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Catalytic Asymmetric Mannich Reactions of Glycine Derivatives with Imines. A New Approach to Optically Active α,β-Diamino Acid Derivatives

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Imines of glycine alkyl esters react with imines in a diastereo- and highly enantioselective Mannich reaction in the presence of chiral copper(I) complexes as the catalyst to give optically active α,β-diamino acid derivatives. A series of imines of glycine esters derived from glycine and aromatic carbonyl compounds has been screened as substrates for the Mannich reaction with different imines in the presence of various combinations of metal salts and chiral ligands. The benzophenone imine of glycine esters was found to react with *N*-protected imines in a diastereoselective fashion giving functionalized α,β-diamino acid esters with excellent enantioselectivities. The most effective chiral catalysts are chiral copper(I) complexes having phosphino-oxazoline (P,N)-ligands, and among these ligands, those derived from (1*R*,2*S*)-dihydroxy-1,2,3,4-tetrahydronaphthalene gave the best results. The scope of this new catalytic asymmetric reaction of the benzophenone imine glycine esters is demonstrated for the reaction with different *N*-protected-*C*-aryl and *C*-alkyl imines giving the Mannich adducts with excellent optical purity. Furthermore, the synthetic aspects of the reaction are presented by converting the Mannich adducts into α,β-diamino acid derivatives. The relative and absolute configuration of the Mannich adduct have been determined and based on the stereochemical outcome of the reaction a tetrahedral chiral-copper(I)-imino glycine alkyl ester intermediate is proposed. In this intermediate the *Re*-face of the benzophenone imine glycine ester is shielded by the chiral ligand leaving the *Si*-face available for approach of the *Si*-face of the imine. A series of semiempirical calculations has been performed to support the structure of the tetrahedral chiral-copper(I) complex and to account for the influence of the substituents in the chiral phosphino-oxazoline ligands.

Introduction

One of the challenges for chemists is to develop reactions that create optically active complex molecules from simple achiral starting materials using asymmetric catalysis. The development of carbon−carbon forming reactions that generate two new stereogenic centers with high diastereo- and enantioselectivity in a single step for the formation of highly valuable optically active compounds is highly desirable from both an academic and industrial point of view. The catalytic enantioselective addition to imines belongs to this class of important carbon−carbon bond forming reaction and the Mannich reaction is one of these reactions.[1]

Imines of glycine alkyl esters are important molecules in organic chemistry that undergo various types of reactions. The imines of glycine alkyl esters can act as azomethine ylide precursors.[2] The azomethine ylide can be obtained either by 1,2-prototropy or by subjecting the imines to a metal salt and a base thereby generating a metal-stabilized azomethine ylide when the metal is considered being covalently bound to the nitrogen atom of the imine. The use of metal-stabilized azomethine ylides for the 1,3-dipolar cycloaddition reaction with various dipolarophiles has been extensively investigated and recently both diastereo-[2,3] and enantioselective[4] 1,3-dipolar cycloaddition reactions have been achieved often via a Lewis acid stabilized azomethine ylide intermediate.

Imines of glycine alkyl ester derivatives[5] have also been

(1) For a recent review dealing with catalytic enantioselective addition to imines see: Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(2) For leading references dealing with the chemistry of azomethine ylides see e.g.: (a) Lown, J. W. Azomethine Ylides. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; p 653. (b) Harwood: L. M.; Vickers, R. J. *Azomethine Ylides* in *Heterocyclic Compounds*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; p 169. (c) Kanemasa, S.; Tsuge, O. *N*-Metalated Azomethine Ylides. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, CT, 1993; Vol. 3, p 91. (d) Grigg, R.; Sridharan, V. Azomethine Ylide Cycloadditions via 1,2-Prototropy and Metallo-dipole Formation from Imines. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, CT, 1993; Vol. 3, p 161. (e) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475.

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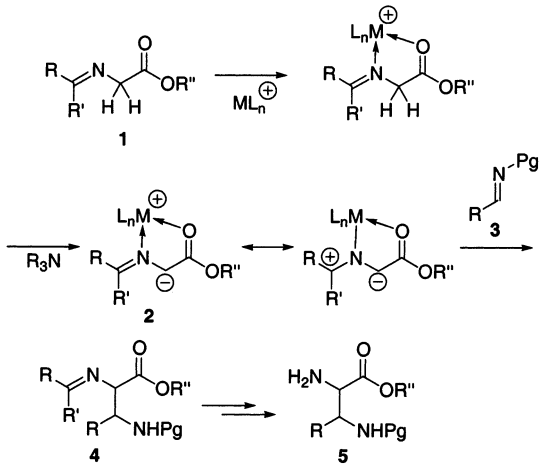
widely used as glycine anion and cation equivalents and have found use as starting compounds for the synthesis of both natural and unnatural α-amino acids. This approach has especially been used in combination with optically active phase-transfer catalysts, such as the *Cinchona* alkaloids, cinchonidine and cinchonine, for, e.g., nucleophilic substitution reactions,[6] Michael additions,[7] and aldol reactions.[8] Furthermore, enantioselective palladium-catalyzed reactions via a π-allyl-palladium intermediate have also been performed with use of α-acetoxy derivatives of the imino glycine alkyl ester as the substrates and mainly BINAP as the chiral ligand.[9]

The formation of two new stereogenic carbon centers by the Mannich reaction with use of a catalytic enantioselective approach has normally been achieved by the addition of enolates to imines;[10] however, one of the disadvantages is the preparation and stability of the enolate used in the addition step. More recently direct Mannich reactions have also been developed with both chiral Lewis acid and organo-catalytic reactions.[11]

The generation of a Lewis acid stabilized imino glycine alkyl ester anion **2** (which can be regarded as a *N*-metalated azomethine ylide when the metal is covalently bound to the imine nitrogen atom giving an overall neutral species) from an imino glycine alkyl ester **1** could lead to the application of **2** as a nucleophile reacting with, e.g., imines **3**. This is a new approach to the catalytic asymmetric Mannich reaction and the Mannich products obtained will give an easy entry to optically active α,β-diamino acid esters **5** (Scheme 1).

SCHEME 1. Generation of Chiral Lewis Acid-Stabilized Imino Glycine Alkyl Ester Anion 2 from an Imino Glycine Alkyl Ester 1 and Its Mannich Reaction with Imines 3



The challenge for the Mannich reaction outlined in Scheme 1 is (i) to "force" the Lewis acid stabilized imino glycine alkyl ester **2** to act as a nucleophile rather than a 1,3-dipolar species and (ii) to develop a chiral catalyst that can catalyze both a diastereo- and enantioselective addition of **2** to imines **3**.

This paper presents the development of the first catalytic enantioselective Lewis acid catalyzed Mannich reaction of imino glycine alkyl esters with imines giving highly functionalized optically active α,β-diamino acid esters.[12] α,β-Diamino acid derivatives **5** (Scheme 1) are highly valuable compounds[13] and the present reaction gives an easy access to optically active compounds of this important class of molecules. The mechanism of the highly enantioselective reaction is discussed on the basis of semiempirical calculations of the chiral intermediate and absolute configuration of the Mannich adduct.

Results and Discussion

Among the different imino glycine alkyl esters **1** obtained from condensation of glycine alkyl esters with different carbonyl compounds, the benzophenone imine glycine methyl ester[4] (**1a**) gave selectively the Mannich reaction with the *N*-tosyl-*C*-phenyl imine **3a** in the presence of various chiral Lewis acid complexes (eq 1). It should be noted that the *N*-*p*-methoxy-benzylidene and *N*-2-naphthylmethylidene glycine alkyl esters both react with **3a** in the presence of different chiral Lewis acid complexes to give a mixture of Mannich and 1,3-dipolar cycloaddition adducts in a ratio of about 1:2 depending on the metal complex and reaction conditions.

