Studies on Asymmetric Synthesis of β-Amino Acids and Related Compounds

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Contents

Chapter 1 General Introduction

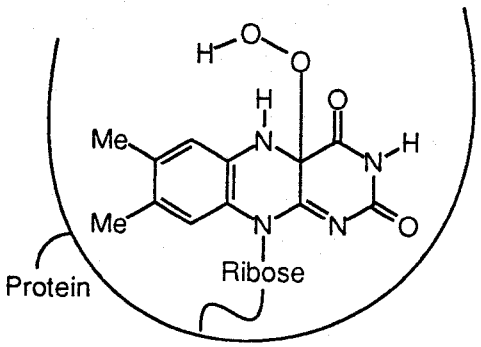
Asymmetric synthesis is of importance in view of life science.[1] In biological systems asymmetry is widely distributed as illustrated by proteins, sugars, alkaloids, and so on. It is expected that metabolites and drugs having stereogenic centers interact stereospecifically with biological systems. In fact, enantiomers are often handled differently during the processes of absorption, distribution, metabolism, and elimination from the body. The first separation of racemic isomers was carried out in 1849 by L. Pasteur on tartrate, and the first recorded observations of differences in biological actions of stereoisomers are attributed to A. Piutti who isolated the two enantiomers of asparagine in 1886; the *S* isomer tasted sweet, while the *R* isomer tasted bland.[1] Further, physically handicapped thalidomide children are chilling evidence of hidden dangers in the use of racemic drugs.[2] Together with the desired tranquilizing effect of its *R* isomer, racemic thalidomide contains an equal amount of the *S* isomer which in retrospect was found to be responsible for these tragic deformities. It is estimated that a half medicines contain drugs exhibiting chirality and a quarter enantiomeric drugs are used as the racemates, thus, two enantiomers in the ratio of 1 : 1 despite the fact that the two enantiomers may have different activities and toxicities.[1]

α-Amino acids are one of the largest classes of nitrogen containing compounds which have asymmetric centers. It is well known that α-amino acids are vital to life itself as the "building blocks" of peptides, proteins, and many other natural products.[3] The importance of amino acids has prompted the development of a multitude of methods for their synthesis.[4]

β-Amino acids, although less abundant than their α analogues, also receive considerable attention. In mammals four β-amino acids were isolated; β-alanine, (*R*)- and (*S*)-β-aminoisobutyrate are catebolites of uracil, thymine, and valine, respectively, and β-leucine is considered to be formed from valine and isofatty acids and is a precursor of leucine.[5] Their metabolism is of current clinical and basic research interest.[5] Peptide bonds involving β-amino acids are resistant to enzymatic hydrolysis, and further interested in the synthesis, hydrolytic stability, and conformational characteristics.[5,6] Further, novel and frequently complex β-amino acids were isolated from plants and microorganisms as free molecules,[7] components of peptides,[8] and other biologically active compounds,[9] and show interesting pharmacological effect.[6] In addition β-amino acids are synthetic precursors of β-lactam antibiotics[10] and other nitrogen containing biologically active compounds.[11] In these respects, several methods for the synthesis of racemic β-amino acids have been developed,[5,6] but only recently has the preparation of optically active compounds emerged as an important and challenging synthetic endeavor.[12] The synthetic methods of optically active forms are classified as follows; i) transformation of α-amino acids,[13] ii) enzymatic reaction,[14] iii) Michael addition of amines to α,β-unsaturated esters

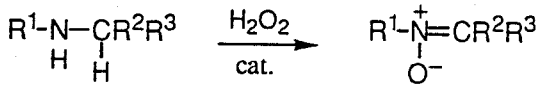
in which both chiral amine derivatives and enoates bearing chiral auxiliaries are used,[15] iv) nucleophilic addition to C-N double bonds such as schiff bases using chiral substrates, which includes the formation of β-lactams,[16] v) catalytic asymmetric hydrogenation of 3-aminoacrylate derivatives,[17] vi) substitution at the α position of β-amino acid derivatives,[18] vii) and other miscellaneous methods have been employed.[12]

Murahashi *et al.* have studied the simulation of the functions of flavoenzyme with metal catalysts.[19] Hepatic flavoenzyme undergoes oxygen atom transfer from molecular oxygen to substrates.[20] The key intermediate of the flavoenzyme is highly reactive hydroperoxyflavin **1**. The simulation of the function of flavoenzyme has been performed



Flavoenzyme **1**

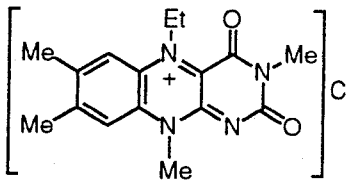
by using flavinium perchlorate **4**.[21] The oxidative transformation of secondary amines **2** to nitrones **3** has been performed by oxidation with a 30% hydrogen peroxide solution in the presence of a catalyst such as sodium tungstate[22,23] and selenium dioxide[24] (eq 1). The biomimetic single step synthesis of nitrones **3** from secondary amines **2** is highly useful, because nitrones **3** thus obtained are highly valuable synthetic intermediates as 1,3-dipole,[25] electrophiles,[26] and spin trapping reagents.[27]



(1)

2 **3**

catalysts;



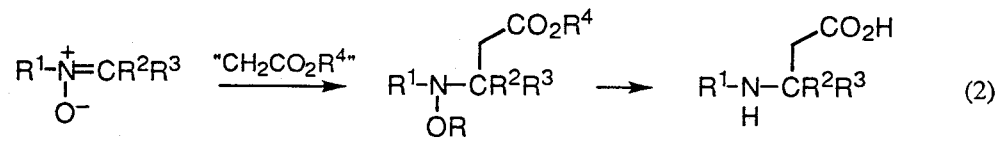
ClO_4^-, Na_2WO_4, SeO_2

4

The introduction of substituents at the carbon α to the nitrogen can be performed by the reactions of nitrones with dipolarophiles or nucleophiles.[28] Chiral nitrones have been utilized mainly for the asymmetric synthesis of nitrogen containing compounds upon treatment with dipolarophiles[29,30] or nucleophiles.[31] The diastereoselective addition of

chiral methyl *p*-tolyl sulfinyl carbanion to achiral nitrones was also reported to give chiral β-sulfinyl hydroxylamines.[32]

The synthesis of α-amino acids has been performed by the reaction of nitrones thus obtained with cyanide, followed by hydrolysis, and hydrogenation.[23b] On the other hand, β-amino acids can be prepared conveniently by the introduction of the carboxymethyl moieties at the carbon α to the nitrogen of nitrones **3** (eq 2). The author describes three

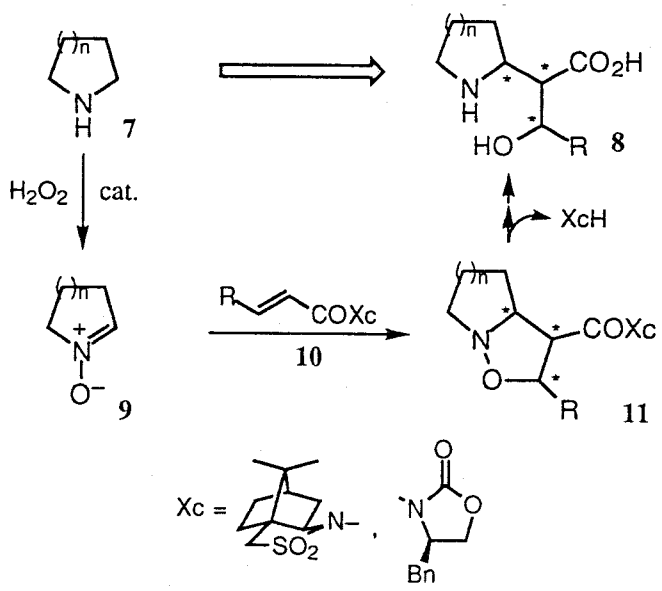


3 **5** **6**

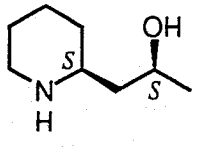
new methods for the asymmetric synthesis of β-amino acids **6** from nitrones **3** as follows; i) asymmetric 1,3-dipolar cycloaddition to chiral enoates, ii) diastereoselective addition of chiral enolates, iii) chiral Lewis acid-catalyzed asymmetric addition of ketene silyl acetals.

In Chapter 2 is described the asymmetric 1,3-dipolar cycloaddition of achiral cyclic nitrones **9** to α,β-unsaturated carboxylic acid derivatives **10** bearing chiral auxiliaries (Xc) such as Oppolzer's camphor sultam[33] and Evans' oxazolidinone,[34] which are recoverable after the reaction (Scheme 1).[35] The author found that the zinc iodide-mediated reaction of

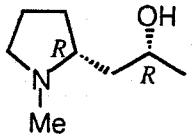
Scheme 1



cyclic nitrones with the dipolarophiles gave the adducts highly diastereoselectively. Optically active isoxazolidines **11** thus obtained are precursors for synthesis of β-amino-β'-hydroxy acids **8**, piperidine and pyrrolidine alkaloids such as (+)-sedridine (**12**)[36] and (+)-hygroline (**13**).[37] In addition the adducts **11** can be used as chiral ligands for the osmium-catalyzed asymmetric dihydroxylation.[38]



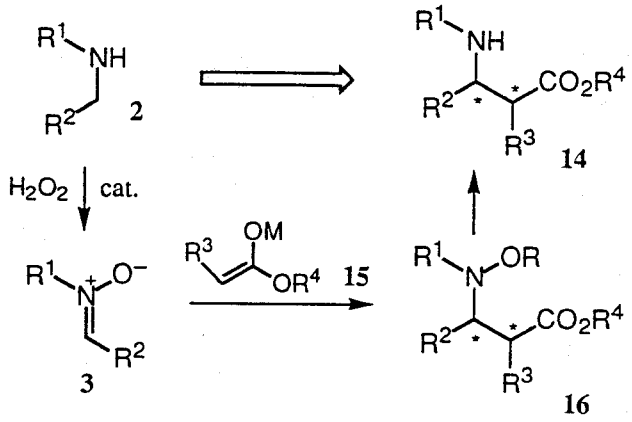
(+)-sedridine (12)



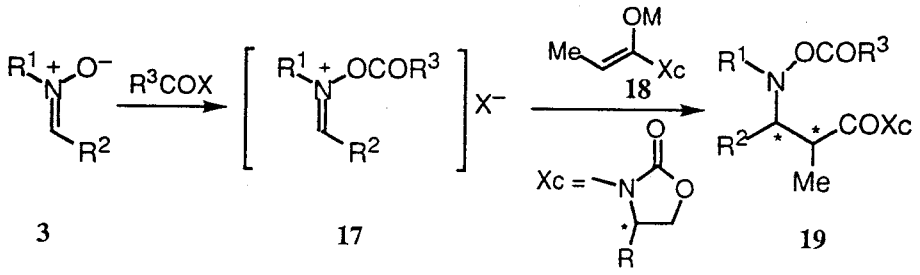
(+)-hygroline (13)

The reaction of nitrones **3** with enolates **15**, which are prepared from carboxylic acid derivatives, will also provide a convenient method for the synthesis of β-amino acids **14** from secondary amines **2** (Scheme 2). The reactivity of nitrones **3** toward soft nucleophiles such as enolates is low in comparison with hard nucleophiles such as Grignard reagents. Therefore, the reactions of nitrones **3** with soft nucleophiles should be activated. The author found two methods for the activation of nitrones.

Scheme 2



In Chapter 3 is described the asymmetric reactions of nitrones **3** with chiral enolates **18** bearing chiral auxiliaries (Xc) such as Evans' oxazolidinones[34] by means of the activation of nitrones upon treatment with acyl halides (eq 3). It is known that the reaction

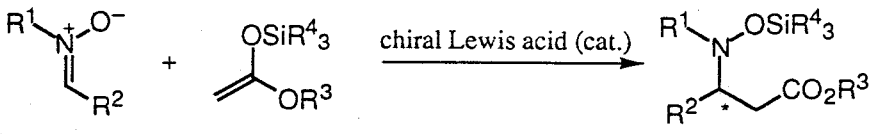


(3)

of nitrone with aroyl chloride gives amide which is an isomeric product of nitrone.[39] Thus, nitrone **3** react with aroyl chloride to give the cationic intermediate which undergoes rearrangement rapidly. By trapping this highly reactive cationic species with nucleophiles, the introduction of substituents at the α carbon of amines can be performed. *N*-Acyloxyiminium intermediates **17** which are formed upon treatment of nitrones **3** with acyl

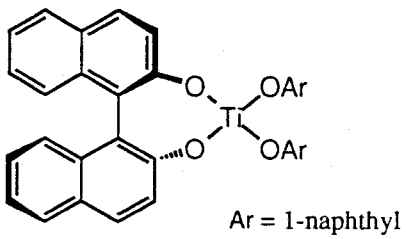
halides, are stable cationic species at low temperature and are characterized by NMR analysis. The intermediates **17** were found to react with chiral enolates **18** readily to give β-amino acid derivatives **19** with high diastereoselectivity. Further, it was found that asymmetric induction occurs by using chiral acyl halides for the reactions of achiral nucleophiles.

Another possibility of the activation of nitrones **3** by using Lewis acids is described in Chapter 4. The catalytic asymmetric reaction is the most attractive method in synthetic organic chemistry.[40] Nitrogen containing substrates such as imines and oximes generally require the stoichiometric amount of Lewis acids for the activation because of its basicity.[41] Although diastereoselective addition of carbon nucleophiles to nitrones have been investigated, the catalytic asymmetric nucleophilic addition to achiral nitrones has never been reported. The reported reaction is limited to the catalytic hydrosilylation of nitrones.[42] The author succeeded in the catalytic asymmetric carbon-carbon bond formation by the reaction of nitrones **3** with ketene silyl acetals **20** in the presence of chiral Lewis acid catalysts. Indeed, optically active *N*-siloxy-β-amino esters **21** were obtained by using chiral Lewis acid catalysts (eq 4). The catalytic activity is influenced by Lewis

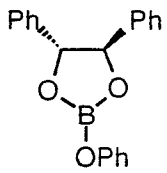


3 **20** **21** (4)

acidity strongly. The Lewis acids prepared from phenol derivatives, such as titanates and borates were found to show the efficient catalysis. While chiral Lewis acids have been developed rapidly,[43] the author designed new catalysts such as titanate **22** and borate **23**.



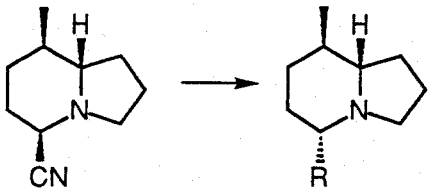
(*R*)-22



(*R*,*R*)-23

The usefulness of the present reactions has been shown by the asymmetric synthesis of (–)-5-cyano-8-methylindolizidine (**24**), which is a key and common precursor for the synthesis of many indolizidine alkaloids which are characterized by GC-MS as illustrated in Scheme 3.[44] Indolizidines (–)-205A and (–)-235B have been synthesized from (–)-**24**,[44b] and the other indolizidines as shown in Scheme 3 can be synthesized.

Scheme 3

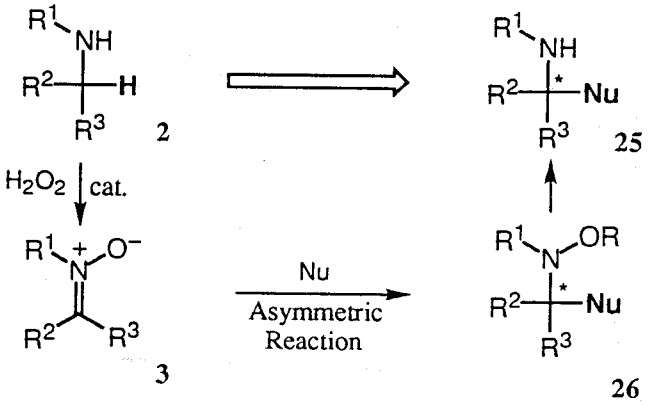


(–)-24

R =
203A; $CH_2CH{=}CHC{\equiv}CH$ (Z)
205A; $(CH_2)_3C{\equiv}CH$
207A; $(CH_2)_3CH{=}CH_2$
209B; n-C_5H_{11}
233D; $(CH_2)_3CH{=}CHCH{=}CH_2$ (Z)
235B; $(CH_2)_3CH{=}CHCH_2CH_3$ (Z)
235B'; $(CH_2)_5CH{=}CH_2$
251B; $(CH_2)_3CH{=}CHCH(OH)CH_3$ (Z)

The methodology which involves the catalytic oxidation of secondary amines to nitrones, followed by the asymmetric addition of the carboxymethyl moieties by using chiral reagents or chiral catalysts, provides a new and convenient method for the asymmetric synthesis of β-amino acids. Especially, the catalytic asymmetric reactions of nitrones with various nucleophiles or dipolarophiles[45] by using chiral Lewis acids will provide the general method for synthesis of optically active amino compounds (Scheme 4).

Scheme 4



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Chapter 2 Asymmetric 1,3-Dipolar Cycloaddition of Cyclic Nitrones to Chiral Crotonic Acid Derivatives

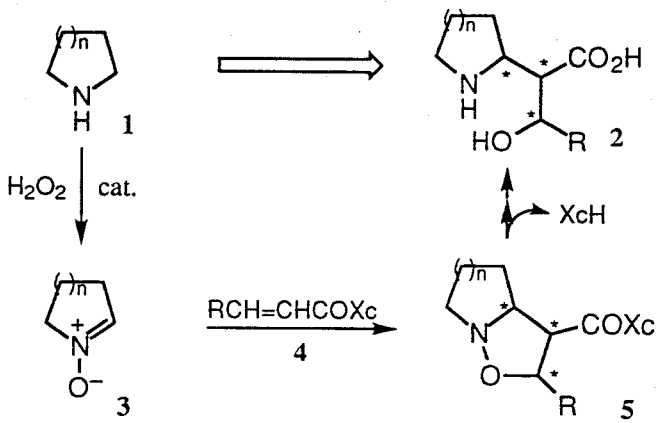
Introduction

Recently the asymmetric synthesis of β-amino acids has attracted considerable interests,[1] because β-amino acids are the partial structures of various naturally occurring biologically active products[2] and useful starting materials for the synthesis of β-lactam antibiotics[3] which are potentially biologically active.[4]

Nitrones are highly valuable synthetic intermediates as excellent 1,3-dipoles and have been utilized for the synthesis of various nitrogen containing biologically active compounds.[5] 1,3-Dipolar cycloaddition of nitrones with alkenes gives isoxazolidines which can be converted into a variety of amino compounds readily.[5,6] Asymmetric inter-[7,8] and intramolecular[9] 1,3-dipolar cycloadditions have been studied for the synthesis of various nitrogen containing biologically active compounds by using chiral nitrones mainly.

Asymmetric 1,3-dipolar cycloaddition of nitrones **3** to enoates bearing chiral auxiliaries **4** gives chiral 3-carboxyisoxazolidines **5**, which will open a new approach to the synthesis of optically active β-amino acids **2** (Scheme 1). The chiral isoxazolidines thus

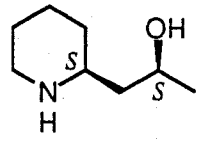
Scheme 1



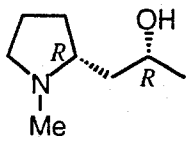
obtained, can be converted into the corresponding optically active β-amino-β'-hydroxy acids **2** by reductive cleavage of the N-O bonds. Since the catalytic oxidation of secondary amines **1** with hydrogen peroxide gives nitrones **3** highly efficiently,[10] the present reaction provides a convenient method for the synthesis of β-amino-β'-hydroxy acids **2** from secondary amines **1** (Scheme 1).

In this chapter, the author describes the asymmetric 1,3-dipolar cycloaddition of cyclic nitrones **3** to chiral crotonic acid derivatives bearing chiral auxiliaries (Xc) such as Oppolzer's camphor sultam (Xc = Xc_1)[11] and Evans' oxazolidinone (Xc = Xc_2).[12,13] This method can be applied to the short step synthesis of piperidine and pyrrolidine alkaloids

such as (+)-sedridine (**6**)[14] and (+)-hygroline (**7**).[15] Good diastereoselectivity was obtained by the zinc iodide-mediated 1,3-dipolar cycloaddition. The optically active isoxazolidines **5** thus obtained, could be readily converted into optically active β-amino-β'-hydroxy acids **2** along with recovering the chiral auxiliaries.



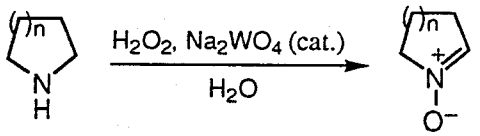
(+)-sedridine (**6**)



(+)-hygroline (**7**)

Results and Discussion

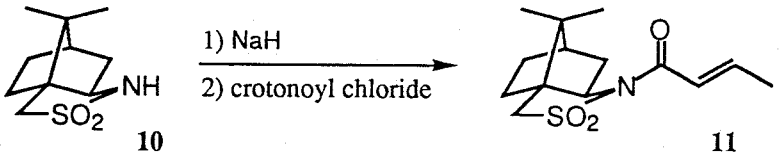
The Reaction of Cyclic Nitrones with Crotonoylsultam 11 in the Absence of Lewis Acids. Asymmetric synthesis of cyclic amines is of importance in view of the preparation of biologically active nitrogen containing compounds such as pyrrolidine and piperidine alkaloids. Previously nitrones have been prepared either by the condensation of carbonyl compounds with hydroxylamines or by the oxidation of the corresponding hydroxylamines.[16] The difficulty of these methods is in the preparation of the starting hydroxylamines. Recently the reliable procedure for the synthesis of nitrones has been established by the oxidation of readily available secondary amines in a single step.[10] Cyclic nitrones such as 1-pyrroline *N*-oxide (**8**) and 2,3,4,5-tetrahydropyridine *N*-oxide (**9**) can be prepared conveniently by the catalytic oxidation of pyrrolidine and piperidine, respectively, with hydrogen peroxide in water using sodium tungstate as a catalyst (eq 1).



(1)

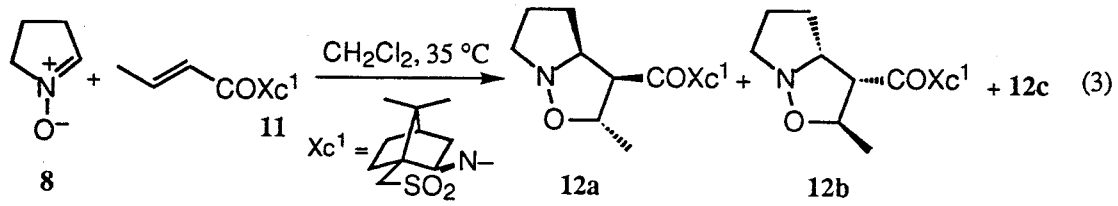
8; n = 1
9; n = 2

(–)-*N*-[(*E*)-2-butenoyl]bornane-10,2-sultam (**11**) (crotonoylsultam) was prepared upon treatment of the sodium salt of (–)-bornane-10,2-sultam (**10**) (sultam) with (*E*)-crotonoyl chloride (eq 2).[11]



10 **11** (2)

Cycloaddition of nitrone **8** (1.5 equiv) to crotonoylsultam **11** in dichloromethane at 35 °C for 24 h gave a mixture of three diastereomers in 86% yield after purification by



(3)

column chromatography on silica gel (eq 3). The ^{1}H NMR spectrum showed three peaks of the methyl groups of the camphor skeletons, although the diastereomeric ratio could not be determined because of signal duplication. The HPLC analysis using chiral column (Daicel CHIRALCEL OD) clearly showed the diastereomeric ratio to be **12a/12b/12c** = 35 : 52 : 13 (Figure 1). Two diastereomers **12a** (mp 207.0–207.5 °C; $[\alpha]^{27}_D$ –187° (*c* 1.01, $CHCl_3$)) and **12b** (mp 164.0–164.5 °C; $[\alpha]^{27}_D$ +15.2° (*c* 1.00, $CHCl_3$)) were isolated as a single diastereomer in 11% and 33% yields, respectively by simple recrystallization from methanol. The relative configurations of the diastereomers **12a** and **12b** were determined to be *endo* (2,3-*trans*; 3,4-*cis*) by NOE experiments. The third diastereomer **12c** may be an *exo* isomer (3,4-*trans*; 4,5-*trans*). For example, signal enhancement of the H-3 (δ 3.74) and the H-4 (δ 4.20) was observed on irradiation at the Me-2 (δ 1.28) of **12b** (Figure 2). The X-ray crystal structure and the derivation to the known alkaloid (*vide infra*) were employed for the determination of the configurations of the diastereomers. The X-ray structure of **12b** is shown in Figure 3, which shows that the absolute configuration of **12b** is 2*R*,3*S*,4*R*. The configuration of the *endo* isomer **12a** is 2*S*,3*R*,4*S*. The adducts **12a** and **12b** themselves can be used as chiral ligands for the osmium-catalyzed asymmetric dihydroxylation of olefins.[17]

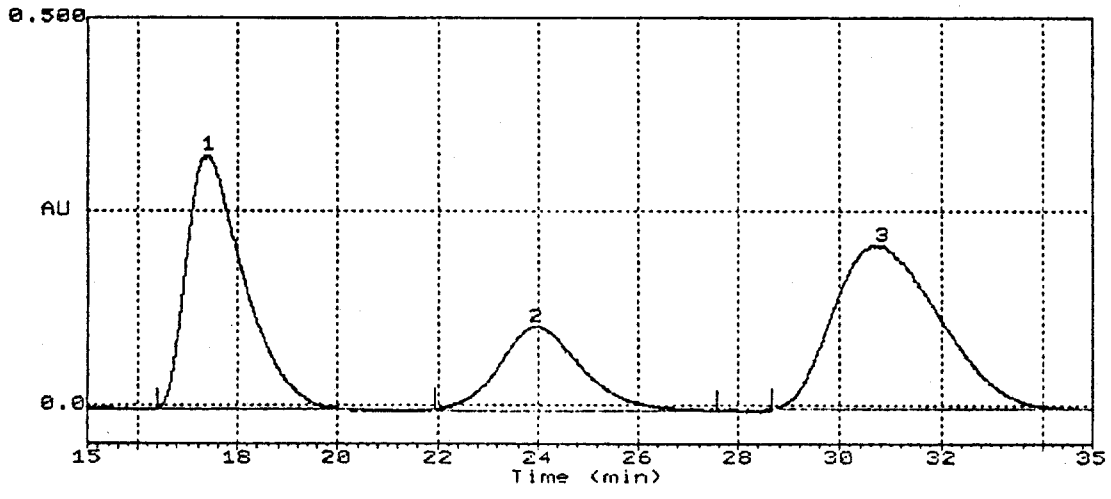


Figure 1. The HPLC spectrum of **12** (Daicel CHIRALCEL OD, 10% IPA in hexane, 1 mL/min). 1, **12a**; 2 , **12c**; 3, **12b**.

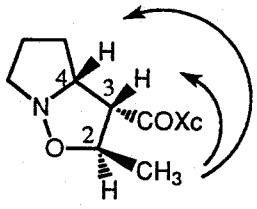
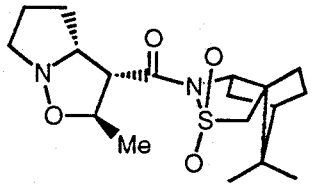


Figure 2. NOE of **12b**.



12b

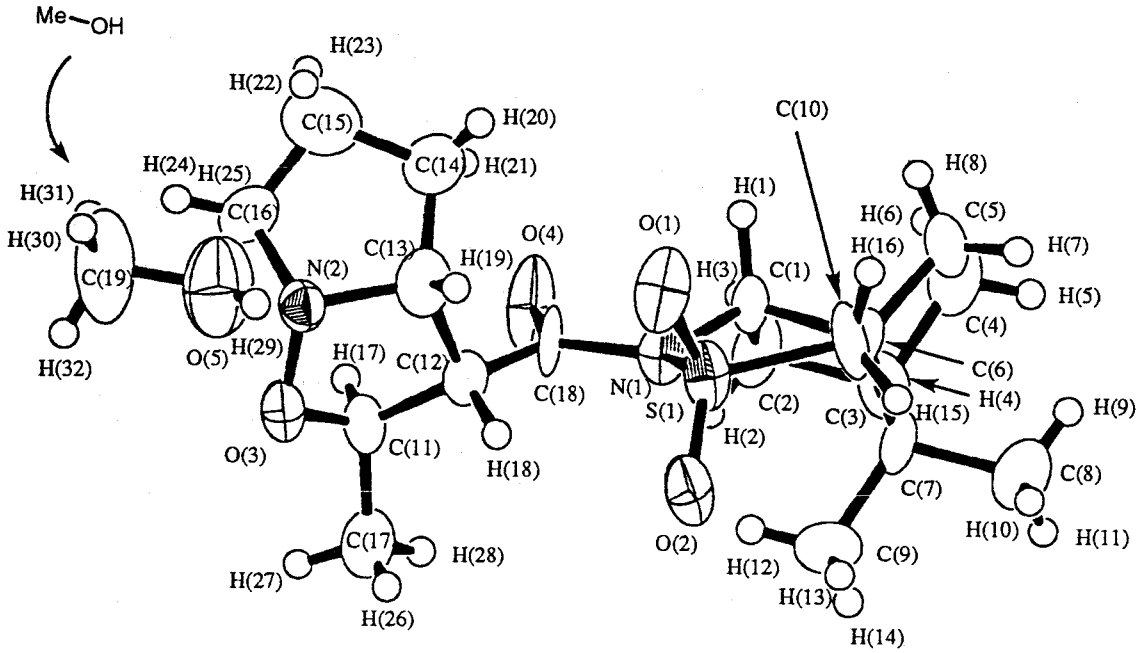
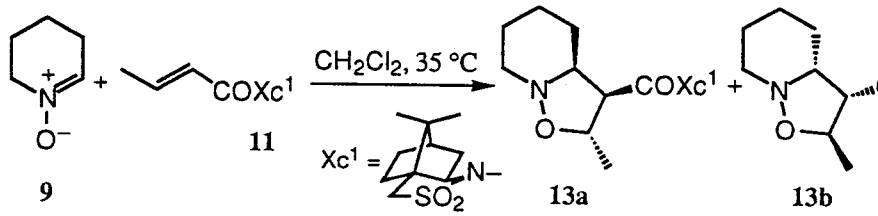


Figure 3. ORTEP drawing of **12b**.

The similar reaction of nitrone **9** with dipolarophile **11** gave a mixture of cycloadducts **13a** and other diastereomers in the ratio of **13a/13b/13c/13d** = 54 : 27 : 16 : 3 (99% yield) (eq 4). The diastereomeric ratio was determined by the HPLC analysis using CHIRALCEL OD (Figure 4). The major diastereomer **13a** (mp 186.0–188.0 °C; $[\alpha]^{30}_D$



(4)

–73.2° (*c* 1.02, $CHCl_3$)) was obtained as a single diastereomer by single recrystallization from ethyl acetate in 41% yield. The configuration of **13a** was determined to be *endo* by NOE experiments, and its absolute configuration was also determined to be 2*S*,3*R*,4*S* by the derivation to the known natural product (*vide infra*). Another diastereomer **13b** is probably an *edno* isomer (2*R*,3*S*,4*R*) and the other isomers **13c** and **13d** are *exo* isomers.

