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Catalytic, Asymmetric Mannich-type Reactions of *N*-Acylimino Esters: Reactivity, Diastereo- and Enantioselectivity, and Application to Synthesis of N-Acylated Amino Acid Derivatives

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Abstract: In the presence of a catalytic amount of $Cu(OTf)_2$-chiral diamine **3e** complex, *N*-acylimino esters reacted with silyl enol ethers to afford the corresponding Mannich-type adducts in high yields with high enantioselectivities. A wide variety of silyl enol ethers derived from ketones, as well as esters and thioesters, reacted smoothly. In the reactions of α-substituted silyl enol ethers (α-methyl or benzyloxy), the desired *syn*-adducts were obtained in high yields with high diastereo- and enantioselectivities. Several intermediates for the synthesis of biologically important compounds were prepared using this novel catalytic asymmetric Mannich-type reaction, and at the same time, absolute and relative stereochemical assignments were made. In addition, it has been revealed that alkyl vinyl ethers reacted with *N*-acylimino esters in the presence of a catalytic amount of the Cu(II) catalyst to give the corresponding Mannich-type adducts in high yields with high enantioselectivities. This is the first example of catalytic asymmetric Mannich-type reactions with alkyl vinyl ethers. The reaction mechanism, structure of chiral catalyst-electrophile complexes, and transition states of these catalytic asymmetric reactions were assumed based on X-ray crystallographic analysis of the Cu(II)-chiral amine complex, PM3 calculations, and FT-IR analyses, etc. Finally, (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12, **1**), a new inhibitor of ceramide trafficking from endoplasmic reticulum to the site of sphingomyerin (SM) synthesis, has been synthesized efficiently using the present Mannich-type reaction as a key step. The synthesis involved three steps (two-pot), and total yield was 82.9%.

Introduction

N-Acylated amino acid derivatives are often observed in biologically important compounds such as peptides, ceramide, etc.[1] For the preparation of these compounds, the use of α-imino esters provides convenient ways.[2] According to typical methods, α-imino esters are treated with nucleophiles, and the protective groups of the amino moieties are removed and then the amino groups are acylated (eq 1).[3] More conveniently, reactions of *N*-acylimino esters would give N-acylated amino acid derivatives directly (eq 2).[4] However, *N*-acylimino esters are unstable and their use in organic synthesis has been rather limited. To address this issue, we have recently developed a convenient method for the preparation of *N*-acylimino esters using a polymer-supported amine.[5] Furthermore, a novel chiral copper catalyst has been developed to achieve enantioselective Mannich-type reactions of *N*-acylimino esters.[6] In this paper, we present a full account of this asymmetric reaction including reactivity, selectivity (diastereo- and enantioselectivity), reaction mechanism, catalyst structure, etc. Facile synthesis of a new inhibitor of ceramide trafficking, (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12, Figure 1, **1**), using this catalytic enantioselective reaction is also reported.

Results and Discussion

First, we searched for an effective catalyst for Mannich-type reactions of *N*-acylimino esters. Although *N*-acylimino esters

(1) (a) Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298. (b) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Wälchli, M. *J. Am. Chem. Soc.* **1989**, *111*, 2582. (c) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243. (d) von Döhren, H.; Keller, U.; Vater, J.; Zocher, R. *Chem. Rev.* **1997**, *97*, 2675. (e) Dickson, R. C. *Annu. Rec. Biochem.* **1998**, *67*, 27. (f) Kolter, T.; Sandhoff, K. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1532.

(2) (a)Weinreb, S. M.; Scola, P. A. *Chem. Rev.* **1989**, *89*, 1525. To our knowledge, α-imino ester was first used as a precursor to α-amino acid by Achmatowicz Jr. (b)Achmatowicz Jr., O.; Pietraszkiewicz, M. *J. Chem. Soc., Chem. Commun.* **1976**, 484.

(3) (a) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450. (b) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168. (c) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3504.

(4) (a) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W. Reuter, H.; Puff, H. *Tetrahedron* **1985**, *41*, 1693. (b) Münster, P.; Steglich, W. *Synthesis* **1987**, 223. (c) Bretschneider, T.; Miltz, W.; Münster, P.; Steglich, W. *Tetrahedron* **1988**, *44*, 5403. (d) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114. (e) Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**. *4*, 387. For a review of *N*-acyliminium ions and related intermediates, see Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(5) Kobayashi, S.; Kitagawa, H.; Matsubara, R. *J. Comb. Chem.* **2001**, *3*, 401.

(6) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143.

10.1021/ja0281840 CCC: $25.00

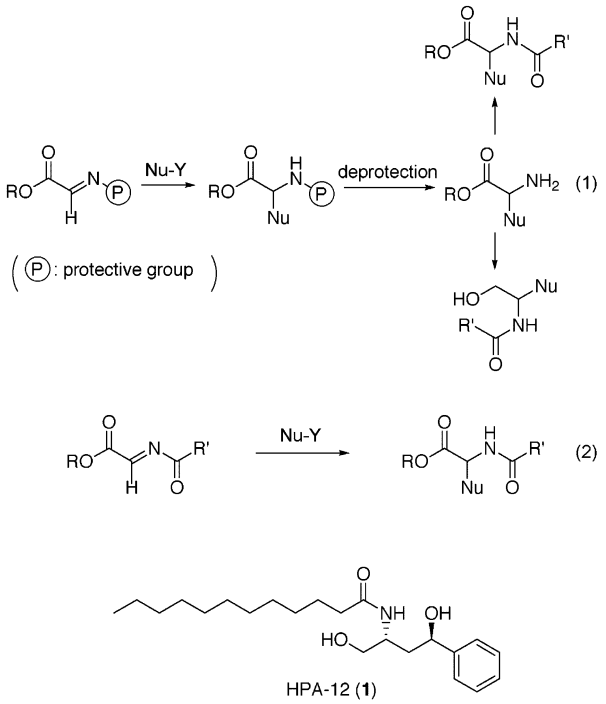
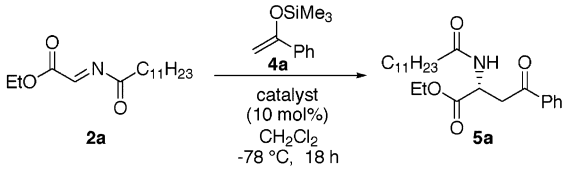


Figure 1. Novel inhibitor of ceramide trafficking, HPA-12.

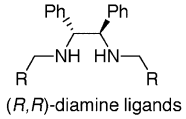
are known to be unstable and are difficult to prepare in high yields, we have recently developed a convenient preparation method of *N*-acylimino esters from the corresponding α-chloroglycine derivatives using a polymer-supported amine. We selected a model Mannich-type reaction of *N*-acylimino ester **2a** with the silyl enol ether **4a** derived from acetophenone, and several reaction factors such as metals, chiral ligands, conditions, etc., were examined. It was revealed that a chiral copper(II) catalyst prepared from $Cu(OTf)_2$ and chiral ligand **3e**[7] was promising. The effects of copper salts, chiral ligands, and reaction conditions are summarized in Table 1. It was already reported by Lectka et al. that $CuClO_4{\cdot}4CH_3CN-$BINAP[8] was effective for Mannich-type reactions of *N*-tosylimino esters with silyl enol ethers.[9−11] In the reaction of **2a**, however, low enantiometic excess was observed (Table 1, entries 1−3). On the other hand, combination of $Cu(OTf)_2$ and chiral diamine **3** gave promising results; for example, to a mixture of $Cu(OTf)_2$ and ligand **3e** (10 mol %), **2a** and the silyl enol ether were added