The results for the reaction of the benzophenone imine glycine ethyl ester **1a** with *N*-tosyl-*C*-phenyl imine **3a** in

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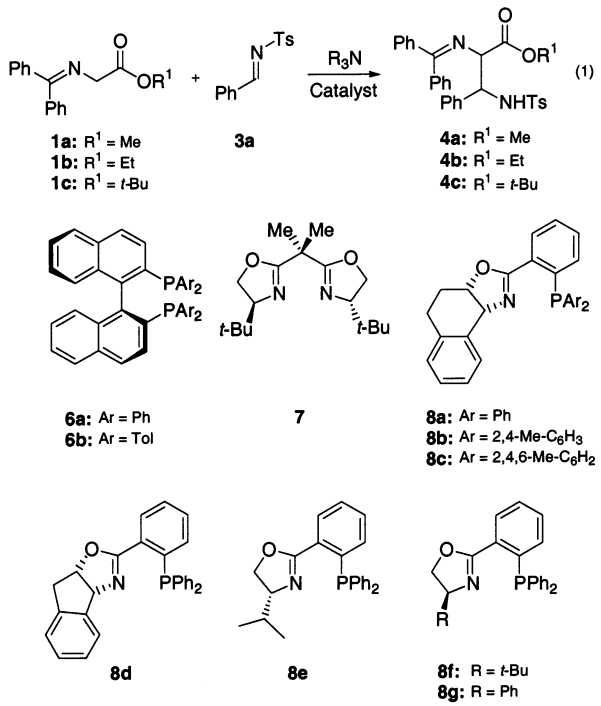

the presence of a series of different chiral Lewis acid complexes **6a**,**b**, **7**, **8a**−**g** under various reaction conditions are presented in Table 1.

The chiral Lewis acids obtained from the combination of copper(I) and the BINAP ligands **6a**,**b** catalyze the diastereoselective Mannich reaction of the benzophenone imine glycine methyl ester **1a** with *N*-tosyl-*C*-phenyl imine **3a** to give **4a** in 95% yield in THF as the solvent (Table 1, entries 2 and 3). Other Lewis acids than copper(I) can also be applied and the use of, e.g., silver(I)-Tol-BINAP (**6b**) gives a diastereoselective reaction; however, the enantioselectivity is low (entry 4). The use of the chiral bisoxazoline ligand **7** and $CuClO_4$ as the Lewis acid gives low yield and diastereoselectivity in the reaction and the Mannich product is obtained as a racemate (entry 5).

Several different phosphino-oxazoline (P,N)-ligands[14] **8a**−**g** have also been tested as chiral ligands for the copper(I)-catalyzed Mannich reaction of **1a** with **3a** and among the ligands tested the P,N-ligands **8a**−**c**, those derived from (1*R*,2*S*)-dihydroxy-1,2,3,4-tetrahydro naphthalene, showed the most promising results. The use of **8a**-$CuClO_4$ as the catalyst gave 76% yield of **4a** in a 72:28 syn:anti diastereomeric ratio and with an enantiomeric excess of 46% of the minor diastereomer (Table 1, entry 7). An exchange of the phenyl substituents with 2,4-dimethylphenyl substituents in the chiral ligand (**8b**) improved the results compared to the use of ligand **8a** in THF as the solvent and applying $CuClO_4$ as the Lewis acid (entry 8). A screening of the application of **8b** as the ligand in combination with $CuClO_4$ and $CuPF_6$ as the Lewis acids in various solvents gave **4a** in good yield and good enantiomeric excess in toluene or THF in the presence of 4 Å molecular sieves (MS) (entries 9−15). Increasing the sterics of the chiral ligand from 2,4-dimethylphenyl (**8b**) to 2,4,6-trimethylphenyl (**8c**) leads to a significant improvement in both yield and diastereo- and enantiomeric excess of the reaction as shown in entries 16−19. In both toluene and THF and in the presence of 4 Å MS very high yield, good diastereoselectivity, and excellent enantiomeric excess of **4a** are obtained at both −20 and 0 °C. Under these conditions the major diastereomer of **4a** is formed with 97% ee with both $CuClO_4$ and $CuPF_6$ as the Lewis acids (entries 16 and 17). The other P,N-ligands **8d**−**g** all showed, with the exception of **8g**, in combination with $CuClO_4$ in THF as the solvent and in the presence of 4 Å MS, good catalytic activity, moderate diastereoselectivity, and good enantioselectivity (entries 20−22).

The results presented in Table 1 are all performed in the presence of 10 mol % of Et_3N as the base. We have also tested other bases for the reaction catalyzed by **8c**-$CuClO_4$ in toluene or THF in the presence of 4 Å MS; Hünigs base gave only 39% yield of **4a** formed in a diastereomeric ratio of 79:21 and with 91% ee of the major diastereomer, while *t*-BuOK leads to a further reduction in the yield of **4a** to 27%, the same diastereomeric ratio, and 81% ee of the major diastereomer.

The reaction course has been investigated for variation of the ester group. The benzophenone imine glycine alkyl esters **1a**−**c** were reacted with *N*-tosyl-*C*-phenyl imine **3a** catalyzed by **8c**-$CuClO_4$ (10 mol %) in toluene or THF in the presence of 4 Å MS. The results are given in Table 2.

It appears from the results from Table 2 that the reaction proceeds well for the different benzophenone imine glycine ethyl esters (**1a**−**c**) tested; the diastereomeric ratio increases (methyl < ethyl < *tert*-butyl) when the size of the ester group increases, while a slight decrease in the enantiomeric excess (methyl > ethyl > *tert*-butyl) is found when the size of the ester group increases (entries 1−4). The reaction course seems thus to be relatively independent of the ester functionality of the benzophenone imine glycine alkyl ester and high enantioselectivities are obtained for the different compounds reacted.

In the following we present the reaction of the benzophenone imine glycine methyl ester **1a** with a series of both *C*-aryl and *C*-alkyl imines **3a**−**i** catalyzed by **8c**-$CuClO_4$ (10 mol %) (eq 2) to show the scope of the catalytic enantioselective Mannich reaction. The results are presented in Table 3.

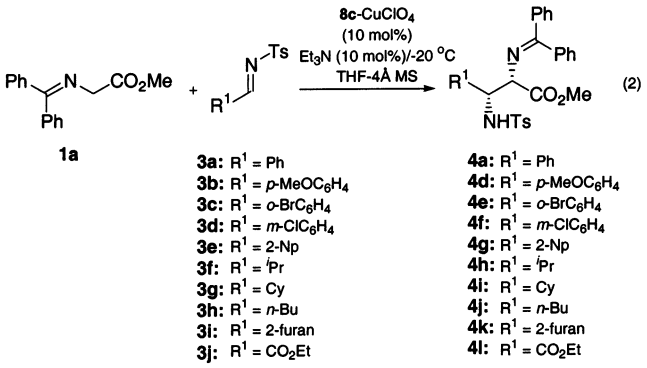

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TABLE 1. Results from the Screening of Lewis Acids (10 mol %), Chiral Ligands (10 mol %), Solvents, and Reaction Temperature for the Catalytic Enantioselective Mannich Reaction of the Benzophenone Imine Glycine Methyl Ester 1a with the *N*-Tosyl-*C*-phenyl Imine 3a

entry	Lewis acid	ligand	solvent	reaction temp (°C)	reaction time (h)	yield[a] (%)	syn:anti[b]	ee[c] (%)
1			THF	rt	25	14	76:24	
2	$CuClO_4$	**6a**	THF	−20	4	95	86:14	7/14
3[d]	$CuClO_4$	**6b**	THF	−20	4	95	88:12	19/51
4	$AgClO_4$	**6b**	THF	−20	6.5	80	71:29	15/22
5	$CuClO_4$	**7**	THF	−20	20	40	73:27	rac/rac
6	$CuClO_4$	**8a**	THF	−20	16	78	70:30	9/24
7	$CuClO_4$	**8a**	THF−4 Å MS	−20	18	76	72:28	14/46
8	$CuClO_4$	**8b**	THF	−20	20	84	71:29	59/70
9	$CuPF_6$	**8b**	toluene	−20	16	72	55:45	54/68
10	$CuClO_4$	**8b**	MeCN	−20	16	37	67:33	rac/rac
11	$CuClO_4$	**8b**	toluene	−20	18	67	60:40	70/83
12	$CuClO_4$	**8b**	CH_2Cl_2	−20	18	25	72:28	rac/rac
13	$CuClO_4$	**8b**	Et_2O	−20	18	51	76:24	10/29
14	$CuClO_4$	**8b**	toluene−4 Å MS	−20	20	80	60:40	81/89
15	$CuClO_4$	**8b**	THF − 4 Å MS	−20	20	78	67:33	84/86
16	$CuClO_4$	**8c**	THF − 4 Å MS	−20	18	94	79:21	97/94
17	$CuPF_6$	**8c**	THF − 4 Å MS	−20	18	98	80:20	97/94
18	$CuClO_4$	**8c**	toluene−4 Å MS	-20	18	92	72:28	97/98
19	$CuClO_4$	**8c**	THF−4 Å MS	0	14	88	77:23	94/92
20	$CuClO_4$	**8d**	THF−4 Å MS	-20	20	>95	63:37	84/82
21	$CuClO_4$	**8e**	THF−4 Å MS	-20	20	81	67:33	64/68
22	$CuClO_4$	**8f**	THF−4 Å MS	-20	20	94	74:26	60/18
23	$CuClO_4$	**8g**	THF−4 Å MS	-20	18	>10		

[a] Isolated yield. [b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excess determined by HPLC. [d] The same results were obtained at −78 °C.