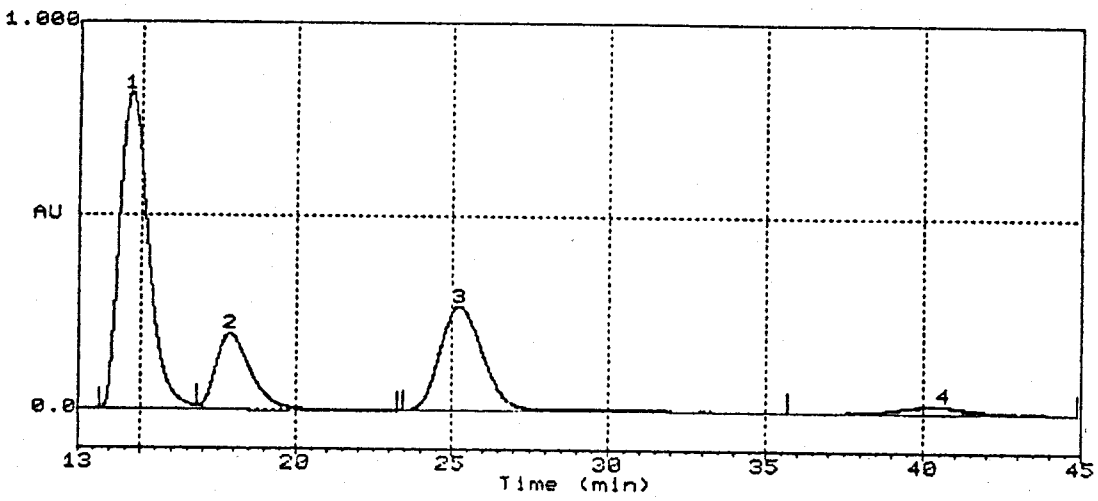


Figure 4. The HPLC spectrum of **13** (Daicel CHIRALCEL OD, 10% IPA in hexane, 1 mL/min). 1, **13a**; 2, **13c**; 3, 13b; 4, **13d**.

Next, in order to obtain the higher diastereoselectivity in the 1,3-dipolar cycloaddition, the effect of solvents was examined (Table 1). The *endo*/*exo* ratio (**a** + **b** : others) didn't change significantly. The diastereomeric ratio of the products by the reaction of **9** in acetonitrile was **13a/13b/13c/13d** = 63 : 19 : 16 : 2 (44% de for the *endo* isomers), whereas when tetrahydrofuran (THF) and methanol were used as a solvent, both of the reactivity and the diastereoselectivity became worse. Compared with the diastereofacial differentiation of dipolarophile **11** in the reaction of nitrone **9**, a reversal of diastereoselectivity was observed in the reaction of nitrone **8** when dichloromethane and toluene were used as a solvent; however, the reaction of nitrone **8** in acetonitrile gave the same diastereofacial differentiation of dienophile **11** in comparison with nitrone **9**. Thus,

the similar tendency toward diastereofacial differentiation was observed by changing solvents, although the diastereoselectivity obtained was not so high.

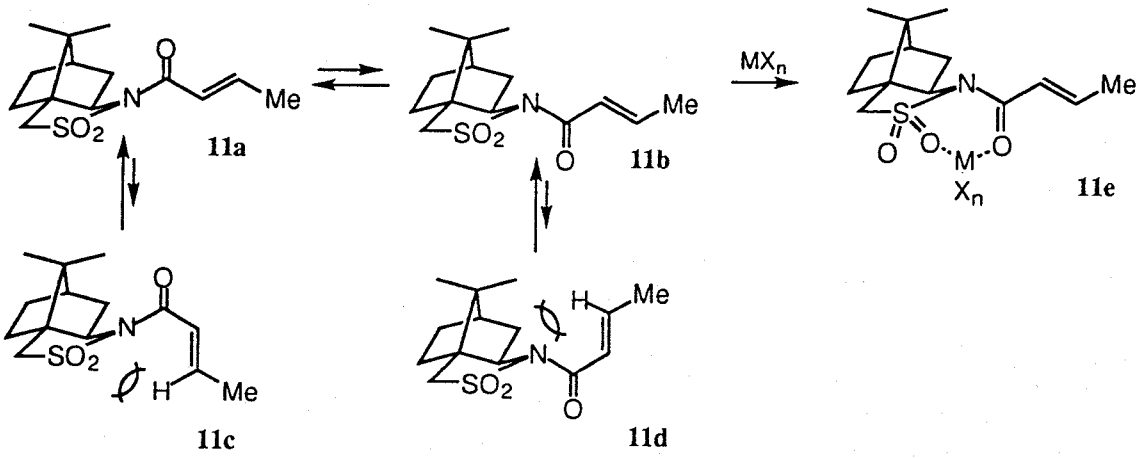
Table 1. The Effect of Solvents toward 1,3-Dipolar Cycloadditions of Nitrone **8** and **9** to Crotonoylsultam **11**[a]

entry	nitrone	solvent	yield,[b] %	ratio[c] a : b : others
1	**9**	CH_3CN	96	63 : 19 : 18
2	**9**	THF	81	47 : 35 : 18
3	**9**	CH_2Cl_2	99	54 : 27 : 19
4	**9**	toluene	96	56 : 31 : 13
5	**9**	CH_3OH	59	43 : 29 : 28
6	**8**	CH_3CN	90	44 : 36 : 21
7	**8**	CH_2Cl_2	82	35 : 52 : 13
8	**8**	toluene	86	38 : 44 : 18

[a]The reactions of nitrones (1.5 mmol) with **11** (1.0 mmol) were carried out in a solvent (2.0 mL) at 35 °C for 24 h. [b]Isolated yield as a diastereomeric mixture. [c]Determined by HPLC analysis (Daicel CHIRALCEL OD).

The Reaction of Cyclic Nitrones with Crotonoylsultam 11 in the presence of Lewis Acids. Next, the effect of the chelation of crotonoylsultam **11** to Lewis acids was examined. As shown in Scheme 2, four conformational structures of **11** are considered. The reaction seems to occur *via* **11a** or **11b** due to the steric repulsion between the camphor sultam skeleton and crotonoyl one.[11c] Poor diastereofacial selectivity of nitrones toward crotonoylsultam **11** is caused by the equilibrium between **11a** and **11b**. When Lewis acids which have more than two coordination sites are present in this system, the conformation will be fixed as **11e**. Oppolzer *et al.* reported that in Diels-Alder reaction the chelated complex of titanium(IV) chloride with crotonoylsultam **11** in which dienes such as cyclopentadiene, attack to the opposite side (the *re* face) of methyl groups of the

Scheme 2



camphor skeleton.[11a] In the addition of nitrone **9** to the chelated complex **11e**, the cycloadduct **13a** should be formed.

It was found that the addition of zinc salts increases diastereoselectivity (Table 2). The reaction of nitrone **9** with dipolarophile **11** in the presence of zinc iodide in dichloromethane for 96 h gave the adduct **13** in the diastereomeric ratio of **13b/13b/13c/13d** = 78 : 4 : 18 : 0 (90% de for the *endo* isomers), although the yield was low (entry 2). The addition of copper(I) chloride improved the diastereoselectivity slightly (entry 6). Other Lewis acids such as copper(II) chloride, titanium(IV) complexes, magnesium chloride, and aluminum salts, however, did not improve the diastereoselectivity.

Table 2. The Effect of Lewis Acids toward 1,3-Dipolar Cycloaddition of Nitrone **9** to Crotonoylsultam **11**[a]

entry	additive (1.5 eq)	time, day	yield,[b] %	ratio[c] 13a : 13b : 13c : 13d
1	none	1	99	54 : 27 : 16 : 3
2	ZnI_2	4	30	78 : 4 : 18 : 0
3	ZnI_2 (0.5 eq)	4	41	68 : 15 : 17 : 0
4	$ZnBr_2$	4	35	76 : 6 : 18 : 0
5	$ZnCl_2$	4	21	74 : 8 : 18 : 0
6	CuCl	4	54	63 : 9 : 28 : 0
7	$CuCl_2$	4	0	—
8	$TiCl_4$	7	0	—
9	$Ti(O\text{-}i\text{-}Pr)_4$	4	28	59 : 27 : 12 : 2
10	$MgCl_2$	4	27	45 : 25 : 24 : 5
11	$AlCl_3$	4	15	52 : 15 : 30 : 2
12	$AlMe_2Cl$	4	0	—

[a] The reaction of nitrone **9** (1.5 mmol) with **11** (1.0 mmol) was carried out in the presence of Lewis acid (1.5 mmol) in CH_2Cl_2 (2 mL) at 35 °C. [b] Isolated yield as a diastereomeric mixture. [c] Determined by HPLC analysis (Daicel CHIRALCEL OD).

The Reaction of Cyclic Nitrones with Crotonoylsultam 11 under High-Pressure. The present reaction can be promoted under high pressure (Table 3).[9h,18] At 10 kbar, in the presence of zinc iodide the cycloadduct **13** was obtained in 74% yield, although the ratio of **13a/13b**/other isomers was changed slightly to be 71 : 18 : 11 (60% de for the *endo* isomers) (entry 4). 4-Å Molecular sieves should be added to avoid the hydrolysis of the cycloadduct by trace amounts of water under high pressure.

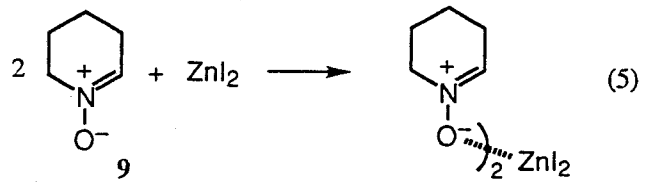
The reaction of nitrone **8** with dipolarophile **11** in the presence of zinc iodide gave the adduct **12** in the ratio of **12a/12b/12c** = 77 : 14 : 9 (68% de for the *endo* isomers), but the yield was low (entry 7). Even under high pressure, both the diastereoselectivity and the yield were low (entry 8).

Table 3. Effects of Pressure and Zinc Iodide toward the 1,3-Dipolar Cycloadditions of Nitrones **8** and **9** to Crotonoylsultam **11**[a]

entry	nitrone	additive (1.5 eq)	pressure, atm	temp, °C	time, h	yield,[b] %	ratio[c] **a** : **b** : others
1	**9**	none	1	35	24	99	54 : 27 : 16
2	**9**	none	10000	r.t.	2	85	54 : 30 : 14
3	**9**	ZnI_2	1	35	96	30	78 : 4 : 18
4	**9**	ZnI_2, MS4A	10000	r.t.	24	74	71 : 18 : 11
5	**8**	none	1	35	24	86	35 : 52 : 13
6	**8**	none	10000	r.t.	2	71	30 : 58 : 12
7	**8**	ZnI_2	1	35	96	12	77 : 14 : 9
8	**8**	ZnI_2, MS4A	10000	r.t.	24	26	54 : 40 : 6

[a] The reactions of nitrones (1.5 mmol) with **11** (1.0 mmol) were carried out in CH_2Cl_2 (2.0 mL). [b] Isolated yield as a diastereomeric mixture. [c] Determined by HPLC (Daicel CHIRALCEL OD).

The Interaction of Nitrone 9 with Zinc Iodide. Zinc iodide is considered to play a role to fix the conformation of crotonoylsultam **11**, but it is insoluble in dichloromethane and chloroform-*d* even in the presence of **11**. Zinc iodide becomes soluble in the presence of nitrones. The NMR analysis showed very strong interaction of nitrone **9** with zinc iodide. Thus, chemical shifts (δ) of the H-2 and the C-2 of nitrone **9** changed from 7.16 to 8.22 and 136.9 to 159.0 (35 °C, zinc iodide (0.091 mmol), **9** (0.091 mmol) in chloroform-*d* (0.6 mL)), respectively (eq 5).



(5)

The titration study of **9** in the presence of zinc iodide showed that 2 equivalents of nitrone **9** coordinate to zinc iodide. Thus, when 2 equivalents of **9** were added to a mixture of zinc iodide in chloroform-*d*, the mixture became a clear solution, while the chemical shift of the H-2 proton of **9** decreased constantly with addition of **9** (Figure 5).

The control of stereochemistry of the addition of nitrones to crotonoylsultam **11** in the presence of ZnI_2 is rationalized by assuming Scheme 3. Zinc iodide is insoluble in dichloromethane in the presence of only dipolarophile **11**, but becomes soluble in the presence of nitrones; therefore, zinc iodide undergoes chelation with crotonoylsultam **11**. Nitrones attack to the *re* face of **11** to give the 2*S*,3*R* configuration, because the *si* face is blocked by the methyl group of the camphor skeleton. The configuration at the C-4 of the adduct is determined by differentiation of the enantiofaces of nitrones. It is understood by the assumption of secondary orbital interaction between nitrones and the carbonyl group of the crotonoyl moiety (an *endo* transition model) to give the 3,4-*cis* configuration.[5,19] Therefore, the 2*S*,3*R*,2*S* configuration is formed.

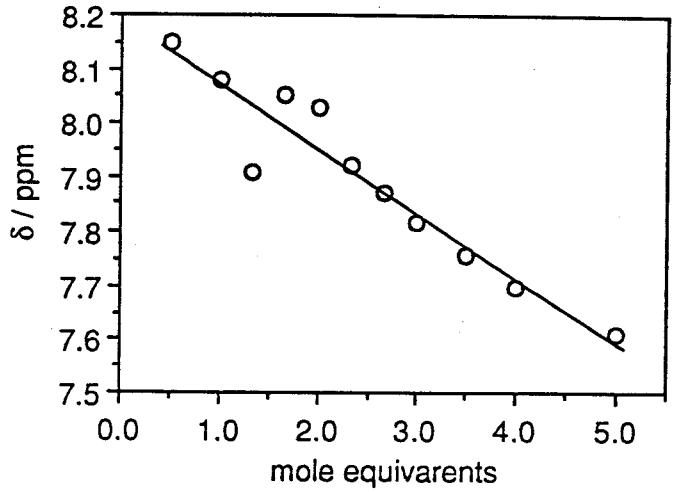
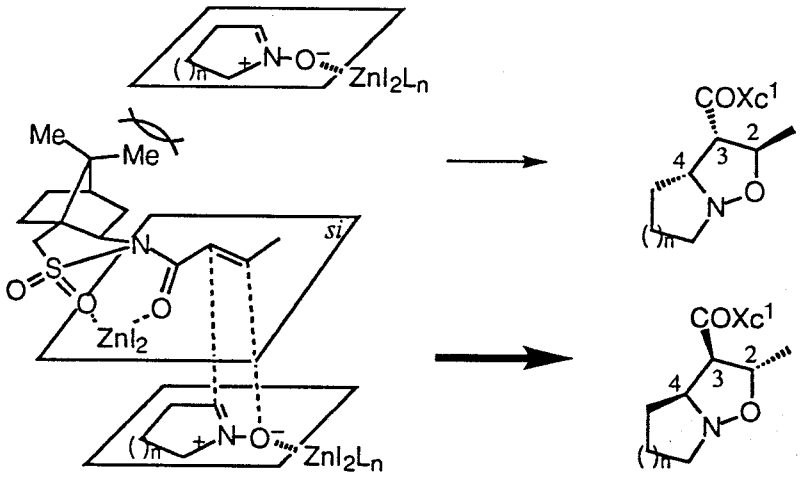
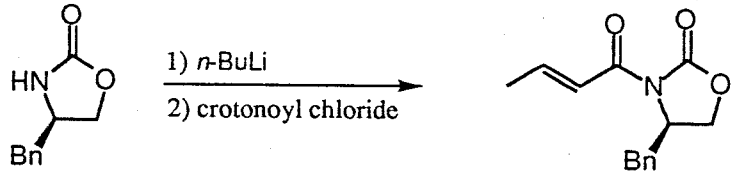


Figure 5. The H-2 chemical shift (δ) of nitrone **9** as the function of added **9** (3.24 M in $CDCl_3$) for ZnI_2 (0.094 mmol) in $CDCl_3$ (0.6 mL).

Scheme 3



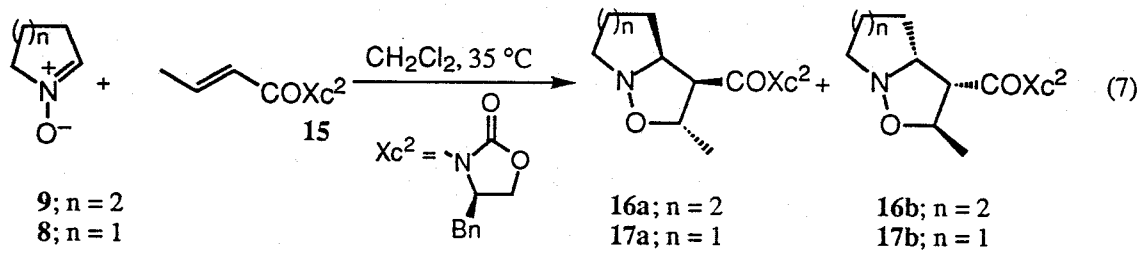
The Reaction of Cyclic Nitrones with Crotonoylimide 15. (4*R*)-3-[(*E*)-2-Butenoyl]-4-phenylmethyl-2-oxazolidinone (**15**) (crotonoylimide), which is prepared by the condensation of the lithium amide of (4*R*)-4-phenylmethyl-2-oxazolidinone (**14**) with (*E*)-crotonoyl chloride (eq 6),[12] is also a bidentate dipolarophile. The reaction of cyclic



14 **15** (6)

nitrones with **15** was found to give good diastereoselectivity (eq 7, Table 4). The reaction of nitrone **9** with crotonoylimide **15** in the presence of zinc iodide gave an adduct **16** in the

ratio of **16a/16b/16c/16d** = 86 : 3 : 11 : 0, 92% de for the *endo* isomers (82% yield) (entry 2), while in the absence of zinc iodide the ratio of **16a/16b/16c/16d** was 34 : 48 : 10 : 8 (entry 1). The reaction of nitrone **8** in the presence of zinc iodide gave an adduct **17** with the ratio of **17a/17b/17c/17d** = 82 : 13 : 5 : 0 (72% de for the *endo* isomers, 53% yield) (entry 4), while in the absence of zinc iodide, the ratio of **17a/17b/17c/17d** was 45 : 50 : 5 : 0 (entry 3).



(7)

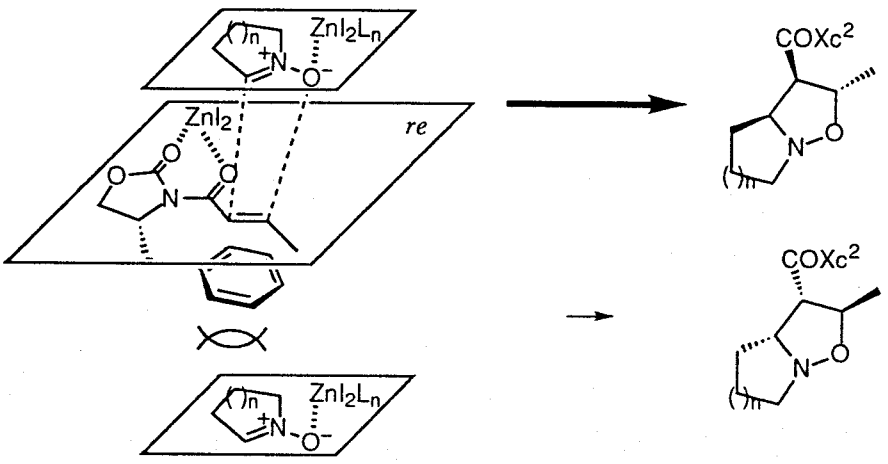
Table 4. 1,3-Dipolar Cycloadditions of Nitrones **8** and **9** to Crotonoylimide **15**[a]

entry	nitrone	additive (1.5 eq)	time, h	yield,[b] %	ratio[c] **a : b : c : d**
1	**9**	none	24	99	34 : 48 : 10 : 8
2	**9**	ZnI_2	48	82	86 : 3 : 11 : 0
3	**8**	none	24	84	45 : 50 : 5 : 0
4	**8**	ZnI_2	48	53	82 : 13 : 5 : 0

[a] The reactions of nitrones (1.5 mmol) with **15** (1.0 mmol) were carried out in CH_2Cl_2 (2.0 mL) at 35 °C. [b] Isolated yield as a diastereomeric mxture. [c] Determined by HPLC analysis (Daicel CHIRALCEL OD).

The addition of zinc iodide improved diastereoselectivity dramatically. This is due to the fact that zinc iodide undergoes chelation to fix the conformation of dipolarophiles (Scheme 4). It is well known that acyl oxazolidinones undergo chelation with Lewis acids.[12] It is proposed that there is the π interaction between the phenyl group and the enoate moiety of crotonoylimide **15** bearing 4-benzyloxazolidinone.[12] Therefore, nitrones

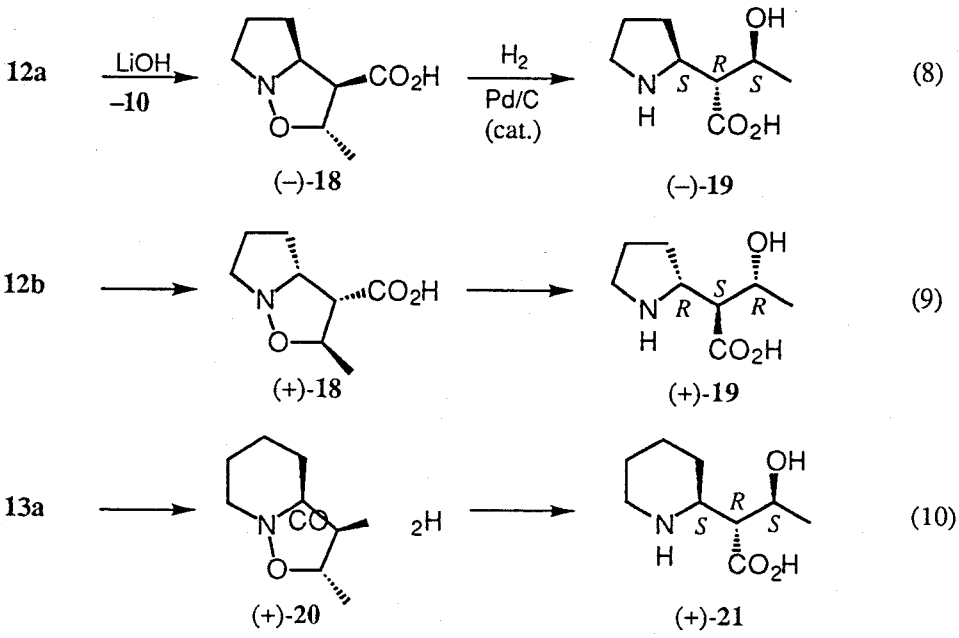
Scheme 4



react with the chelated dipolarophile to the opposite side (the *re* face) of the substituent of the oxazolidinone ring to give the major diastereomers *via* an *endo* transition state.

The retardation of the zinc iodide-mediated cycloaddition is considered to be caused by the coordination of basic nitrones to zinc iodide. If the chelation of the dipolarophiles to zinc iodide is performed effectively, the reaction will be improved. The reaction with crotonoylimide **15** is faster than that with crotonoylsultam **11**. This is provably due to the stability of the chelated dipolarophiles. The difference between **11** and **15** is the size of the chelate rings with zinc iodide. For example, the C=O bond (1.2 Å) of **15** is shorter than the S=O bond (1.4 Å) of **11**. This is considered to cause the difference of the reactivity.

Synthesis of β-Amino-β'-hydroxy Acids, (+)-Sedridine, and (+)-Hygroline. The cycloadducts **12a**, **12b**, and **13a**, which were obtained by the reaction of nitrone **8** or **9** with crotonoylsultam **11**, were converted to β-amino acids (–)-**19**, (+)-**19**, and (+)-**21**, respectively (eqs 8–10). Hydrolysis of the cycloadducts **12a** and **12b** with lithium hydroxide, followed by the ion exchange column chromatography gave carboxylic acids (–)-**18** (68% yield; mp 176 °C dec; $[\alpha]^{27}_D$ –130° (*c* 1.01, H_2O)) and (+)-**18** (57% yield; mp 172 °C dec; $[\alpha]^{26}_D$ +131° (*c* 1.21, H_2O)), respectively along with recovering sultam **10**. The N-O bond cleavages of (–)-**18** and (+)-**18** by catalytic hydrogenation gave (–)-**19** (84% yield; mp 230 °C dec; $[\alpha]^{25}_D$ –33.2° (*c* 1.05, H_2O)) and (+)-**19** (97% yield; mp 229 °C dec; $[\alpha]^{25}_D$ +31.0° (*c* 1.02, H_2O)), respectively. β-Amino acid (+)-**21** (99% yield based on (+)-**20**; mp 225 °C dec; $[\alpha]^{25}_D$ +6.6° (*c* 0.96, H_2O)) was obtained by the similar procedure *via* the carboxylic acid (+)-**20** (68% yield; mp 158 °C dec; $[\alpha]^{24}_D$ +94.2° (*c* 1.25, $CHCl_3$)). The methyl esters of (±)-**18** and (±)-**20** were converted to the corresponding β-lactams as models of thienamycin.[20]

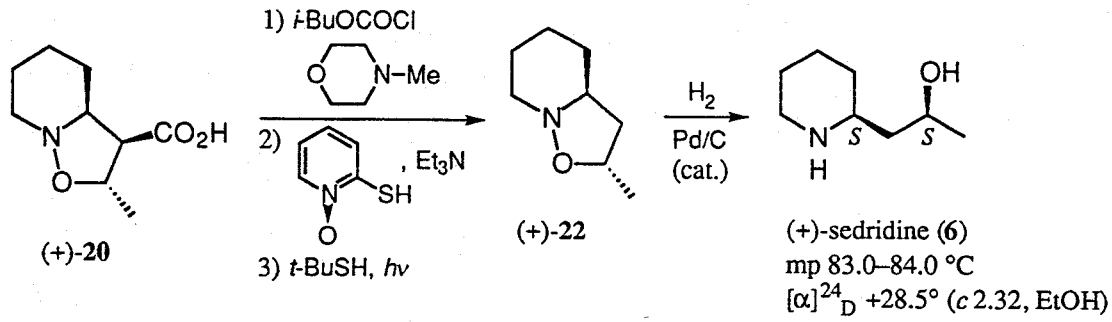


The cycloadducts are also useful precursors for synthesis of piperidine and pyrrolidine alkaloids. Typically, (+)-sedridine (**6**)[14] which is a natural piperidine alkaloid

isolated from *Sedum acre* (Crassulaceae), and (+)-hygroline (**7**)[15] which is a natural pyrrolidine alkaloid isolated from *Carallia brachiata* (Rhizophoraceae), can be synthesized simply.

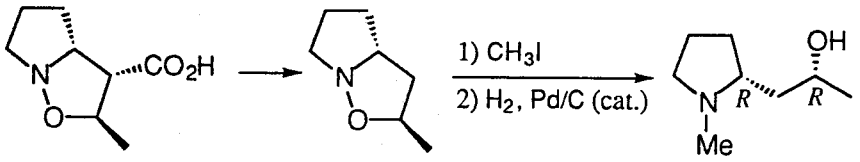
Decarboxylation of (+)-**20** by means of Barton's method[21] gave isoxazolidine (+)-**22** ($[\alpha]^{24}_D$ +86.8° (*c* 1.09, $CHCl_3$)) in 56% yield. Then, catalytic hydrogenation of (+)-**22** gave (+)-sedridine (**6**) (mp 83.0–84.0 °C; $[\alpha]^{24}_D$ +28.5° (*c* 2.32, EtOH)) in 83% yield (Scheme 5). The absolute configuration of (+)-sedridine is 2*S*,2'*S*; therefore, the cycloadduct **13a** has the 2*S*,3*R*,4*S* configuration.

Scheme 5



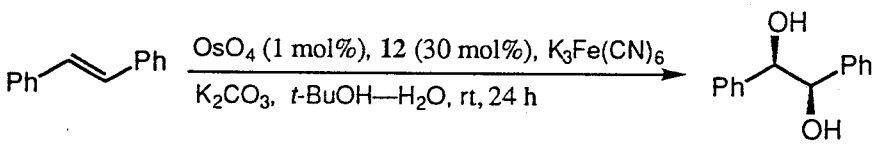
Similarly, the cycloadduct (+)-**18** can be converted into (+)-hygroline (**7**) (mp 32.5–34.5 °C; $[\alpha]^{24}_D$ +50.7° (*c* 0.869, EtOH)) *via* isoxazolidine (+)-**23** ($[\alpha]^{23}_D$ +45.3° (*c* 0.766, $CHCl_3$)) (Scheme 6). The configuration of (+)-hygroline (**7**) is 2*R*,2'*R*; therefore, the configuration of **12b** is 2*R*,3*S*,4*R*, while the configuration of **12a** is 2*S*,3*R*,4*S*.

Scheme 6



The cycloadducts are useful chiral ligands for the osmium-catalyzed asymmetric dihydroxylation of olefins.[17] The oxidation of *trans*-stilbene with $K_3Fe(CN)_4$ in the

Scheme 7



12	yield,[a] %	ee,[b] %
12a	99	56 (*S*,*S*)
12b	>99	73 (*R*,*R*)

[a] GC yield. [b] Determined by HPLC.

presence of the cycloadduct **12a** or **12b** (30 mol%) and osmium tetroxide (1 mol%) in *t*-BuOH—H_2O (1 : 1) gave hydrobenzoin in quantitative yield. The enantiomeric excess of the oxidation products were 56% (*S*,*S*) and 73% (*R*,*R*), respectively (Scheme 7). The use of these cycloadducts as chiral ligands is expected in other asymmetric reactions.

Asymmetric cycloadditions of nitrones to crotonic acid derivatives bearing chiral auxiliaries such as camphor sultam and oxazolidinone were performed. The cycloadducts were obtained as a single diastereomer by simple crystallization, respectively. This reaction was applied to the short step synthesis of alkaloids such as (+)-sedridine and (+)-hygroline. In this reaction, the addition of zinc iodide lowers the reactivity, but the diastereoselectivity is enhanced because of the fixation of the conformation of dipolarophiles. The rate enhancement of the 1,3-dipolar cycloadditions of nitrones to olefins is difficult because of Lewis basicity of nitrones. Quite recently, Kanemasa *et al.* reported that $TiCl_2(O\text{-}i\text{-}Pr)_4$ promotes the cycloaddition of acyclic nitrones to α,β-unsaturated ketone or allyl alcohol.[22] Jørgensen *et al.* applied this system to the catalytic asymmetric reaction using the chiral titanate,[23] and obtained moderate enantiomeric excess up to 62% ee. Scheeren *et al.* also reported the catalytic asymmetric reaction with ketene acetals using chiral oxaborolidine,[24] and obtained enantiomeric excess up to 62% ee. The development of highly stereoselective 1,3-dipolar cycloaddition of nitrones attracts considerable attention.