Table 1. Effects of Copper Salts, Chiral Ligands, and Reaction Conditions

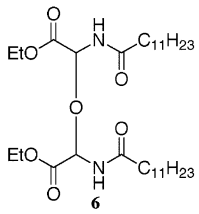


entry	catalyst	yield (%)[a]	Ee (%)[b]
1	$CuClO_4{\cdot}4CH_3CN$ + BINAP	44	15
2	$CuClO_4{\cdot}4CH_3CN$ + xylyl-BINAP[c]	69	12
3	$CuClO_4{\cdot}4CH_3CN$ + **3a**	62	8
4	$Cu(OTf)_2$ + BINAP	71	36
5	$Cu(OTf)_2$ + **3a**	25	63
6	$Cu(OTf)_2$ + **3b**	32	63
7	$Cu(OTf)_2$ + **3c**	24	75
8	$Cu(OTf)_2$ + **3d**	12	52
9	$Cu(OTf)_2$ + **3e**	20	80
10	$Cu(OTf)_2$ + **3f**	32	64
11[d]	$Cu(OTf)_2$ + **3e**	65	75
12[d,e]	$Cu(OTf)_2$ + **3e**	91	85
13[d,f]	$Cu(OTf)_2$ + **3e**	92	94
14[d,g]	$Cu(OTf)_2$ + **3e**	67	89
15[d,f]	$Cu(OTf){\cdot}1/2C_6H_6$ + **3e**	91	0
16[d,f]	$Cu(SbF_6)_2$ + **3e**	63	65

[a] Isolated yield from the corresponding α-chloroglycinate (imino ester was generated in situ). [b] Determined by chiral HPLC analysis. [c] (S)-(-)-Bis[bis(3,5-dimethylphenyl)phosphino]-1,1′-binaphthyl. [d] **2a** was added slowly after the addition of the silyl enol ether to the catalyst. [e] At −20 °C. [f] At 0 °C. [g] At rt.



3a: R = Ph
3b: R = 4-MePh
3c: R = 3,5-diMePh
3d: R = 3,5-di^{t}BuPh
3e: R = 1-Nap
3f: R = 2-Nap



successively to afford the desired adduct in 80% ee, but in low yield (entry 9). In this case, formation of a dimer of **2a** (**6**) was observed, presumably due to contamination by water. We carefully performed the reaction under anhydrous conditions, and the silyl enol ether was added to the catalyst first and then **2a** was slowly charged over 20 min to this mixture. The yield was dramatically improved, and the desired adduct was obtained in 92% yield with 94% ee (entry 13). For the copper salt, $Cu(OTf)_2$ was much better than $CuClO_4$, CuOTf, and even $Cu(SbF_6)_2$.[12] In addition, interesting temperature effects on selectivity were observed in this reaction. When the reactions

(7) (a) Mimoun, H.; Laumer, J. Y. S.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158. (b) Cavallo, L.; Cucciolito, M. E.; Martino, A. D.; Giordano, F.; Orabona, I.; Vitagliano, A. *Chem. Eur. J.* **2000**, *6*, 1127. (c) Kobayashi, S.; Hamada. T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640, and references therein.

(8) For the preparation of $CuClO_4{\cdot}4CH_3CN$, see: Kubas, G. J. *Inorganic Synthesis*; Shriver, D. F., Ed.; Plenum: New York, 1979; Vol. XIX, p 90.

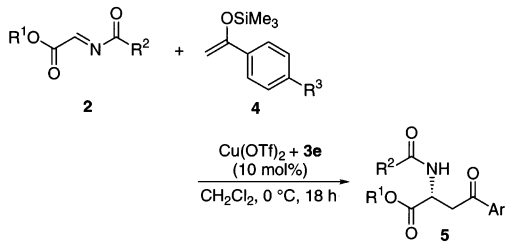
(9) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67.

(10) For the use of the Cu−BINAP system in enantioselective reactions of α-imino esters, see: (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (b) Drury, W. J., III.; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11 006. (c) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3121. (d) Yao, S.; Fang, X.; Jørgensen, K. A. *Chem. Commun.* **1998**, 2547. (e) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844. (f) Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293. (g) Johannsen, M. *Chem. Commun.* **1999**, 2233. (h) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4114. (i) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435. (j) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (k) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2992. Cf. (l) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.

(11) For other chiral Cu-catalyzed reactions, see, for example: (a) Wei, C.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (d) Bromidge, S.; Wilson, P. C.; Whiting, A. *Tetrahedron Lett.* **1998**, *39*, 8905. (e) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617. (f) Audrain, H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 11 543. (g) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12 517.

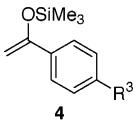
(12) $Cu(SbF_6)_2$-diamine complex was prepared according to the reported method. Evans, D. A.; Scheidt, K. A.; Johnston, J. N. Wills, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

Table 2. Mannich-type Reactions with Silyl Enol Ethers Derived from Ketones



	imine					
entry	R^1	R^2	Nu	yield (%)[a]	Ee(%)[b]	product
1	Et	CH_3 (**2b**)	**4a**	85	94	**5b**
2		$C_{10}H_{21}$ (**2c**)	**4a**	88	94	**5c**
3		$C_{11}H_{23}$ (**2a**)	**4a**	92	94	**5a**
4		$C_{12}H_{25}$ (**2d**)	**4a**	91	92	**5d**
5		$C_{13}H_{27}$ (**2e**)	**4a**	91	92	**5e**
6		$C_{11}H_{23}$ (**2a**)	**4b**	97	92	**5f**
7		$C_{11}H_{23}$ (**2a**)	**4c**	88	93	**5g**
8		$C_{11}H_{23}$ (**2a**)	**4d**	85	94	**5h**
9	Bn	$C_{11}H_{23}$ (**2f**)	**4a**	75	93	**5i**

[a] Isolated yield from the corresponding α-chloroglycinate (imino ester was generated in situ). [b] Determined by chiral HPLC analysis.



4	R^3
4a	H
4b	OMe
4c	Cl
4d	C_5H_{11}

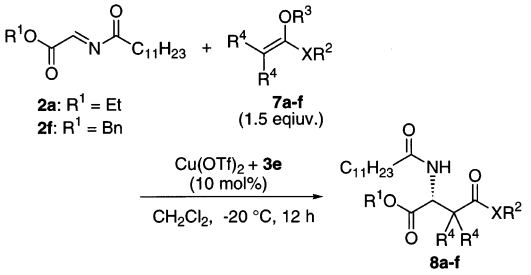
were carried out at −78 °C, −45 °C, −20 °C, 0 °C, and room temperature, the best selectivity was obtained at 0 °C. As the temperature was lowered, the selectivity was decreased. When the catalyst prepared at room temperature was cooled to −78 °C, a white precipitate was observed and the solution color changed from green to blue. This observation indicates that the catalyst structure was changed at lower temperature such as −78 °C. On the other hand, a slight loss of the selectivity was observed at room temperature. The loss was mainly ascribed to an uncatalyzed reaction pathway because this reaction proceeded to some extent without a catalyst to give a racemic adduct.

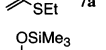
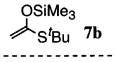
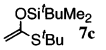
Several examples of the Mannich-type reactions of *N*-acylimino esters with silyl enol ethers derived from ketones in the presence of 10 mol % of the copper catalyst are shown in Table 2. In all cases, the desired adducts were obtained in high yields with high enantioselectivities.