TABLE 2. Reaction of Benzophenone Imine Glycine Alkyl Esters 1a−c with the *N*-Tosyl-*C*-phenyl Imine 3a Catalyzed by 8c-$CuClO_4$ (10 mol %) in Toluene or THF in the Presence of 4 Å MS at −20 °C

entry	azomethine ylide	solvent	yield[a] (%)	syn:anti[b]	ee[c] (%)
1	**1a**	THF−4 Å MS	**4a**, 94	79:21	97/94
2	**1b**	THF−4 Å MS	**4b**, 90	83:17	96/94
3	**1c**	THF−4 Å MS	**4c**, 90	92:8	85/71
4	**1c**	toluene−4 Å MS	**4c**, 50	90:10	88/79

[a] Isolated yield. [b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excess determined by HPLC.

TABLE 3. Catalytic Enantioselective Mannich Reaction of the Benzophenone Imine Glycine Ethyl Ester 1a with Different Imines 3a−j Catalyzed by 8c-$CuClO_4$ (10 mol %) in THF in the Presence of 4 Å MS at −20 °C

entry	imine	yield[a] (%)	syn:anti[b]	ee[c] (%)
1	**3a**	**4a**, 94	79:21	97/94
2	**3b**	**4d**, 90	82:18	97/95
3	**3c**	**4e**, 99	61:39	96/>99
4	**3d**	**4f**, 93	84:16	95/−
5	**3e**	**4g**, 90	86:14	97/92
6	**3f**	**4h**, 73	>95:<5	96/−
7	**3g**	**4i**, 85	>95:<5	92/−
8	**3h**	**4j**, 61	>95:<5	88/−
9	**3i**	**4k**, 88	54:46	90/95
10	**3j**	**4l**, 84	60:40	60/57

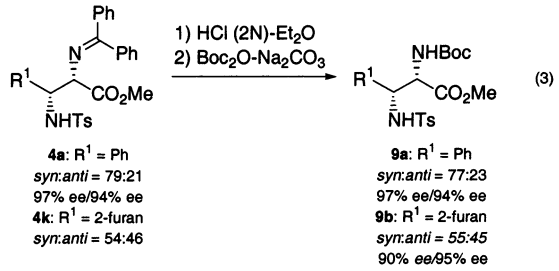
[a] Isolated yield. [b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excess determined by HPLC.

The aromatic imines **3a**−**e** all reacted with the benzophenone imine glycine ethyl ester **1a** catalyzed by **8c**-$CuClO_4$ (10 mol %) to give the corresponding optically active α,β-diamino acid esters **4a**,**d**−**g** in high yields, moderate to good diastereoselectivity, and excellent enantioselectivity (>95% ee) (Table 3, entries 1−5). A highly diastereo- and enantioselective Mannich reaction also takes place for the aliphatic imines (**3f**−**h**); for these imines only one diastereomer could be detected by ^{1}H NMR spectroscopy. For the isopropyl and cyclohexyl substituted imines (**3f**,**g**) excellent enantioselectivities of **4h** and **4i** were obtained, 96% and 92% ee, respectively (entries 6 and 7), while the *n*-butyl-substituted imine gave **4j** with 88% ee (entry 8). The imine (**3i**) derived from 2-furaldehyde reacts with **1a** in a nondiastereoselective reaction as the syn:anti ratio was 54:46; however, the enantioselectivity of the two diastereomers was very high (entry 9). For comparison we also present the results for the highly activated *N*-tosyl-α-imino ester **3j**, which has been used as the substrate for many catalytic enantioselective reactions.[11c,15] However, under the present reaction conditions, **3j** reacts with **1a** to give **4l** with moderate diastereo- and enantioselectivity (entry 10).

(15) See e.g.: (a) Kagoshima, H.; Uzawa, T.; Akiyama, T. *Chem. Lett.* **2002**, 298. (b) Fang, X.; Johansen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844. (c) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114. (d) Johannsen, M. *Chem. Commun.* **1999**, 2233. (e) Juhl, K.; Hazell, R. G.; Jørgsensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293. Mannich reactions: (f) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090. (g) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (h) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. Hetero Diels−Alder reactions: (i) Yao, S.; Johansen, M.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121. (j) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435. Ene reactions: (k) Yao, S.; Fang, X.; Jørgensen, K. A. *Chem. Commun.* **1998**, 2547. (l) Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006. Synthesis of β-lactams. (m) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Letcka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831. (n) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett.* **2000**, *2*, 3963. (o) Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 10853. (p) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, *4*, 627. (q) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626. (r) France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 1603.

The relative and absolute configuration of the Mannich product has been assigned by X-ray analysis (see Supporting Information). The configuration of the major diastereomer **4b**, formed by reaction of benzophenone imine glycine ethyl ester **1b** with *N*-tosyl-*C*-phenyl imine **3a** catalyzed by **8c**-$CuClO_4$, was found to be (2*S*,3*R*), i.e., the *Si*-face of **1b** is approached by the *Si*-face of **3a** (vide infra).

The optically active *N*-protected α,*β*-diamino acid derivatives formed in this new catalytic enantioselective reaction can be converted into the corresponding Boc-protected α,*β*-diamino acid ester by hydrolysis of the Mannich adducts (eq 3). Reaction of the Mannich adducts



4a: R^1 = Ph
syn:*anti* = 79:21
97% ee/94% ee
4k: R^1 = 2-furan
syn:*anti* = 54:46

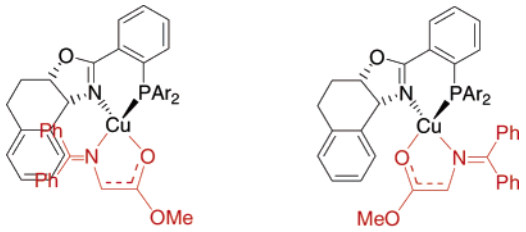
9a: R^1 = Ph
syn:*anti* = 77:23
97% ee/94% ee
9b: R^1 = 2-furan
syn:*anti* = *55:45*
90% *ee*/95% ee

(3)

4a and **4k** with first HCl, followed by protection by Boc_2O, gave **9a** and **9b**, respectively. The diastereomers can be separated by chromatography and the reactions proceeded with only a small decrease in the diastereomeric ratio while enantiomeric excess was unchanged. It has previously been shown that the *N*-tosyl group can be removed by first *N*-Boc protection, followed by treatment with Mg/MeOH.[16]

To obtain some information about the intermediate, binding of the chiral catalyst to the substrate(s), and the reaction course we have performed a series of experimental and theoretical investigations. ^{1}H NMR spectroscopic studies of the possible coordination of $CuClO_4$ to the benzophenone imine glycine methyl ester **1a** and/or the *N*-tosyl-*C*-phenyl imine **3a** show that it is only the former which coordinates to the Lewis acid.[17] We have therefore in the following assumed that the catalyst activates **1a** by coordination, followed by deprotonation by the base (NEt_3) to give the chiral ligand copper(I)-stabilized imino glycine alkyl ester anion (**2** in Scheme 1), a neutral intermediate.

