$, 173.01$_{anti}$. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH 85:15, flow rate 0.8 mL/min, 254 nm): t_R = 13.6 min (2*R*,3*S*)-isomer, 17.8 min (2*R*,3*R*)-isomer, 22.6 min (2*S*,3*R*)-isomer, 23.9 min (2*S*,3*S*)-isomer. HRMS calcd for $C_{31}H_{31}N_2O_4S$ $[M + H]^+$ 527.2000, found 527.2011.

Methyl 2-[(diphenylmethylene)amino]-3-(*p*-methoxyphenyl)-3-(tosylamino)propanoate *syn*-3i + *anti*-4i:[3,5] ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H, Me_{anti}), 2.35 (s, 3H, Me_{syn}), 3.50 (s, 3H + 3H, $OMe_{syn+anti}$), 3.74 (s, 3H + 3H, $OMe_{syn+anti}$), 4.13 (d, J = 2.4 Hz, 1H$_{syn}$), 4.35 (d, J = 5.8 Hz, 1H$_{anti}$), 4.68 (dd, 1H$_{anti}$, J = 5.7, 7.4 Hz), 5.10 (dd, 1H$_{syn}$, J = 2.3, 8.4 Hz), 5.70 (d, 1H, J = 7.7 Hz, NH_{anti}), 6.32 (d, 1H, J = 8.8 Hz, NH_{syn}), 6.45 (d, 2H$_{syn}$ J = 7.2 Hz), 6.64−7.82 (m, 16H$_{syn}$, 18H$_{anti}$). ^{13}C NMR ($CDCl_3$) δ 21.4 ($Me_{syn+anti}$), 52.1 (C_{anti}NH), 52.3 (C_{syn}NH), 55.2 (OMe_{anti}), 55.3 (OMe_{syn}), 59.0 (OMe_{syn}), 59.4 (OMe_{anti}), 69.4 (OMe_{anti}), 70.0 (OMe_{syn}), 113.45 (OMe_{anti}), 113.50 (OMe_{syn}), 113.5−142.9 (several Ar signals), 158.8$_{syn}$, 159.0$_{anti}$, 169.7$_{syn}$, 170.0$_{anti}$, 173.0$_{anti}$, 173.1$_{syn}$. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH 85:15, flow rate 0.8 mL/min, 254 nm): t_R = 16.7 min (2*R*,3*S*)-isomer, 25.0 min (2*R*,3*R*)-isomer, 29.8 min (2*S*,3*S*)-isomer, 48.6 min (2*S*,3*R*)-isomer. HRMS calcd for $C_{31}H_{31}N_2O_5S$ $[M + H]^+$ 543.1948, found 543.1939.

General Procedure for the Amination Reaction of Glycine Schiff Base. In a 20-mL Schlenk tube containing a stirring bar, ThioClickFerrophos **L6** (4.7 mg, 0.0075 mmol) and AgOAc (1.1 mg, 0.0070 mmol) were dissolved in Et_2O (1.3 mL) and the mixture was stirred at room temperature for 30 min under nitrogen. The mixture was cooled to 0 °C, and then a Et_2O (1.2 mL) solution of Glycine Schiff base **1** (Ar = Ph) (58 mg, 0.23 mmol) was added followed by di-*tert*-butyl azodicarboxylate (0.12 mL, 0.27 mmol, 2.2 M). The resulting solution was stirred at the same temperature for 3 h and then filtered through Celite and concentrated. The crude product was purified by preparative TLC (*n*-hexane/EtOAc = 2/1) to afford **6a** (Ar = Ph, R= *t*-Bu) as a colorless oil, yield 98 mg (99%). The enantiomeric excess (96% ee) was determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 254 nm): t_R = 11.8 min (major), 13.1 min (minor). $[\alpha]^{29}_D$ −40.87 (*c* 0.3, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21−1.51 (m, 18H), 3.72 (s, 3H), 6.08 (br s, 1H), 6.75 (br s, 1H), 7.31−7.66 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 27.9, 28.0, 52.6, 73.4, 80.7, 81.8, 127.9, 128.2, 128.4, 128.9, 129.2, 129.9, 130.7, 132.3, 135.7, 138.9, 154.1, 154.7, 169.0. HRMS cacld for $C_{26}H_{34}N_3O_6$ $[M + H]^+$ 484.2447, found 484.2442.

Diethyl 1-{1-[(diphenylmethylene)amino]-2-methoxy-2-oxoethyl}hydrazine-1,2dicarboxylate 6b: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18−1.34 (m, 6H), 3.75 (s, 3H), 4.15−4.34 (m, 4H), 6.06 (br s, 1H), 6.94 (br s, 1H), 7.30−7.46 (m, 8H), 7.66 (d, 2H, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$) δ 14.0, 14.3, 52.7, 61.8, 62.8, 74.3, 127.6, 127.9, 128.1, 128.3, 129.0, 129.1, 129.9, 130.8, 135.5, 138.7, 155,2, 155.7, 168.6, 173.8. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH 90:10, flow rate 0.7 mL/min, 254 nm): t_R = 25.4 min (minor), 27.3 min (major). $[\alpha]^{30}_D$ −45.19 (*c* 0.1, $CHCl_3$). HRMS calcd for $C_{22}H_{26}N_3O_6$ $[M + H]^+$ 428.1821, found 428.1837.

Di-*tert*-butyl 1-{1-[(di-*p*-tolylmethylene)amino]-2-methoxy-2-oxoethyl}hydrazine-1,2-dicarboxylate 6c: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24−1.51 (m, 18H, *t*-Bu), 2.35 (s, 3H), 2.40 (s, 3H), 3.71 (br s, 3H), 6.08 (s, 1H), 6.75 (s, 1H), 7.09−7.26 (m, 8H), 7.54 (d, 2H, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$) δ 21.3, 21.6, 27.9, 28.0, 52.6, 80.6, 81.6, 127.8, 128.5, 128.8, 129.0, 129.2, 130.1, 132.9, 135.1, 136.5, 138.7, 141.0, 142.8, 154.2, 154.7, 166.2, 169.1. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 254 nm): t_R = 10.0 min (minor), 11.5 min (major). $[\alpha]^{30}_D$ −43.37 (*c* 0.2, $CHCl_3$). HRMS calcd for $C_{28}H_{38}N_3O_6$ $[M + H]^+$ 512.2760, found 512.2729.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. ^1H and ^{13}C NMR spectra (PDF) and HPLC analytical dada for the products (**3a** and **4a**−**3i** and **4i**) of Mannich reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: orgsynth@kc.chuo-u.ac.jp.

■ ACKNOWLEDGMENT

This study was financially supported by a Grant-in-Aid, No. 22550044, for Scientific Research from the Japan Society for the Promotion of Science (JSPS) and a Chuo University Grant for Special Research.

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