We then investigated Mannich-type reactions of *N*-acylimino esters with silyl enol ethers derived from thioesters and esters (Table 3). This type of reaction provides one of the most efficient methods for the preparation of optically active *N*-acyl aspartic acid derivatives, which are versatile intermediates for several kinds of biologically important natural products and pharmaceutical chemicals.[13] Although asymmetric Mannich-type reactions of *N*-tosylimino esters or *N*-*p*-methoxyphenylimino esters using chiral copper(I) or palladium(II) catalysts were

(13) For examples using aspartic acid derivatives as chiral synthons, see: (a) Yoshida, T.; Takeshita, M.; Orita, H.; Kado, N.; Yasuda, S.; Kato, H.; Itoh, Y. *Chem. Pharm. Bull.* **1996**, *44*, 1128. (b) Humphrey, J. M.; Bridges R. J.; Hart, J. A.; Chamberlin, A. R. *J. Org. Chem.* **1994**, *59*, 2467. (c) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017. (d) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943.

Table 3. Asymmetric Mannich-type Reactions with Silyl Enol Ethers Derived from Esters or Thioesters



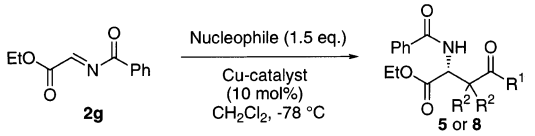
entry	imine	ketene acetal	solvent	yield (%)[a]	Ee (%)[b]	product
1	**2a**	 **7a**	CH_2Cl_2	89	6	**8a**
2	**2a**	 **7b**	CH_2Cl_2	77	31	**8b**
3	**2a**	 **7c**	CH_2Cl_2	89	60	**8b**
4	**2a**	**7c**	toluene	80	87	**8b**
5[c]	**2a**	**7c**	toluene	85	90	**8b**
6	**2a**	**7c**	xylene	86	68	**8b**
7	**2a**	**7c**	mesitylene	80	34	**8b**
8[c]	**2f**	**7d**	CH_2Cl_2	80	16	**8d**
9	**2a**	**7e**	CH_2Cl_2	96	72	**8e**
10	**2a**	**7f**	CH_2Cl_2	90	92	**8f**
11[d]	**2a**	**7f**	CH_2Cl_2	81	94	**8f**

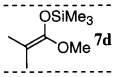
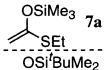
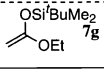
[a] Isolated yield from the corresponding α-chloroglycinate (imino ester was generated in situ). [b] Determined by chiral HPLC analysis. [c] At 0 °C. [d] 5 mol % of the catalyst was used.

already reported, silyl enol ethers derived from ketones were used in most cases and few examples using silyl enol ethers derived from thioesters and esters are known.[14] In the presence of 10 mol % of the $Cu(OTf)_2$-ligand **3e**, *N*-acylimino ester **2a** was treated with 1-ethylthio-1-trimethylsiloxyethene (**7a**) in dichloromethane at −20 °C. The reaction proceeded smoothly to afford the corresponding adduct in high yield, but in low selectivity (entry 1). The selectivity was improved when bulky silyl enol ethers were used. When 1-*tert*-butylthio-1-*tert*-butyldimethylsiloxyethene (**7c**) was used as a nucleophile and the reaction was conducted in toluene at 0 °C, the desired product was obtained in 85% yield with 90% ee (entry 5). Other solvents such as dichloromethane, xylene, and mesitylene gave lower selectivities. For α,α-disubstituted enol ethers, the ketene silyl acetal (**7e**) derived from the corresponding phenyl ester gave much better selectivity than the ketene silyl acetal (**7d**) derived from the methyl ester. High yield and selectivity (90% yield and 92% ee) were attained when 1-ethylthio-1-trimethylsilyl-2-methyl-1-propene (**7f**) was used (entry 10). The high

(14) The asymmetric Mannich-type reaction with ester-derived ketene acetals using a Cu(I)-BINAP catalyst was already reported by Lectka et al; however, the enantioselectivity for simple ester-derived ketene silyl acetals was moderate (~72% ee) except for the coumarinone derived ketene silyl acetals. See ref 9.

Table 4. Mannich-type Reactions of N−Benzoylimino Esters



entry	Nu	Cu-catalyst	yield (%)[a]	Ee (%)[b]	product
1[c]	 **4a**	$Cu(OTf)_2$ + **3e**	95	27	**5j**
2[d]	**4a**	$CuClO_4$•$4CH_3CN$ + (*R*)-BINAP	84	-70	**5j**
3[d]	**4a**	$CuClO_4$•$4CH_3CN$ + (*R*)-Tol-BINAP	73	-81	**5j**
4	**4a**	$CuClO_4$•$4CH_3CN$ + (*S*)-xylyl-BINAP	79	97	**5j**
5	 **7d**	$CuClO_4$•$4CH_3CN$ + (*S*)-xylyl-BINAP	81	96	**8g**
6	 **7a**	$CuClO_4$•$4CH_3CN$ + (*S*)-xylyl-BINAP	76	90	**8h**
7	 **7g**	$CuClO_4$•$4CH_3CN$ + (*S*)-xylyl-BINAP	69	79	**8i**

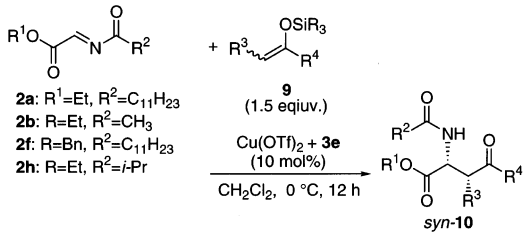
[a] Isolated yield from the corresponding α-bromoglycinate (imino ester was generated in situ). [b] Determined by chiral HPLC analysis. [c] At 0 °C. [d] 20 mol % of the catalyst was used.

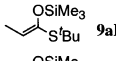
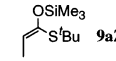
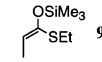
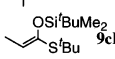
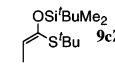
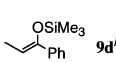
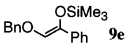
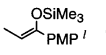
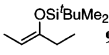
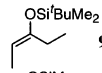
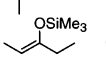
yield and selectivity were retained even when 5 mol % of the catalyst was employed (entry 11).

Although wide substrate scope was observed in the present Mannich-type reactions, lower selectivity was obtained in the reaction of *N*-benzoylimino ester **2g**. When **2g** was treated with the silyl enol ether derived from acetophenone (**4a**) in the presence of 10 mol % of $Cu(OTf)_2$-ligand **3e**, the Mannich-type adduct was produced in 95% yield with only 27% ee (Table 4, entry 1). On the other hand, the yield and selectivity were improved when $CuClO_4$•$4CH_3CN$−BINAP systems were used as the catalysts. In particular, the desired product was obtained in 79% yield with 97% ee in the presence of $CuClO_4$•$4CH_3CN$−(*S*)-xylyl-BINAP[15] (10 mol %) (entry 4). As for enolate components, silyl enol ethers derived from a ketone as well as an ester and a thioester worked well to afford the corresponding adducts in high yields with high ee's.