The mechanistic investigations were performed with the phenyl and 2,4,6-trimethylphenyl phosphino-oxazoline ligands, **8a** and **8c**, respectively, as these ligands are significantly different in enantioinduction; the former gives <20% ee, while the latter produces 97% ee of the major diastereomer and nearly the same diastereoselectivity for the reaction of the benzophenone imine glycine methyl ester **1a** with the *N*-tosyl-*C*-phenyl imine **3a** (Table 1, entries 7 and 16). The coordination of the imino



10a: Ar = Ph
10b: Ar = 2,4,6-Me-C_6H_2

11a: Ar = Ph
11b: Ar = 2,4,6-Me-C_6H_2

FIGURE 1. The two possible coordination modes of the benzophenone imine glycine methyl ester anion to the nonsymmetric chiral ligand P,N-copper(I) complex.

glycine alkyl ester anion to the chiral ligand copper(I) can take place in two manners due to the nonsymmetric chiral ligand. The two possibilities are shown in Figure 1. The structures of **10a**,**b** and **11a**,**b** have been optimized by using semiempirical PM3 calculations.[18]

The optimized structures of **10a**,**b** and **11a**,**b** all gave the geometry at the copper(I) center as tetrahedral. The intermediates **10a** and **11a** obtained from coordination of the benzophenone imine glycine methyl ester **1a** to the copper(I)-phenyl phosphino-oxazoline ligand **8a** are of very similar energy; the intermediate **10a** is <1 kcal/mol less stable compared to the energy of **11a**.[19]

For the two intermediates, **10a** and **11a**, respectively, obtained from benzophenone imine glycine methyl ester **1a** anion coordination to the Cu(I)-**8a** catalyst, which are of similar energy, an analysis of the face-shielding by the chiral ligand of the nucleophilic carbon atom shows no significant shielding for both intermediates. This is in accordance with the experimental results obtained as the enantiomeric excess of the Mannich adduct using this chiral catalyst was found to be less than 20% ee. Figure 2 shows the optimized structure of intermediate **10a** in which the low shielding of the nucleophilic carbon atom of the benzophenone imine glycine methyl ester anion by the chiral P,N-ligand **8a** can be seen (the arrow shows the nucleophilic carbon atom).

The energy of the two intermediates formed from coordination of the benzophenone imine glycine methyl ester **1a** anion to the Cu(I)-**8c** catalyst, **10b** and **11b**, respectively, differs significantly compared with that of **10a** and **11a**.[19] The most stable of the two intermediates (**10b**) is 12.4 kcal/mol more stable than **11b**, and the difference in stability of the two intermediates can be traced to steric repulsion in **11b** between the 2- and 6-methyl substituents of the 2,4,6-trimethylphenyl group of the chiral ligand with the phenyl groups of the benzophenone fragment of the coordinated benzophenone imine glycine methyl ester anion. Figure 2 also gives the optimized structure **10b**, and it appears that the *Re*-face of the carbon atom of the **1a**, which acts as the nucleophile (the arrow in Figure 2 shows this carbon atom), is shielded by the methyl substituent of the 2,4,6-trimethylphenyl group of the chiral ligand.

The geometries of the optimized structures of the intermediates shown in Figure 2 thus account for the

(16) The *N*-tosyl substituent can be removed as described by first *N*-Boc protection followed by treatment with Mg/MeOH: see ref 11c and Nyasse et al. (Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017). Removal can also be achieved by treatment with phenol in a refluxing HBr/HOAc solution by addition of H_2O: see ref 15g. Treatment with SmI_2 in THF at room temperature has been found to be able to remove the *N*-tosyl substituent from *β*-lactams: see ref 15m.

(17) We have previously postulated that highly activated imines such as the *N*-tosyl-α-imino ester **3j** coordinate to the catalyst in various types of addition reactions to this imine: see e.g. ref 15j.

(18) The structures have been optimized by using PM3 calculations applying the PC-Spartan program.

(19) The heat of formation calculated for **10a** and **11a** is −10.9 and −11.1 kcal/mol, respectively. For **10b** and **11b**, the calculated heat of formation values are −39.2 and −26.8 kcal/mol, respectively.

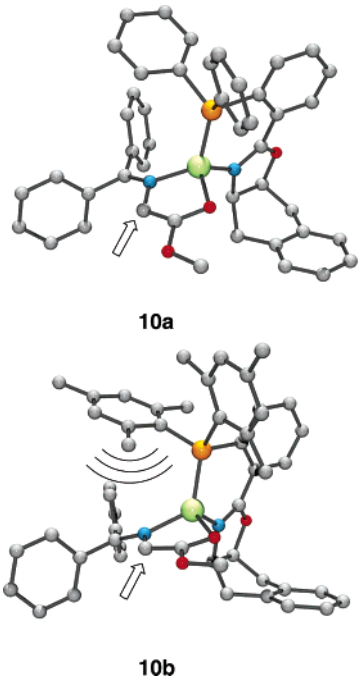


FIGURE 2. Optimized structure of intermediates **10a** of the benzophenone imine glycine methyl ester **1a** anion coordinated to the copper(I)-phenyl phosphino-oxazoline ligand **8a** (top) and the optimized structure of the most stable intermediate (**10b**) of the benzophenone imine glycine methyl ester **1a** anion coordinated to the copper(I)-phenyl phosphino-oxazoline ligand **8c** (bottom).

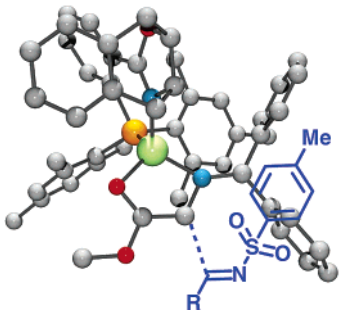


FIGURE 3. Proposed diastereo- and enantioselective approach of the imine (blue) to the *Si*-face of the benzophenone imine glycine methyl ester **1a** anion in intermediate **10b**. The dotted blue line shows the carbon−carbon bond being formed.

experimental observations that ligand **8a**, which has diphenyl phosphine groups, gives low enantioselectivity in this Mannich reaction, while ligand **8c**, having 2,4,6-trimethylphenyl phosphine groups, gives excellent enantioselectivity. Figure 3 shows the proposed approach of the imines **3** to the *Si*-face of the benzophenone imine glycine methyl ester **1a** anion in intermediate **10b** to account for observed diastereo- and enantioselectivity. An approach of the *Re*-face of the imines **3** instead of the *Si*-face would lead to a significant steric repulsion between the R-substituent of the imine and the tetrahydronaphthalene fragment of the chiral ligand that projects out from the plane.

In summary, we have developed the first chiral Lewis acid diastereo- and enantioselective Mannich reaction of imines of glycine esters. This reaction proceeds in high yield and with good to excellent diastereoselectivity and excellent enantioselectivity for both *N*-protected-*C*-aryl and *C*-alkyl imines catalyzed by a copper(I)-phosphino-oxazoline ligand complex derived from (1*R*,2*S*)-dihydroxy-1,2,3,4-tetrahydronaphthalene. It is demonstrated that the reaction gives access to optically active α,*β*-diamino acid derivatives. Experimental and theoretical investigations show that the high enantioselectivity of the Mannich reaction can be accounted for by face shielding of the *Re*-face of the nucleophilic carbon atom of the imine glycine methyl ester anion by the methyl substituent of the 2,4,6-trimethylphenyl group of the chiral ligand.

Experimental Section

General Methods. All reactions were carried out under anhydrous conditions in flame-dried Schlenk tubes. Solvents were dried according to standard procedures and distilled prior to use. The ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent, and were reported in ppm relative to $CHCl_3$ (δ 7.23) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ 77.00) for ^{13}C NMR. Enantiomeric excess was determined by HPLC, using a Chiralpack AD column or Chiracel OD column as stated below, and checked with the corresponding racemic samples, obtained using racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP). Optical rotations were measured with use of a sodium lamp and reported as follows: $[\alpha]^{rt}_D$ (*c* in g per 100 mL, solvent). Melting points were determined on an electrothermal melting point apparatus and were uncorrected.