Experimental Section

General. All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 polarimeter. IR spectra were recorded on a Shimadzu FTIR 4100 spectrometer. NMR spectra were obtained on a JEOL JNM-GSX-270 (^1H, 270 MHz, ^{13}C 68 MHz) spectrometer; chemical shifts (δ) were expressed in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad. Coupling constants (*J*) are reported in hertz. Elemental analyses were carried out on a Yanagimoto Model MT-3 CHN corder. Mass spectra were obtained on a JEOL JMS-DX303 mass spectrometer. Analytical GC evaluations of product mixtures were performed on a Shimadzu GC-9A flame ionization chromatography by using a glass spiral column packed with 10% silicon SE-30 on 60–80 mesh Uniport HP, under the condition of injection temperature (200 °C), column temperature (100–250 °C), and nitrogen gas flow (40 mL/min). HPLC analyses were performed on a JASCO TRI ROTAR-VI system with a JASCO MULTI 340 UV detector by using a 250 mm x 4.6 mm analytical column packed with Daicel CHIRALCEL® OD. Analytical TLC was performed on E. Merck silica gel 60 F254 (Art. 5714) or E. Merck DC-Fertigplatten RP-18F245S (Art. 15685). Flash chromatography was carried out on E. Merck silica gel 60 (230–400 mesh). High-pressure (10 kbar) experiments were performed

in a stainless steel die and compressed *via* a piston. A X-ray analysis was performed on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation and a 12kW rotating anode generator.

Materials. Isobutyl chlorocarbonate, *t*-butyl mercaptan, 2-mercaptopyridine *N*-oxide, methyliodide, *trans*-stilbene, *t*-buthanol, lithium hydroxide monohydrate, aluminum chloride, dimethylalminum chloride in hexane, copper(I) chloride, copper(II) chloride, zinc chloride, zinc bromide, zinc iodide, palladium on charcoal (K-type) (Nippon Engelhard), potassium ferricyanide, and osmium tetroxide (Wako Pure Chemical Ind.) were commercially available and used without further purification. Triethylamine, 4-methylmorpholine, titanium(IV) chloride, titanium(IV) isopropoxide, dichloromethane, acetonitrile, methanol, toluene, and tetrahydrofuran (THF) were commercially available and distilled before use. 4-Å Molecular sieves is commercially available and dried over P_2O_5 at 120 °C *in vacuo* before use.

Preparation of Nitrones. 1-Pyrroline *N*-oxide (**8**) and 2,3,4,5-tetrahydropyridine *N*-oxide (**9**) were prepared by the catalytic oxidation of the corresponding secondary amines with 30% hydrogen peroxide in the presence of Na_2WO_4 (4 mol%).[10]

Preparation of Dipolarophiles. (–)-*N*-Crotonoylbornane-10,2-sultam (**11**) was prepared by the condensation of (*E*)-crotonoyl chloride and (–)-bornane-10,2-sultam (**10**)[11d,e] upon treatment with sodium hydride by reported procedure.[11] (4*R*)-3-[(*E*)-2-Butenoyl]-4-(phenylmethyl)-2-oxazolidinone (**15**) was prepared by the condensation of (*E*)-crotonoyl chloride and (4*R*)-4-(phenylmethyl)-2-oxazolidinone[12b] upon treatment with *n*-butyl lithium by reported procedure.[12]

General Procedure for the Reaction of Nitrones with Olefins. A mixture of nitrone (1.5 mmol), olefin (1.0 mmol), and a solvent (2.0 mL) were stirred at 35 °C under argon. After the reaction evaporation, followed by column chromatography on silica gel (ethyl acetate in hexane) gave the adducts. The product was analyzed by HPLC (Daicel CHIRALCEL OD) and ^{1}H NMR. The results were shown in Table 1, 3, and 4. The product was purified by crystallization from ethyl acetate or methanol.

General Procedure for the Reaction of Nitrones and Olefins with Lewis acids. To a mixture of olefin (1.0 mmol) and Lewis acid (1.5 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of nitrone in CH_2Cl_2 (1.5 mmol, 1.0 mL), and the mixture was stirred at 35 °C under argon. After the reaction ethyl acetate (5 mL) and sat. $NaHCO_3$ (10 mL) were added to the reaction mixture, and the mixture was filtered through Celite and the cake was washed with ethyl acetate (30 mL). The organic layer was separated and washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL), and dried over $MgSO_4$. Filtration, evaporation, followed by column chromatography on silica gel gave the adducts. The product was analyzed by HPLC and ^{1}H NMR. The results were shown in Table 2, 3, and 4.

General Procedure for the Reaction of Nitrones and Olefins under High-pressure condition. In a Teflon capsule (1.5–10 mL capacity) were placed olefin, Lewis acid (1.5 eq), nitrone (1.5 eq), 4-Å molecular sieves, and CH_2Cl_2 (0.5 M). High pressure (10 kbar) experiment was performed in a stainless steel die which was compressed *via* a piston. After the reaction water was added to the mixture, and the mixture was filtered through Celite and the cake was washed with ethyl acetate. The mixture was extracted with ethyl acetate (20 mL x 3), and the combined extracts were dried over $MgSO_4$. Filtration, evaporation, followed by column chromatography on silica gel gave adducts. The product was analyzed by HPLC and ^1H NMR. The results were shown in Table 3.

***N*-[{2-Methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*]isoxazolidin-3-yl}carbonyl]bornane-10,2-sultam (12).** The tittle compound **12** was prepared by the reaction of nitrone **8** with crotonoylsultam **11** following general procedures. The diastereomeric ratio was determined by HPLC analysis using Daicel CHIRALCEL OD (10 % isopropyl alcohol in hexane, 1 mL/min).

***N*-[{(2*S*,3*R*,4*S*)-2-Methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*]isoxazolidin-3-yl}carbonyl]bornane-10,2-sultam (12a).** The diastereomeric mixture of **12** (12.8 g, 34.8 mmol) was recrystallized from methanol twice to give **12a** (2.2 g) as a colorless crystal: R_f 0.40 (SiO_2, hexane—ethyl acetate = 1 : 1); mp 207.0–207.5 °C (methanol); $[\alpha]^{27}_D$ –187° (*c* 1.01, $CHCl_3$); IR (KBr) 2970, 1675, 1405, 1375, 1330, 1310, 1300, 1270, 1240, 1220, 1165, 1130, 1055, 765, cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 0.98 (s, 3 H, C*H*$_3$), 1.14 (s, 3 H, C*H*$_3$), 1.29 (d, *J* = 5.9 Hz, 3 H, C*H*$_3$), 1.26–1.49 (m, 3 H, C*H*$_2$, C*H*), 1.52–2.13 (m, 8 H, 4 C*H*$_2$), 3.07 (ddd, *J* = 7.1, 7.1, and 11.4 Hz, 1 H, *H*CHNO), 3.25 (ddd, *J* = 6.4, 11.4, and 11.4 Hz, 1 H, *H*CHNO), 3.46 (d, *J* = 13.9 Hz, 1 H, *H*CHSO$_2$), 3.52 (d, *J* = 13.9 Hz, 1 H, *H*CHSO$_2$), 3.74 (dd, *J* = 8.8 and 8.8 Hz, 1 H, C*H*CON), 3.90 (dd, *J* = 5.2 and 7.4 Hz, 1 H, C*H*NSO$_2$), 4.17 (ddd, *J* = 7.8, 7.8, and 8.1 Hz, 1 H, C*H*NO), and 4.50 (dq, *J* = 5.9, 8.8 Hz, 1 H, CH$_3$C*H*O); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 17.4, 19.9, 20.7, 24.3, 26.4, 26.7, 32.9, 38.6, 44.7, 47.8, 48.3, 53.2, 56.5, 59.0, 65.3, 66.8, 73.6, 169.0 (C=O); Anal. Calcd for $C_{18}H_{28}N_2O_4S$: C, 58.67; H, 7.66; N, 7.60. Found: C, 58.61; H, 7.88; N, 7.49.

***N*-[{(2*R*,3*S*,4*R*)-2-Methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*]isoxazolidin-3-yl}carbonyl]bornane-10,2-sultam (12b).** The recovered solid from the first mother liquid from **12a** was further recrystallized from methanol several times to give **12b** (6.3 g) as a colorless crystal (containing methanol): R_f 0.42 (SiO_2, hexane—ethyl acetate = 1 : 1); mp 164.0–164.5 °C (methanol); $[\alpha]^{27}_D$ +15.2° (*c* 1.00, $CHCl_3$); IR (KBr) 2969, 1688, 1402, 1323, 1310, 1298, 1267, 1236, 1134, 1059, 534 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 0.98 (s, 3 H, C*H*$_3$), 1.15 (s, 3 H, C*H*$_3$), 1.28 (d, *J* = 5.9 Hz, 3 H, C*H*$_3$), 1.31–1.46 (m, 2 H, C*H*$_2$), 1.69–1.99 (m, 7 H, 3 C*H*$_2$, C*H*), 2.10 (ddd, *J* = 1.8, 1.8, and 6.4 Hz, 2 H, C*H*$_2$CHNSO$_2$), 3.08 (ddd, *J* = 7.5, 7.5, and 11.5 Hz, 1 H, *H*CHNO), 3.29 (ddd, *J* = 6.4, 11.2, and 11.2 Hz, 1 H, *H*CHNO), 3.43 (d, *J* = 13.9 Hz, 1 H, *H*CHSO$_2$), 3.53 (d, *J* = 13.9 Hz, 1 H, *H*CHSO$_2$), 3.74 (dd, *J* = 8.8 and 8.8 Hz, 1 H, C*H*CON), 3.89 (dd, *J* = 6.3 and 6.3 Hz, 1 H, C*H*NSO$_2$), 4.20 (ddd, *J* = 7.5, 7.5, and 8.3 Hz, 1 H, C*H*NO), 4.49 (dq, *J* = 5.9 and 8.8 Hz, 1 H, CH$_3$C*H*O); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 17.3, 19.9, 20.8, 24.2, 26.5,

26.6, 32.9, 38.7, 44.7, 47.9, 48.5, 53.2, 56.5, 58.5, 65.4, 67.4, 76.1, 169.3 (C=O); HRMS (EI) calcd for $C_{18}H_{28}N_2O_4S$ (M^+) 368.1770, found 368.1798.

***N*-[{2-Methyl-3*H*-4,5,6,7-tetrahydropyrido[1,2-*b*]isoxazolidin-3-yl}carbonyl]bornane-10,2-sultam (13).** The adduct **13** was prepared by the reaction of nitrone **9** with crotonoylsultam **11** following general procedures. The diastereomeric ratio was determined by HPLC analysis using Daicel CHIRALCEL OD (10 % isopropyl alcohol in hexane, 1 mL/min).

***N*-[{(2*S*,3*R*,4*S*)-2-Methyl-3*H*-4,5,6,7-tetrahydropyrido[1,2-*b*]isoxazolidin-3-yl}carbonyl]bornane-10,2-sultam (13a).** The diastereomeric mixture of **13** (11.2 g) was recrystallized form ethyl acetate to give **13a** (4.81 g) as a colorless crystal: R_f 0.39 (SiO_2, hexane—ethyl acetate = 3 : 2); mp 186.0–188.0 °C (ethyl acetate); $[\alpha]^{30}_D$ –73.2° (*c* 1.02, $CHCl_3$); IR (KBr) 2882, 2862, 2828, 1670, 1456, 1446, 1410, 1335, 1325, 1318, 1310, 1270, 1250, 1238, 1220, 1168, 1135, 1125, 1113, 1064, 1055, 1041, 544 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 0.98 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.26–1.44 (m, 4 H, $2CH_2$), 1.35 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.60–1.80 (m, 3 H, CH_2, CH), 1.80–2.18 (m, 6 H, $3CH_2$), 2.35–2.43 (m, 1 H, HCHNO), 2.53–2.60 (m, 1 H, HCNO), 3.45 (d, *J* = 13.8 Hz, 1 H, $HCHSO_2$), 3.59 (dd, *J* = 8.1 and 5.2 Hz, 1 H, HCCON), 3.93 (dd, *J* = 7.0 and 5.6 Hz, 1 H, $HCNSO_2$), 4.52 (dq, *J* = 5.9 and 5.6 Hz, 1 H, CH_3CHO); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 18.8, 19.9, 20.8, 23.5, 24.1, 26.0, 26.4, 33.0, 38.0, 44.6, 47.7, 48.0, 53.3, 55.3, 57.5, 65.7, 70.7, 75.6, 170.9 (*C*=O); Anal. Calcd for $C_{19}H_{30}N_2O_4S$: C, 59.96; H, 7.91; N, 7.33; S, 8.37. Found: C, 59.96; H, 7.86; N, 7.35; S, 8.60.

(4*R*)-3-[{2-Methyl-3*H*-4,5,6,7-tetrahydropyrido[1,2-*b*]isoxazolidin-3-yl}carbonyl]-4-(phenylmethy)-2-oxazolidinone (16). The adduct **16** was prepared by the reaction of nitrone **9** with crotonoylimide **15** following general procedures. Diastereomeric ratio was determined by HPLC analysis using Daicel CHIRALCEL OD (2% isopropyl alcohol in hexane, 1 mL/min).

(4*R*)-3-[{(2*S*,3*R*,4*S*)-2-Methyl-3*H*-4,5,6,7-tetrahydropyrido[1,2-*b*]isoxazolidin-3-yl}carbonyl]-4-(phenylmethy)-2-oxazolidinone (16a). The diastereomeric mixture of **16** (86 : 3 : 11, 325 mg) was purified by column chromatography on silica gel to give **16a** (219 mg, 64%) as a foam, and the analytical sample was obtained by crystallization from chloroform—isopropyl alcohol as a colorless crystal: R_f 0.38 (SiO_2, hexane—ethyl acetate = 3 : 2); mp 132.0–133.0 °C; $[\alpha]^{29.5}_D$ –41.1° (*c* 1.24, $CHCl_3$); IR (KBr) 2926, 1782, 1765, 1701, 1689, 1400, 1383, 1348, 1238, 1211, 1198, 1109, 750, 702, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.221.42 (m, 2 H), 1.33 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.552.08 (m, 3 H), 1.862.08 (m, 1 H), 2.45 (br t, *J* = 10.0 Hz, 1 H, NCHH), 2.59 (dd, *J* = 11.0 and 13.0 Hz, 1 H, PhCHH), 2.69 (br t, *J* = 8.0 Hz, 1 H, ONCH), 3.463.58 (m, 1 H, NCHH), 3.51 (dd, *J* = 3.2 and 12.9 Hz, 1 H, PhCHH), 4.144.22 (m, 3 H, OCH_2, CHCO), 4.624.78 (m, 2 H, $OCHCH_3$, $NCHCH_2Ph$), 7.22–7.39 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 19.4, 23.6, 24.2, 26.2, 38.2, 55.3, 55.7, 66.2, 70.2, 74.6, 127.3, 129.0, 129.3, 135.4, 153.4 (NCO_2), and 171.2 (CON); Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.15; H, 6.99; N, 8.13.

(4*R*)-3-[{(2*R*,3*S*,4*R*)-2-Methyl-3*H*-4,5,6,7-tetrahydropyrido[1,2-*b*]isoxazolidin-3-yl}carbonyl]-4-(phenylmethy)-2-oxazolidinone (16b): R_f 0.32 (SiO_2, hexane—ethyl acetate = 3 : 2); IR (Nujol) 1784, 1699, 1460, 1445, 1395, 1352, 1211, 1114 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.12–1.42 (m, 2 H), 1.36 (d, J = 6.4 Hz, 3 H, CH_3), 1.56–1.89 (m, 4 H), 2.43 (br t, J = 9.0 Hz, 1 H, NC*H*H), 2.61 (br, 1 H, ONC*H*), 2.81 (dd, J = 9.5 and 13.4 Hz, 1 H, PhC*H*H), 3.30 (dd, J = 3.2 and 13.4 Hz, 1 H, PhC*H*H), 3.50 (br d, J = 9.3 Hz, 1 H, NC*H*H), 4.17–4.25 (m, 2 H, OCH_2), 4.29 (dd, J = 5.4 and 8.3 Hz, 1 H, C*H*CO), 4.62–4.78 (m, 2 H, OC*H*CH_3, NC*H*CH_2Ph), 7.15–7.38 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 19.4, 23.5, 24.1, 26.0, 37.9, 55.2, 55.4, 55.7, 66.2, 69.7, 75.0, 76.5, 127.4, 128.9, 129.3, 135.1, 153.5 (N*C*O_2), 171.3 (*C*ON); HRMS (EI) calcd for $C_{19}H_{24}N_2O_4$ (M^+) 344.1736, found 344.1719.

(4*R*)-3-[{2-Methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*]isoxazolidin-3-yl}carbonyl]-4-(phenylmethy)-2-oxazolidinone (17). The adduct **17** was prepared by the reaction of nitrone **8** with crotonoylimide **15** following general procedures. The diastereomeric ratio was determined by HPLC analysis using Daicel CHIRALCEL OD (5% ethanol in hexane, 1 mL/min).

(4*R*)-3-[{(2*S*,3*R*,4*S*)-2-Methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*]isoxazolidin-3-yl}carbonyl]-4-(phenylmethy)-2-oxazolidinone (17a). The diastereomeric mixture of **17** (50 : 45 : 5, 554 mg) was purified by column chromatography on silica gel to give **17a** (192 mg) as a foam: R_f 0.57 (SiO_2, hexane—ethyl acetate = 1 : 2); IR (KBr) 2976, 1778, 1692, 1391, 1211, 764, 708 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.31 (d, J = 6.1 Hz, 3 H, CH_3), 1.54–2.10 (m, 4 H, 4 CH_2), 2.62 (dd, J = 10.5 and 13.2 Hz, 1 H, PhC*H*H), 3.10 (ddd, J = 7.3, 7.3, and 11.2 Hz, 1 H, NC*H*H), 3.28 (ddd, J = 5.4, 6.1, and 11.5 Hz, 1 H, NC*H*H), 3.40 (dd, J = 3.2 and 12.9 Hz, 1 H, PhC*H*H), 4.02 (t, J = 9.0 Hz, 1 H, C*H*CO), 4.12 (dd, J = 3.7 and 9.3, 1 H, OC*H*H), 4.22 (dd, J = 9.3 and 9.3, 1 H, OC*H*H), 4.36 (q, J = 8.3 Hz, 1 H, NC*H*), 4.62 (dq, J = 9.0 and 5.9 Hz, 1 H, OC*H*CH_3), 4.69 (dq, J = 10.5 and 3.4, 1 H, NC*H*CH_2Ph), 7.16–7.40 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 17.5, 24.3, 26.9, 38.1, 55.3, 56.3, 58.5, 65.9, 66.4, 73.2, 127.4, 129.0, 129.2, 135.1, 152.8 (N*C*O_2), 170.0 (*C*ON); Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.42; H, 6.72; N, 8.48. Found: C, 65.18; H, 6.76; N, 8.42.

(4*R*)-3-[{(2*R*,3*S*,4*R*)-2-Methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*]isoxazolidin-3-yl}carbonyl]-4-(phenylmethy)-2-oxazolidinone (17b): R_f 0.46 (SiO_2, hexane—ethyl acetate = 1 : 2); IR (KBr) 2973, 1777, 1694, 1385, 1358, 1238, 1198, 762, 704 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.34 (d, J = 5.9 Hz, 3 H, CH_3), 1.46–1.98 (m, 4 H, 4 CH_2), 2.82 (dd, J = 9.5 and 13.4 Hz, 1 H, PhC*H*H), 3.10 (ddd, J = 6.4, 6.4, and 13.7 Hz, 1 H, NC*H*H), 3.21–3.32 (m, 1 H, NC*H*H), 3.29 (dd, J = 3.9 and 13.4 Hz, 1 H, PhC*H*H), 4.12 (t, J = 9.0 Hz, 1 H, C*H*CO), 4.17–4.28 (m, 3 H, OC*H*H, OC*H*H, NC*H*), 4.62 (dq, J = 8.8 and 5.9 Hz, 1 H, OC*H*CH_3), 4.65–4.74 (m, 1 H, NC*H*CH_2Ph), 7.15–7.39 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 17.6, 24.3, 27.0, 37.9, 55.4, 56.3, 58.8, 65.6, 66.4, 73.6, 127.5, 129.0, 129.3, 134.9, 152.7 (N*C*O_2), 170.3 (*C*ON); Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.42; H, 6.72; N, 8.48. Found: C, 65.36; H, 6.72; N, 8.48.

Preparation of (2*S*,3*R*,4*S*)-2-Methyl-3*H*-4,5,6,7-tetrahydropyrido[1,2-*b*]isoxazolidine-3-carboxylic acid (20). A mixture of **13a** (1.24 g, 3.24 mmol), $LiOH{\cdot}H_2O$ (1.37 g, 32.7 mmol), THF (30 mL), and water (15 mL) was stirred at room temperature for 17 h. After THF was removed under reduced pressure, the remaining aqueous solution was washed with chloroform (30 mL x 3). Ion exchange column chromatography (Dowex* 50W-X2, 3 N NH_3 aqueous), evaporation, followed by crystallization from ethanol gave (+)-**20** (0.406 g, 68%) as a colorless crystal. The others, the combined chloroform extracts were dried over $MgSO_4$, and evaporated to give sultam **10** (635 mg, 91%). (+)-**20**: mp 158.0 °C dec; $[\alpha]^{24}_D$ +94.2° (*c* 1.25, $CHCl_3$); IR (KBr) 2950, 2930, 1686, 1445, 1379, 1300, 1149, 1055, 1024, 945, 922, 848, 766, 702, 630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.16–1.41 (m, 1 H, *H*CH), 1.34 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$), 1.43–1.89 (m, 4 H), 1.97–2.08 (m,1 H, *H*CHCH), 2.48 (ddd, *J* = 2.9, 9.7, and 12.3 Hz, 1 H, *H*CH), 2.56 (ddd, *J* = 2.4, 7.4, and 10.0 Hz, 1 H, *H*CH$_2$), 2.90 (dd, *J* = 3.8 and 6.7 Hz, 1 H, C*H*CO_2H), 3.54 (ddd, *J* = 2.6, 2.6, and 9.5 Hz, 1 H, *H*CHN), 4.47 (dq, *J* = 3.7 and 6.3 Hz, 1 H, C*H*CH); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 20.3, 23.3, 24.1, 26.1, 55.0, 57.6, 67.8, 75.5, 174.4 (*C*=O); Anal. Calcd for $C_9H_{15}NO_3$: C, 58.35; H, 8.17; N, 7.50. Found: C, 58.17; H, 8.04; N, 7.46.

(2*R*,3*S*,4*R*)-2-Methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*]isoxazolidine-3-carboxylic Acid ((+)-18). Prepared from **12b** by the similar procedure for (+)-**20** in 57% yield as a colorless crystal: mp 172 °C dec; $[\alpha]^{26}_D$ +131° (*c* 1.21, H_2O); IR (KBr) 3234, 2943, 1593 (C=O), 1413, 1059, 862 cm^{-1}; ^1H NMR (270 Hz, $CDCl_3$, 35 °C) δ 1.35 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.71–2.06 (m, 4 H, C*H*$_2$C*H*$_2$), 3.16 (ddd, *J* = 6.0, 6.0 and 12.0 Hz, 1 H, NC*H*$_2$), 3.21 (dd, *J* = 7.5 and 9.9 Hz, 1 H, C*H*COO), 3.37 (ddd, *J* = 6.0, 6.0 and 12.0 Hz, 1 H, NC*H*$_2$), 4.16 (ddd, *J* = 7.5, 7.5 and 7.5 Hz, 1 H, NC*H*), 4.37 (dq, *J* = 6.0 and 9.9 Hz, 1 H, NOC*H*), 7.52 (br, 1 H, CO_2H); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 18.0, 24.5, 27.4, 57.0, 59.7, 67.1, 75.1, 174.4; HRMS (EI) calcd for $C_8H_{13}NO_3$ (M^+) 171.0895, found 171.0899; Anal Calcd for $C_8H_{13}NO_3$: C, 56,13; H, 7.65; N, 8.18. Found: C, 55.77; H, 7.59; N, 8.16.

(2*S*,3*R*,4*S*)-2-Methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*]isoxazolidine-3-carboxylic Acid ((–)-18): Prepared in 68% yield by hydrolysis of **12a** as a colorless crystal: mp 176 °C dec; $[\alpha]^{27}_D$ –130° (*c* 1.01, H_2O).

Preparation of (2*R*,3*S*,2'*S*)-3-Hydroxy-2-(2'-pyrrolidinyl)butanoic Acid ((–)-19). A mixture of (–)-**18** (138 mg, 0.81 mmol), 10% Pd/C (86 mg, 0.08 mmol) and methanol (8 mL) was stirred at room temperature at 1 atm of H_2 for 4 h. The catalyst was removed by filtration. Evaporation gave (–)-**19** (117 mg, 84%) as a colorless crystal: mp 230 °C dec; $[\alpha]^{25}_D$ –33.2° (*c* 1.05, H_2O); IR (KBr) 3405, 3310, 2965, 1618, 1595, 1393, 1136, 1112, 1100, 1072, 748 cm^{-1}; ^1H NMR (270 MHz, CD_3OD, 35 °C) δ 1.28 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$), 1.70–2.24 (m, 4 H), 2.42 (dd, *J* = 2.4 and 6.8 Hz, 1 H, C*H*CO_2H), 3.20–3.35 (m, 2 H, C*H*$_2$N), 3.89 (ddd, *J* = 2.4, 7.1, and 10.0 Hz, 1 H, C*H*N), 4.00 (quint, *J* = 6.6 Hz, 1 H,

*H*CCH$_3$); ^{13}C NMR (68 MHz, CD$_3$OD, 35 °C) δ 23.4, 25.8, 31.3, 57.1, 59.7, 69.1, 179.9; HRMS (FAB) calcd for $C_8H_{15}NO_3$ (M+H$^+$) 174.1130, found 174.1163.

(2*S*,3*R*,2'*R*)-3-Hydroxy-2-(2'-pyrrolidinyl)butanoic Acid ((+)-19): Prepared from (+)-**18** in 97% yield as a colorless crystal: mp 229 °C dec; $[\alpha]^{26}_D$ +31.0° (*c* 1.02, H_2O)

(2*R*,3*S*,2'*S*)-3-Hydroxy-2-(2'-piperidyl)butanoic Acid ((+)-21). Prepared from (+)-**20** by the similar procedure for **19** in 99% yield as a colorless crystal: mp 225–230 °C; $[\alpha]^{25}_D$ +6.6° (*c* 0.96, H_2O); IR (KBr) 3400 (br), 3135, 2950, 1626, 1578, 1460, 1405, 1390, 1375, 1314, 1086; ^{1}H NMR (270 MHz, CD$_3$OD, 35 °C) δ 1.28 (d, *J* = 6.3 Hz, 3 H, C*H*$_3$), 1.46–1.95 (m, 6 H), 2.28 (dd, *J* = 3.2 and 6.6 Hz, 1 H, C*H*CO$_2$H), 2.91 (dt, *J* = 3.2 and 12.7 Hz, 1 H, C*H*N), 3.37–3.48 (m, 2 H, C*H*$_2$N), 4.15 (quint, *J* = 6.4 Hz, 1 H, *H*CCH$_3$); ^{13}C NMR (68 MHz, CD$_3$OD, 35 °C) δ 23.3, 24.2, 24.5, 29.6, 46.5, 57.2, 59.1, 68.4, 179.5; HRMS (FAB) calcd for $C_9H_{17}NO_3$ (M+H$^+$) 188.1287, found 188.1284.

Preparation of (2*S*,4*S*)-2-Methyl-3*H*-4,5,6,7-tetrahydropyrido[1,2-*b*]isoxazolidine (22). To a solution of (+)-**20** (450 mg, 2.43 mmol) in CH_2Cl_2 (12 mL) were added isobutyl chlorocarbonate (0.315 mL, 2.45 mmol) and 4-methylmorpholine (0.267 mL, 2.43 mmol), and the mixture was stirred at –10 °C under argon. After 20 min, triethylamine (0.677 mL, 4.86 mmol) and 2-mercaptopyridine *N*-oxide (309 mg, 2.43 mmol) were added and the stirring continued at –10 °C for 45 min. After addition of *t*-butyl mercaptan (1.32 mL, 12.2 mmol), the solution was irradiated with 150 W tungsten lamp cooling with cold water for 2 h. After evaporation, 2 M hydrochloric acid (10 mL) was added and the mixture was washed with ether (20 mL x 3). To the aqueous phase was added K_2CO_3 (3 g) and the mixture was extracted with ether (15 mL x 3). The combined extracts were dried over $MgSO_4$ and evaporated, followed by bulb-to-bulb distillation gave (+)-**22** (194 mg, 56%) as a pale yellow oil: R_f 0.49 (SiO_2, ethyl acetate); $[\alpha]^{21}_D$ +86.8° (*c* 1.09, $CHCl_3$); IR (neat) 2947, 2901, 2870, 2827, 1454, 1381, 1262, 1115, 1038, 907, 856 , 775; ^{1}H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.14–1.52 (m, 2 H), 1.24 (d, *J* = 6.1 Hz, C*H*$_3$), 1.56–1.84 (m, 4 H), 1.87–1.97 (m, 1 H), 1.98–2.12 (m, 1 H), 2.12–2.27 (m, 1 H), 2.40–2.52 (m, 1 H), 3.38–3.48 (m, 1 H), 4.11–4.24 (m, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 20.9, 24.0, 24.8, 29.4, 41.6, 55.2, 66.4, 71.8; HRMS (EI) calcd for $C_8H_{15}NO$ (M$^+$) 141.1154, found 141.1172.

(2*R*,4*R*)-2-Methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*]isoxazolidine (23). Prepared from (+)-**18** by the similar procedure for (+)-**22** in 29% yield as a pale yellow oil: R_f 0.26 (SiO_2, ethyl acetate); $[\alpha]^{23}_D$ +45.4° (*c* 0.766, $CHCl_3$); IR (neat) 2980, 1455, 1707, 1383, 1293, 1082; ^{1}H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.25 (d, *J* = 6.2 Hz, 3 H, C*H*$_3$), 1.46–1.76 (m, 2 H, C*H*$_2$), 1.71–2.07 (m, 4 H, C*H*$_2$), 3.03–3.22 (m, 2 H, C*H*$_2$N), 3.75 (dddd, *J* = 5.6, 5.6, 5.6, and 7.6 Hz, 1 H, C*H*N), 4.18 (ddq, *J* = 6.1, 7.3, and 6.1 Hz, 1 H, C*H*O); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 19.0, 24.3, 31.8, 44.2, 57.2, 65.0, 72.1; HRMS (EI) calcd for $C_7H_{13}NO$ (M$^+$) 127.0997, found 127.0981.