Diastereo- and Enantioselective Reactions. Diastereoselection in this Mannich-type reaction is of great interest not only from a synthetic point of view but also from a mechanistic aspect. We investigated reactions of *N*-acylimino esters with α-substituted silyl enol ethers in the presence of 10 mol % of $Cu(OTf)_2$-ligand **3e** (Table 5). When the reaction of *N*-acylimino ester **2a** with (*E*)-1-*tert*-butylthio-1-trimethylsiloxy-1-propene (**9aE**) was conducted in dichloromethane at 0 °C, the desired Mannich-type adduct was obtained in 89% yield with high *syn*-selectivity (*syn*/*anti* = 96/4), and the enantiomeric excess of the *syn*-adduct was 72% (entry 1). The geometrically isomeric enolate, (*Z*)-1-*tert*-butylthio-1-trimethylsiloxy-1-propene (**9aZ**), also reacted smoothly to give *syn*-adduct (*syn*/*anti* = 96/4), and the enantioselectivity of the adduct was improved to 90% ee

Table 5. Diastereo- and Enantioselective Mannich-type Reactions with α-Monosubstituted Silyl Enol Ethers



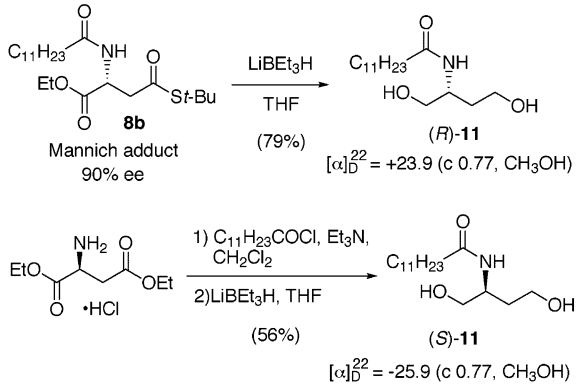
entry	imine	Nu	yield(%)[a]	*syn*:*anti*[b]	Ee(%)[c]	product
1	**2a**	 **9aE**[d]	89	96:4	72	**10a**
2[e]	**2a**	 **9aZ**[f]	90	96:4	90	**10a**
3	**2a**	 **9b**[g]	95	88:12	67	**10b**
4	**2a**	 **9cE**[h]	73	95:5	77	**10a**
5[e]	**2a**	 **9cZ**[f]	82	98:2	92	**10a**
6[i]	**2a**	**9cZ**[f]	65	78:22	80	**10a**
7[e]	**2f**	**9cZ**[f]	80	99:1	91	**10c**
8[e]	**2b**	**9aZ**[f]	70[j]	91:9	87	**10d**
9[e]	**2b**	**9cZ**[f]	68[j]	97:3	87	**10d**
10[e]	**2h**	**9cZ**[f]	96[j]	93:7	71	**10e**
11	**2a**	 **9d**[k]	79	92:8	93	**10f**
12	**2f**	**9d**[k]	81	85:15	93	**10g**
13	**2b**	**9d**[k]	75[j]	90:10	94	**10h**
14	**2a**	 **9e**[k]	77	89:11	92	**10i**
15	**2a**	 **9f**[k]	92	86:14	94	**10j**
16	**2b**	**9f**[k]	78[j]	81:19	90	**10k**
17	**2f**	 **9g**[m]	81	85:15	74	**10l**
18	**2f**	 **9h**[n]	82	52:48	42	**10l**
19	**2f**	 **9i**[k]	44	69:31	77	**10l**

[a] Isolated yield from the corresponding α-chloroglycinate (imino ester was generated in situ). [b] Determined by ^1H NMR. [c] Ee of the major diastereomer (determined by chiral HPLC analysis). [d] *E*/*Z* = 94/6. [e] 2 equiv of enolate were used. [f] *E*/*Z* = 3/97. [g] *E*/*Z* = 4/96. [h] *E*/*Z* = 98/2. [i] Toluene was used as a solvent. [j] Isolated yield from the corresponding α-hydroxyglycinate (α-halogenoglycinate was not isolated). [k] *E*/*Z* = <1/>99. [l] PMP = *p*-methoxyphenyl. [m] *E*/*Z* = 8/92. [n] *E*/*Z* = 76/24.

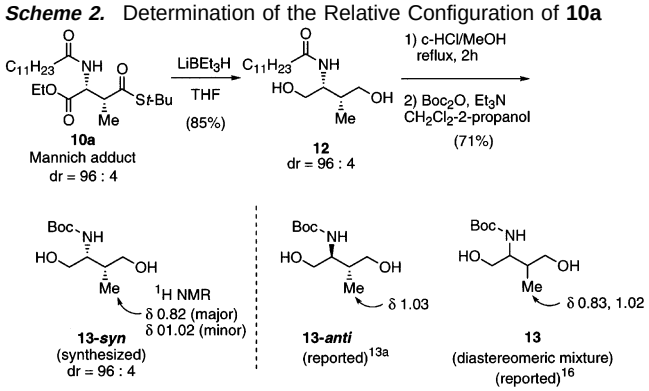
(entry 2). It is noted that *syn*-adducts were obtained from both (*E*)- and (*Z*)-enolates with high selectivities. Although the use of an *S*-ethyl group instead of the *S*-*tert*-butyl group decreased both diastereo- and enantioselectivities (entry 3), *tert*-butyldimethylsilyl enol ethers in place of trimethylsilyl enol ethers gave higher selectivities (entries 4 and 5). Regarding the solvents, dichloromethane gave better selectivity than toluene in this case

(15) Provided from Takasago Chemical Co. Ltd. For the preparation of xylyl-BINAP, see: 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. The use of xylyl-BINAP, see, e.g.: Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13 529.

Scheme 1. Determination of the Absolute Configuration of **8b**



Scheme 2. Determination of the Relative Configuration of **10a**



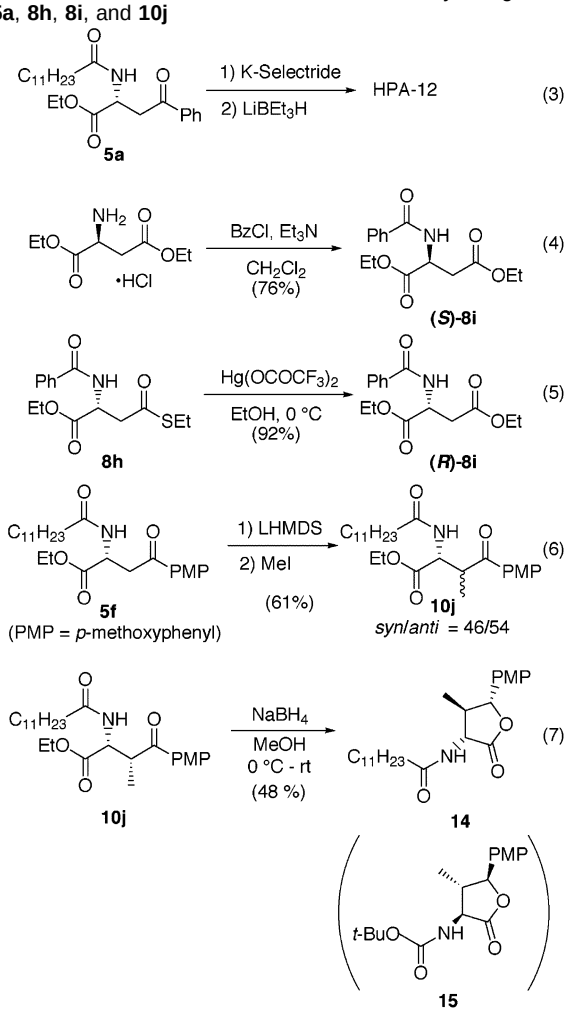
(entry 6). We tested other *N*-acylimino esters and the results are summarized in entries 7−10. In all cases, the desired adducts were obtained in high yields with good to high disatereo- and enantioselectivities. We also examined reactions of silyl enol ethers derived from ketones. Interestingly, *syn*-adducts were obtained stereoselectively in most cases (entries 11−19). It is noteworthy that 2-benzyloxy-1-phenyl-1-trimethylsiloxyethene (**9e**) reacted with *N*-acylimino ester **2a** with high *syn*-selectivity and that the enantiomeric excess of the *syn*-adduct was high (entry 14). In the reactions of the silyl enol ethers derived from 3-pentanone, the (*Z*)-*tert*-butyldimethylsilyl enol ether (**9g**) gave the best result (entry 17).