Materials. The phosphino-oxazoline ligands **8a**−**c** were prepared following literature or modified procedure.[20] The benzophenone imines **1a**−**c** were prepared from the corresponding amine hydrochlorides and benzophenone imine.[21] Imines **3a**,**b**,[22a] **3b**−**h**,[22b] and **3j**[22c] were prepared following literature procedures. $CuClO_4$·4MeCN was prepared as described in the literature.[23] Et_3N was distilled over CaH_2 and stored over 4 Å MS, which were stored at 120 °C and flame dried under vacuum in the reaction Schlenk before use.

General Procedure for the Catalytic Reactions. $CuClO_4$·4MeCN (3.3 mg, 0.01 mmol) and the phosphino-oxazoline ligand **8c** (5.7 mg, 0.011 mmol) were added under N_2 to a flame-dried Schlenk tube, containing activated 4 Å MS and a stirring bar. The mixture was dried for 30 min under vacuum with stirring, then freshly distilled anhydrous THF (1 mL) was added. After being stirred for 15 min, the yellow solution was cooled to −20 °C (NaCl/ice bath), before the benzophenone imine **1a**−**c** was added (0.1 mmol), followed by Et_3N (1.4 μL, 0.01 mmol) and by the *N*-tosylimine **3a**−**j** (0.11 mmol). The reaction mixture was stirred at −20 °C overnight, then filtered through a short plug of silica gel. After evaporation of the solvent, the crude product was analyzed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio, and then purified by chromatography on silica gel (CH_2Cl_2/Et_2O mixtures).

Methyl 2-[(Diphenylmethylene)amino]-3-phenyl-3-(*p*-toluenesulfonylamino)propanoate (4a). According to the

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general procedure, the reaction of the benzophenone imine of the glycine methyl ester **1a** with the *N*-tosyl imine **3a** afforded after chromatographic purification on silica gel the white solid **4a** in 94% yield, as a mixture of diastereomers (dr = 79:21 determined by ^{1}H NMR analysis of the crude product). According to HPLC with a Chiralpak AD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), the enantiomeric excess of the major diastereomer is 97% ee, and the enantiomeric excess of the minor diastereomer is 94% ee. ^{1}H NMR: δ 7.60−6.80 (m, 17 H_{maj}, 19 H_{min}), 6.35 (d, J = 8.4 Hz, 1H_{maj}), 6.27 (d, J = 6.8 Hz, 2H_{maj}), 5.76 (d, J = 7.6 Hz, 1H_{min}), 5.10 (dd, J = 8.4, 2.4 Hz, 1H_{maj}), 4.64 (dd, J = 7.2, 5.6 Hz, 1H_{min}), 4.28 (d, J = 6.0 Hz, 1H_{min}), 4.07 (d, J = 2.0 Hz, 1H_{maj}), 3.43 (s, 3H_{maj}), 3.42 (s, 3H_{min}), 2.26 (s, 3H_{maj}), 2.19 (s, 3H_{min}). ^{13}C NMR (minor isomer in parentheses): δ 173.05, (170.01), 169.62, (142.91), 142.75, 138.87, (138.69), 138.37, 138.07, (137.54), (137.09), (135.46), 135.42, 130.86, (129.20), 129.15, (128.89), 128.85, 128.55, 128.29, 128.11, 128.08, (128.05), (128.01), (127.64), (127.64), (127.41), (127.36), (127.23), (127.16), 127.02, 126.82, 126.69, 69.93, (69.42), (59.95), 59.42, 52.31, (52.07), 21.36. HRMS: exact mass calcd for $C_{30}H_{28}N_2O_4S$ [M + Na]$^+$ 535.1667, found 535.1710.

Ethyl 2-[(Diphenylmethylene)amino]-3-phenyl-3-(*p*-toluenesulfonylamino)propanoate (4b). According to the general procedure, the reaction of the benzophenone imine of the glycine alkyl ester **1b** with the *N*-tosylimine **3a** afforded after chromatographic purification on silica gel the white solids **4b** and **4b′** in 87% overall yield, as single diastereomers. The diastereomeric ratio, determined by ^{1}H NMR analysis of the crude product, is 83:17. According to HPLC with a Chiralcel OD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), the enantiomeric excess of the major diastereomer **4b** is 96% ee, and the enantiomeric excess of the minor diastereomer **4b′**, detected by HPLC with a Chiralpack AD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), is 94% ee.

Major diastereomer (2*S*,3*R*)-**4b**: mp 129−130 °C; $[\alpha]^{rt}_D$ −168 (*c* 1.25 in $CHCl_3$). ^{1}H NMR: δ 7.80−6.95 (m, 17H), 6.38 (d, J = 8.4 Hz, 1H), 6.30 (d, J = 7.2 Hz, 2H), 5.16 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 4.08 (d, J = 2.4 Hz, 1H), 4.00−3.87 (m, 2H), 2.30 (s, 3H), 1.14 (t, J = 8.0 Hz, 3H). ^{13}C NMR: δ 172.91, 169.13, 142.71, 138.84, 138.44, 138.12, 135,53, 130.81, 129.09, 128.84, 128.52, 128.27, 128.08, 127.19, 126.99, 126.85, 126.76, 69.97, 61.48, 59.45, 21.36, 13.99. HRMS: exact mass calcd for $C_{31}H_{30}N_2O_4S$ [M + Na]$^+$ 549.1824, found 549.1833.

Minor diastereomer **4b′**: mp 52−54 °C; $[\alpha]^{rt}_D$ −26 (*c* 0.350 in $CHCl_3$). ^{1}H NMR: δ 7.60−6.80 (m, 19H), 5.80 (d, J = 7.6 Hz, 1H), 4.68 (t, J = 6.4 Hz, 1H), 4.31 (d, J = 5.6 Hz, 1H), 3.94−3.88 (m, 2H), 2.24 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 173.00, 169.52, 142.89, 138.78, 137.61, 137.20, 135.60, 130.85, 129.21, 128.93, 128.87, 128.58, 128.04, 127.64, 127.58, 127.41, 127.19, 69.28, 61.19, 59.90, 21.40, 13.86. HRMS: exact mass calcd for $C_{31}H_{30}N_2O_4S$ [M + Na]$^+$ 549.1824, found 549.1830.

***tert*-Butyl 2-[(Diphenylmethylene)amino]-3-phenyl-3-(*p*-toluenesulfonylamino)propanoate (4c).** According to the general procedure, the reaction of the benzophenone imine of the glycine alkyl ester **1c** with the *N*-tosylimine **3a** afforded after chromatographic purification on silica gel the white solids **4c** and **4c′** in 90% overall yield, as single diastereomers. The diastereomeric ratio, determined by ^{1}H NMR analysis of the crude product, is 92:8. According to HPLC with a Chiralcel OD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), the enantiomeric excess of the major diastereomer **4c** is 85% ee, and the enantiomeric excess of the minor diastereomer **4c′**, detected by HPLC with a Chiralpack AD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), is 71% ee.

Major diastereomer (2*S*,3*R*)-**4c**: mp 100−101 °C; $[\alpha]^{rt}_D$ −105 (*c* 0.247 in $CHCl_3$). ^{1}H NMR: δ 7.60−6.95 (m, 17H), 6.35 (d, J = 7.2 Hz, 2H), 6.30 (d, J = 8.4 Hz, 1H), 5.17 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 3.99 (d, J = 2.4 Hz, 1H), 2.26 (s, 3H), 1.40 (s, 9H). ^{13}C NMR: δ 172.41, 168.10, 142.54, 138.69, 138.62, 138.31, 135,75, 130.66, 129.01, 128.77, 128.43, 128.22, 128.04, 127.92, 127.02, 126.91, 126.89, 82.31, 70.61, 59.66, 27.85, 21.32. HRMS: exact mass calcd for $C_{33}H_{34}N_2O_4S$ [M + Na]$^+$ 577.2137, found 577.2145.

Minor diastereomer **4c′**: mp 42−46 °C; $[\alpha]^{rt}_D$ −32 (*c* 0.22 in $CHCl_3$). ^{1}H NMR: δ 7.80−6.90 (m, 19H), 5.76 (d, J = 8.0 Hz, 1H), 4.68 (t, J = 6.4 Hz, 1H), 4.26 (d, J = 5.6 Hz, 1H), 2.24 (s, 3H), 1.16 (s, 9H). ^{13}C NMR: δ 172.89, 168.26, 142.79, 138.96, 137.73, 137.41, 135.81, 130.74, 129.19, 128.87, 128.74, 128,-48, 128.03, 127.99, 127.92, 127.48, 127.13, 82.09, 69.44, 59.62, 27.68, 21.41. HRMS: exact mass calcd for $C_{33}H_{34}N_2O_4S$ [M + Na]$^+$ 577.2137, found 577.2164.