Preparation of (+)-Sedridine (6). A mixture of (+)-**22** (131 mg, 0.928 mmol) and 5% Pd/C (K type) (395 mg, 0.19 mmol) in methanol (10 mL) was stirred at room temperature at 1 atm of H_2 for 2 h. The catalyst was removed by filtration. Evaporation gave (+)-sedridine (**6**) (110 mg, 83%) as a colorless crystal: mp 83.0–84.0 °C (lit.[14a] mp 83–84 °C); $[\alpha]^{24}_D$ +28.5° (*c* 2.32, EtOH) (lit.[14a] $[\alpha]^{23}_D$ +29.3 ° (*c* 2.28, EtOH)); IR (KBr) 3420 (br), 2975, 2859, 1630 (br), 1094, 1055; ^{1}H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.25 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.32–1.51 (m, 4 H), 1.53–1.64 (m, 3 H), 1.79–1.85 (m, 1 H), 2.58 (ddd, *J* = 3.0, 12.0, and 12.0 Hz, 1 H, *H*CHNH), 2.67 (br, 2 H, *H*N, *H*O), 2.89 (ddd, *J* =3.0, 6.5, and 12.0 Hz, 1 H, *H*CHNH), 3.02–3.11 (m, 1 H, *H*CNH), 4.11 (ddq, *J* = 3.5, 4.5, and 9.0 Hz, 1 H, *H*CCH$_3$); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 23.6, 24.8, 26.1, 31.4, 43.9, 47.0, 54.87, 65.2; HRMS (EI) calcd for $C_8H_{17}NO$ (M^+) 143.1310, found 143.1305.

Preparation of (+)-Hyglorine (7). To a solution of (+)-**23** (120 mg, 0.943 mmol) in $CHCl_3$ (4.5 mL) was added CH_3I (0.12 mL, 1.9 mmol) at room temperature under argon. The mixture was stirred for 2 h, then evaporated. The residue was dissolved in methanol (4.5 mL), and to the solution was added 5% Pd/C (K type) (395 mg, 0.19 mmol). The suspension was stirred at room temperature at 1 atm of H_2 for 19 h. The catalyst was removed by filtration. Evaporation and extraction with CH_2Cl_2 (15 mL x 6) from sat. $NaHCO_3$ (5 mL) gave (+)-hyglorine (**7**) (107 mg, 83%) as a colorless crystal: mp 32.5–34.5 °C (lit[15b] 29–30 °C); $[\alpha]^{24}_D$ +50.7° (*c* 0.868, EtOH) (lit[15b] $[\alpha]^{21}_D$ +50° (*c* 0.77, EtOH); IR (KBr) 3400, 2966, 1456, 1375, 1217, 1186, 1150, 1148, 1111, 1071, 1038; ^{1}H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.15 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$), 1.46 (dt, *J* = 5.6 and 2.7 Hz, 1 H, C*H*H), 1.67–1.99 (m, 5 H), 2,10–2.28 (m, 1 H, C*H*HN), 2.37 (s, 3 H, C*H*$_3$), 2.56–2.65 (m 1 H, C*H*HN), 3.07–3.16 (m, 1 H, C*H*N), 4.16 (ddq, *J* = 2.2, 10.0, and 6.1 Hz, 1 H, C*H*OH), 4.43 (br, 1 H, O*H*); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 23.3, 23.7, 28.4, 37.2, 40.5, 57.1, 64.6, 65.0; HRMS (EI) calcd for $C_8H_{17}NO$ (M^+) 143.1310, found 143.1336.

General procedure for asymmetric dihydroxylations of olefins. To a mixture of olefin (1.0 mmol), $K_3Fe(CN)_6$ (0.988 g, 3.0 mmol), K_2CO_3 (0.415 g, 3.0 mmol), and chiral ligand (30 mol%) in *t*-butyl alcohol—water (1 : 1, 15 mL) was added a 0.2 M solution of osmium tetroxide in toluene (50 μL, 0.01 mmol). The mixture was stirred at room temperature for 24 h. The reaction mixture was added Na_2SO_3 (0.756 g, 6.0 mmol) and diluted with ethyl acetate (30 mL) and water (30 mL). Extraction of the aqueous phase, followed by column chromatography on silica gel of extracts gave diols. The chemical yields were determined by GC analysis, and the optical purity were determined by the HPLC analysis.

(*R,*R**)-1,2-Diphenyl-1,2-ethanediol (Hydrobenzoin).** The optical purity was determined by HPLC (Daicel CHIRALCEL OB , 5% ethanol in hexane): IR (KBr) 3402, 3086, 2928, 1452, 1402, 1217, 1046, 1012, 777, 706 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$, 35 °C) δ 2.82 (br, 2 H, O*H*), 4.71 (s, 2 H, C*H*), 6.95–7.25 (m, 10 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 79.1, 126.9, 127.9, 128.1, 139.9.

X-Ray Structure Analysis of *N*-[{(2*R*,3*S*,4*R*)-2-Methyl-4,5,6,7-tetrahydropyrrolo[1,2-*b*]isoxazolidin-3-yl}carbonyl]bornane-10,2-sultam (12b). The single crystal of **12b** was grown in methanol. Crystal data, collection parameters, and refinement parameters were summarized in Table 5.[25] Atomic coordinates, anisotropic thermal parameters, bond lengths, and selected bond angles were shown in Table 6, 7, 8, and 9, respectively. Hydrogen atoms were idealized with C-H = 0.95 Å.

Table 5. Crystal Data, Collection Parameters, and Refinement Parameters for **12b**

molecular formula	$C_{19}H_{32}N_2O_5S$
fw	400.53
crystal color, habit	colorless, prismatic
dimensions, mm	0.15 x 0.20 x 0.30
radiation, Å	Mo-Kα (0.71069)
crystal system	orthorhombic
lattice type	primitive
lattice parameters	
a, Å	9.415(3)
b, Å	28.193(6)
c, Å	7.738(3)
V, Å^3	2054(1)
space group	$P2_12_12_1$ (#19)
Z	4
D_{calc}, g/cm^3	1.295
reflections collected	2171
reflections observed	1051
scan width, °	1.47 + 0.30 tan θ
F (000)	864.00
temp, °C	20.0
μ, cm^{-1}	1.89
no. of variables	245
shift/error at final cycle	0.05
ρ_{max}, e^-/Å^3	0.27
ρ_{min}, e^-/Å^3	–0.24
R	0.055
R_w	0.052
goodness of fit	1.69

Table 6. Atomic coordinates and B_{eq} of **12b**[a]

atom	x	y	z	B_{eq}
S(1)	0.2469(3)	0.11777(10)	0.9725(3)	3.51(6)
O(1)	0.3107(7)	0.0720(2)	0.9572(9)	4.8(2)
O(2)	0.3339(7)	0.1566(3)	1.0247(9)	4.9(2)
O(3)	0.5936(6)	0.1315(2)	0.4471(8)	3.6(2)
O(5)	0.8199(9)	0.0356(3)	0.586(1)	7.7(3)
O(4)	0.1599(7)	0.1319(3)	0.4949(8)	5.1(2)
N(2)	0.5759(8)	0.0826(3)	0.478(1)	3.0(2)
N(1)	0.1653(7)	0.1320(3)	0.7831(9)	2.8(2)
C(1)	0.0087(9)	0.1275(3)	0.796(1)	2.6(2)
C(2)	–0.079(1)	0.1668(4)	0.707(1)	4.3(3)
C(3)	–0.177(1)	0.1837(4)	0.853(1)	4.1(3)
C(4)	–0.273(1)	0.1426(4)	0.904(1)	4.9(3)
C(5)	–0.178(1)	0.1083(3)	1.005(1)	4.2(3)
C(6)	–0.0328(9)	0.1332(3)	0.989(1)	2.7(2)
C(7)	–0.0717(10)	0.1860(3)	1.006(1)	3.5(2)
C(8)	–0.142(1)	0.1971(4)	1.183(1)	5.2(3)
C(9)	0.047(1)	0.2225(3)	0.984(2)	5.0(3)
C(10)	0.086(1)	0.1131(4)	1.098(1)	3.8(2)
C(11)	0.455(1)	0.1533(3)	0.462(1)	3.4(2)
C(12)	0.3939(10)	0.1281(3)	0.619(1)	2.9(2)
C(13)	0.451(1)	0.0783(4)	0.603(1)	4.1(3)
C(14)	0.358(1)	0.0398(4)	0.528(2)	7.6(4)
C(15)	0.442(2)	0.0206(5)	0.377(2)	9.6(5)
C(16)	0.534(1)	0.0577(4)	0.319(1)	4.7(3)
C(17)	0.476(1)	0.2052(4)	0.481(2)	6.3(3)
C(18)	0.234(1)	0.1304(4)	0.623(1)	3.6(2)
C(19)	0.907(1)	0.0251(5)	0.447(2)	7.4(4)
H(1)	–0.0187	0.0921	0.7568	5.5682
H(2)	–0.0198	0.1918	0.6679	5.5682
H(3)	–0.1322	0.1545	0.6130	4.9108
H(4)	–0.2260	0.2125	0.8300	5.5253
H(5)	–0.3488	0.1534	0.9747	4.9108
H(6)	–0.3103	0.1275	0.8039	5.1150
H(7)	–0.2065	0.1056	1.1218	5.5682
H(8)	–0.1761	0.0777	0.9530	4.6943

Table 6. (continued)

atom	x	y	z	B_{eq}
H(9)	–0.2188	0.1757	1.2018	5.5682
H(10)	0.0744	0.1937	1.2725	6.1954
H(11)	–0.1775	0.2287	1.1820	6.1954
H(12)	0.0976	0.2159	0.8802	5.5682
H(13)	0.1096	0.2209	1.0794	5.7326
H(14)	0.0067	0.2533	0.9768	3.6700
H(15)	0.0954	0.1308	1.2019	5.5253
H(16)	0.0678	0.0809	1.1251	5.7295
H(17)	0.3997	0.1467	0.3628	5.5253
H(18)	0.4307	0.1422	0.7213	8.8663
H(19)	0.4859	0.0682	0.7122	5.7326
H(20)	0.3413	0.0156	0.6104	7.8912
H(21)	0.2705	0.0526	0.4896	7.8912
H(22)	0.4963	–0.0060	0.4126	9.7260
H(23)	0.3793	0.0115	0.2868	6.3086
H(24)	0.6146	0.0449	0.2621	3.6700
H(25)	0.4850	0.0785	0.2432	4.9550
H(26)	0.5307	0.2115	0.5815	6.3086
H(27)	0.5242	0.2171	0.3822	6.3086
H(28)	0.3861	0.2203	0.4909	5.5253
H(29)	0.8278	0.0359	0.6709	5.6053
H(30)	0.9672	–0.0007	0.4758	5.5682
H(31)	0.8496	0.0166	0.3504	8.8663
H(32)	0.9624	0.0520	0.4188	5.6838

[a] $B_{eq} = (8/3)\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$.

Table 7. Anisotropic Displacement Parameters of **12b**[a]

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S(1)	0.033(1)	0.077(2)	0.023(1)	0.004(2)	–0.004(2)	0.010(2)
O(1)	0.059(5)	0.077(5)	0.045(4)	0.035(4)	–0.001(4)	0.019(4)
O(2)	0.043(4)	0.110(6)	0.033(4)	–0.029(4)	–0.006(4)	–0.010(5)
O(3)	0.035(4)	0.059(4)	0.044(4)	–0.002(4)	0.009(4)	0.002(4)
O(4)	0.037(4)	0.141(7)	0.018(3)	0.020(5)	–0.010(4)	0.000(4)
O(5)	0.094(7)	0.145(8)	0.055(5)	0.015(7)	–0.002(5)	0.012(6)
N(2)	0.033(5)	0.041(5)	0.040(5)	0.005(4)	0.002(5)	0.001(5)
N(1)	0.024(4)	0.060(6)	0.022(4)	0.005(4)	–0.007(4)	0.002(4)
C(1)	0.021(5)	0.056(7)	0.023(5)	–0.001(5)	0.000(5)	–0.005(5)
C(2)	0.049(7)	0.077(8)	0.036(6)	0.019(7)	0.003(6)	–0.004(6)
C(3)	0.038(7)	0.070(8)	0.049(7)	0.003(6)	0.006(6)	0.007(6)
C(4)	0.034(7)	0.095(9)	0.056(7)	0.009(7)	0.000(6)	–0.020(7)
C(5)	0.045(7)	0.069(7)	0.045(7)	–0.014(6)	0.013(6)	–0.002(7)
C(6)	0.029(5)	0.050(6)	0.023(5)	0.001(5)	0.004(5)	–0.005(5)
C(7)	0.041(6)	0.057(7)	0.034(6)	0.004(5)	0.011(6)	–0.011(5)
C(8)	0.063(8)	0.077(8)	0.056(7)	0.013(7)	0.006(7)	–0.017(7)
C(9)	0.056(7)	0.054(6)	0.078(8)	–0.003(6)	–0.002(8)	–0.013(7)
C(10)	0.033(6)	0.083(8)	0.026(5)	–0.008(6)	0.009(5)	0.012(6)
C(11)	0.048(7)	0.043(6)	0.038(6)	–0.003(5)	0.010(6)	0.008(6)
C(12)	0.031(6)	0.047(6)	0.032(5)	0.005(5)	–0.002(5)	–0.001(6)
C(13)	0.052(8)	0.059(8)	0.047(6)	0.009(7)	0.004(6)	0.014(6)
C(14)	0.070(9)	0.067(9)	0.15(1)	–0.014(7)	0.05(1)	–0.04(1)
C(15)	0.14(2)	0.13(1)	0.10(1)	–0.06(1)	0.01(1)	–0.03(1)
C(16)	0.067(8)	0.063(8)	0.048(7)	–0.017(7)	0.004(7)	–0.019(6)
C(17)	0.10(1)	0.070(8)	0.076(9)	0.007(7)	0.040(9)	0.001(8)
C(18)	0.044(7)	0.068(7)	0.025(5)	0.012(7)	0.015(6)	0.000(5)
C(19)	0.057(8)	0.16(1)	0.061(8)	0.019(10)	0.003(8)	0.012(10)

[a]The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 8. Bond Lengths (Å) of **12b**

atom	atom	distance	atom	atom	distance
S(1)	O(1)	1.429(6)	S(1)	O(2)	1.427(7)
S(1)	N(1)	1.702(7)	S(1)	C(10)	1.801(9)
O(3)	N(2)	1.409(8)	O(3)	C(11)	1.45(1)
O(4)	C(18)	1.21(1)	O(4)	C(19)	1.39(1)
N(2)	C(13)	1.52(1)	N(2)	C(16)	1.47(1)
N(1)	C(1)	1.48(1)	N(1)	C(18)	1.40(1)
C(1)	C(2)	1.54(1)	C(1)	C(6)	1.55(1)
C(2)	C(3)	1.54(1)	C(3)	C(7)	1.55(1)
C(4)	C(3)	1.52(1)	C(4)	C(5)	1.53(1)
C(5)	C(6)	1.54(1)	C(7)	C(6)	1.54(1)
C(7)	C(8)	1.55(1)	C(7)	C(9)	1.53(1)
C(10)	C(6)	1.51(1)	C(11)	C(17)	1.48(1)
C(12)	C(11)	1.52(1)	C(12)	C(13)	1.51(1)
C(12)	C(18)	1.51(1)	C(13)	C(14)	1.51(2)
C(14)	C(15)	1.50(2)	C(15)	C(16)	1.43(2)

Table 9. Bond Angles (°) of **12b**

atom	atom	atom	angle	atom	atom	atom	angle
O(1)	S(1)	O(2)	118.4(4)	O(1)	S(1)	N(1)	109.4(4)
O(1)	S(1)	C(10)	109.4(5)	O(2)	S(1)	N(1)	108.8(4)
O(2)	S(1)	C(10)	112.6(4)	N(2)	S(1)	C(10)	95.9(4)
N(2)	O(3)	C(8)	107.3(6)	O(3)	N(2)	C(13)	106.0(7)
O(3)	N(2)	C(16)	111.0(8)	C(13)	N(2)	C(16)	106.6(7)
S(1)	N(1)	C(1)	111.8(6)	S(1)	N(1)	C(18)	123.2(6)
C(1)	N(1)	C(18)	121.0(7)	N(1)	C(1)	C(2)	116.2(8)
N(1)	C(1)	C(6)	107.8(7)	C(2)	C(1)	C(6)	102.6(7)
S(1)	C(10)	C(6)	107.0(6)	C(1)	C(2)	C(3)	102.7(8)
C(5)	C(4)	C(3)	105.4(9)	C(4)	C(5)	C(6)	101.0(8)
C(2)	C(3)	C(4)	108.1(9)	C(2)	C(3)	C(7)	100.8(8)
C(4)	C(3)	C(7)	102.4(9)	C(3)	C(7)	C(8)	114.0(8)
C(3)	C(8)	C(9)	114.2(9)	C(3)	C(7)	C(6)	92.5(7)
C(8)	C(7)	C(9)	106.2(8)	C(8)	C(7)	C(6)	112.0(8)
C(9)	C(7)	C(6)	117.8(8)	C(1)	C(6)	C(10)	108.2(7)
C(1)	C(6)	C(5)	104.7(8)	C(1)	C(6)	C(7)	104.2(8)
C(10)	C(6)	C(5)	116.2(8)	C(10)	C(6)	C(7)	119.2(8)
C(5)	C(6)	C(7)	102.9(7)	C(11)	C(12)	C(13)	103.4(8)
C(11)	C(12)	C(18)	111.9(8)	C(13)	C(12)	C(18)	113.6(8)
O(3)	C(11)	C(12)	102.0(7)	O(3)	C(11)	C(17)	108.1(8)
C(12)	C(11)	C(17)	115.7(9)	N(2)	C(13)	C(12)	104.8(8)
N(2)	C(13)	C(14)	104.9(9)	C(12)	C(13)	C(14)	119.4(9)
C(13)	C(14)	C(15)	104(1)	C(14)	C(15)	C(16)	107(1)
O(4)	C(18)	N(1)	117.3(8)	O(4)	C(18)	C(12)	124.0(8)
N(1)	C(18)	C(12)	118.7(8)	N(2)	C(16)	C(15)	104.5(10)

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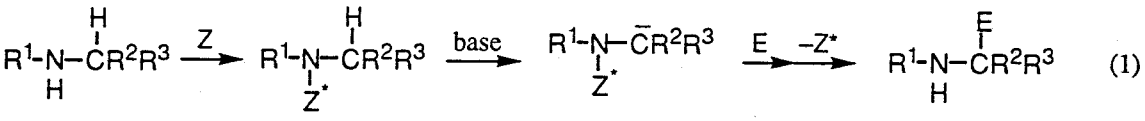
Chapter 3 Diastereoselective Addition of Chiral Enolates to Nitrones *via* *N*-Acyloxyiminium Intermediates

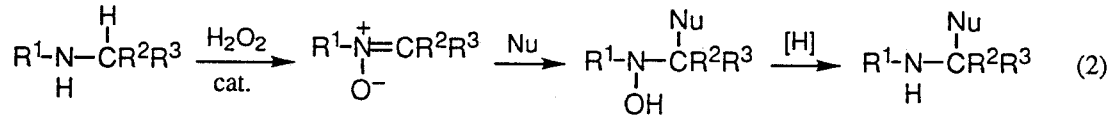
Introduction

Asymmetric induction at the α carbon of amines is of importance in view of synthesis of nitrogen containing biologically active compounds and chiral ligands for asymmetric synthesis. The introduction of substituents has been performed by using electrophiles. Thus, treatment of *N*-protected secondary amines **2** bearing electron-withdrawing groups with strong base such as organolithium reagents gives carbanions **3**. The reaction of **3** with electrophiles (E) and removal of the protecting group give α-substituted amines **4** (eq 1).[1–4] This method has been applied to the asymmetric reactions by using chiral protecting groups (Z*) such as formamidine[1] and aminooxazoline.[2]



1 **2** **3** **4** (1)

On the other hand, Murahashi *et al.* have reported that substituents can be introduced at the α carbon of secondary amines **1** by means of the catalytic oxidation of amines, followed by addition of nucleophiles (eq 2).[5] Thus, the oxidation of secondary amines **1**



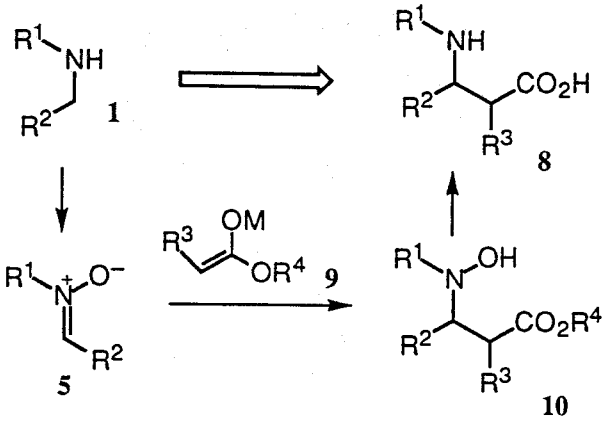
1 **5** **6** **7** (2)

with hydrogen peroxide in the presence of a catalyst such as sodium tungstate,[5,6a,d,e] selenium dioxide,[6b] or flavinium perchlorate[6c] gives nitrones **5**[7] conveniently. The addition of nucleophiles to nitrones gives α-substituted hydroxylamines **6**, which are converted into the corresponding amines **7** readily by catalytic hydrogenation,[8a] reduction with Zn/H^+ [8b] or $TiCl_3$.[8c] In this system, various hard nucleophiles such as Grignard reagents, organolithiums, potassium cyanide, and metal hydrides, can be used. Further, asymmetric synthesis of α-substituted amines can be performed by the addition of methyl *p*-tolyl α-sulfinyl carbanion,[9] catalytic hydrosilylation,[10] and the Lewis acid-promoted addition of Grignard reagents.[11] Asymmetric addition of nucleophiles to chiral nitrones is also available.[12]

β-Amino acids **8** show interesting pharmacological properties[13,14] and are useful starting materials for synthesis of β-lactam antibiotics[15] and nitrogen containing

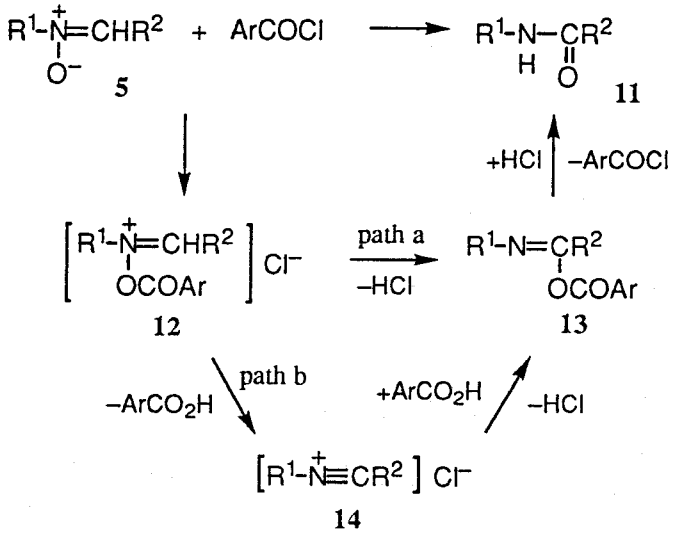
biologically active compounds.[16] Therefore, some approaches to the asymmetric synthesis of β-amino acids are in progress.[17] The reaction of nitrones **5** with enolates **9** will provide a new and convenient method for the synthesis of β-amino acids **8** (Scheme 1); however, the reactivity of soft nucleophiles such as enolates **9** toward nitrones **5** is low in comparison with that of hard nucleophiles.[18] Therefore, the activation of the reaction of nitrones with soft nucleophiles is required.

Scheme 1



It is known that the reaction of nitrones **5** with aroyl chlorides gives amides **11** (Scheme 2).[19] It is considered that the reaction proceeds *via* following path; first, the reaction of nitrones **5** with aroyl chlorides gives intermediates **12** which rearranged to **13** along with leaving hydrogen chloride, then the reaction of **13** with hydrogen chloride gives amides **11** (path a).[19a] An alternative pathway which involves nitronium ions **14** which react with carboxylic acids to give the intermediates **13** (path b).[19b]

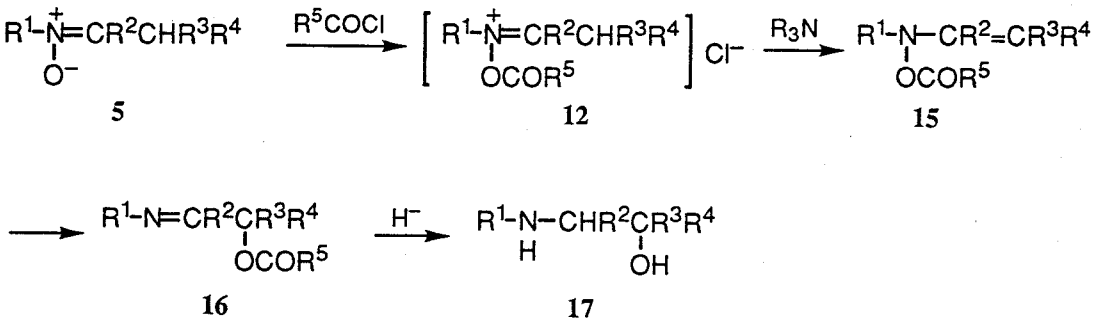
Scheme 2



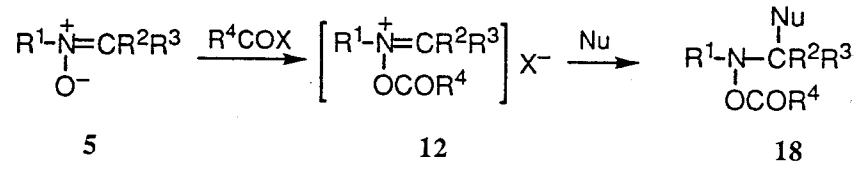
Another report has been done that the acyloxy group rearranges to the β carbon to the nitrogen in the presence of tertiary amines (Scheme 3).[20] Thus, intermediates **12**

rearrange to α-acyloxy imines **16** *via* **15**, then **16** is reduced to β-amino alcohols **17** in the presence of reducing reagents such as sodium borohydride.

Scheme 3

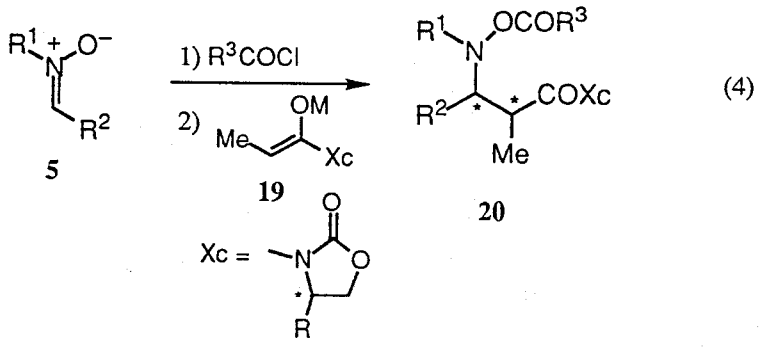


In the view of the reaction with nucleophiles, the intermediates **12** are considered to be more reactive than nitrones themselves. Indeed, it was succeeded that highly reactive intermediates **12** were trapped with nucleophiles at low temperature to give α-substituted amines **18** before the rearrangement (eq 3). The soft nucleophiles such as enolates could be introduced to give β-amino acid derivatives. The present reaction provides a useful and convenient method for the generation of iminium ion species[21,22] and the synthesis of α-substituted amines.



(3)

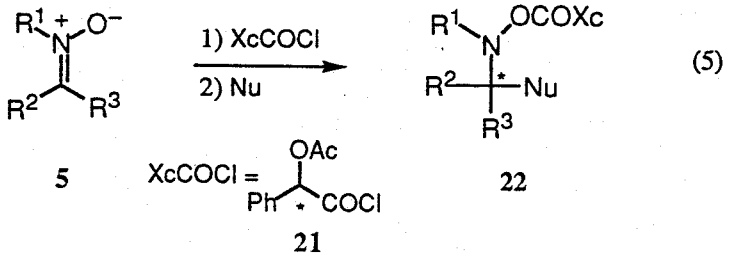
The *N*-acyloxyiminium species **12** could be detected by NMR analysis. Further, the principle was applied to asymmetric synthesis by the two methods; first, chiral enolates such as Evans' chiral enolates **19**[23] were used as chiral nucleophiles to give β-amino acid derivatives **20** (eq 4). Second, chiral acyl chloride was used as a chiral auxiliary (eq 5).



(4)

The reaction of nitrones **5** with acetylmandelyl chloride (**21**)[24] gives the chiral *N*-acyloxyiminium intermediates, which react with achiral nucleophiles diastereoselectively

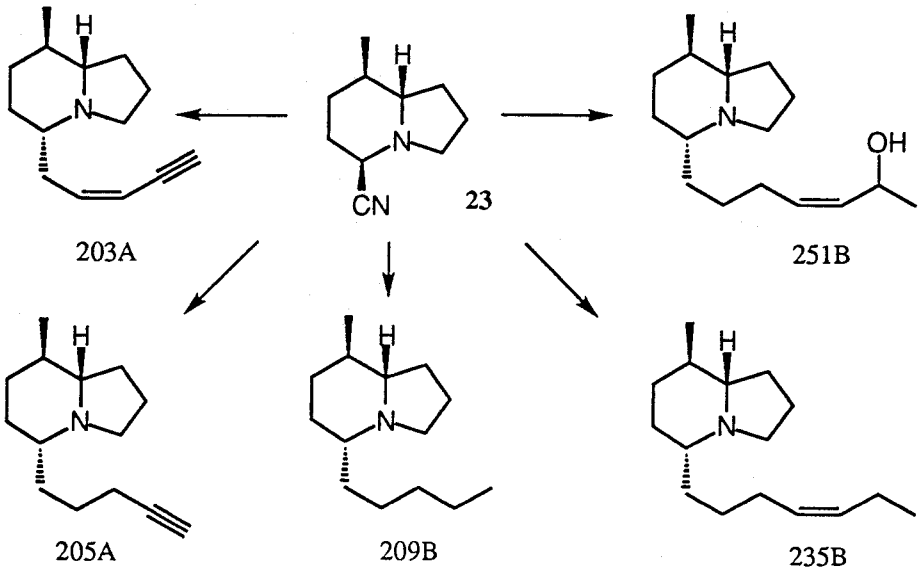
to give chiral amino compounds **22**. This is a convenient method for the generation of the chiral iminium species.