Absolute and Relative Stereochemistry Assignments. The Mannich-type adducts obtained in this reaction were successfully converted to intermediates of biologically important compounds, and at the same time, absolute and relative stereochemistry assignments were made. Mannich-type adduct **8b** was reduced to give diol **11** without epimerization. A natural aspartic acid ester was converted to (*S*)-**11**, and comparison of optical rotations revealed that the absolute configuration of **8b** was *R* (Scheme 1). On the other hand, Mannich-type adduct **10a** was reduced and the N-substituent was converted to a *tert*-butoxycarbonyl (Boc) group to afford diol **13**, whose C-3 epimer was known to be a promising substituent of quinolone antibacterial agents.[13a] The relative stereochemistry was assigned to be syn determined by ^{1}H NMR analysis (see Scheme 2).[16]

Furthermore, Mannich-type adduct **5a** was transferred to HPA-12 (vide infra) and its absolute configuration was determined to be *R* (Scheme 3, eq 3).[17] Authentic enantiomerically

(16) ^{1}H NMR spectrum data for the *anti*-isomer of **13**: See ref 13(a). ^{1}H NMR spectrum data for the diastereomeric mixture of **13**: Hirabayashi, S.; Ike, K.; Zanka, A.; Kawakami, T., Ichihara, M. *World Intellectual Property Organization Patent* 1992, WO9220652.

Scheme 3. Absolute and Relative Stereochemistry Assignments of **5a**, **8h**, **8i**, and **10j**



pure **8i** was synthesized by the *N*-acylation of (*S*)-asparatic acid diethyl ester, and the absolute configuration of Mannich-adduct **8i** was determined to be also *R* (eq 4). Also, the Mannich adduct **8h** was converted to **8i** and the absolute configuration was determined to be *R* (eq 5).[18] The absolute configuration of Mannich adduct **10j**-***syn*** was also determined to be *R* by converting optically active (*R*)-**5f** to a diastereomer mixture of **10j**-***syn*** and **10j**-***anti*** (eq 6). Relative stereochemical assignment of **10j**-***syn*** and **10j**-***anti*** was made after converting to lactone **14** by NMR analysis (eq 7).[19]

In addition, we carefully conducted absolute and relative stereochemistry assignments of Mannich-adduct **10i**. It has been reported that stereochemical courses were sometimes different between α-methyl substituted and α-benzyloxy substituted enolates.[20] The ketone moiety of Mannich-adduct **10i** was reduced using lithium triethylborohydride ($LiBEt_3H$), followed by deprotection of the benzyl ether to afford diastereomeric triols **17** and **18** along with diol **19** (Scheme 4, eq 8). These

(17) Ueno, M.; Kitagawa, H.; Ishitani, H.; Yasuda, S.; Nishijima, K.; Hanada, K.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 7863.
(18) Experimental details were shown in the Supporting Information.
(19) The NMR spectra of **14** was compared with one of known compound **15**. Details were shown in Supprting Information. (a) Barluenga, J.; Viado, A. L.; Aguilar, E.; Fustero, S.; Olano, B. *J. Org. Chem.* **1993**, *58*, 5972. (b) Gair, S.; Jackson, R. F. W.; Brown, P. A. *Tetrahedron Lett.* **1997**, *38*, 3059.
(20) (a)Kobayashi, S.; Ueno, M.; Ishitani, H. *J. Am. Chem. Soc.* **1998**, *120*, 431. (b)Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1708.

Scheme 4. Absolute and Relative Stereochemistry Assignments of **10i**

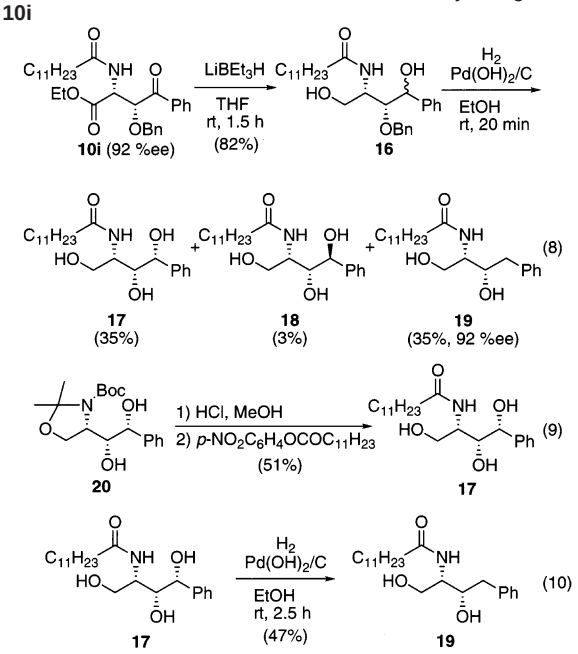
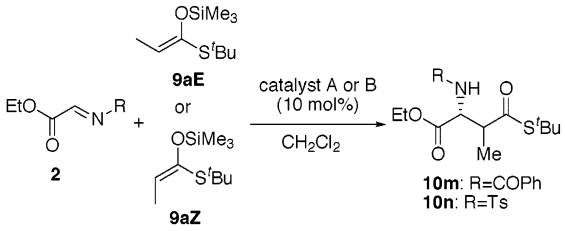


Table 6. Cu(I)-xylyl-BINAP Catalyzed Mannich-Type Reactions



catalyst A: $Cu(OTf)_2$ + (*R,R*)-ligand **3e**
catalyst B: $CuClO_4 \cdot 4CH_3CN$ + (*S*)-xylyl-BINAP

entry	imine	Nu	catalyst	yield (%)	*syn*:*anti*[a]	Ee(%)[b]
1	R═COPh	**9aZ**[c]	A	76[e]	89:11	20[g]
2		**9aZ**[c]	B	86[e]	78:22	99
3		**9aE**[d]	B	94[e]	36:64	94
4	R═Ts (**2i**)	**9aZ**[c]	A	73[f]	20:80	2
5[d]		**9aZ**[c]	B	83[f]	<1:>99	87
6[d]		**9aE**[d]	B	90[f]	<1:>99	98

[a] Determined by ^{1}H NMR. [b] Ee of the major diastereomer (determined by chiral HPLC analysis). [c] *E*/*Z* = 3/97. [d] *E*/*Z* = 94/6. [e] Isolated yield from the corresponding α-bromoglycinate (imino ester was generated in situ). [f] Isolated yield from *N*-Ts-imino ester. [g] Reverse enationselectivity was observed.

compounds are the phytosphingosine analogues.[21] On the other hand, authentic sample **20** was synthesized according to literature,[22] and deprotection of the protective group under acidic conditions and acylation made it possible to confirm the absolute and relative stereochemistry of **17** (eq 9). Moreover, optically pure **17** was reduced to afford optically pure authentic sample **19** (eq 10), and the absolute configuration of **19** was determined by HPLC analysis. It is noted that *syn*-adducts with the same absolute configuration were obtained using both α-methyl substituted and α-benzyloxy substituted enolates in this Mannich-type reaction using chiral $Cu(OTf)_2$-ligand **3e** as the catalyst.