Methyl 2-[(Diphenylmethylene)amino]-3-(*p*-methoxyphenyl)-3-(*p*-toluenesulfonylamino)propanoate (4d). According to the general procedure, the reaction of the benzophenone imine of the glycine methyl ester **1a** with the *N*-tosyl imine **3b** afforded after chromatographic purification on silica gel the white solid **4d** in 90% yield, as a mixture of diastereomers (dr = 82:18 determined by ^{1}H NMR spectroscopy of the crude product). According to HPLC with a Chiralpak AD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), the enantiomeric excess of the major diastereomer is 97% ee, and the enantiomeric excess of the minor diastereomer is 95% ee. ^{1}H NMR: δ 7.60−6.50 (m, 16 H_{maj}, 18 H_{min}), 6.33 (d, J = 6.8 Hz, 2H_{maj}), 6.26 (d, J = 8.0 Hz, 1H_{maj}), 5.66 (d, J = 7.2 Hz, 1H_{min}), 5.00 (dd, J = 8.0, 2.0 Hz, 1H_{maj}), 4.58 (t, J = 6.8 Hz, 1H_{min}), 4.25 (d, J = 6.0 Hz, 1H_{min}), 4.04 (d, J = 2.4 Hz, 1H_{maj}), 3.64 (s, 3H_{min}), 3.62 (s, 3H_{maj}), 3.39 (s, 3H_{maj}), 3.38 (s, 3H_{min}), 2.23 (s, 3H_{maj}), 2.17 (s, 3H_{min}). ^{13}C NMR (minor isomer in brackets): δ (173.04), 172.95, (170.01), 169.67, (158.97), 158.76, (142.83), 142.66, (138.75), 138.43, 138.14, (137.20), 135.49, (131.06), 130.85, 130.81, (129.18), 129.12, 128.85, (128.64), (128.57), (128.53), 128.32, 128.09, (128.01), 127.88, (127.38), (127.17), 127.03, 126.88, 113.48, (113.41), 69.99, (69.45), (59.43), 58.99, 55.21, (55.12), 52.24, (52.04), 21.36. HRMS: exact mass calcd for $C_{31}H_{30}N_2O_5S$ [M + Na]$^+$ 565.1773, found 565.1779.

Methyl 3-(*o*-Bromophenyl)-2-[(diphenylmethylene)amino]-3-(*p*-toluenesulfonylamino)propanoate (4e). According to the general procedure, the reaction of the benzophenone imine of the glycine methyl ester **1a** with the *N*-tosyl imine **3c** afforded after chromatographic purification on silica gel the white solid **4e** in 99% yield, as a mixture of diastereomers (dr = 61:39 determined by ^{1}H NMR analysis of the crude product). According to HPLC with a Chiralpak AD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), the enantiomeric excess of the major diastereomer is 96% ee, and the enantiomeric excess of the minor diastereomer is >99% ee. ^{1}H NMR: δ 7.60−6.85 (m, 16 H_{maj}, 18 H_{min}), 6.43 (d, J = 8.4 Hz, 1H_{maj}), 6.33 (d, J = 4.8 Hz, 1H_{min}), 6.17 (d, J = 6.0 Hz, 2H_{maj}), 5.42 (dd, J = 8.0, 2.0 Hz, 1H_{maj}), 4.73 (t, J = 5.6 Hz, 1H_{min}), 4.45 (d, J = 6.0 Hz, 1H_{min}), 4.23 (d, J = 2.0 Hz, 1H_{maj}), 3.36 (s, 3H_{maj}, 3H_{min}), 2.25 (s, 3H_{maj}), 2.14 (s, 3H_{min}). ^{13}C NMR: δ 173.56, 172.50, 169.80, 169.36, 143.04, 142.97, 138.46, 138.12, 137.65, 137.61, 136.22, 135.25, 132.55, 132.46, 130.92, 129.30, 129.27, 129.23, 129.18, 128.99, 128.91, 128.83, 128.80, 128.62, 128.56, 128.31, 128.08, 127.54, 127.61, 127.48, 127.26, 127.09, 126.96, 126.61, 122.24, 66.48, 58.35, 52.28, 51.93, 21.37. HRMS: exact mass calcd for $C_{30}H_{27}BrN_2O_4S$ [M + Na]$^+$ 613.0773, found 613.0740.

Methyl 3-(*m*-Chlorophenyl)-2-[(diphenylmethylene)amino]-3-(*p*-toluenesulfonylamino)propanoate (4f). According to the general procedure, the reaction of the benzophenone imine of the glycine methyl ester **1a** with the *N*-tosyl imine **3d** afforded after chromatographic purification on silica gel the white solid **4f** in 93% yield, as a mixture of diastereomers (dr = 84:16 determined by ^{1}H NMR analysis of the crude product). According to HPLC with a Chiralpak AD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), the enantiomeric excess of the major diastereomer is 95% ee. ^{1}H NMR: δ 7.60−6.85 (m, 16 H_{maj}, 18 H_{min}), 6.35 (m, 3H_{maj}), 5.73 (d, J = 7.2 Hz, 1H_{min}), 5.04 (dd, J = 8.4, 2.0 Hz, 1H_{maj}), 4.65 (t, J = 6.8 Hz, 1H_{min}), 4.26 (d, J = 6.0 Hz, 1H_{min}), 4.06 (d, J = 2.4 Hz, 1H_{maj}), 3.42 (s, 3H_{maj}, 3H_{min}), 2.27 (s, 3H_{maj}), 2.21 (s, 3H_{min}). ^{13}C NMR

(minor isomer in brackets): δ 173.52, (173.46), (169.70) 169.35, (143.22), 143.06, 140.98, (139.44), (138.56), 138.18, 137.81, (136.84), 135.33, 134.05, (133.86), 131.00, (130.95), 129.42, 129.26, (128.99), (128.89), 128.85, 128.75, (128.61), 128.40, 128.12, (128.05), (127.84), (127.76), 127.38, (127.33), (127.09), 126.98, 126.74, (125.94), 124.91, 69.57, (69.07), (59.42), 58.90, 52.38, (52.22), 21.37. HRMS: exact mass calcd for $C_{30}H_{27}ClN_2O_4S$ $[M + H]^+$ 547.1458, found 547.1468.

Methyl 2-[(Diphenylmethylene)amino]-3-(2-naphthyl)-3-(*p*-toluenesulfonylamino)propanoate (4g). According to the general procedure, the reaction of the benzophenone imine of the glycine methyl ester **1a** with the *N*-tosyl imine **3e** afforded after chromatographic purification on silica gel the white solid **4g** in 90% yield, as a mixture of diastereomers (dr = 86:14 determined by ^{1}H NMR analysis of the crude product). According to HPLC with a Chiralpak AD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), the enantiomeric excess of the major diastereomer is 97% ee, and the enantiomeric excess of the minor diastereomer is 92% ee. ^{1}H NMR: δ 7.60−6.70 (m, 19 H_{maj}, 21 H_{min}), 6.39 (d, J = 8.4 Hz, $1H_{maj}$), 6.12 (d, J = 6.8 Hz, $2H_{maj}$), 5.76 (d, J = 8.0 Hz, $1H_{min}$), 5.18 (dd, J = 8.4, 2.0 Hz, $1H_{maj}$), 4.77 (dd, J = 7.6, 6.0 Hz, $1H_{min}$), 4.34 (d, J = 6.0 Hz, $1H_{min}$), 4.15 (d, J = 2.4 Hz, $1H_{maj}$), 3.39 (s, $3H_{maj}$), 3.34 (s, $3H_{min}$), 2.05 (s, $3H_{maj}$), 1.96 (s, $3H_{min}$). ^{13}C NMR (minor isomer in parentheses): δ 173.19, (170.01), 169.67, (142.92), 142.81, (138.71), 138.36, 138.00, (137.03), 136.08, (135.44), 135.34, (134.70), 132.88, (132.80), (132.73), 132.51, 130.86, (130.83), 129.08, (128.89), 128.83, (128.53), 128.22, 128.07, (128.00), (127.88), 127.84, (127.78), 127.39, (127.10), 126.99, 126.78, 126.03, 125.97, (125.90), 125.85, (125.11), 124.47, 69.82, (69.40), (60.13), 59.61, 52.36, (52.12), 21.20. HRMS: exact mass calcd for $C_{34}H_{30}N_2O_4S$ $[M + Na]^+$ 585.1824, found 585.2013.