5 **21** **22** (5)

The usefulness of these methods was shown by the asymmetric synthesis of some alkaloids. 5-Substituted-8-methylindolizidines are a major class of indolizidine alkaloids. These have been isolated from the skin extracts of neotoropical poison-dart frogs (family Dendrobatidae) such as *Dendrobates pumilio*, *Dendrobates speciosus*, and *Dendrobates aurafus*,[25] and have been interested because of their activity as noncompetitive inhibitors of the acetylcholine receptor complex.[26] 5-Cyano-8-methylindolizidne (**23**) is a key synthetic precursor for the synthesis of 8-methylindolidines such as 203A, 205A, 209B, 235B, and 251B (Scheme 4).[26a]

Scheme 4



203A **23** 251B

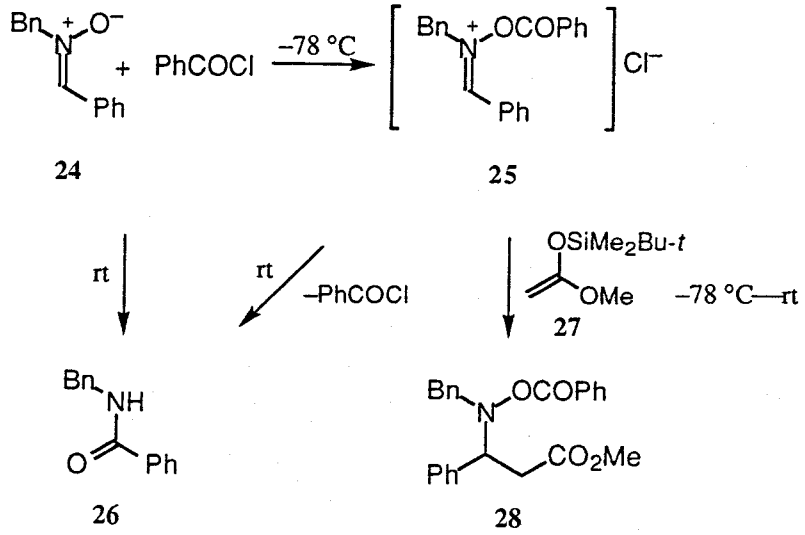
205A 209B 235B

Results and Discussion

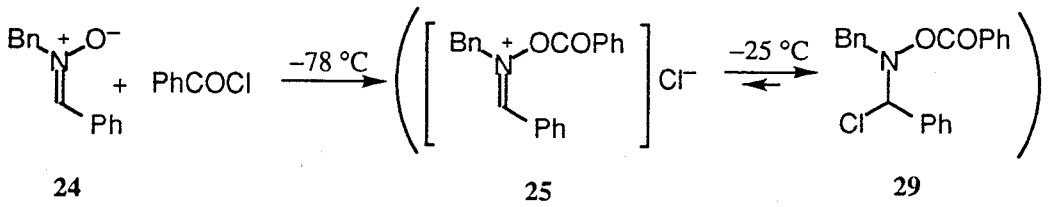
The Generation and the Reaction of *N*-Acyloxyiminium Species. First, the condition of generation of *N*-acyloxyiminium species was examined upon treatment of nitrones with acylating regents at low temperature (Scheme 5). When *N*-benzylidenebenzylamine *N*-oxide (**24**) was allowed to react with benzoyl chloride in dichloromethane at –78 °C in the presence of 4-Å molecular sieves, **24** disappeared within

30 min. When the solution was warmed up to room temperature, *N*-benzylbenzamide (**26**) was obtained *via* well-known rearrangement. Addition of ketene silyl acetal **27** to the cold solution gave methyl 3-(*N*-benzoyloxy-*N*-benzylamino)-3-phenylpropanoate (**28**) in quantitative yield, and the amide **26** could not be detected (Scheme 5). Since the reaction of nitrone **24** with **27** did not proceed without benzoyl chloride, this reaction provides a convenient method for the activation of nitrones by the generation of iminium species. The details of the reaction of nitrones with acylating reagents and further reaction with nucleophiles will be described in Ohtake's doctoral thesis.

Scheme 5



Next, the NMR study of *N*-acyloxyiminium species was carried out. The ^{1}H NMR spectrum (–25 °C) of the intermediate prepared from nitrone **24** and benzoyl chloride in chloroform-*d* at –78 °C *in situ* showed complicated signals. This is due to the equilibrium of α-chloroamine derivative **29** along with a small amount of *N*-benzoyloxyiminium ion **25** (eq 6). When acetyl chloride was employed instead of benzoyl chloride, the ^{1}H NMR

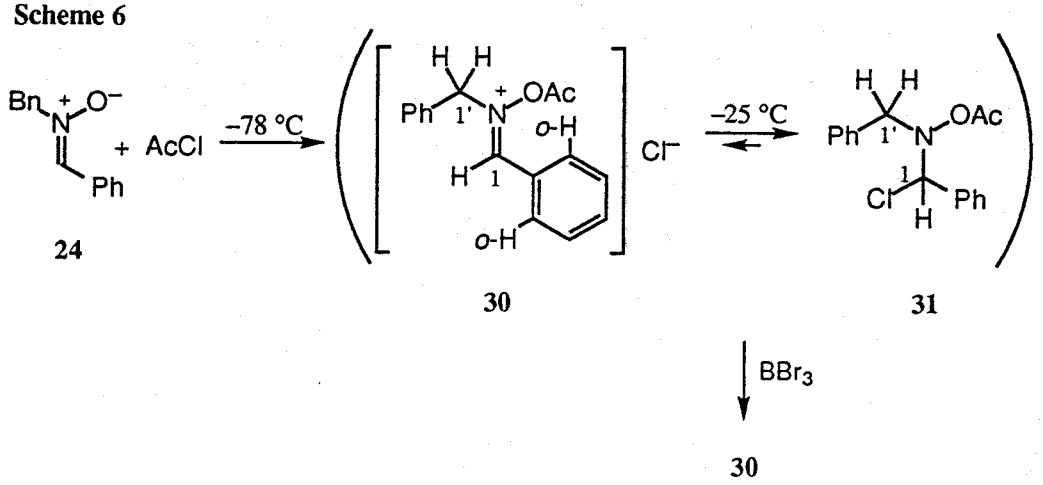


(6)

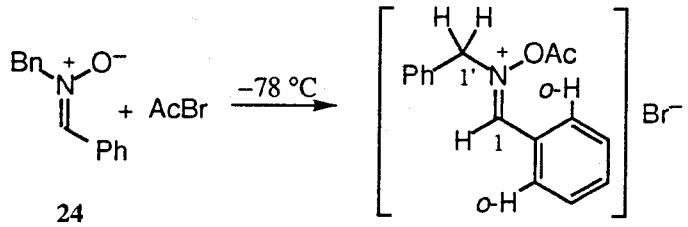
spectrum showed two sets of signals as shown in Figure 1. α-Chloroamine derivative **31** is in equilibrium with a small amount of *N*-acetyloxyiminium ion **30** (Scheme 6). The signals of 4.21 and 6.57 ppm correspond to the protons H-1' and H-1 of **31**, respectively. In the ^{13}C NMR spectrum, the signals of **31** were observed at 57 and 89 ppm. The signal at 5.56 ppm seemed to correspond to the H-1' of **30**, although no signal of the H-1 of **30** was observed. The doublet signal at 8.20 ppm corresponds to the *o*-H of **30**. When boron

tribromide (0.2 equiv) was added to the mixture, the spectrum changed as shown in Figure 2. The intermediate **30** appeared clearly, and **31** disappeared. The signal of the H-1 of **30** was observed at 9.63 ppm, and the ^{13}C NMR spectrum showed the C-1 signal at 164 ppm. Thus, boron tribromide seems to play a role of trapping chloride anion.[27] This result

Scheme 6



indicates that the intermediate bearing a better leaving group than chloride may form the *N*-acyloxyiminium species predominantly. When acetyl bromide was employed (eq 7), the remarkable ^1H NMR spectrum was obtained (Figure 3). No signal corresponding to α-bromoamine derivative appeared, while the signals of *N*-acetyloxyiminium ion **32** were observed clearly. The signal of the H-1 of **32** appeared at down-field (11.47 ppm) in comparison with that of **30**, while in the ^{13}C NMR spectrum the broad signal of C-1 of **32** was observed at 159 ppm, which was at up-field in comparison with that of **30**. The signals of H-1' (5.75 ppm) and *o*-H (8.22 ppm) were identified, although the other minor signals could not be assigned.



(7)

Now, the generation of the *N*-acyloxyiminium species upon treatment of nitrones with acyl halides at low temperature was established. The next problem is the geometry of the *N*-acyloxyiminium ion. The difference NOE experiment was performed (Figure 4), and are summarized in Figure 5. When the H-1' of **32** (5.75 ppm) was irradiated, the signal enhancement was observed at the signals of the H-1, $MeCO_2$-, and aromatic protons. These data indicate that **32** has (i) the *Z* geometry for the C-N double bond and (ii) the *anti* conformation of the N-O bond. When the *o*-H of **32** (8.23 ppm) was

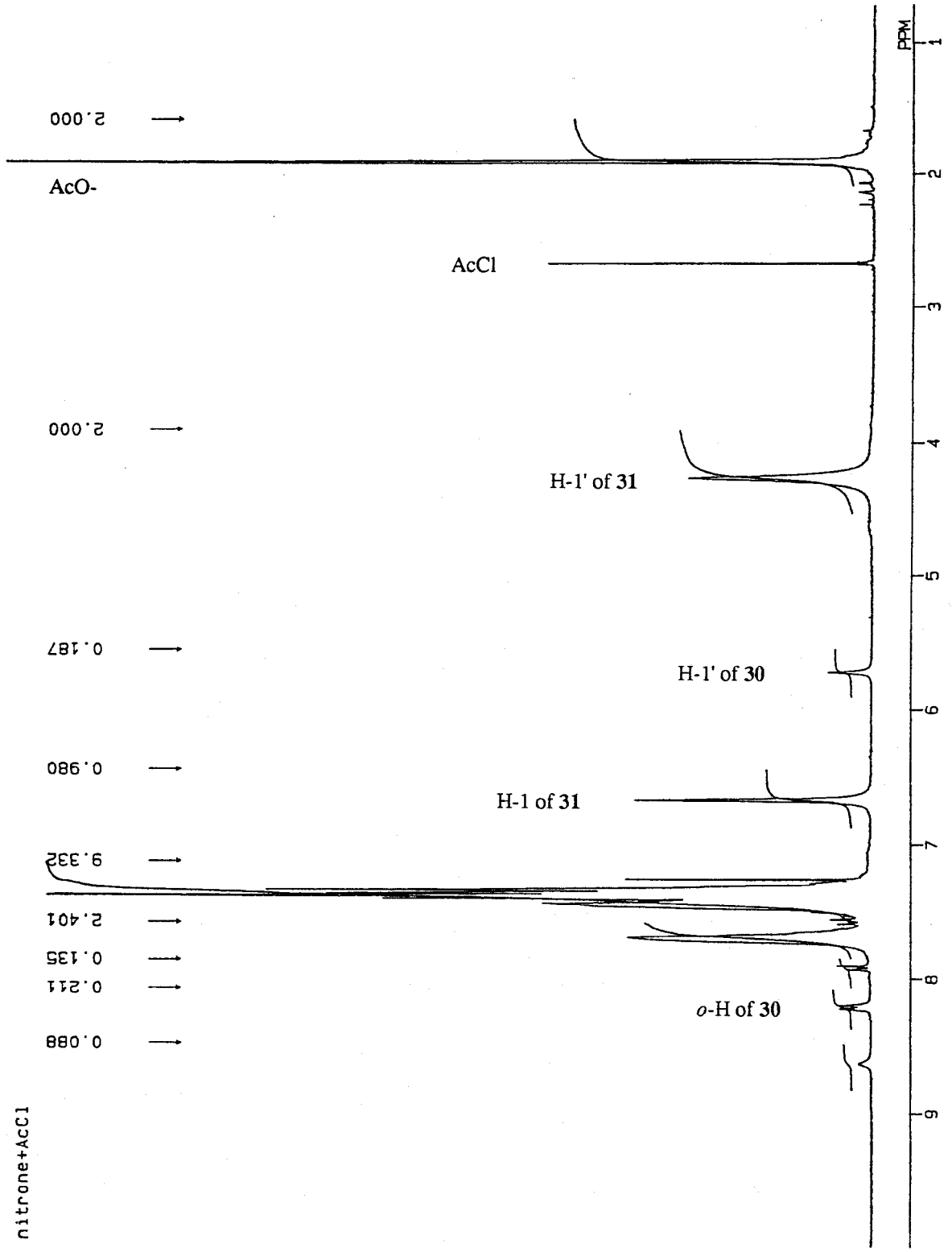


Figure 1. The ^{1}H NMR spectrum (–25°C) of the products prepared from nitrone **24** (0.15 mmol) and acetyl chloride (0.15 mmol) in $CDCl_3$ (0.60 mL) at –78 °C.

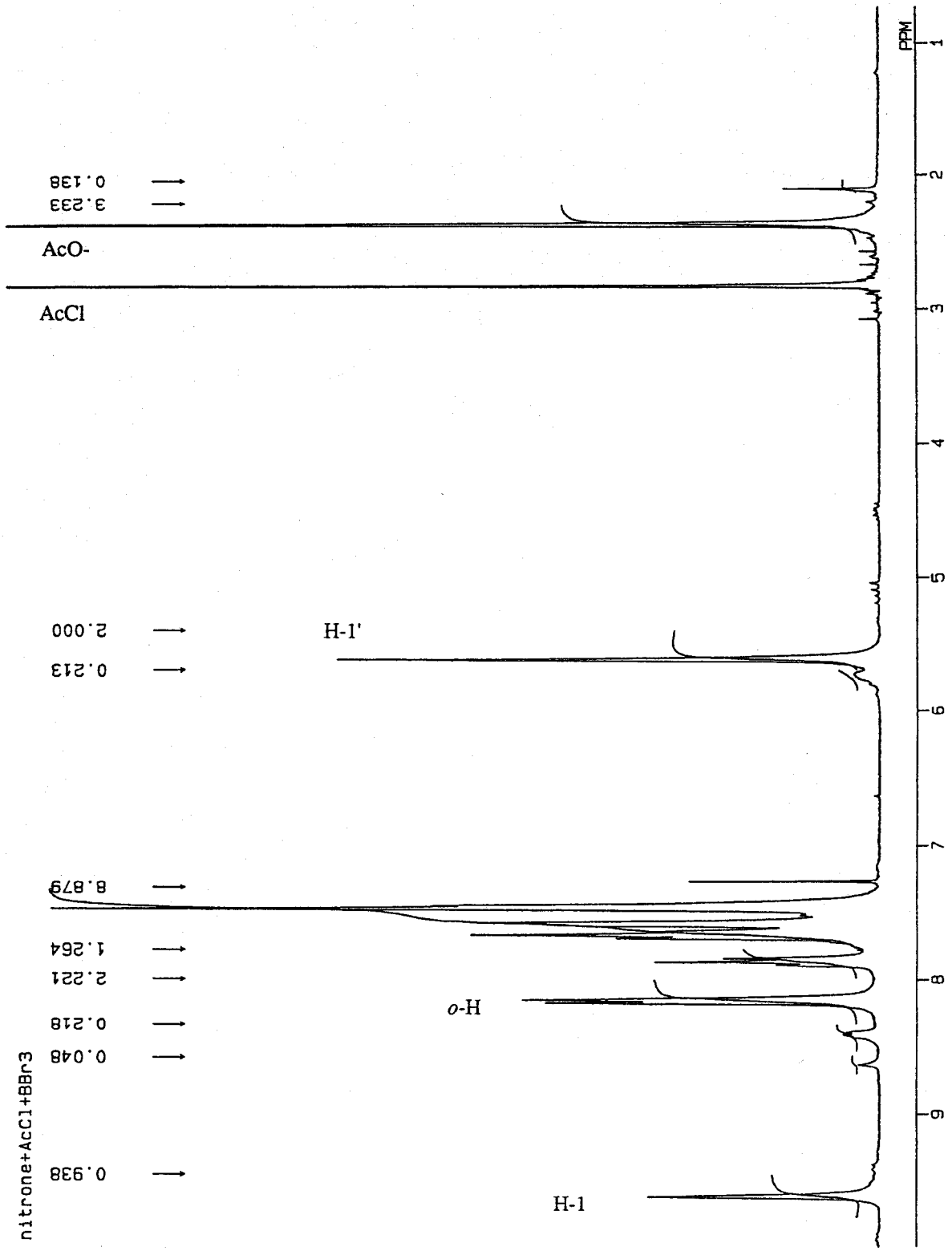


Figure 2. The ^{1}H NMR spectrum (–25 °C) of the *N*-acetyloxyiminium ion **30** prepared from nitrone **24** (0.15 mmol), acetyl chloride (0.15 mmol), and BBr_3 (0.03 mmol) in $CDCl_3$ (0.60 mL) at –78 °C.

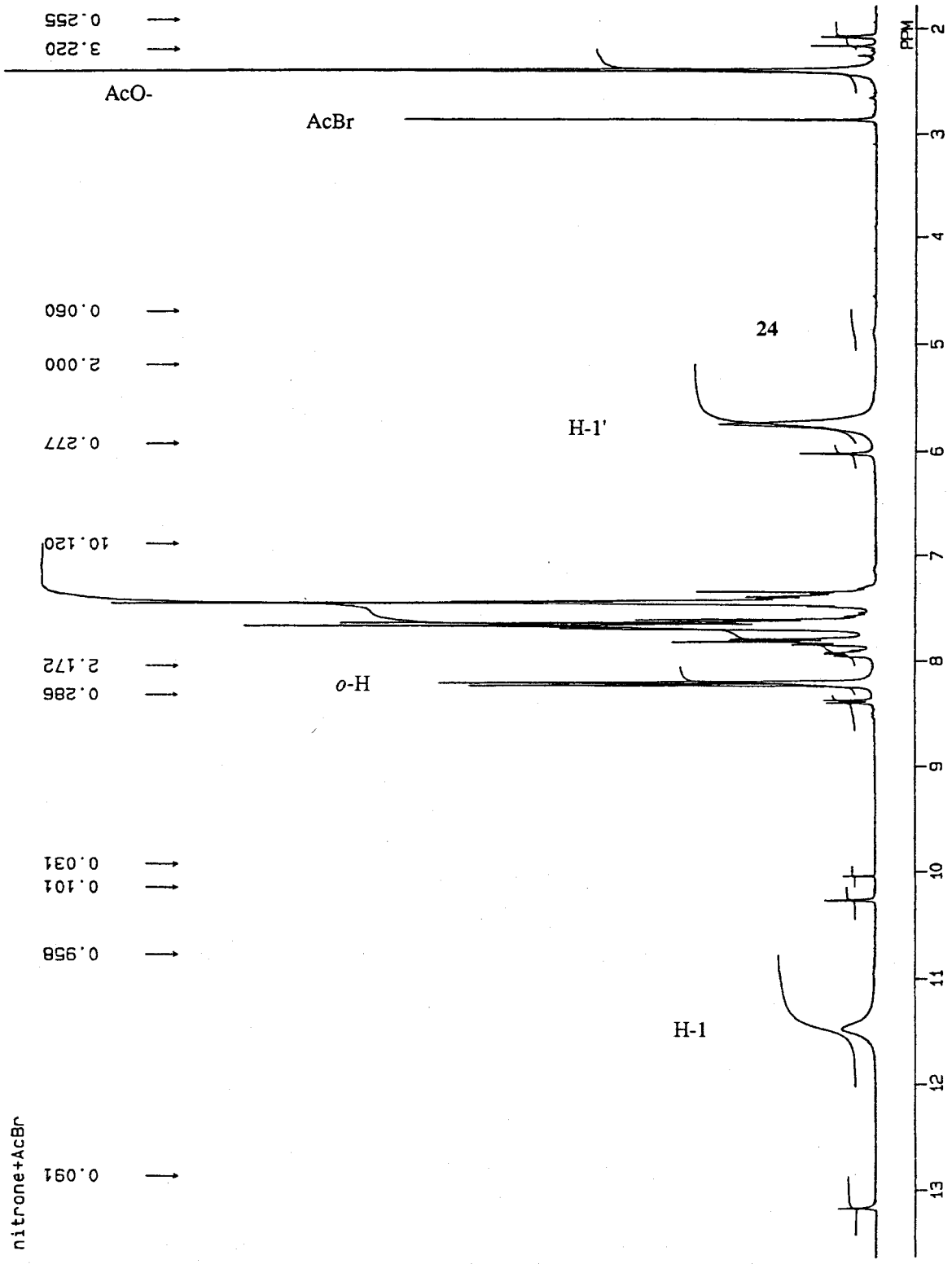


Figure 3. The ^{1}H NMR spectrum (–25 °C) of the *N*-acetyloxyiminium ion **32** prepared from nitrone **24** (0.15 mmol) and acetyl bromide (0.15 mmol) in $CDCl_3$ (0.60 mL) at –78 °C.

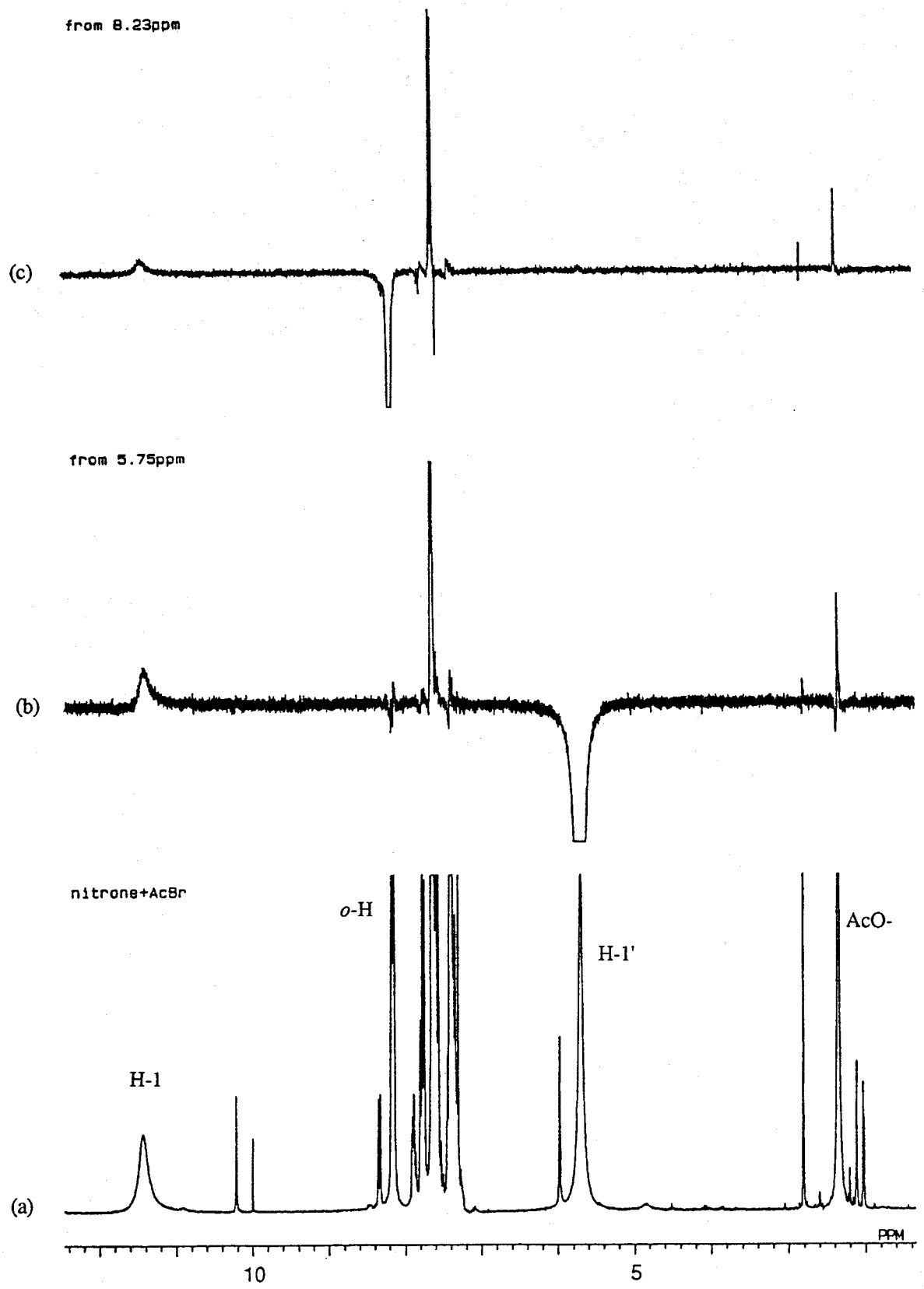
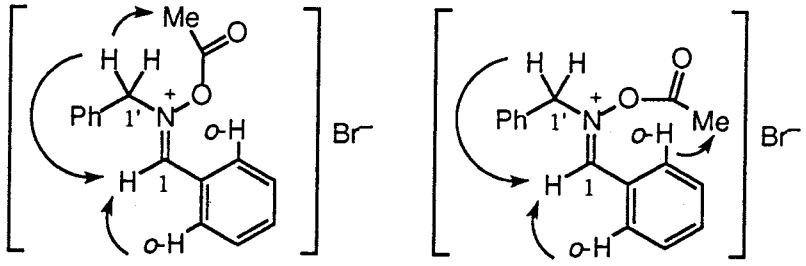


Figure 4. The difference NOE spectra (–25 °C) of the *N*-acetyloxyiminium ion **32** prepared from nitrone **24** (0.15 mmol) and acetyl bromide (0.15 mmol) in $CDCl_3$ (0.60 mL) at –78 °C: (a) no irradiation; (b) irradiated at 5.75 ppm (H-1'); (c) irradiated at 8.23 ppm (*o*-H).

irradiated, the signals of the H-1, $MeCO_2$-, and aromatic protons were enhanced. These results indicate that **32** has (i) the *Z* geometry for the C-N double bond and (ii) the *syn* conformation of the N-O bond. Thus, (i) *N*-acetyloxyiminium ion **32** has the *Z* geometry for the C-N double bond, (ii) the rotation of the N-O bond is free. The irradiation of the minor signal at 6.02 or 8.40 ppm showed no significant enhancement, and the presence of the *E* isomer of **32** could not be evident. Thus, the geometry of the *N*-acyloxyiminium ion is *Z* in the majority.



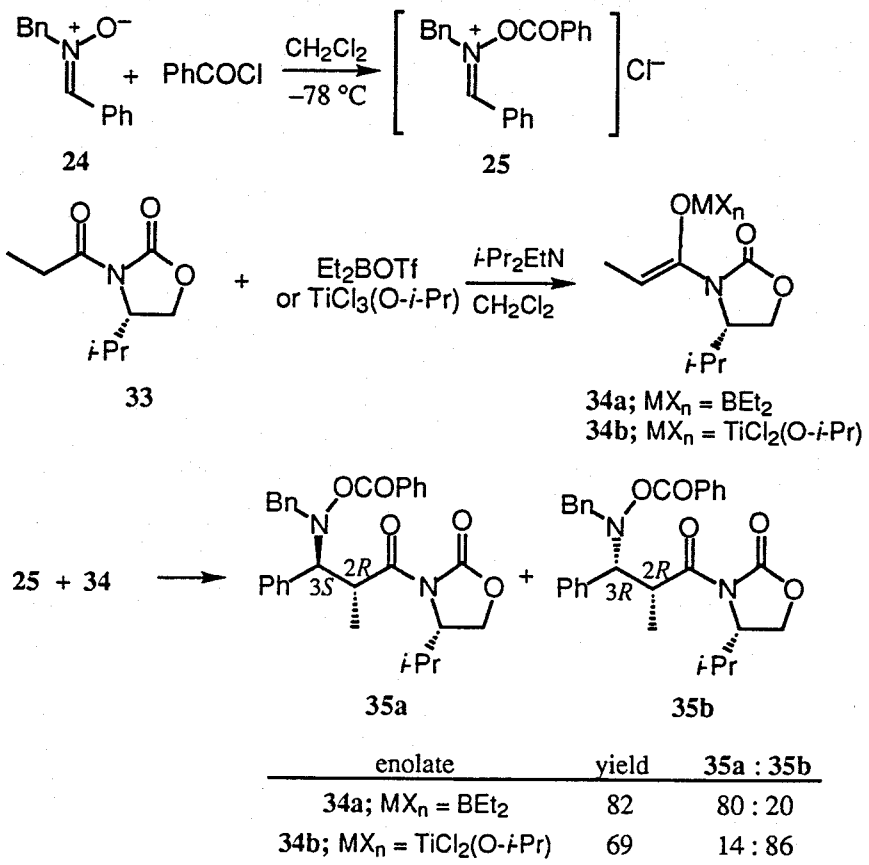
(*Z*)-*anti*-**32** (*Z*)-*syn*-**32**

Figure 5. The NOE of *N*-acetyloxyiminium ion **32**.

The other point is the discrepancy of the reactivity between *N*-acyloxyiminium chloride and *N*-acyloxyiminium bromide. Although the significant difference could not be observed, acyl chloride is better as an activator because of easier handling.

The Reaction of Nitrone 24 Activated by Acyl Halides with Chiral Enolates. The present reaction can be applied to the asymmetric synthesis of β-amino acids. The reaction of Evans' chiral enolate **34**[23] with the *N*-acyloxyiminium intermediate **25** prepared from nitrone **24** and benzoyl chloride, proceeded efficiently to give β-amino acid derivative **35** as a mixture of only two diastereomers selectively (Scheme 7). The reversal of diastereoselectivity was observed by changing a metal of the enolate. The addition of chiral boron enolate **34a** (M = BEt_2) gave an *anti* isomer **35a** as a major isomer (82%, *anti*/*syn* = 80 : 20 by ^1H NMR analysis, **35a**: mp 153.5–154.0 °C; $[\alpha]^{29}_D$ +103.6° (*c* 1.02, $CHCl_3$)). When titanium enolate **34b** (M = $TiCl_2$(O-*i*-Pr)) was used, a *syn* isomer **35b** was obtained predominantly (69%, *anti*/*syn* = 16 : 84, **35b**: mp 158.0–159.0 °C; $[\alpha]^{20}_D$ –41.4° (*c* 0.99, $CHCl_3$)). When benzoyl bromide was employed as an activator for nitrone **24**, a similar result was observed. Thus, the reaction with the boron enolate **34a** gave the adduct **35** in 70% yield with the ratio of *anti*/*syn* = 83 : 17. In each case, only two diastereomers were obtained among four isomers possible, and each diastereomer can be separated simply by column chromatography on silica gel. These adducts can be transformed to the corresponding β-amino acids (*vide infra*).