Use of Other Imines and Catalysts. The reaction of *N*-benzoylimino ester **2g** with (*Z*)-1-*tert*-butylthio-1-trimethylsiloxy-1-propene (**9aZ**) using $Cu(OTf)_2$-ligand **3e** proceeded in 76% yield with *syn*/*anti* = 89/11, but the enantiomeric excess of the *syn*-adduct was low (20% ee) (Table 6, entry 1). When $CuClO_4 \cdot 4CH_3CN$−(*S*)-xylyl-BINAP (10 mol %) was used instead of the copper (II) catalyst, the desired *syn*-adduct was obtained preferentially (*syn*/*anti* = 78/22), and the enantiomeric excess of the *syn*-adduct was very high (99% ee) (entry 2). Interestingly, the geometrically isomeric enolate, (*E*)-1-*tert*-butylthio-1-trimethylsiloxy-1-propene (**9aE**), gave the *anti*-adduct predominantly (*syn*/*anti* = 36/64) with high enantiomeric excess (entry 3). In the reactions with *N*-tosylimino ester **2i**, the $CuClO_4$ system gave better results, and *anti*-adducts were obtained from both (*E*)- and (*Z*)-enolates with high diastereo- and enantioselectivities (entries 4−6).

Vinyl Ethers. In the presence of $Cu(OTf)_2$-ligand **3e** (10 mol %), alkyl vinyl ethers reacted with *N*-acylimino esters smoothly to afford the corresponding N-acylated amino acid derivatives in high yields with high selectivities. Several examples of the reactions are summarized in Table 7, and in all cases, the Mannich-type reactions proceeded cleanly. It is noteworthy that this is the first example of a catalytic enantioselective Mannich-type reaction using alkyl vinyl ethers.[23]

Mechanism and Catalyst Structure of the Mannich-type Reactions. In the Mannich-type reaction of *N*-acylimino esters, a mixture of the desired product **24** and vinyl ether **23** was obtained after quenching the reaction with water (Scheme 5). The vinyl ether **23** was converted to **24** by treatment with hydrochloric acid. Because it is difficult to monitor this catalytic reaction by NMR analysis due to the paramagnetic character of Cu(II), we conducted the NMR study of the reaction without the Cu catalyst to get information on the reaction mechanism (R^1 = ^{t}BuMe$_2$Si, R^2 = PMP). The reaction was found to proceed at room temperature without the catalyst, and it was interesting to find that no Mannich adduct **24** was observed in the ^{1}H NMR spectra of the reaction mixture. Instead, vinyl ether **23** and an unidentified product were observed before quenching the reaction with water. Contrary to the NMR study, TLC analysis of the reaction mixture showed formation of both **23** and **24**, which were found to be stable on TLC. These experiments indicate formation of a reactive intermediate, which was easily transferred to **24** on TLC. We also confirmed that no N-silylated compounds such as **25** were produced in this reaction.[24] From these experimental results and considerations, we assumed that the reaction proceeded via [4 + 2] cycloaddition as shown in Scheme 5.[25] The initially formed cycloadduct **22** would be partially transformed to vinyl ether **23** in situ via hydrogen transfer, and then the resultant mixture of **22** and **23** would be converted to the desired Mannich adduct **24** after acidic workup.

X-ray crystallographic analysis of asymmetric catalysts are sometimes helpful to presume the geometry of a catalyst-substrate complex as well as to interpret the sense of asymmetric induction. Although X-ray analysis of the most effective catalyst in this Mannich-type reaction composed of $Cu(OTf)_2$ and

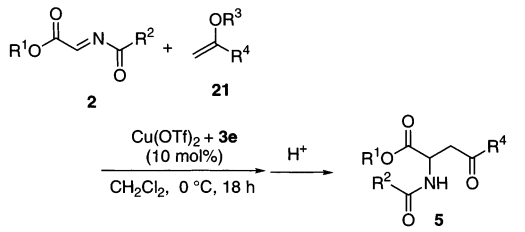
(21) (a)Merrill, A. H., Jr.; Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins, and Membranes*; Vance, D. E., Vance, J., Eds; Elsevier Science B. V.: Amsterdam, 1996; pp 309−339. (b)Hannun, Y. A. *Science* **1996**, *274*, 1855. See also, (c)Hanada, K.; Nishijima, M.; Kiso, M.; Hasegawa, A.; Fujita, S.; Ogawa, T.; Akamatsu, Y. *J. Biol. Chem.* **1992**, *267*, 23 527. (d) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc*. **1998**, *120*, 908.

(22) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10 657.

(23) For catalytic enantioselective aldol reactions using alkyl vinyl ethers, see Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649.

(24) Experimental details were shown in Supporting Information.

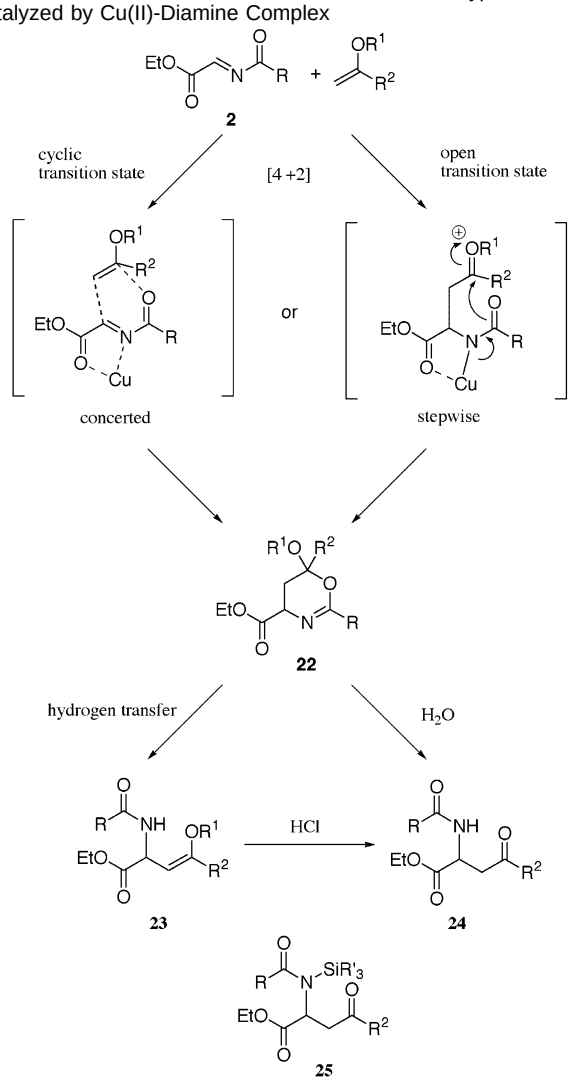
Table 7. Mannich-Type Reactions with Alkyl Vinyl Ethers



entry	R^1	R^2	Nu	yield (%)[a]	Ee (%)[b]	product
1	Et	$C_{11}H_{23}$	OMe, Ph **21a**	85	90	**5a**
2	Bn	$C_{11}H_{23}$	**21a**	82	84	**5i**
3[c]	Et	CH_3	**21a**	67	91	**5b**
4[d]	Et	Ph	**21a**	77	95	**5j**
5	Et	$C_{11}H_{23}$	OMe, PMP **21b**	62	89	**5f**
6	Bn	$C_{11}H_{23}$	**21b**	52	79	**5k**
7	Et	$C_{11}H_{23}$	OEt, Ph **21c**	74	90	**5a**
8	Bn	$C_{11}H_{23}$	**21c**	70	89	**5i**
9	Et	$C_{11}H_{23}$	OEt, PMP **21d**	47	89	**5f**
10	Bn	$C_{11}H_{23}$	**21d**	47	80	**5k**
11[e]	Bn	$C_{11}H_{23}$	OMe **21e**	79	71	**5l**

[a] Isolated yield from the corresponding α-halogenoglycinate. [b] Determined by chiral HPLC analysis. [c] Isolated yield from the corresponding α-hydroxyglycinate (α-halogenoglycinate was not isolated). [d] $CuClO_4$·$4CH_3CN$-(*S*)-xylyl-BINAP catalyst was used at −78 °C. [e] **3d** was used instead of **3e** as a diamine ligand.