(2*S*,3*R*)-Methyl 2-[(Diphenylmethylene)amino]-4-methyl-3-(*p*-toluenesulfonylamino)pentanoate (4h). According to the general procedure, the reaction of the benzophenone imine of the glycine methyl ester **1a** with the *N*-tosyl imine **3f** afforded after chromatographic purification on silica gel the white solid **4h** in 73% yield, as a single diastereomer (dr >95:5 determined by ^{1}H NMR analysis of the crude product). According to HPLC with a Chiralpak AD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), the enantiomeric excess of the product is 96% ee; mp 134−135 °C; $[\alpha]^{rt}_D$ −43 (*c* 0.673 in $CHCl_3$). ^{1}H NMR: δ 7.70−6.95 (m, 14 H), 5.93 (d, J = 8.8 Hz, 1H), 3.98 (d, J = 1.6 Hz, 1H), 3.62 (dt, J_t = 9.2 Hz, J_d = 1.6 Hz, 1H), 3.19 (s, 3H), 2.29 (s, 3H), 1.70−1.60 (m, 1H), 0.76 (d, J = 6.8 Hz, 3H), 0.63 (d, J = 6.8 Hz, 3H). ^{13}C NMR: δ 172.27, 170.95, 142.64, 139.14, 138.67, 136.16, 130.92, 129.31, 129.03, 128.91, 128.66, 128.15, 127.01, 66.00, 61.69, 52.03, 32.12, 21.43, 19.57, 18.85. HRMS: exact mass calcd for $C_{27}H_{30}N_2O_4S$ $[M + Na]^+$ 501.1824, found 501.1848.

(2*S*,3*R*)-Methyl 3-Cyclohexyl-2-[(diphenylmethylene)-amino]-3-(*p*-toluenesulfonylamino)propanoate (4i). According to the general procedure, the reaction of the benzophenone imine of the glycine methyl ester **1a** with the *N*-tosylimine **3g** afforded after chromatographic purification on silica gel the white solid **4i** in 85% yield, as a single diastereomer (dr >95:5 determined by ^{1}H NMR analysis of the crude product). According to HPLC with a Chiralcel OD column (hexane/*i*-PrOH 95:5, 1.0 mL min^{-1}), the enantiomeric excess of the product is 92% ee; mp 64−66 °C; $[\alpha]^{rt}_D$ −39 (*c* 1.088 in $CHCl_3$). ^{1}H NMR: δ 7.80−6.95 (m, 14 H), 5.95 (d, J = 8.8 Hz, 1H), 4.08 (d, J = 1.2 Hz, 1H), 3.73 (dt, J_t = 8.4 Hz, J_d = 1.2 Hz, 1H), 3.21 (s, 3H), 2.36 (s, 3H), 1.80−0.75 (m, 11H). ^{13}C NMR: δ 172.26, 170.99, 142.56, 139.25, 138.68, 136.19, 130.91, 129.26, 129.02, 128.93, 128.62, 128.16, 126.97, 126.95, 64.83, 61.06, 51.96, 41.49, 29.82, 29.28, 26.15, 26.12, 26.09, 21.41. HRMS: exact mass calcd for $C_{30}H_{34}N_2O_4S$ $[M + Na]^+$ 541.2137, found 541.2111.

(2*S*,3*R*)-Methyl 2-[(Diphenylmethylene)amino]-3-(*p*-toluenesulfonylamino)heptanoate (4j). According to the general procedure, the reaction of the benzophenone imine of the glycine methyl ester **1a** with the *N*-tosyl imine **3h** afforded after chromatographic purification on silica gel the colorless thick oil **4j** in 61% yield, as a single diastereomer (dr >95:5 determined by ^{1}H NMR analysis of the crude product). According to HPLC with a Chiralpak AD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), the enantiomeric excess of the product is 88% ee; $[\alpha]^{rt}_D$ −33 (*c* 1.05 in $CHCl_3$). ^{1}H NMR: δ 7.75−6.95 (m, 14 H), 5.70 (d, J = 9.2 Hz, 1H), 3.94 (d, J = 1.6 Hz, 1H), 3.75 (ddt, J_t = 6.8 Hz, J_d = 8.0 Hz, J_d = 2.4 Hz, 1H), 3.28 (s, 3H), 2.33 (s, 3H), 1.50−0.70 (m, 6H), 0.69 (t, J = 6.8 Hz, 3H). ^{13}C NMR: δ 172.86, 170.73, 142.77, 138.91, 138.70, 135.95, 130.93, 129.37, 129.99, 128.93, 128.65, 128.16, 127.23, 126.99, 66.27, 56.47, 52.00, 33.80, 27.77, 22.29, 21.45, 13.87. HRMS: exact mass calcd for $C_{27}H_{30}N_2O_4S$ $[M + Na]^+$ 515.1980, found 515.1988.

Methyl 2-[(Diphenylmethylene)amino]-3-(2-furyl)-3-(*p*-toluenesulfonylamino)propanoate (4k). According to the general procedure, the reaction of the benzophenone imine of the glycine methyl ester **1a** with the *N*-tosyl imine **3i** afforded after chromatographic purification on silica gel the white solid **4k** in 88% yield, as a mixture of diastereomers (dr = 54:46 determined by ^{1}H NMR analysis of the crude product). ^{1}H NMR: δ 7.70−6.70 (m, $15H_{maj}$, $15H_{min}$), 6.19 (d, J = 9.2 Hz, $1H_{maj}$), 6.15 (d, J = 3.2 Hz, $1H_{min}$), 6.14−6.10 (m, $1H_{maj}$, $1H_{min}$), 6.05 (d, J = 3.2 Hz, $1H_{maj}$), 5.31 (d, J = 9.2 Hz, $1H_{min}$), 5.18 (dd, J = 9.2, 2.0 Hz, $1H_{maj}$), 5.00 (dd, J = 9.6, 6.0 Hz, $1H_{min}$), 4.45 (d, J = 6.0 Hz, $1H_{min}$), 4.35 (d, J = 2.4 Hz, $1H_{maj}$), 3.58 (s, $3H_{min}$), 3.48 (s, $3H_{maj}$), 2.34 (s, $3H_{maj}$), 2.31 (s, $3H_{min}$). ^{13}C NMR: δ 173.99, 173.69, 169.83, 169.63, 152.28, 150.71, 143.34, 143.19, 142.16, 141.99, 139.18, 138.99, 138.36, 137.55, 135.96, 135.70, 131.14, 131.10, 129.60, 129.56, 129.24, 129.18, 129.13, 128.76, 128.74, 128.34, 128.30, 127.89, 127.45, 127.30, 127.29, 110.69, 110.54, 108.87, 108.04, 68.62, 67.90, 54.47, 54.17, 52.63, 52.59, 21.71. HRMS: exact mass calcd for $C_{28}H_{26}N_2O_5S$ $[M + Na]^+$ 525.1460, found 525.1429.