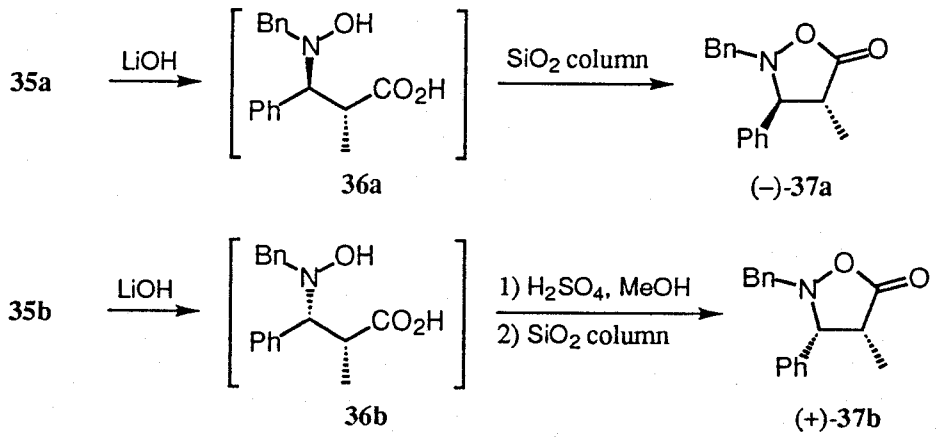
Scheme 7



enolate	yield	35a : 35b
34a; $MX_n = BEt_2$	82	80 : 20
34b; $MX_n = TiCl_2(O\text{-}i\text{-}Pr)$	69	14 : 86

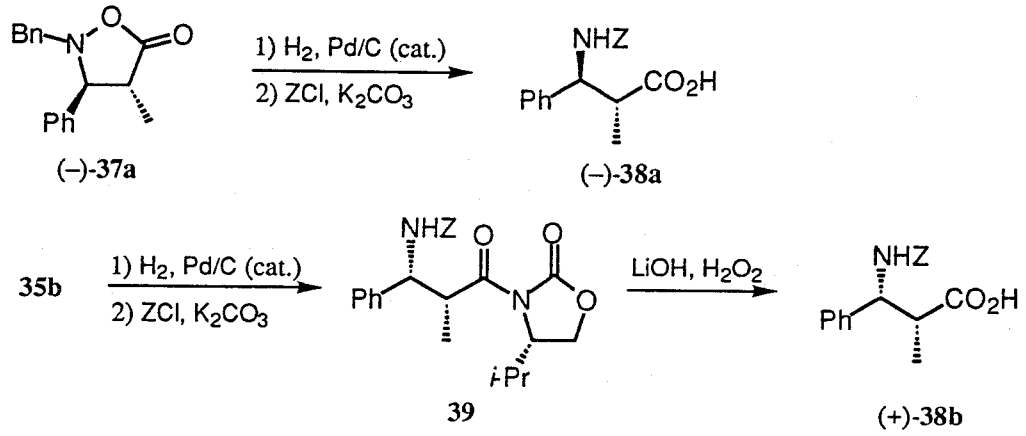
Determination of the Absolute Configuration of the β-Amino Acid derivative 35. The relative configurations of the β-amino acid derivative **35a** and **35b** were determined as shown in Scheme 8. Hydrolysis of **35a** followed by column chromatography on silica gel gave (–)-**37a** in 58% yield, which was formed by cyclization of β-hydroxylamino acid **36a** on silica gel column, while (+)-**37b** was obtained in 31% yield from **35b**. The relative configurations of **37a** and **37b** were determined to be *trans* and *cis*, respectively by NOE experiments. Therefore, the relative configurations of **35a** and **35b** are *anti* and *syn*, respectively.

Scheme 8



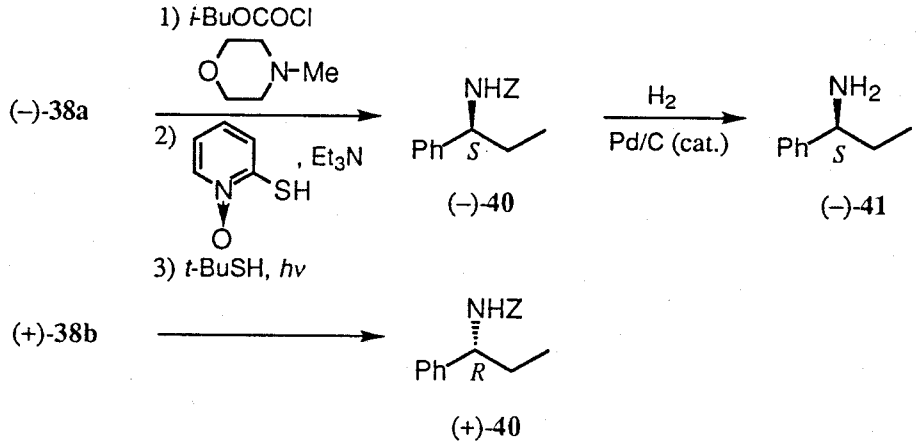
The diastereomers **35a** and **35b** were transformed to *N*-protected β-amino acids[28] (–)-**38a** (mp 135.0–137.5 °C; $[\alpha]^{28}_D$ –21.6° (*c* 1.01, $CHCl_3$)) and (+)-**38b** (mp 167.0–169.0 °C; $[\alpha]^{31}_D$ +36.1° (*c* 0.97, MeOH)) in 52% and 71% yields, respectively with recovering the chiral oxazolidinone auxiliary (Scheme 9). The β-amino acid (–)-**38a** was obtained by catalytic hydrogenation of (–)-**37a** followed by protection of the amino group by benzyloxycarbonyl (Z) group (90% yield). On the other hand, (–)-**38b** was obtained from **35b** by another method because of the low yield of (+)-**37b**. Thus, cleavage of the N-O bond of **35b** by catalytic hydrogenation followed by protection of the amino group gave the *N*-protected β-amino acid derivative **39** in 75% yield. Then, hydrolysis of **39** gave (–)-**38b** in 95% yield with recovering the oxazolidinone.

Scheme 9



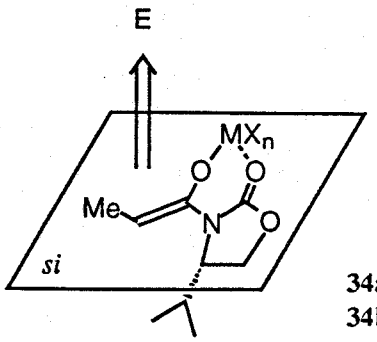
These β-amino acids (–)-**38a** and (+)-**38b** were decarboxylated by means of Barton's method[29] to give *N*-benzyloxycarbonyl-α-phenylpropylamine (**40**), whose optical rotations showed opposite signs each other (Scheme 10). Further, the absolute configuration of (–)-**40** was determined to be *S* after deprotection by catalytic hydrogenation to known amine (–)-**41**.[30] Therefore, the absolute configurations of β-amino acid derivatives **35a** and **35b** were 2*R*, 3*S* and 2*R*, 3*R*, respectively.

Scheme 10



Mechanistic Consideration. The control of stereochemistry of the present reaction can be rationalized by assuming Schemes 11 and 12. The complete stereocontrol at the C-2 position of **35** is induced by the bulky *i*-Pr group of the chelated *Z*-enolate **34**;[23] thus, *N*-acyloxyiminium ion (E) approaches to the *si* face of the enolate (Scheme 11).

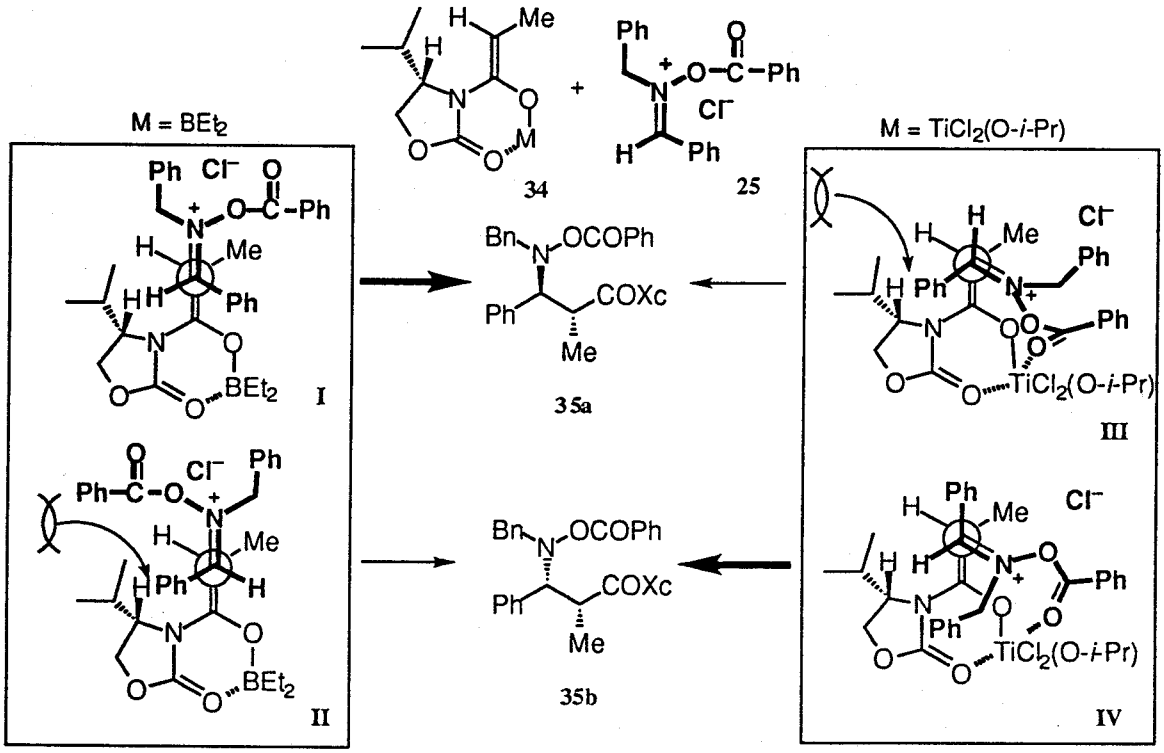
Scheme 11



34a; $MX_n = BEt_2$
34b; $MX_n = TiCl_2(O\text{-}i\text{-}Pr)$

The relative configurations at the C-2 and C-3 positions are dependent on whether the carbonyl group of *N*-acyloxyiminium ion coordinates to the metal of the enolate in the transition state (Scheme 12). The geometry of **25** is *Z* from the relationship with *N*-acetyloxyiminium bromide **32** (Figure 5). It is important that *N*-acyloxyiminium ions need no more activation. Thus, the reaction of *N*-acyloxyiminium ion **25** with the boron enolate **34a** proceeds without further coordination to the boron, because there is no coordination

Scheme 12



site after the intramolecular chelation of the enolate **34a**. Thus, **25** and **34a** occupy the open transition state as shown in the model **I** or **II**. In these transition models, **I** is predominant to give the *anti* isomer **35a** because of repulsion between the phenyl group of **25** and the oxazolidinone ring of **34a**. On the other hand, the titanium enolate **34b** has further coordination site after the intramolecular chelation. Thus, the carbonyl oxygen of **25** coordinates to the titanium of **34b** to give the *syn* isomer **35b** *via* the closed transition state as shown in the model **IV** which is predominant more than **III** because of repulsion between the phenyl group of **25** and the oxazolidinone ring of **34b**.

The Reaction of Nitrone 24 Activated by Benzoyl Chloride with Chiral Enolates Bearing Various Chiral Auxiliaries. The bulkiness of a chiral auxiliary is considered to be important to the diastereoselectivity. Therefore, various kinds of chiral oxazolidinones and pyrimidinone[31] were examined as a chiral auxiliary. The results are summarized in Table 1. Both *anti* and *syn* isomers could be prepared with very high diastereoselectivity, respectively. For an *anti* isomer, the reaction of **24** with the boron enolate bearing (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone auxiliary *via* the *N*-acyloxyiminium ion in toluene gave **45a** in 92% yield with 97% de (entry 9), while a *syn* isomer **47b** was obtained in 79% yield with 96% de by using the titanium enolate bearing (*S*)-2-*t*-butyl-2,3-dihydro-4(1*H*)pyrimidinone auxiliary (entry 15). These isomers **45a** and **47b** can be isolated as a single diastereomer and are converted into the *N*-protected β-amino acids (+)-**38a** and (–)-**38b**, respectively as antipodes for adducts **35a** and **35b** (Scheme 13).

Scheme 13

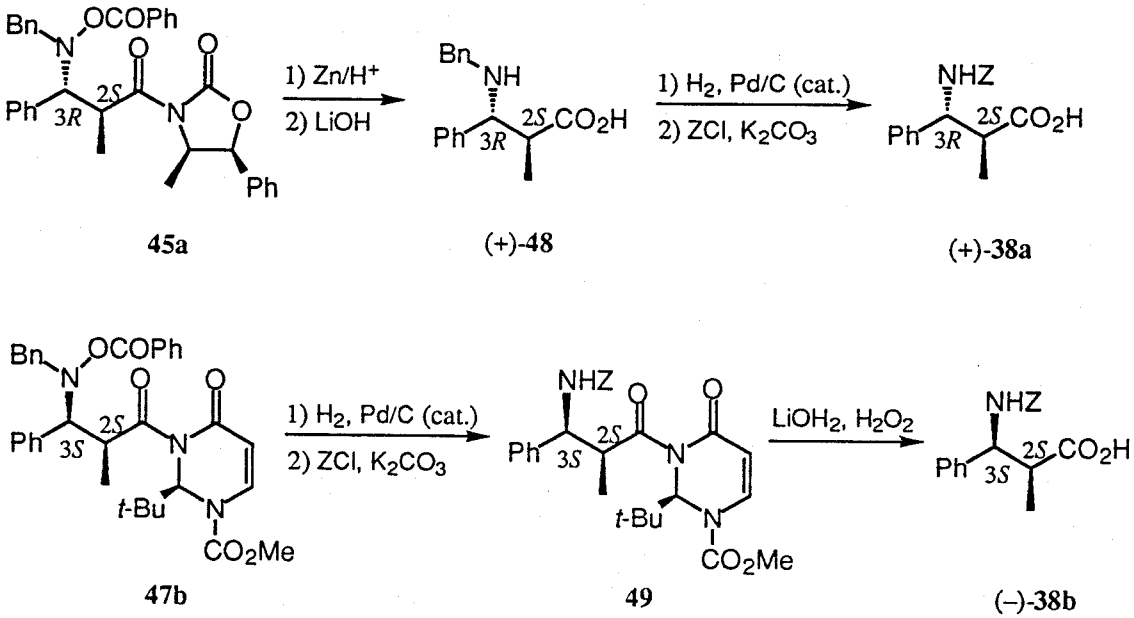
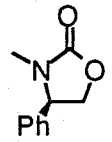
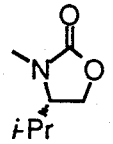
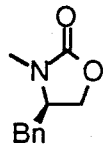
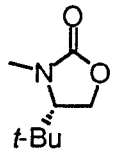
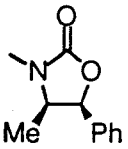
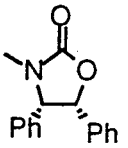
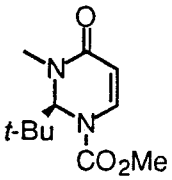
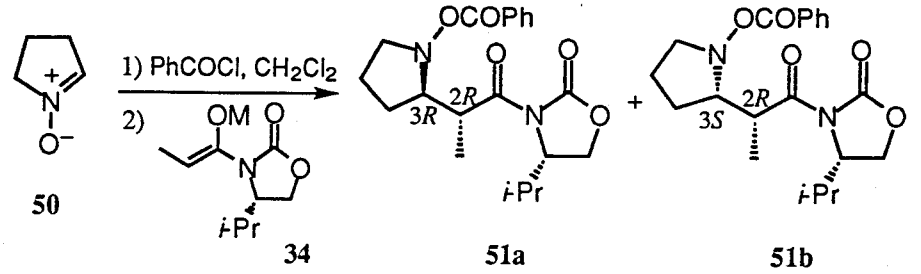


Table 1. The Additions of Various Chiral Enolates to Nitrone 24 Acitivated by Benzoyl Chloride[a]

entry	chiral auxiliary (Xc)	metal of enolate	yield[b] %	ratio[b] a : b	product No.[c]
1		BEt_2	70	86 : 14	**42**
2		$TiCl_2$(O-*i*-Pr)	45	8 : 92	
3		BEt_2	82[d]	80 : 20	**35**
4		$TiCl_2$(O-*i*-Pr)	69[d]	14 : 86	
5		BEt_2	83	71 : 29	**43**
6		$TiCl_2$(O-*i*-Pr)	49	11 : 89	
7		BEt_2	91	95 : 5	**44**
8		$TiCl_2$(O-*i*-Pr)	85	16 : 84	
9		BEt_2	81 (92)[e]	93 : 7 (98 : 2)[e]	**45**
10		$TiCl_2$(O-*i*-Pr)	65	15 : 85	
11		BEt_2	70	87 : 13	**46**
13		$TiCl_2$(O-*i*-Pr)	46	13 : 87	
14		BEt_2	98	80 : 20	**47**
15		$TiCl_2$(O-*i*-Pr)	71	2 : 98	

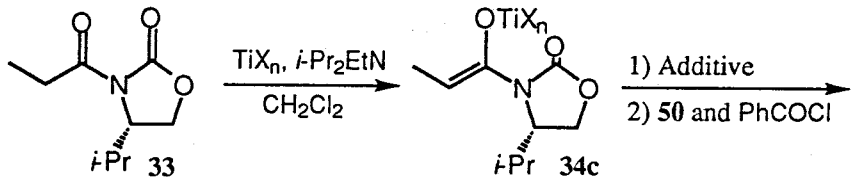
[a]The reaction was carried out as follows; nitrone **24** (2.6 mmol) was treated with benzoyl chloride (2.6 mmol) in the presence of 4Å-MS in CH_2Cl_2 (6.0 mL) at –78 °C for 30 min under argon. This solution was added to the solution of enolate (2.0 mmol) prepared in CH_2Cl_2 (6.0 mL) *in situ* at –78 °C, then, the mixture was stirred for 1 h. [b]Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]See the experimental section. [d]Isolated yield as a mixture of two diastereomers. [e]The reaction was carried out in toluene.

The Reaction of Cyclic Nitrone 50 with Chiral Enolates. Cyclic nitrone **50** reacted with benzoyl chloride at –78 °C smoothly. The solution obtained was added to a solution of the chiral enolate **34** at –78 °C (eq 8). The reaction of nitrone **50** activated by benzoyl chloride with the boron enolate **34a** proceeded smoothly to give a mixture of two diastereomers **51a** and **51b** in 78% yield with the ratio of 80 : 20. However, in the reaction



(8)

with the titanium enolate **34b**, the adduct **51** was obtained in only 16% yield. Since *N*-acyloxyiminium ion prepared from nitrone **50** is unstable toward strong Lewis acids, the titanium enolate was modified by adding external ligands. After the enolization of **33** with TiX_4 and *i*-Pr_2EtN,[23b] external ligands were added, then a solution of nitrone **50** activated by benzoyl chloride was added (eq 9). The results were shown in Table 2.



(9)

Table 2. The Effect of Additives to the Reaction of Titanium Enolate with Nitrone **50** Activated by Benzoyl Chloride[a]

entry	TiX_n	additive (equiv)	yield,[b] %	ratio[c] 51a : 51b
1	$TiCl_4$	—	0	—
2	$TiCl_3$(O-*i*-Pr)	—	16	72 : 28
3	$TiCl_4$	*i*-Pr_2EtN (1.3)	13[e]	58 : 42
4	$TiCl_3$(O-*i*-Pr)	*i*-Pr_2EtN (1.3)	20[e]	73 : 27
5	$TiCl_4$	AcOH (1.2), *i*-Pr_2EtN (1.3)	40	88 : 12
6	$TiCl_4$	AcOH (1.2), *i*-Pr_2EtN (1.3)[d]	0	—
7	$TiCl_4$	AcOH (1.2), *i*-Pr_2EtN (1.3)	59[e]	84 : 16
8	$TiCl_4$	AcOH (2.3), *i*-Pr_2EtN (2.5)	0	—
9	$TiCl_4$	$PhCO_2H$ (1.2), *i*-Pr_2EtN (1.3)	55[e]	86 : 14
10	$TiCl_4$	*t*-$BuCO_2H$ (1.2), *i*-Pr_2EtN (1.3)	35[e]	88 : 12

[a]After enolization of **33** (2.0 mmol) with TiX_n (2.2 mmol) and *i*-Pr_2EtN (2.3 mmol) in the presence of 4-Å MS in CH_2Cl_2 (3.0 mL), a solution of additive in CH_2Cl_2 (3.0 mL) was added at –78 °C, then the mixture was stirred at 0 °C for 30 min under argon. To this solution was added at –78 °C the solution of the intermediate prepared from nitrone **50** (3.0 mmol) and benzoyl chloride (3.0 mmol) in the presence of 4-Å MS in CH_2Cl_2 (6.0 mL), then, the mixture was stirred at –78 °C for 1 h. [b]Isolated yield as a diastereomeric mixture. [c]Determined by ^1H NMR analysis. [d]Treated at –78 °C. [e]The reaction was carried out at 0 °C.

After treatment of the titanium enolate **34c** with a mixture of acetic acid and *i*-Pr_2EtN, the adduct **51** was obtained in 40% yield (entry 5). Thus, ligand exchange of the titanium enolate **34c** upon treatment with acetic acid and *i*-Pr_2EtN should occur at 0 °C, while upon treatment at –78 °C the adduct **51** was not obtained (entry 6). Furthermore, the reaction at 0 °C raised the yield up to 59% (entry 7). The diastereomeric ratio was **51a/51b** = 84 : 16 by ^1H NMR analysis. Other carboxylic acids such as benzoic acid and pivalic acid were employed as additive, and the adduct **51** was obtained in 55 and 35% yields with the similar diastereomeric ratio, respectively. In the present reaction the isomer **51a** was obtained predominantly by using either boron or titanium as a metal of the enolate.[32] The configuration of the isomer **51a** was determined to be 2*R*,3*R* (*anti*) by derivation to the known alkaloid (*vide infra*). The configuration of the diastereomer **51b** is maybe 2*R*,3*S* (*syn*), because of the assumption in Scheme 10.

Next, in order to improve the diastereoselectivity, various chiral auxiliaries were examined. The results are summarized in Table 3. Only two diastereomers among four possible were obtained in satisfactory yields with good diastereomeric ratios. The best result was obtained in 75% yield with 82% de by using the titanium enolate bearing (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone in dichloromethane (entry 10). Furthermore, the examination of acyl chlorides is shown later.

These adducts can be converted into the corresponding β-amino esters. The adducts **51a** and **53a** are illustrated as antipodes (Scheme 14). Although **51a** could not be obtained as a single diastereomer, after catalytic hydrogenation of the diastereomeric mixture of **51** followed by protection of the amino group, **58** was obtained as a single diastereomer by column chromatography on silica gel in 82% yield. Then, hydrolysis of **58** gave *N*-

Scheme 14

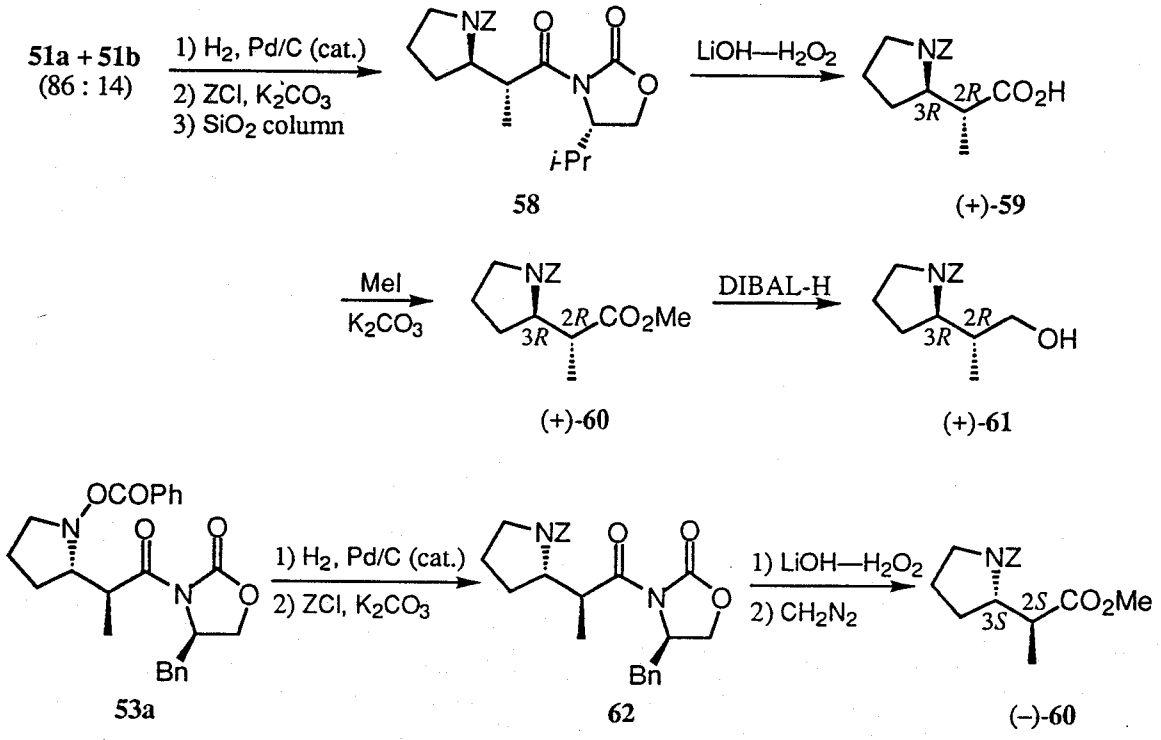
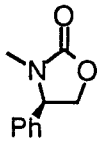
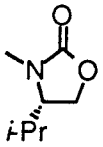
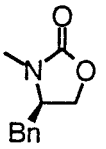
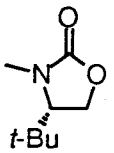
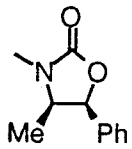
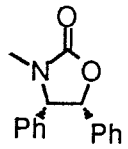
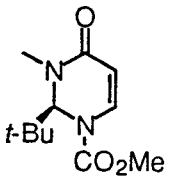


Table 3. The Additions of Various Chiral Enolates to Nitrone **50** Acitivated by Benzoyl Chloride[a]

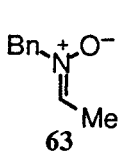
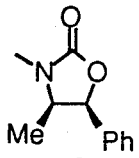
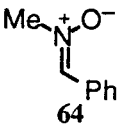
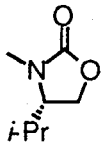
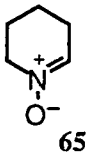
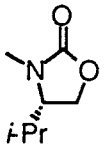
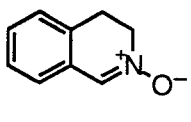
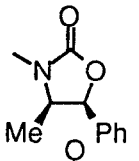
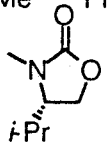
entry	chiral auxiliary (Xc)	metal of enolate	yield[b] %	ratio[b] a : b	product No.[c]
1		BEt_2	74	77 : 23	**52**
2		$TiCl_2(OCOPh)$	48	86 : 14	
3		BEt_2	78[d]	80 : 20	**51**
4		$TiCl_2(OCOPh)$	55[d]	86 : 14	
5		BEt_2	69[d]	86 : 14	**53**
6		$TiCl_2(OCOPh)$	75[d]	83 : 17	
7		BEt_2	72	81 : 19	**54**
8		$TiCl_2(OCOPh)$	49	80 : 20	
9		BEt_2	85	88 : 12	**55**
10		$TiCl_2(OCOPh)$	75	91 : 9	
11		BEt_2	71	73 : 27	**56**
13		$TiCl_2(OCOPh)$	67	69 : 30	
14		BEt_2	81	81 : 19	**57**
15		$TiCl_2(OCOPh)$	79	69 : 31	

[a]The reaction was carried out as follows; nitrone **50** (3.0 mmol) was treated with benzoyl chloride (3.0 mmol) in the presence of 4Å-MS in CH_2Cl_2 (6.0 mL) at –78 °C for 30 min under argon. This solution was added to the solution of enolate (2.0 mmol) prepared in CH_2Cl_2 (6.0 mL) *in situ* at –78 °C, then, the mixture was stirred for 1 h. Titanium enolate was employed after treatment with a mixture of benzoic acid (2.3 mmol) and *i*-Pr_2EtN (2.4 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C for 30 min. [b]Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]See the experimental section. [d]Isolated yield as a mixture of two diastereomers.

benzyloxycarbonyl β-amino acid (+)-**59** ($[\alpha]^{22}_D$ +26.3° (*c* 1.45, MeOH)) in 97% yield, and the chiral auxiliary was recovered. The β-amino acid (+)-**59** could be converted into the β-amino ester (+)-**60** ($[\alpha]^{22}_D$ +11.6° (*c* 0.92, MeOH)) in 96% yield, further, (+)-**60** was transformed into amino alcohol (+)-**61** ($[\alpha]^{23}_D$ +31.7° (*c* 0.89, MeOH)) by reduction with diisobutylaluminum hydride (DIBAL-H) in 67% yield. On the other hand, the adduct **53a** was isolated as a single diastereomer easily by crystallization from ethyl acetate—hexane. Then, **53a** was converted into the *N*-protected β-amino ester (–)-**60** ($[\alpha]^{24}_D$ –14.3° (*c* 0.98, MeOH)) by the similar method.

The Reactions of Various Nitrones Activated by Benzoyl Chloride with Chiral Enolates. The reactions of other nitrones with chiral enolates[33] are summarized in Table 4. All cases were not optimized, but good selectivity and satisfactory yield were obtained in most cases. In the reaction of nitrone **63**, a reversal of diastereoselectivity was not observed by changing the metal of the enolate (entries 1 and 2). In the reaction of cyclic nitrones **65** and **66**, the diastereoselectivity was reversed by changing the metal (entries 5 and 6, 7 and 8). It is considered that the diastereoselectivity is dependent on the bulkiness

Table 4. The Reactions of Nitrones Acitivated by Benzoyl Chloride with Various Chiral Enolates[a]

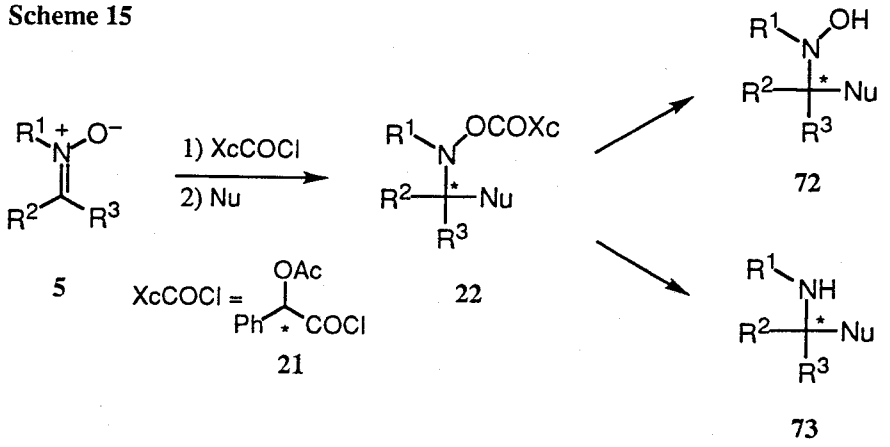
entry	nitrone	chiral auxiliary (Xc)	metal of enolate	yield[b] %	ratio[c] a : b	product No.[d]
1	 **63**		BEt_2	79	95 : 5	**67**
2			$TiCl_2$(O-*i*-Pr)	68	84 : 16	
3	 **64**		BEt_2	84	83 : 17	**68**
4			$TiCl_2$(O-*i*-Pr)	76	13 : 87	
5	 **65**		BEt_2	78	89 : 11	**69**
6			$TiCl_2$(O-*i*-Pr)	76	42 : 58	
7	 **66**		BEt_2	83	92 : 8	**70**
8			$TiCl_2$(O-*i*-Pr)	72	20 : 80	**71**

[a]The reaction was carried out as follows; nitrone (3.0 mmol) was treated with benzoyl chloride (3.0 mmol) in the presence of 4Å-MS in CH_2Cl_2 (6.0 mL) at –78 °C for 30 min under argon. This solution was added to the solution of enolate (2.0 mmol) prepared in CH_2Cl_2 (6.0 mL) *in situ* at –78 °C, followed by, the mixture was stirred for 1 h. [b]Isolated yield as a diastereomeric mixture. [c]Determined by ^{1}H NMR analysis. [d]See the experimental section.