Scheme 5. Presumed Mechanism for the Mannich-type Reactions Catalyzed by Cu(II)-Diamine Complex



diamine ligand **3e** failed, X-ray structure for the complex of $Cu(ClO_4)_2$·$6H_2O$ and diamine **3d** was successfully obtained[26] after extensive screening of copper salts and diamine ligands. The X-ray structure obtained is illustrated in Figure 2 (Structure A),[27] and it displays monomeric, bidentate coordination of the diamine ligand to the copper center in a little distorted square-planar geometry.[28] Two molecules of water also bind to the metal center in the distorted square-planar face, and two perchlorate counteranions are arrayed in the apical position. It is noteworthy that one of the oxygen atoms of the perchlorate anions interacts with the N-hydrogen atom of the diamine ligand.

On the other hand, PM3 calculations[29] suggested the lowest energy structure of $Cu(OTf)_2$-ligand **3e**-*N*-acylimino ester **2b** complex (Figure 2, structure B).[30] In this model, the Cu(II) has a tetrahedral geometry,[31] and both the ester carbonyl oxygen and the imine nitrogen coordinate to the copper center. In addition, the amide carbonyl oxygen may interact with the amine hydrogen atom of the diamine ligand via hydrogen bonding. To get more information about the structure of the catalyst-imine complex, we monitored interaction of the imine with the diamine-copper catalyst by an FT-IR spectrometer, which made it possible to conduct the reaction under strictly anhydrous conditions. As a result, the ester carbonyl stretch shifted as expected, and also the band of the amide carbonyl group shifted, which might indicate that the amide oxygen atom also coordinated to the catalyst as the ester carbonyl oxygen atom did. The C═N absorption was unclear and no information about the coordination of the imine nitrogen atom was obtained. It is noted

(25) Similar reaction pathways were reported. (a)Gizecki, P.; Dhal, R.; Toupet, L.; Dujardin, G. *Org. Lett*. **2000**, *2*, 585, and ref 2a. See also, (b)Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568. See also, ref 12.
(26) The blue-color crystal of the complex composed of $Cu(ClO_4)_2$·$6H_2O$ and diamine **3d** was grown in a THF-hexane solvent system.
(27) Two water molecules are abbreviated for clarification.
(28) The copper center in a little distorted square planar geometry was also reported by Evans et al.: See ref 12.
(29) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−221.
(30) Although the reliability of PM3 calculations for transition metal complexes with partially filled d-orbitals is controversial, there are several examples of PM3 calculations of Cu(II)-complexes. For examples, Evans et al. used PM3 calculations for Cu(II)-bisoxazoline complexes, and optimized structures were reported to be almost consistent with X-ray structures. They also reasonably explained enantioselectivity in several catalytic asymmetric reactions: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325, and references therein.
(31) Although Cu(II) complexes usually adopt a square planar geometry rather than a tetrahedral geometry, several examples of tetrahedral Cu(II) complexes have been reported. For recent examples, see: (a) Beheshti, A.; Clegg, W.; Hyvadi, R.; Hekmat, H. F. *Polyhedron* **2002**, *21*, 1547. Jørgensen et al. also proposed tetrahedral transition state models to explain enantioselectivity in asymmetric hetero Diels−Alder Reactions and ene reactions catalyzed by chiral Cu(II) complexes. (b) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757. (c) Johannsen, M.; Yao, S.; Graven, A.; Jørgensen, K. A. *Pure Appl. Chem.* **1998**, *70*, 1117.

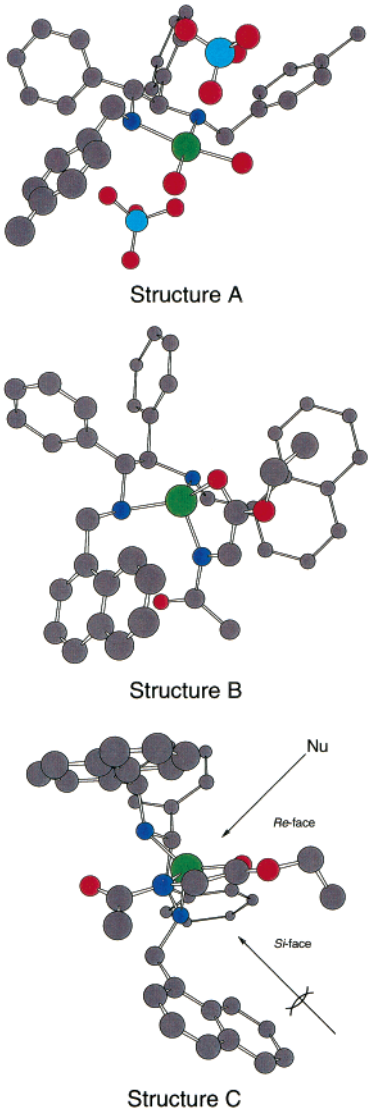


Figure 2. X-ray structure of $Cu(ClO_4)_2$-ligand **3d** (structure A), the assumed structure of $Cu(OTf)_2$-**3e**-**2b** calculated using PM3 (structure B), and a model for understanding the enantioselectivity (structure C).

that these IR experimental results do not contradict the calculation model, structure B. In this model, the *Si*-face of the imine was shielded by one of the naphthyl rings of the chiral catalyst, and silyl enol ethers or vinyl ethers attacked the imine from the opened *Re*-face (Figure 2, Structure 3).

For diastereoselectivity, the present Mannich-type reactions using the Cu(II)-diamine complex exhibited high *syn*-selectivity regardless of the enolate geometry. From the structure for the catalyst-imino ester complex, we assume that the reaction proceeds via a stepwise manner (Scheme 1). The observed *syn*-preference can also be explained more reasonably by the stepwise open transition state model than by the concerted cyclic model.[32] Among the possible transition states that lead to the

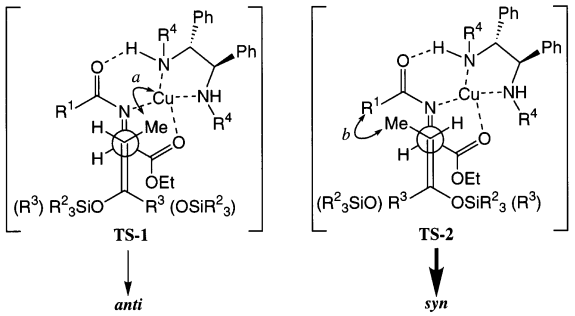


Figure 3. Assumed transition state models for the diastereoselective reactions.

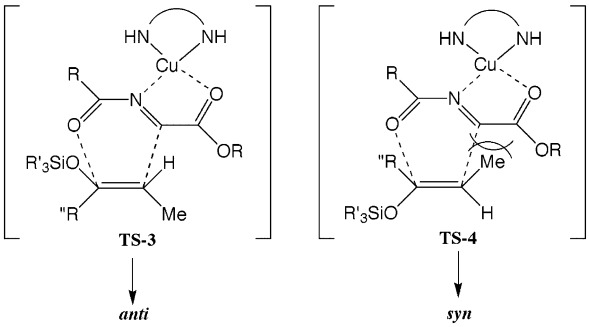


Figure 4. Assumed cyclic transition state models.