Ethyl 3-[(Diphenylmethylene)amino]-3-methyloxocarbonyl-2-(*p*-toluenesulfonylamino)propanoate (4l). According to the general procedure, the reaction of the benzophenone imine of the glycine methyl ester **1a** with the *N*-tosyl imine **3j** afforded after chromatographic purification on silica gel the white solid **4l** in 84% yield, as a mixture of diastereomers (dr = 60:40 determined by ^{1}H NMR analysis of the crude product). According to HPLC with a Chiralpak AD column (hexane/*i*-PrOH 90:10, 1.0 mL min^{-1}), the enantiomeric excess of the major diastereomer is 60% ee, and the enantiomeric excess of the minor diastereomer is 57% ee. ^{1}H NMR: δ 7.70−6.90 (m, $14H_{maj}$, $14H_{min}$), 5.94 (d, J = 10.4 Hz, $1H_{maj}$), 5.33 (d, J = 7.6 Hz, $1H_{min}$), 4.57 (dd, J = 10.0, 2.4 Hz, $1H_{maj}$), 4.52 (dd, J = 7.6, 2.8 Hz, $1H_{min}$), 4.43 (d, J = 2.8 Hz, $1H_{maj}$), 4.15 (d, J = 2.4 Hz, $1H_{min}$), 4.15−4.07 (m, $1H_{min}$), 4.04−3.99 (m, $1H_{min}$), 3.96−3.89 (m, $1H_{maj}$), 3.84−3.76 (m, $1H_{maj}$), 3.63 (s, $3H_{min}$), 3.45 (s, $3H_{maj}$), 2.32 (s, $3H_{maj}$, $3H_{min}$), 1.11 (t, J = 7.2 Hz, $3H_{min}$), 0.98 (t, J = 7.2 Hz, $3H_{maj}$). ^{13}C NMR (minor isomer in brackets): δ (174.23), 173.99, (169.16), 169.10, (168.93), 168.88, (143.61), 143.29, (138.73), 138.61, 137.80, (136.60), 135.53, (135.35), (132.40), 131.03, (130.90), (129.68), 129.39, 129.16, 129.12, (129.08), (128.95), (128.64), 128.61, (128.25), 128.07, (128.03), (127.64), 127.33, 127.21, (127.13), (68.14), 66.36, (62.33), 61.82, 58.48, (58.42), 52.47, (52.34), (21.52), 21.47, 13.91, (13.88). HRMS: exact mass calcd for $C_{27}H_{28}N_2O_6S$ $[M + Na]^+$ 531.1566, found 531.1570.

General Procedure for the Hydrolysis of the Imines 4a,k. A 2 N aq solution of HCl (1.5 mL) was added to a suspension of the benzophenone imine **4a**,**k** (0.05 mmol) in Et_2O (1 mL). The mixture was vigorously stirred for 3 h (two clear layers), then diluted with HCl (2 N, 2 mL). The layers were separated and the aq layer was washed with Et_2O (1 mL), then taken to pH 9 with solid Na_2CO_3 and extracted with CH_2Cl_2 (4 × 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated, affording in quantitative yield the crude free amines, which were used in the subsequent step with no further purification.

General Proceure for the Synthesis of Compounds

9a,b. Di-*tert*-butyl dicarbonate (0.06 mmol) in EtOAc (0.5 mL) was added to a stirred solution of the crude amines (0.05 mmol) in EtOAc (0.5 mL), followed by H_2O (0.5 mL) and Na_2CO_3 (0.06 mmol). The mixture was stirred overnight, then diluted with EtOAc (3 mL). The layers were separated, and the organic layer was washed with H_2O (2 mL) and brine (2 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Chromatographic purification (CH_2Cl_2/Et_2O) afforded the *N*-Boc-protected amines **9a**,**b** as single diastereomers.

Methyl 2-(*tert*-Butoxycarbonylamino)-3-(*p*-toluenesulfonylamino)-3-phenylpropanoate (9a). Following the general procedure, the white solids **9a** and **9a′** were obtained, after chromatography on silica gel, in 94% overall yield, as single diastereomers. According to HPLC with a Chiralcel OD column (hexane/*i*-PrOH 88:12, 1.0 mL min^{-1}), the enantiomeric excess of the major diastereomer **9a** is 97% ee, and the enantiomeric excess of the minor diastereomer **9a′**, detected with use of a Chiralpack AD column (hexane/*i*-PrOH 80:20, 1.0 mL min^{-1}), is 94% ee.

Major diastereomer (2*S*,3*R*)-**9a**: mp 185−187 °C; $[\alpha]^{rt}_D$ +6 (*c* 0.78 in $CHCl_3$). ^{1}H NMR: δ 7.49 (d, J = 7.2 Hz, 2H), 7.15−6.95 (m, 7H), 5.94 (br s, 1H), 5.29 (d, J = 8.4 Hz, 1H), 4.70 (br s, 1H), 4.52 (t, J = 7.2 Hz, 1H), 3.53 (s, 3H), 2.29 (s, 3H), 1.36 (s, 9H). ^{13}C NMR: δ 170.16, 155.50, 143.11, 137.32, 136.68, 129.28, 128.42, 128.00, 126.99, 126.80, 80.62, 59.85, 58.44, 52.61, 28.17, 21.41. HRMS: exact mass calcd for $C_{22}H_{28}N_2O_6S$ $[M + Na]^+$ 471.1566, found 471.1576.

Minor diastereomer **9a′**: mp 179−180 °C; $[\alpha]^{rt}_D$ +55 (*c* 0.25 in $CHCl_3$). ^{1}H NMR: δ 7.55 (d, J = 7.6 Hz, 2H), 7.10−6.90 (m, 7H), 6.50 (br s, 1H), 5.08 (br s, 1H), 4.92 (br s, 1H), 4.51 (dd, J = 3.6, 7.6 Hz, 1H), 3.62 (s, 3H), 2.32 (s, 3H), 1.41 (s, 9H). ^{13}C NMR: δ 169.70, 154.88, 143.09, 137.52, 135.67, 129.36, 128.33, 127.98, 127.00, 126.75, 81.02, 59.50, 58.30, 52.70, 28.18, 21.46. HRMS: exact mass calcd for $C_{22}H_{28}N_2O_6S$ $[M + Na]^+$ 471.1566, found 471.1556.

Methyl 2-(*tert*-Butoxycarbonylamino)-3-(2-furyl)-3-(*p*-toluenesulfonylamino)propanoate (9b). Following the general procedure, the white solids **9b** and **9b′** were obtained, after chromatography on silica gel, in 92% overall yield, as single diastereomers. According to HPLC with a Chiralcel OD column (hexane/*i*-PrOH 85:15, 1.0 mL min^{-1}), the enantiomeric excess of the major diastereomer **9b** is 90% ee, and the enantiomeric excess of the minor diastereomer **9b′**, detected with use of a Chiralpack AD column (hexane/*i*-PrOH 85:15, 1.0 mL min^{-1}), is 95% ee.

Major diastereomer (2*S*,3*R*)-**9b**: mp 143−144 °C; $[\alpha]^{rt}_D$ +8 (*c* 0.800 in $CHCl_3$). ^{1}H NMR: δ 7.59 (d, J = 8.0 Hz, 2H), 7.20−7.05 (m, 3H), 6.10 (dd, J = 2.0, 3.2 Hz, 1H), 5.98 (d, J = 2.0 Hz, 1H), 5.58 (br s, 1H), 5.28 (d, J = 8.4 Hz, 1H), 4.85 (br s, 1H), 4.60 (br s, 1H), 3.67 (s, 3H), 2.34 (s, 3H), 1.37 (s, 9H). ^{13}C NMR: δ 169.87, 155.02, 149.46, 142.54, 137.16, 129.44, 126.99, 110.26, 108.17, 80.49, 56.77, 53.46, 52.87, 28.15, 21.47. HRMS: exact mass calcd for $C_{20}H_{26}N_2O_7S$ $[M + Na]^+$ 461.1358, found 461.1364.

Minor diastereomer **9b′**: mp 125−126 °C; $[\alpha]^{rt}_D$ +68 (*c* 0.80 in $CHCl_3$). ^{1}H NMR: δ 7.64 (d, J = 7.6 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.15−7.12 (m, 1H), 6.14 (m, 1H), 6.03−5.98 (m, 2H), 5.17 (br s, 1H), 4.97 (dd, J = 3.6, 9.6 Hz, 1H), 4.51 (br s, 1H), 3.66 (s, 3H), 2.36 (s, 3H), 1.40 (s, 9H). ^{13}C NMR: δ 169.52, 155.86, 143.36, 142.64, 137.25, 129.51, 128.33, 127.00, 110.30, 108.62, 80.87, 57.02, 53.50, 52.82, 28.15, 21.49. HRMS: exact mass calcd for $C_{20}H_{26}N_2O_7S$ $[M + Na]^+$ 461.1358, found 461.1354.

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Supporting Information Available: Complete X-ray data for compound **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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