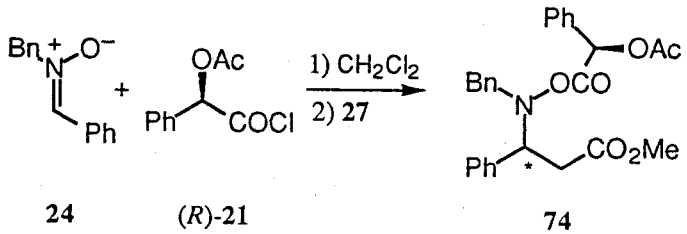
of the substituents at the carbon of nitrones; when the substituent is large enough, a reversal of diastereoselectivity may be observed.

Asymmetric Induction of Nitrones by Using Optically Active Acyl Chlorides. Asymmetric induction of nitrones using chiral acyl chlorides as a chiral auxiliary will provide a convenient method for the synthesis of optically active amino compounds, since nitrones are prepared easily by the oxidation of the corresponding secondary amines.[5,6] If optically active *N*-acyloxyiminiun intermediate can be generated, various achiral nucleophiles will be introduced diastereoselectively.[34] Then, the corresponding optically active hydroxylamines **72** and amines **73** can be obtained after removal of the acyl unit (Scheme 15). Acetylmandelyl chloride (**21**), which is prepared easily from mandelic acid, was examined as a chiral activator for nitrones.[24]

Scheme 15



First, the reactions with enolates were examined. Nitrone **24** was allowed to react with (*R*)-**21** in the presence of 4-Å molecular sieves in dichloromethane at –78 °C. To the solution was added ketene silyl acetal **27** at –78 °C. The β-amino acid derivative **74** was obtained in quantitative yield, but significant diastereoselectivity was not observed (53 : 47 by ^{1}H NMR analysis) (eq 10).

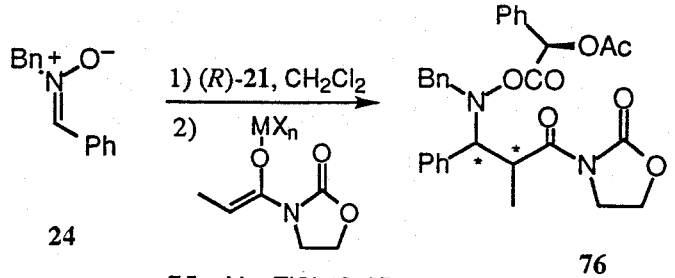


(10)

Low diastereoselectivity is caused by free rotation of the N-O and C-C=O bonds of the chiral *N*-acyloxyiminium ion, therefore the reaction of **24** activated by (*R*)-**21** with enolate **75** which has a Lewis acidic metal was examined. A reversal of diastereoselectivity occurred by changing the metal of the enolate (boron and titanium) (Scheme 16). In the reaction with the titanium enolate **75a** (M = $TiCl_2$(O-*i*-Pr)) the *syn* isomer of **76** was obtained predominantly (74% yield, *syn*/*anti* = 91 : 9 by ^{1}H NMR analysis), and the diastereomeric excess was 16% for the *syn* isomer, while in the reaction

with the boron enolate **75b** (M = Et_2B), the selectivity obtained was quite low (8% de for the *anti* isomer). The reaction of *N*-acyloxyiminium ion with the titanium enolate **75a** proceeds *via* the closed transition state that the *N*-acyloxyiminium ion coordinates to the titanium, although the *N*-acyloxyiminium ion doesn't coordinate to the boron of the chelated enolate **75b**. Thus, the interaction of the *N*-acyloxyiminium ion with the metal of enolates is important for the diastereoselection.

Scheme 16

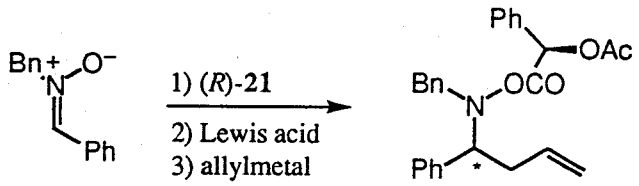


24 **76**

75a; M = $TiCl_2$(O-*i*-Pr)
75b; M = BEt_2

MX_n	yield	ratio		
		syn : *anti*	*syn*	*anti*
$TiCl_2$(O-*i*-Pr)	74	91 : 9	58 : 42	52 : 48
BEt_2	97	39 : 61	54 : 46	54 : 46

Next, the chelation effect of the chiral *N*-acyloxyiminium intermediate itself was examined with employing allyl nucleophiles. The reaction with allyltributyltin or allyltrimethylsilane in the presence or absence of Lewis acids was carried out (eq 11). The results are summarized in Table 5.



24 **77** (11)

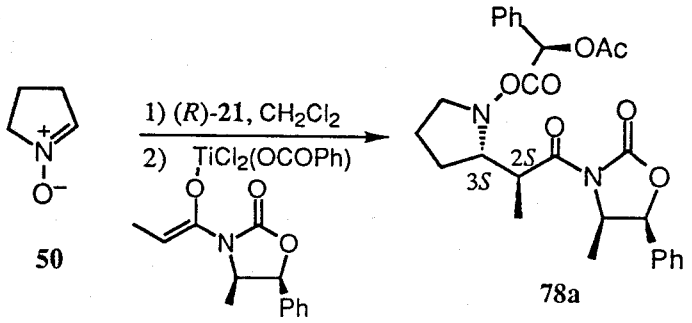
Nitrone **24** activated by (*R*)-**21** reacted with allyltributyltin in the absence of Lewis acids in dichloromethane at –78 °C to give a homoallylamine derivative **77** in 99% yield, and the diastereomeric excess was quite low (2% de) (entry 1); however, in the presence of $TiCl_4$, **77** was obtained in 36% de (entry 2). When BF_3•OEt_2 was used, the diastereomeric excess was only 4% (entries 3 and 5). Therefore, Lewis acids which have more than two coordination sites are important for the diastereoselection. On the other hand, the reaction with allyltrimethylsilane did not proceed in the absence of Lewis acids, but in the presence of $TiCl_4$, **77** was obtained in 71%, and the diastereomeric excess was 64% (entry 6). Dichloromethane was the best solvent among the solvents examined such as toluene, THF, and propionitrile. Unfortunately, the major diastereomer of **77** could not be isolated as a single diastereomer, and the configuration of **77** was not determined.

Table 5. The Reaction of Nitrone 24 Acitivated by (*R*)-21 with Allylmetals[a]

entry	Lewis acid	allylmetal	yield,[b] %	de,[b] %
1	none	allyltributyltin	99	2
2	$TiCl_4$ (1 eq)	"	43	36
3	BF_3•OEt_2 (1 eq)	"	97	4
4	BF_3•OEt_2 (2 eq)	"	93	4
5	none	allyltrimethylsilane	0	—
6	$TiCl_4$ (1 eq)	"	71	64
7[c]	$TiCl_4$ (1 eq)	"	80	48
8[d]	$TiCl_4$ (1 eq)	"	11	—
9[e]	$TiCl_4$ (1 eq)	"	97	6
10	BF_3•OEt_2 (1 eq)	"	30	4
11	BF_3•OEt_2 (2 eq)	"	58	2

[a] The reaction was carried out as follows; nitrone 24 (0.50 mmol) was treated with (*R*)-21 (0.50 mmol) in the presence of 4Å-MS in CH_2Cl_2 (1.5 mL) at –78 °C for 30 min under argon. Lewis acid was added at –78 °C, and the mixture was stirred at 0 °C for 30 min. After cooling to –78 °C, allylmetal (0.60 mmol) was added, then the mixture was stirred at –78 °C (for allyltributyltin) or at 0 °C (for allyltrimethylsilane) for 1 h. [b]Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]Toluene was used as a solvent. [d]THF was used as a solvent. [e]EtCN was used as a solvent.

The Reaction of Cyclic Nitrone 50 Activated by Acetylmandelyl Chloride with the Chiral Titanium Enolate. The reaction of *N*-acyloxyiminium ions with titanium enolate proceeds *via* coordination of the carbonyl oxygen of the *N*-acyloxyiminium ions to the titanium of the enolates. Therefore, it is considered that the acyl unit plays an important role for the diastereoselection. The reaction of cyclic nitrone **50** activated by acetylmandelyl chloride **21** with the chiral titanium enolate was examined (eq 12). When

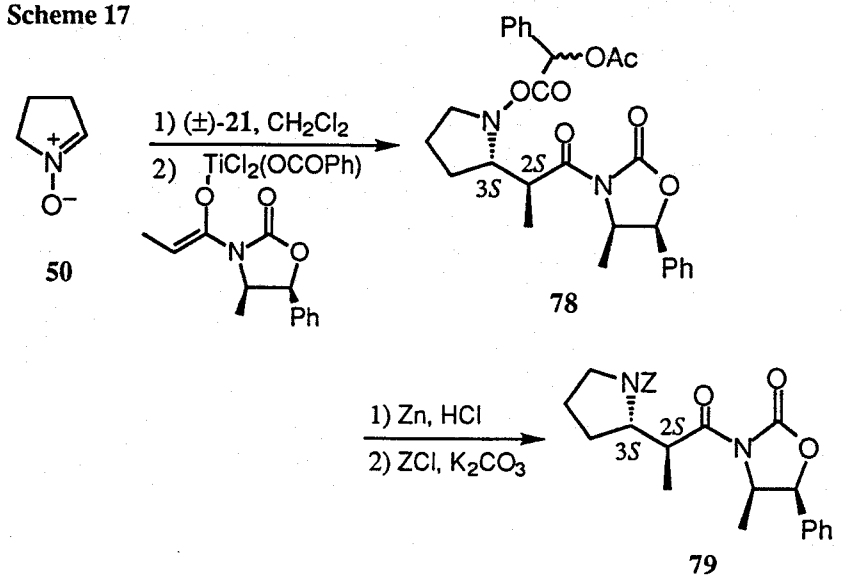


50 **78a** (12)

(*R*)-**21** was employed as an optically active activator, an isomer **78a** was obtained in 56% yield, and the diastereomeric excess was 94%. Surprisingly, almost same selectivity was obtained (96% de) when (*S*)-**21** was used. Double asymmetric synthesis is known in some cases, which concern the interaction of two chiral reactants.[35] However, in the present reaction neither matched nor mismatched pair is observed. Therefore, the reaction using racemic acetylmandelyl chloride (±)-**21** was carried out (Scheme 17). The isomer **78** was

obtained in 84% yield, and the diastereomeric excess was 96% at the C-2 and C-3 positions. Reduction of **78** with Zn/HCl, followed by protection of the amino group with benzyloxycarbonyl (Z) group gave **79** in 88% yield as a single diastereomer.

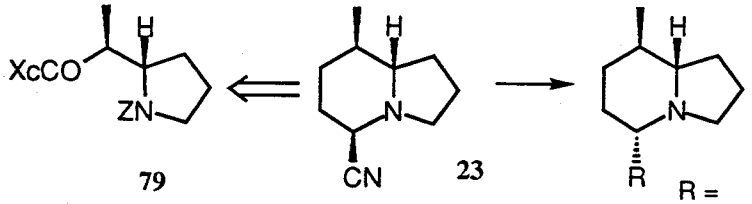
Scheme 17



Asymmetric Synthesis of 8-Methylindolizidines. The present reaction was applied to asymmetric synthesis of indolizidine alkaloids. A large number of alkaloids have been isolated in minute quantity from skin extracts of neotropical poison-dart frogs (family Dendrobatidae).[25] The Dendrobatdae are a family of small Neotropical frogs, which are currently partitioned among five genera: *Colostethus*, *Dendrobates*, *Epipedobates*, *Minyobates*, and *Phyllobates*. The last four genera are single evolutionary lineage of "poison frogs" characterized by bright warning coloration and defensive skin alkaloids. Alkaloids have been characterized by GC-MS analysis, and many novel alkaloids have been reported. Alkaloids of the following classes have been detected: batrachotoxins, histrionicotoxins, pumiliotoxins, indolizidines, decahydroquinolines, azatricyclododecenes, amidines and so on. A major subclass of indolizidine alkaloids is the 5-substituted-8-methylindolizidines. Indolizidines 203A, 205A, 207A, 209A, 233D, 235B, 235B', and 251B are isolated from poison frogs such as *Dendrobates pumilio*, *Dendrobates sppeciosus*, and *Dendrobates aurafus* (Scheme 18).[25] These alkaloids have been interested in because of their activity as noncompetitive inhibitors of the acetylcholine receptor complex.[26a] (–)-5-Cyano-8-methylindolizidine (**23**) is a common key intermediate for the synthesis of these 8-methylindolizidines.[26a] The β-amino acid derivative **79** thus obtained has the suitable configuration for the synthesis of these alkaloids.

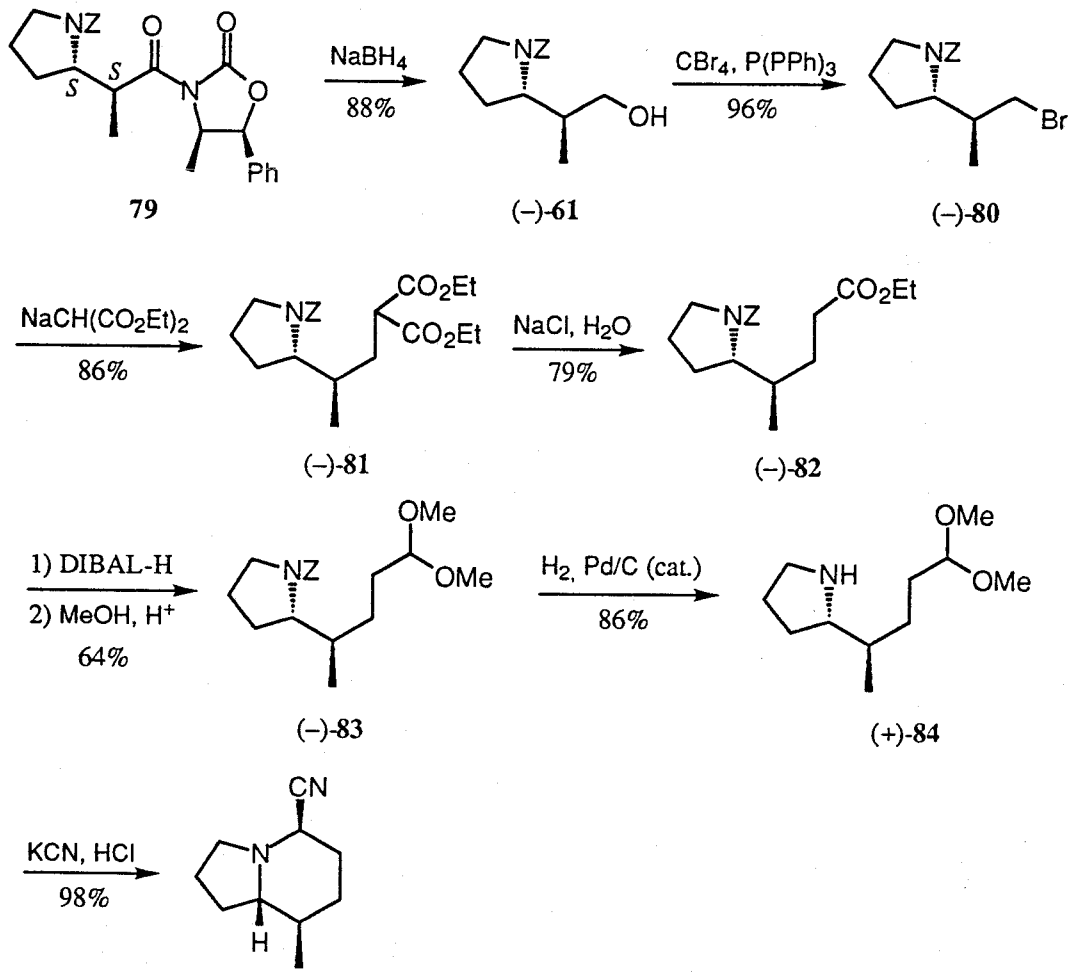
The α-amino nitrile (–)-**23** was synthesized as shown in Scheme 19. Thus, the reduction of **79** with $NaBH_4$ gave amino alcohol (–)-**61** ($[\alpha]^{23}_D$ –37.3° (*c* 1.43, MeOH)) in 88% yield along with recovering the chiral auxiliary (82%). The alcohol **61** was converted into bromide (–)-**80** in 96% yield. Then, substitution by diethyl malonate gave diester (–)-**81** (86% yield), which was decarboxylated to (–)-**82** in 79% yield. The reduction of the

Scheme 18



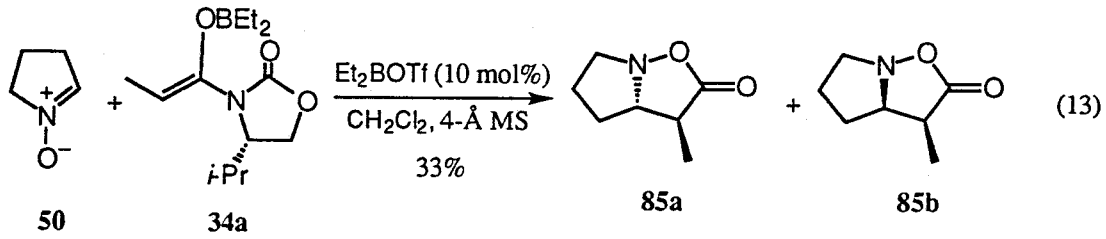
203A; $CH_2CH{=}CHC{\equiv}CH$ (Z)
205A; $(CH_2)_3C{\equiv}CH$
207A; $(CH_2)_3CH{=}CH_2$
209B; *n*-C_5H_{11}
233D; $(CH_2)_3CH{=}CHCH{=}CH_2$ (Z)
235B; $(CH_2)_3CH{=}CHCH_2CH_3$ (Z)
235B'; $(CH_2)_5CH{=}CH_2$
251B; $(CH_2)_3CH{=}CHCH(OH)CH_3$ (Z)

Scheme 19



ester (–)-**82** upon treatment with 1 equiv of DIBAL-H followed by acetalyzation with methanol in the presence of toluenesulfonic acid gave acetal (–)-**83** in 64% yield. Deprotection of (–)-**83** by catalytic hydrogenation afforded amino acetal (+)-**84** ($[\alpha]^{23}_D$ +7.8° (*c* 1.12, CH_2Cl_2)) in 86% yield. The ^1H and ^{13}C NMR spectra, the IR spectrum, and the optical rotation of (+)-**84** were good argument with the reported data (lit.[26a] $[\alpha]^{23}_D$ +7.4° (*c* 1.1, CH_2Cl_2)). No epimerization was observed by the ^1H and ^{13}C NMR analysis. The treatment of (+)-**84** with potassium cyanide and hydrochloric acid in dichloromethane,[26a] gave (–)-**23** including another diastereomer in 7%, which was probably a epimer at the C-5 position. The α-amino nitrile (–)-**23** can be converted into various 5-substituted-8-methylindolizidines such as 205A and 235B by the reported procedure.[26a]

The *N*-acyloxyiminium species generated by the reaction of nitrones with acyl chlorides show higher reactivity toward soft nucleophiles than nitrones themselves. *O*-Protected α-substituted hydroxylamines thus obtained are more stable and easily handled than hydroxylamines themselves. For example, the reaction of nitrone **50** itself with chiral enolate **34a** in the presence of diethylboryl triflate as a catalyst at 0 °C became complicated. The corresponding hydroxylamine could not be isolated, and the cyclyzed products **85a** and **85b** were obtained in low yield (eq 13). After treatment of nitrones with



50 **34a** **85a** **85b** (13)

benzoyl chloride, the reaction with the chiral enolates proceeds at –78 °C, and the adducts are isolated easily. Then, *O*-protected α-substituted hydroxylamines thus obtained are converted into other nitrogen containing compounds such as β-amino acids. Another advantage is the convenient generation of the chiral *N*-acyloxyiminium species by using chiral acyl chlorides. The chiral *N*-acyloxyiminium species undergoes reaction with various nucleophiles diastereoselectively to give various amino compounds.

Experimental Section

General. All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 polarimeter. IR spectra were recorded on a Shimadzu FTIR 4100 spectrometer. NMR spectra were obtained on a JEOL JNM-GSX-270 (^1H, 270 MHz, ^{13}C 68 MHz) spectrometer; chemical shifts (δ) were expressed in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q,

quartet; quint; quintet; m, multiplet; br, broad. Coupling constants (*J*) are reported in hertz. Elemental analyses were carried out on a Yanagimoto Model MT-3 CHN corder. Mass spectra were obtained on a JEOL JMS-DX303 mass spectrometer. Analytical TLC was performed on E. Merck silica gel 60 F254 (Art. 5714) or E. Merck DC-Fertigplatten RP-18F245S (Art. 15685). Flash chromatography was carried out on E. Merck silica gel 60 (230–400 mesh).

Materials. Benzoic acid, trimethylacetic acid, *N*-methylhydroxylamine hydrochloride, benzaldehyde, acetaldehyde, benzyl chloroformate (ZCl), toluenesulfonic acid, carbon tetrabromide, triphenyl phosphine, boron tribromide, sodium borohydride, diisobutylaluminum hydride (DIBAL-H) (1.0 M in hexane), sodium hydride (60% dispersion in mineral oil), 30% hydrogen peroxide, lithium hydroxide monohydrate, potassium cyanide, zinc powder (Aldrich Chem. Co.), sodium tungstate dihydrate, and 10% palladium on charcoal were commercially available and used without further purification. *N*,*N*-Diisopropylethylamine, triethylamine, iodomethane, acetyl chloride, benzoyl chloride, diethyl malonate, acetic acid, titanium(IV) chloride, titanium(IV) isopropoxide, boron trifluoride diethyl etherate (BF_3•OEt), triethylborane (Toyo Stauffer Chemical Co.), 1,1,2,2-tetrachloroethane, *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), tetrahydrofuran (THF), pyridine, and benzene were commercially available and distilled before use. Dichloromethane (Hayashi Pure Chemical Industry Ltd.) is commercially available and dried over 4-Å molecular sieves. 4-Å Molecular sieves is commercially available and dried over P_2O_5 at 120 °C *in vacuo* before use. Ketene silyl acetal **27**[36] and diethylboryl triflate (Et_2BOTf)[37] were prepared by reported procedures.

Preparation of Nitrones. *N*-Benzylidenebenzylamine *N*-oxide (**24**), 1-pyrroline *N*-oxide (**50**), tetrahydropyridine *N*-oxide (**65**), and 3,4-dihydroisoquinoline *N*-oxide (**66**) were prepared by the catalytic oxidation of the corresponding secondary amines with 30% hydrogen peroxide in the presence of sodium tungstate dihydrate (4 mol%).[5,6] Cyclic nitrones **50** and **65** were used as possible as readily, but can be stored as a solution in CH_2Cl_2 at –20 °C under argon for one week. *N*-Ethylidenebenzylamine *N*-oxide (**63**) and *N*-benzylidenemethylamine *N*-oxide (**64**) were prepared by condensation of hydroxylamines and aldehydes as shown below.

Preparation of *N*-Benzylhydroxylamine.[38] A mixture of nitrone **24** (32.4 g, 153 mmol) and conc. H_2SO_4 (9.0 mL, 169 mmol) in H_2O (100 mL) was steam-distilled until benzaldehyde was not distilled (4 h). To the resultant aqueous solution was added 4 M NaOH (80 mL) to pH 9, the mixture was extracted with ethyl acetate (180 mL, 50 mL x 5). The combined extracts were dried over Na_2SO_4, filtered, and evaporated. The residue was crystallized from diisopropyl ether (*i*-Pr_2O) to give a colorless crystal (13.3 g, 71%): mp 58.0–58.5 °C (*i*-Pr_2O); IR (KBr) 3620, 3275, 2910, 2855, 1512, 1499, 1454, 1427, 1350, 1065, 1035, 853, 748, 700, 608 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 3.95 (s, 2 H, CH_2), 7.23–7.37 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 58.2, 127.6, 128.4, 129.1, 137.0.

Preparation of *N*-Benzylidenemethylamine *N*-oxide (64). A mixture of *N*-methylhydroxylamine hydrochloride (1.01 g, 12.0 mmol), benzaldehyde (1.82 mL, 18.0 mmol), K_2CO_3 (1.65 g, 11.97 mmol), water (5 mL), and CH_2Cl_2 (10 mL) was stirred for 30 h under argon at room temperature. The organic layer was separated, washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL), and dried over $MgSO_4$. Removal of the solvent and purification by column chromatography on silica gel (40 mL, 0—5% MeOH in CH_2Cl_2) gave **64** (76%): IR (Nujol) 1650, 1412, 1158, 940 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 3.87 (s, 3 H, C*H*$_3$), 7.36 (s, 1 H, NC*H*), 7.38–7.45 (m, 3 H, Ph), 8.16–8.25 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 54.4 (*C*H_3N), 128.4, 128.5, 130.4, 130.5, 135.1 (N=*C*); Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N; 10.36. Found: C, 71.07; H, 6.71; N, 10.29.

***N*-Ethylidenebenzylamine *N*-Oxide (63).** Nitrone **63** was prepared from *N*-benzylhydroxylamine and acetaldehyde by the similar procedure for **64**: IR (Nujol) 1609, 1170, 1097, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 2.00 (d, J = 5.9 Hz, 3 H, C*H*$_3$), 4.90 (s, 2 H, C*H*$_2$), 6.72 (q, J = 5.9 Hz, 1 H, C*H*), 7.35–7.44 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 12.7 (*C*H_3), 69.0 (*C*H_2), 128.9, 129.3, 132.7, 134.6.

General Procedure for the Formation of *N*-Acyloxyiminium Ions from Nitrones and Acyl Chloride. To a mixture of nitrone (2.0 mmol) and 4-Å molecular sieves (300 mg) in CH_2Cl_2 (6.0 mL) was added acyl chloride (2.0 mmol) dropwise at –78 °C under argon. Then, the solution was stirred below –50 °C for 0.5 h.

NMR Studies of *N*-Acyloxyiminium Ions. To a solution of nitrone **24** (32 mg, 0.15 mmol) in $CDCl_3$ (0.60 mL) in a NMR tube was added acyl halide (0.15 mmol) at –78 °C under argon. After checking the reaction by the TLC analysis, ^1H and ^{13}C NMR were measured at –25 °C on a JEOL JNM-GSX-270 (^1H, 270 MHz; ^{13}C, 68 MHz) spectrometer. The ^1H NMR spectra are shown in Figure 1, 2, and 3. In the spectrum in Figure 2, boron tribromide (0.06 mmol) was added to the sample prepared from nitrone **24** and acetyl chloride at –78 °C. The difference NOE spectra of the sample prepared from nitrone **24** and acetyl bromide were also measured, and are shown in Figure 4.

Preparation of Propanoic Acid Derivatives Bearing Chiral Auxiliaries. Propanoic acid derivatives were prepared by the reported procedures that the condensations of the corresponding auxiliaries with propionyl chloride upon treatment with *n*-butyl lithium.[23f] (*S*)-3-Propanoyl-4-(1-methylethyl)-2-oxazolidinone (**34**),[23a,e] (*R*)-3-propanoyl-4-phenyl-2-oxazolidinone,[23g] (*R*)-3-propanoyl-4-phenylmethyl-2-oxazolidinone,[23f] (*S*)-3-propanoyl-4-(*tert*-butyl)-2-oxazolidinone,[23g] (4*R*,5*S*)-3-propanoyl-4-methyl-5-phenyl-2-oxazolidinone,[23a] (4*S*, 5*R*)-3-propanoyl-4,5-diphenyl-2-oxazolidinone,[39,23f] (*S*)-2-*tert*-butyl-1-carbomethoxy-3-propanoyl-2,3-dihydro-4(1*H*)-pyrimidinone.[31]

General Procedure for the Preparation of Boron Enolates.[23f] To a solution of propanoic acid derivative (2.0 mmol) in CH_2Cl_2 (6.0 mL) in the presence of 4-Å molecular

sieves are added successively Et_2BOTf (0.395 mL, 2.3 mmol) and *i*-Pr_2EtN (0.401 mL, 2.4 mmol) at –78 °C under argon , and the mixture was stirred at 0 °C for 0.5 h.

General Procedure for the Preparation of Titanium Enolates ($TiCl_3$(O-*i*-Pr)).[23b] To a solution of Ti(O-*i*-Pr)$_4$ (0.17 mL, 0.60 mmol) in CH_2Cl_2 (4.0 mL) in the presence of 4-Å molecular sieves was added $TiCl_4$ (0.19 mL, 1.7 mmol) under argon, and the mixture was stirred at room temperature until it was a clear solution. After cooling at –78 °C, to the solution were added a solution of propionic acid derivative (2.0 mmol) in CH_2Cl_2 (2.0 mL), followed by *i*-Pr_2EtN (0.418 mL, 2.4 mmol). Then, the mixture was stirred at 0 °C for 0.5 h.

General Procedure for the Preparation of Titanium Enolates Modified by Carboxylic Acid—*i*-Pr_2EtN. To a solution of propanoic acid derivatives (2.0 mmol) and 4-Å molecular (300 mg) in CH_2Cl_2 (4 mL) were added $TiCl_4$ (2.2 mmol), followed by *i*-Pr_2EtN (2.4 mmol) at –78 °C under argon. The mixture was stirred at 0 °C for 0.5 h. After cooling at –78 °C again, a mixture of carboxylic acid (2.4 mmol), *i*-Pr_2EtN (2.6 mmol), and 4-Å molecular sieves (200 mg) in CH_2Cl_2 (2.0 mL) was added to the mixture. Then, the mixture was stirred at 0 °C for 0.5 h.

General Procedure for the Reaction of *N*-Acyloxyiminium Ions with Boron Enolates. To a solution of enolate (2.0 mmol) was added a solution of *N*-acyloxyiminium ion (3.0 mmol) which was prepared from nitrone (3.00 mmol) and acyl chloride (3.00 mmol), dropwise at –78 °C under argon, and the reaction mixture was stirred at the same temperature for 1 h. To the mixture were added hexane (15 mL), sat. $NaHCO_3$ (5 mL), and ethyl acetate (30 mL). The organic layer was separated, washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL x 2), and dried over $MgSO_4$. After filtration and removal of the solvent, $CHCl_2CHCl_2$ was added as an internal standard, and the yield and diastereomeric ratio were determined by ^1H NMR analysis. The product was purified by column chromatography on silica gel (50 mL, 5—25% ethyl acetate in hexane). The results are summarized in Tables and Schemes.