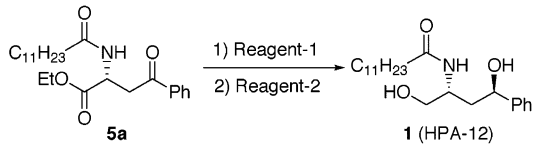
syn-adduct, *antiperiplanar* transition state model **TS-2** would be the most reasonable to minimize the number of repulsive interactions (Figure 3). On the contrary, **TS-1** that affords the *anti*-adduct has severe steric interaction between the methyl group of the nucleophile and the chelated copper catalyst (repulsion *a*), and *synclinal* transition state models are apparently disfavored by steric repulsions between nucleophiles and the chelated copper complex or N-acyl groups (COR). In this model (**TS-2**), both (*E*)- and (*Z*)-enolates would provide the *syn*-adduct stereoconvergently. On the other hand, cyclic transition state models cannot explain the observed high *syn*-selectivity and the stereoconvergency (Figure 4). The decrease of the *syn*-selectivity for the bulky N-acyl group such as N−CO^{i}Pr or N−Bz would be rationalized by the increase of the steric repulsion between the N-acyl group and the methyl group (repulsion *b*). In such bulky *N*-acylimino esters, enantioselectivity was also decreased, probably because the bulkiness of *N*-acylimine inhibits the coordination to the catalyst. This consideration would be not inconsistent with IR experiments that revealed almost no shift of the carbonyl stretches in the mixture of *N*-Bz-imino ester and the catalyst.

Facile Synthesis of HPA-12. Recently, our laboratories have focused on (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12, **1**), a new inhibitor of ceramide trafficking from endoplasmic reticulum to the site of sphingomyerin (SM) synthesis. HPA-12 is the first compound of a specific inhibitor for SM synthesis in mammalian cells, and is expected as a drug that inhibits intracellular trafficking of sphingolipids.[33] Although we have completed the first asymmetric synthesis of HPA-12 using zirconium-catalyzed enantioselective Mannich-type reactions,[34] we planned to develop a more convenient way using the present Mannich-type reactions with *N*-acylimino esters. The Mannich-type adduct (**5a**) was

(32) Diastereoselections in additions of π-based nucleophiles (silyl enol ethers, allylic metals, etc.) to aldehydes or ketones have been discussed very well using open or cyclic transition state models. For aldol reactions, see: (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095, and references therein. For allylations, see: (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207, and references therein. For effects of olefin geometry of nucleophiles on the diastereoselection, see: (c) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889. (d) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.

(33) Yasuda, S.; Kitagawa, H.; Ueno, M.; Ishitani, H.; Fukasawa, M.; Nishijima, M.; Kobayashi, S.; Hanada, K. *J. Biol. Chem.* **2001**, *276*, 43 994.

Table 8. Synthesis of HPA-12 (*Anti*-selective Reduction of β-Carbamoyl Ketone)



5a **1** (HPA-12)

entry	solvent	reagent-1	reagent-2[a]	yield (%)	*syn*:*anti*
1	THF	9-BBN[b]	none	0	
2	THF	LS-Selectride[c,d]	none	0	
3	THF	$LiBEt_3H$[e]	none	63	55:45
4	THF	$LiAl(O^tBu)_3H$[b]	none	86	65:35
5	THF	L-Selectride[f]	$LiBH_4$[k]	92	41:59
6	THF	(S)-Alpine-Hydride[b,g]	$LiBH_4$[k]	96[h]	53:47
7	THF	(R)-Alpine-Hydride[b,g]	$LiBH_4$[k]	99[h]	53:47
8	THF	K-Selectride[b]	$LiBEt_3H$[l]	99	9:91
9	MeOH	$NaBH_4$[b]	$LiBEt_3H$[l]	90	44:56
10	Et_2O	K-Selectride[b]	$LiBEt_3H$[l]	90	60:40
11	DME	K-Selectride[i]	$LiBEt_3H$[l]	92	19:81
12	DME	K-Selectride[j]	$LiBEt_3H$[m]	95	16:84

[a] At rt. [b] At −78 °C for 2 h. [c] LS-Selectride: lithium triisoamylborohydride. [d] At −78 °C for 26 h. [e] At −78 °C for 20 min. [f] At −78 °C for 1 h. [g] Alpine-Hydride: lithium B-isopinocampheyl-9-bora-bicyclo[3.3.1]nonyl hydride. [h] Containing a small amount of unknown compounds. [i] At −45 °C for 2 h. [j] At −45 °C for 15 min. [k] 2 h. [l] 1 h. [m] 45 min.

obtained from *N*-acylimino ester **2a** with 1-trimethylsiloxy-1-phenylethene (**3a**) or 1-methoxy-1-phenylethene (**21a**) using the chiral Cu(II) catalyst in high yield and selectivity. We then examined reduction conditions of **5a** to afford HPA-12 directly. Although 9-bora-bicyclo[3.3.1]nonyl hydride (9-BBN) or lithium triisoamylborohydride (LS−Selectride) was not effective, $LiBEt_3H$ or tri-*tert*-butoxyaluminum hydride gave the desired product directly, but diastereomer ratios (*syn*/*anti*) were moderate. After examination of several reducing agents, it was revealed that combination of K−Selectride and $LiBEt_3H$ in THF gave the best result, and that HPA-12 was obtained in 99% yield with high diastereoselectivity (*syn*/*anti* = 9/91). Interestingly, the solvents had significant effects on the selectivity, and moderate selectivity was obtained in ether (*syn*/*anti* = 60/40). The use of a bulky reducing agent in a polar solvent prevented a cyclic intermediate in which both the ketone carbonyl oxygen and the amide nitrogen coordinated to the reducing agent, leading to *anti*-selective reduction of the β-amino ketone.[35] It should be noted that HPA-12 has been synthesized from **2a** in three steps (two-pot), and that the total yield was 82.9%.[36] Gram-scale preparation has also been performed successfully, and the preparation of many other HPA-12 analogues is feasible according to this efficient synthetic pathway.

Conclusion

We have developed catalytic asymmetric Mannich-type reactions of *N*-acylimino esters with silyl enol ethers or alkyl vinyl ethers using $Cu(OTf)_2$-chiral diamine complexes as the catalysts. The reactions proceeded smoothly at 0 °C in most cases, and high yields and high diastereo- and enantioselectivities were attained. On the basis of X-ray crystallographic analysis of the chiral Cu(II) catalyst, PM3 calculations, and FT-IR analyses, we assumed the reaction mechanism, the most stable chiral catalyst-*N*-acylimino ester complex, and the transition states of these Mannich-type reactions. Moreover, several useful intermediates for the synthesis of biologically important compounds were prepared by using these novel Mannich reactions. In particular, HPA-12 (**1**), a new inhibitor of ceramide trafficking from endoplasmic reticulum to the site of sphingomyerin (SM) synthesis, has been synthesized in three steps in 82.9% total yield using the present Cu(II)-catalyzed Mannich-type reaction.

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Note Added after ASAP Publication: The version published on the Web 2/6/2003 contained an error in entry 8 of Table 5. The final Web version published 2/18/2003 and the print version are correct.

Supporting Information Available: Experimental section (PDF) and X-ray data of Figure 2, Structure A. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) (a) Ueno, M.; Kitagawa, M.; Ishitani, H.; Yasuda, S.; Hanada, K.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 7863. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180. (d) Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* **2001**, *57*, 861. See also, 20(a).

(35) Pilli, R. A.; Russowsky, D.; Dias, L. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1213. *Syn*-selective reduction of *N*-acyl-β-amino ketones has been reported recently. Keck, G. E.; Truong, A. P. *Org. Lett.* **2002**, *4*, 3131.

(36) Direct recrystallization gave diastereo- and enantiomerically pure HPA-12. See Supporting Information.