General Procedure for the Reaction of *N*-Acyloxyiminium Ions with Titanium Enolates. To a solution of enolate (2.0 mmol) was added a solution of *N*-acyloxyiminium ion (3.0 mmol) which was prepared from nitrone (3.00 mmol) and acyl chloride (3.00 mmol), dropwise at –78 °C under argon, and the mixture was stirred at the same temperature for 1.0 h. When the titanium enolate modified by carboxylic acid and *i*-Pr_2EtN was used, the reactions were carried out at 0 °C. To the mixture were added hexane (15 mL), sat. $NaHCO_3$ (5 mL), and 10 M KF (2 mL), and the mixture was stirred at room temperature for 0.5 h. The mixture was filtered through Celite and the cake was washed with ethyl acetate (30 mL). The organic layer was separated, washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL x 2), and dried over $MgSO_4$. After filtration and removal of the solvent, $CHCl_2CHCl_2$ was added as an internal standard, and the yield and diastereomeric ratio were determined by ^1H NMR analysis. The product was purified by

column chromatography on silica gel (50 mL, 5—25% ethyl acetate in hexane). The results are summarized in Tables and Schemes.

(4*R*)-3-[(2*S*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4-phenyl-2-oxazolidinone (42a): $[\alpha]^{26}_{D}$ –7.13° (*c* 1.01, $CHCl_3$); IR (Nujol) 1781, 1742, 1701, 1256, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 1.54 (d, *J* = 6.6 Hz, 3 H, CH_3), 3.72 (d, *J* = 12.5 Hz, 1 H, CH_3CHCH), 3.96 (dd, *J* = 4.4 and 8.8 Hz, 1 H, HCHO), 4.10 (d, *J* = 11.0 Hz, 1 H, HCHPh), 4.14 (d, *J* = 12.7 Hz, 1 H, HCHPh), 4.50 (t, *J* = 3.3 Hz, 1 H, $PhCHCH_2$), 4.97 (dt, *J* = 11.6 and 11.2 Hz, 1 H, CH_3CH), 5.18 (dd, *J* = 4.4 and 8.8 Hz, 1 H, HCHO), 6.45–6.48 (m, 2 H, Ph), 6.97–7.59 (m, 16 H, Ph), 7.98–8.01 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 16.4, 39.9, 57.7, 59.4, 69.4, 69.8, 124.7, 127.6, 127.7, 128.1, 128.4, 128.5, 128.8, 129.3, 129.4, 130.6, 133.0, 135.4, 136.0, 138.1, 153.2 (CH_2CON), 165.1 (NCOO), 174.9 (OCO); Anal. Calcd for $C_{28}H_{30}N_2O_5$: C, 74.13; H, 5.66; N, 5.24. Found: C, 74.40; H, 5.81; N, 5.31.

(4*R*)-3-[(2*S*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4-benzyl-2-oxazolidinone (42b): mp 99–102 °C (ethyl acetate—hexane); $[\alpha]^{26}_{D}$ +33.1° (*c* 0.737, $CHCl_3$); IR (KBr) 1788, 1769, 1738, 1686, 1287, 1248, 1223, 1053, 721, 706, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.89 (d, *J* = 6.8 Hz, 3 H, CH_3CHCO), 3.00 (br t, *J* = 12.0 Hz, 1 H, CHCHHPh), 3.89 (d, *J* = 12.9 Hz, 1 H, NHCHPh), 3.92 (dd, *J* = 3.2 and 13.7 Hz, 1 H, CHCHHPh), 3.99 (d, *J* = 13.2 Hz, 1 H, NHCHPh), 4.11 (t, *J* = 8.6 Hz, 1 H, CHHO), 4.16 (dd, *J* = 3.8 and 8.9 Hz, 1 H, CHHO), 4.49 (d, *J* = 11.2 Hz, 1 H, NCHPh), 4.71 (dddd, *J* = 3.4, 3.7, 7.8, and 11.5 Hz, 1 H, $NCHCH_2O$), 4.84 (dq, *J* = 11.3 and 6.8 Hz, 1 H, $COCHCH_3$), 7.12–7.68 (m, 18 H, Ph), 7.79–8.00 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 15.7, 37.6, 38.9, 56.2, 60.7, 66.3, 72.3, 126.9–137.0 (Ph), 153.4 (CH_2CON), 165.1 (NCOO), 176.2 (OCO); Anal. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.43; H, 5.88; N, 5.11. Found: C, 74.18; H, 5.89; N, 5.14.

(4*R*)-3-[(2*S*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4-benzyl-2-oxazolidinone (43a): mp 99–102 °C; $[\alpha]^{26}_{D}$ +33.1° (*c* 0.737, $CHCl_3$); IR (KBr) 1788, 1769, 1738, 1686, 1287, 1248, 1223, 1053, 721, 706, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.89 (d, *J* = 6.8 Hz, 3 H, CH_3CHCO), 3.00 (br t, *J* = 12.0 Hz, 1 H, CHCHHPh), 3.89 (d, *J* = 12.9 Hz, 1 H, NHCHPh), 3.92 (dd, *J* = 3.2 and 13.7 Hz, 1 H, CHCHHPh), 3.99 (d, *J* = 13.2 Hz, 1 H, NHCHPh), 4.11 (t, *J* = 8.6 Hz, 1 H, CHHO), 4.16 (dd, *J* = 3.8 and 8.9 Hz, 1 H, CHHO), 4.49 (d, *J* = 11.2 Hz, 1 H, NCHPh), 4.71 (dddd, *J* = 3.4, 3.7, 7.8, and 11.5 Hz, 1 H, $NCHCH_2O$), 4.84 (dq, *J* = 11.3 and 6.8 Hz, 1 H, $COCHCH_3$), 7.12–7.68 (m, 18 H, Ph), 7.79–8.00 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 15.7, 37.6, 38.9, 56.2, 60.7, 66.3, 72.3, 126.9–137.0 (Ph), 153.4 (CH_2CON), 165.1 (NCOO), 176.2 (OCO); Anal. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.43; H, 5.88; N, 5.11. Found: C, 74.18; H, 5.89; N, 5.14.

(4*R*)-3-[(2*S*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4-phenylmethyl-2-oxazolidinone (43b): mp 101–104 °C (ethyl acetate—hexane); $[\alpha]^{24}_{D}$ +36.3° (*c* 0.985, $CHCl_3$); IR (KBr) 1788, 1769, 1738, 1688, 1287, 1248, 1223, 1053, 721, 708, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 1.56 (d, *J* = 6.6 Hz, 3 H, CH_3CHCO), 1.79 (dd, *J* = 10.0 and 13.4 Hz, 1 H, CHCHHPh), 2.33 (dd, *J* = 3.2 and 13.4

Hz, 1 H, CHC*H*HPh), 3.82 (d, J = 12.7 Hz, 1 H, N*H*CHPh), 3.89 (dd, J = 2.9 and 9.0 Hz, 1 H, *H*CHO), 3.98 (dd, J = 7.8 and 8.8 Hz, 1 H, *H*CHO), 4.21 (d, J = 12.7 Hz, 1 H, NC*H*HPh), 4.23 (d, J = 11.0 Hz, 1 H, NC*H*Ph), 4.34–4.43 (m, 1 H, NC*H*CH_2O), 4.90 (dq, J = 11.0 and 6.6 Hz, 1 H, COC*H*CH_3), 6.83–6.93 (m, 2 H, Ph), 7.14–7.62 (m, 16 H, Ph), 7.97–8.04 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 16.1, 36.7, 40.0, 54.9, 59.5, 65.5, 70.5, 127.0, 127.7, 128.1, 128.3, 128.4, 128.5, 128.8, 129.1, 129.3, 129.4, 129.4, 130.7, 133.0, 135.4, 135.8, 136.0, 152.8 (CH_2*C*ON), 165.1 (N*C*OO), 175.4 (O*C*O); Anal. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.43; H, 5.88; N, 5.11. Found: C, 74.28; H, 5.90; N, 5.12.

(4*S*)-3-[(2*R*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4-*tert*-butyl-2-oxazolidinone (44a): $[\alpha]^{26}_D$ +119.8° (*c* 0.97, $CHCl_3$); IR (Nujol) 1774, 1752, 1705, 1183, 1103, 976, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.79 (d, J = 7.8 Hz, 3 H, COCHC*H*$_3$), 1.17 (s, 9 H, C(C*H*$_3$)$_3$), 3.85 (d, J = 12.9 Hz, 1 H of C*H*$_2$Ph), 4.04 (d, J = 12.7 Hz, 1 H of C*H*$_2$Ph), 4.17 (dd, J = 7.6 and 9.0 Hz, 1 H), 4.28 (dd, J = 1.7 and 9.3 Hz, 1 H), 4.47 (dd, J = 1.6 and 7.6 Hz, 1 H) 4.52 (d, J = 11.2 Hz, 1 H, NC*H*), 4.70–4.91 (m, 1 H, NCHC*H*), 7.12-7.57 (m, 13 H of 3 x Ph), 7.81–7.92 (m, 2 H of Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 16.4, 25.7, 36.1, 38.9, 60.7, 62.0, 65.1, 71.1, 127.5, 128.0, 128.1, 128.2, 128.3, 129.4, 129.6, 131.1, 132.6, 134.3, 135.8, 154.1 (CH_2*C*ON), 164.8 (N*C*OO), 175.6 (O*C*O).Anal Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66; N, 5.44. Found: C, 72.24; H, 6.64; N, 5.41.

(4*S*)-3-[(2*R*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4-*tert*-butyl-2-oxazolidinone (44b): $[\alpha]^{27}_D$ –24.4° (*c* 1.02, $CHCl_3$); IR (Nujol) 1779, 1748, 1701, 1319, 1184, 959, 760, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.37 (s, 9 H, $(CH_3)_3$), 1.51 (d, J = 6.6 Hz, 3 H, C*H*$_3$CHCO), 3.81 (d, J = 13.0 Hz, 1 H of C*H*$_2$Ph), 4.01–4.18 (m, 3 H of C*H*$_2$O, C*H*CH_2O, and 1 H of PhC*H*$_2$), 4.21 (d, J = 10.3 Hz, 1 H, NC*H*), 4.96 (dq, J = 11.2 and 6.6 Hz, 1 H, NCHC*H*), 7.19–7.60 (m, 13 H of 3 x Ph), 7.92–8.02 (m, 2 H of Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 16.5, 24.9, 35.2, 39.4, 59.4, 61.0, 64.7, 70.3, 127.6, 128.2, 128.4, 128.5, 129.3, 129.4, 129.5, 130.8, 132.9, 135.4, 136.1, 154.2 (CH_2*C*ON), 165.1 (N*C*OO), 175.2 (O*C*O); Anal Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66; N, 5.44. Found: C, 72.08; H, 6.67; N, 5.41.

(4*R*,5*S*)-3-[(2*S*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4-methyl-5-phenyl-2-oxazolidinone (45a): mp 140.5–142.0 °C (MeOH); $[\alpha]^{24}_D$ +20.2° (*c* 1.02, $CHCl_3$); IR (KBr) 1778, 1750, 1698, 1454, 1387, 1370, 1346, 1260, 1234, 1196, 1057, 1024, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.90 (d, J = 7.1 Hz, 3 H, C*H*$_3$CHCO), 1.20 (d, J = 6.6 Hz, C*H*$_3$CHN), 3.84 (d, J = 12.9 Hz, 1 H, N*H*CHPh), 4.00 (d, J = 13.2 Hz, 1 H, N*H*CHPh), 4.46 (d, J = 11.2 Hz, 1 H, NC*H*Ph), 4.78–4.94 (m, 2 H, NC*H*CHO, COC*H*CH_3), 5.63 (d, J = 7.8 Hz, 1 H, OC*H*Ph), 7.16–7.58 (m, 18 H, Ph), 7.88–7.93 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.4, 15.9, 39.0, 55.2, 60.4, 71.8, 78.7, 126.1, 127.5, 128.0, 128.2, 128.3, 128.6, 128.6, 129.3, 129.4, 129.7, 130.9, 132.7, 133.9, 134.2, 135.9, 153.0 (CH_2*C*ON), 165.0 (N*C*OO), 175.8 (O*C*O); Anal. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.42; H, 5.88 N, 5.11. found: C, 74.60; H, 5.95; N, 5.07.

(4*R*,5*S*)-3-[(2*S*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4-methyl-5-phenyl-2-oxazolidinone (45b): $[\alpha]^{24}_D$ +73.4° (*c* 1.02, $CHCl_3$); IR (KBr) 1780, 1744, 1699, 1454, 1383, 1368, 1342, 1256, 1240, 1196, 1055, 1024, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.08 (d, *J* = 6.6 Hz, 3 H, CH_3CHN), 1.58 (d, *J* = 6.6 Hz, 3 H, CH_3CHCO), 3.82 (d, *J* = 12.7 Hz, 1 H, C*H*HPh), 4.18 (d, *J* = 11.2 Hz, 1 H, C*H*Ph), 4.20 (d, *J* = 12.7 Hz, 1 H, C*H*HPh), 4.50 (dq, *J* = 7.3 and 6.6 Hz, 1 H, NC*H*CH_3), 4.94 (dq, *J* = 11.0 and 6.6 Hz, 1 H, COC*H*CH_3), 5.48 (d, *J* = 7.3 Hz, 1 H, OC*H*), 7.13–7.60 (m, 18 H, Ph), 8.00–8.04 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 13.2, 16.2, 39.9, 54.2, 59.5, 70.3, 78.3, 125.6, 127.7, 128.0, 128.1, 128.4, 128.5, 128.6, 128.6, 129.3, 129.4, 129.5, 130.6, 133.0, 133.3, 135.8, 136.0, 152.5 (CH_2CON), 165.1 (N*C*OO), 175.2 (O*C*O); Anal. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.42; H, 5.88 N, 5.11. Found: C, 74.70; H, 6.09; N, 5.09.

(4*S*,5*R*)-3-[(2*R*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4,5-diphenyl-2-oxazolidinone (46a): $[\alpha]^{24.5}_D$ –27.9° (*c* 0.756, $CHCl_3$); IR (KBr) 3063, 3032, 2934, 1782, 1748, 1703, 1454, 1349, 1260, 1240, 1184, 1061, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.90 (d, *J* = 6.8 Hz, 3 H, CHCH_3), 3.74 (d, *J* = 12.9 Hz, 1 H, *H*CHPh), 4.03 (d, *J* = 12.7 Hz, 1 H, *H*CHPh), 4.38 (d, *J* = 11.0 Hz, 1 H, NC*H*Ph), 4.98 (br, 1 H, C*H*CH_3), 5.69 (d, *J* = 8.1 Hz, 1 H, C*H*Ph), 5.86 (d, *J* = 8.0 Hz, 1 H, C*H*Ph), 6.83–7.58 (m, 23 H, Ar), 7.95–8.05 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 16.1, 60.4, 63.8, 70.7, 77.2, 79.9, 126.5, 126.6, 126.6, 127.3, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.3, 129.4, 129.4, 130.0, 131.1, 132.6, 133.4, 133.8, 134.6, 135.4, 153.3 (CH_2CON), 165.0 (N*C*OO), 175.4 (O*C*O); HRMS(FAB) calcd for $C_{39}H_{35}N_2O_5$ ($M+H^+$) 611.2546, found 611.2546; Anal. Calcd for $C_{39}H_{34}N_2O_5$: C, 76.70; H, 5.61; N, 4.59. Found: C, 76.33; H, 5.92; N, 4.50.

(4*S*,5*R*)-3-[(2*R*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4,5-diphenyl-2-oxazolidinone (46b): mp 76.5–80.0 °C (ethyl acetate—hexane); $[\alpha]^{26}_D$ –65.8° (*c* 0.814, $CHCl_3$); IR (KBr) 3065, 2930, 1780, 1744, 1701, 1454, 1341, 1256, 1238, 1184, 1055, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 1.62 (d, *J* = 6.6 Hz, 3 H, CHCH_3), 3.74 (d, *J* = 12.7 Hz, 1 H, *H*CHPh), 4.14 (d, *J* = 11.0 Hz, 1 H, NC*H*Ph), 4.18 (d, *J* = 12.4 Hz, 1 H, *H*CHPh), 5.12 (dq, *J* = 11.0 and 6.6 Hz, 1 H, C*H*CH_3), 5.41 (d, *J* = 7.8 Hz, 1 H, C*H*Ph), 5.72 (d, *J* = 7.6 Hz, 1 H, C*H*Ph), 6.07 (d, J = 8.3 Hz, 2 H, Ar), 6.66–7.63 (m, 21 H, Ph), 7.98–8.10 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 16.8, 40.1, 59.4, 62.9, 69.7, 79.8, 125.7, 126.2, 126.9, 127.2, 127.6, 127.9, 128.1, 128.2, 128.3, 128.4, 128.6, 129.3, 129.4, 129.5, 130.8, 132.7, 133.0, 133.5, 135.5, 136.0, 153.2 (CH_2CON), 165.2 (N*C*OO), 174.8 (O*C*O); HRMS(FAB) calcd for $C_{39}H_{35}N_2O_5$ ($M+H^+$) 611.2546, found 611.2534.

(2*S*)-3-[(2*S*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-2-*tert*-butyl-1-carbomethoxy-2,3-dihydro-4(1*H*)-pyrimidinone (47a): $[\alpha]^{26}_D$ +5.1° (*c* 1.05, $CHCl_3$); IR (Nujol) 1742, 1689, 1626, 1313, 1171, 806 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.72 (d, *J* = 7.1 Hz, 3 H, CH_3CHCO), 1.15 (s, 9 H, $(CH_3)_3$), 3.82 (d, *J* = 12.9 Hz, 1 H, C*H*HPh), 3.85 (s, 3 H, CH_3CO_2), 4.11 (d, *J* = 12.7 Hz, C*H*HPh), 4.52 (d, *J* = 10.7 Hz, 1 H, C*H*Ph), 4.88 (dq, J = 11.0 and 7.1 Hz, 1 H, CH_3CHCO) 5.23 (d, *J* = 7.8 Hz,

1 H, COC*H*=CH), 6.90 (s, 1 H, C*H*C_4H_9), 7.20–7.55 (m, 13 H, Ph). 7.60 (br d, J = 7.9 Hz, 1 H, COCH=C*H*), 7.90–7.96 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 16.5, 27.0, 40.6, 40.7, 54.1, 60.4, 69.6, 70.9, 105.2, 127.5, 128.0, 128.1, 128.2, 129.3, 129.6, 130.3, 131.1, 132.4, 134.7, 136.0, 138.9, 139.0, 152.8, 164.0, 164.8, 176.3; Anal Calcd for $C_{34}H_{37}N_3O_6$: C, 69.97; H, 6.39; N, 7.20. Found: C, 70.01; H, 6.50; N, 7.16.

(2*S*)-3-[(2*S*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-2-*tert*-butyl-1-carbomethoxy-2,3-dihydro-4(1*H*)-pyrimidinone (47b): $[\alpha]^{27}_D$ +98.2° (*c* 0.97, $CHCl_3$); IR (Nujol) 1741, 1684, 1624, 1215, 1177, 806, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.49 (s, 9 H, (C*H*$_3$)$_3$) 1.44 (d, J = 6.8 Hz, 3 H, C*H*$_3$CHCO), 3.79 (s, 3 H, C*H*$_3$CO$_2$), 3.84 (d, J = 12.9 Hz, 1 H, C*H*HPh), 4.17 (d, J = 12.7 Hz, 1 H, C*H*HPh), 4,28 (d, J = 11.0 Hz, 1 H, C*H*Ph), 4.98 (dq, J = 10.8 and 7.0 Hz, 1 H, CH$_3$C*H*CO) 5.23 (d, J = 7.8 Hz, 1 H, COC*H*=CH), 6.58 (s, 1 H, C*H*C_4H_9), 7.20–7.65 (m, 14 H, COCH=C*H* and Ph), 7.95–8.03 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 16.8, 26.2, 39.7, 41.9, 54.1, 59.5, 68.5, 70.1, 104.7, 127.6, 127.8, 127.9, 128.3, 128.5, 128.6, 129.3, 129.5, 131.0, 132.9, 136.1, 136.3, 139.3, 152.5, 164.1, 165.0, 175.7; Anal Calcd for $C_{34}H_{37}N_3O_6$: C, 69.97; H, 6.39; N, 7.20. Found: C, 69.86; H, 6.49; N, 7.15.

(4*S*)-3-{(2*R*)-2-[((2*R*)-*N*-Benzoyloxypyrrolidin-2-yl)propanoyl]}-4-(1-methylethyl)-2-oxazolidinone (51a): ^{1}H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.82 (d, J = 6.8 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.86 (d, J = 6.8 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.22 (d, J = 7.0 Hz, 3 H, NCOCHC*H*$_3$), 1.88–2.04 (m, 4 H, C*H*$_2$C*H*$_2$), 2.24–2.43 (m, 1 H, C*H*(CH$_3$)$_2$), 3.05–3.22 (m, 1 H, NC*H*H), 3.50–3.66 (m, 1 H, NC*H*H), 3.73–3.85 (m, 1 H, NC*H*CH$_2$), 4.07–4.19 (m, 1 H, NCOC*H*CH$_3$), 4.19 (dd, J = 8.0 and 12.0 Hz, 1 H, *H*CHO), 4.22 (dd, J = 8.0 and 12.0 Hz, 1 H, *H*CHO), 4.38–4.49 (m, 1 H, C*H*CH$_2$O), 7.38–8.05 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.4, 14.6, 18.0, 21.3, 28.2, 39.4, 57.0 58.5, 62.9, 69.3, 153.6 (CH$_2$*C*ON), 165.0 (N*C*OO), 174.9 (O*C*O); HRMS (FAB) calcd for $C_{20}H_{27}N_2O_5$ (M+H$^+$) 375.1920, found 375.1914.

(4*R*)-3-{(2*S*)-2-[((2*S*)-*N*-Benzoyloxypyrrolidin-2-yl)propanoyl]}-4-phenyl-2-oxazolidinone (52a): IR (Nujol) 1784, 1750, 1713, 1340, 1325, 770, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 1.19 (d, J = 6.8 Hz, 3 H, C*H*$_3$), 1.53–1.65 (m, 2 H, C*H*$_2$CH), 1.77–1.89 (m, 2 H, CH$_2$C*H*$_2$CH$_2$), 3.03 (dt, J = 8.0 and 11.0 Hz, 1 H, CH$_2$C*H*CH), 3.56–3.72 (m, 2 H, CH$_3$C*H* and NC*H*), 4.13–4.25 (m, 2 H, 1 H of *H*CHCHPh and 1 H of NCH$_2$), 4.64 (t, J = 9.0 Hz, 1 H, PhC*H*), 5.42 (dd J = 4.4 and 8.8 Hz, 1 H, *H*CHCHPh), 7.18–7.61 (m, 8 H, Ph), 7.92–8.04 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 11.9, 20.8, 23.2, 39.3, 56.5, 58.0, 68.4, 69.7, 125.8, 128.3, 128.4, 128.5, 129.0, 129.5, 132.8, 138.8, 153.2 (CH$_2$*C*ON), 165.1 (N*C*OO), 174.7 (O*C*O); Anal. Calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.45; H, 5.94; N, 6.83.

(4*R*)-3-{(2*S*)-2-[((2*S*)-*N*-Benzoyloxypyrrolidin-2-yl)propanoyl]}-4-phenylmethyl-2-oxazolidinone (53a): mp 143.5–146.0 °C (ethyl acetate—hexane); $[\alpha]^{27}_D$ +3.9° (*c* 1.04, $CHCl_3$); IR (KBr) 2957, 2924, 2855, 1784, 1736, 1701, 1453, 1387 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 1.24 (d, J = 7.1 Hz, 3 H, NCOCHC*H*$_3$), 1.70–2.17 (m, 4 H, C*H*$_2$C*H*$_2$), 2.67 (dd, J = 10.4 and 13.5 Hz, 1 H, CHC*H*HPh), 3.22 (dt, J = 12.4 and 7.3 Hz, 1 H, NC*H*H), 3.43 (d, J = 13.2 Hz, 1 H, CHC*H*HPh), 3.55 (dt, J = 12.5 and 6.3 Hz, 1 H,

NC*H*H), 3.82 (q, *J* = 8.3 Hz, 1 H, NC*H*CH_2), 4.05–4.17 (m, 3 H, NCOC*H*CH_3, CH_2O), 4.64 (dq, *J* = 13.2 and 3.7 Hz, 1 H, NC*H*CH_2Ph) 7.19–7.56 (m, 8 H, Ph), 7.96–8.01 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 22.1, 25.5, 37.7, 39.7, 39.7, 55.5, 66.0, 70.4, 127.0, 128.3, 128.8, 129.4, 132.8, 135.9, 153.1 (CH_2*C*ON), 165.0 (N*C*OO), 175.3 (O*C*O); Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.00; H, 6.20; N, 6.63.

(4*S*)-3-{(2*R*)-2-[((2*R*)-*N*-Benzoyloxypyrrolidin-2-yl)propanoyl]}-4-*tert*-butyl-2-oxazolidinone (54a): IR (neat) 1777, 1740, 1700, 1453, 1387, 1217, 711 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.92 (s, 9 H, (CH_3)$_3$), 1.21 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.72–2.02 (m, 4 H, CH_2CH_2), 3.06–3.24 (m, 1 H, C*H*NO), 3.53–3.70 (m, 1 H, C*H*HN), 3.81 (q, *J* = 8.0 Hz, 1 H, C*H*Me), 4.15–4.30 (m, 3 H, C*H*HNO and CH_2), 4.44 (dd, *J* = 2.9 and 7.0 Hz, 1 H, C*H*-*t*-Bu), 7.35–7.64 (m, 3 H, Ph), 7.95–8.16 (m, 3 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 12.2, 21.2, 23.9, 25.6, 35.7, 38.9, 56.8, 61.2, 65.0, 69.2, 128.3, 129.4, 129.6, 132.7, 154.2, 165.1, 175.1; HRMS (FAB) calcd for $C_{21}H_{29}N_2O_5$ ($M+H^+$) 389.2076, found 389.2063.

(4*R*,5*S*)-3-{(2*S*)-2-[((2*S*)-*N*-Benzoyloxypyrrolidin-2-yl)propanoyl]}-4-methyl-5-phenyl-2-oxazolidinone (55a): IR (KBr) 2980, 1782, 1738, 1699, 1453, 1385, 1370, 1346, 1256, 1196, 1123, 1088, 1065, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.87 (d, *J* = 6.6 Hz, 3 H, CH_3CHN), 1.25 (d, *J* = 6.8 Hz, 3 H, NCOCHC*H*$_3$), 1.7–1.84 (m, 4 H, CH_2CH_2), 3.16 (ddd, *J* = 7.0, 7.6, and 12.3 Hz, 1 H, NC*H*H), 3.58 (ddd, *J* = 5.8, 6.4 and 12.0 Hz, 1 H, NC*H*H), 3.78 (q, *J* = 7.8 Hz, 1 H, NC*H*CH_2), 4.15 (dq, *J* = 8.3 and 6.8 Hz, 1 H, NCOC*H*CH_3), 4.75 (quint, *J* = 6.8 Hz, 1 H, NC*H*CHPh), 5.60 (d, *J* = 7.3 Hz, 1 H, C*H*O), 7.22–7.58 (m, 8 H, Ph), 7.95–8.01 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 67.9 MHz, 35 °C) δ 14.0, 14.5, 21.8, 25.2, 39.8, 54.9, 57.4, 69.9, 78.7, 125.7, 128.3, 128.6, 128.6, 129.4, 129.6, 132.8, 133.5, 152.6 (CH_2*C*ON), 165.0 (N*C*OO), 175.1 (O*C*O); Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.23; H, 6.28; N, 6.49.

(4*S*,5*R*)-3-{(2*R*)-2-[(2*R*)-*N*-Benzoyloxypyrrolidin-2-ly)propanoyl]}-4,5-diphenyl-2-oxazolidinone (56a): IR (KBr) 3069, 3000, 2965, 2938, 1773, 1734, 1692, 1339, 1269, 1258, 1088, 1067, 1024, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 1.24 (d, *J* = 7.1 Hz, 3 H, CH_3CHN), 1.58–1.71 (m, 2 H, 2 *H*CH), 1.79–1.92 (m, 2 H, 2 *H*CH), 3.04 (dt, *J* = 11.8 and 8.5 Hz, 1 H, *H*CHN), 3.70 (dt, *J* = 11.0 and 6.1 Hz, 1 H, *H*CHN), 3.76 (dt, *J* = 6.8 and 8.8 Hz, 1 H, NC*H*CH_2), 4.18 (br, 1 H, C*H*CH_3), 5.68 (d *J* = 7.9 Hz, 1 H, C*H*Ph), 5.83 (d *J* = 7.6 Hz, 1 H, C*H*Ph), 6.83–7.15 (m, 9 H, Ar), 7.38–7.58 (m, 4 H, Ar), 8.15–8.19 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 12.3, 20.5, 23.1, 39.7, 56.4, 63.0, 68.0, 80.1, 126.2, 126.6, 128.0, 128.0, 128.0, 128.2, 128.4, 129.4, 129.5, 132.8, 132.9, 134.4, 153.1 (CH_2*C*ON), 165.2 (N*C*OO), 174.4 (O*C*O); HRMS (FAB) calcd for $C_{29}H_{29}N_2O_5$ ($M+H^+$) 485.2076, found 485.2083.

(2*S*)-3-{(2*S*)-2-[((2*S*)-*N*-Benzoyloxypyrrolidin-2-yl)propanoyl]}-2-*tert*-butyl-1-carbomethoxy-2,3-dihydro-4(1*H*)-pyrimidinone (57a): IR (neat) 2971, 1748, 1686, 1624, 1443, 1425, 1372, 1333, 1294, 1215, 1111, 761, 709 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.93 (s, 9 H, (CH_3)$_3$), 1.16 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.76–2.04 (m, 4 H, CH_2CH_2), 3.01–3.14 (m, 1 H, C*H*NO), 3.62–3.75 (m, 1 H, C*H*H), 3.87 (s, 3 H, CH_3),

3.85–3.97 (m, 1 H, C*H*H), 4.03 (quint, *J* = 6.9 Hz, C*H*Me), 5.30 (d, *J* = 7.2 Hz, 1 H, C*H*=CH), 6.83 (s, 1 H, C*H*-*t*-Bu), 7.39–7.71 (m, 4 H, Ph and C*H*=CH), 8.09–8.13 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 12.4, 20.8, 22.8, 26.9, 40.2, 40.8, 54.2, 56.4, 68.2, 69.1, 104.9, 128.3, 129.4, 129.7, 132.7, 132.8, 139.2, 163.8, 164.2, 165.3, 175.9; HRMS (FAB) calcd for $C_{24}H_{32}N_3O_6$ ($M+H^+$) 458.2291, found 458.2307.

(4*R*,5*S*)-3-[(2*S*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methylbutanoyl]-4-methyl-5-phenyl-2-oxazolidinone (67a): IR (KBr) 2942, 1785, 1743, 1696, 1603, 1453, 1368, 1198, 1059, 959, 703 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.11 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$), 1.15 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 1.31 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$), 3.59 (dq, *J* = 6.6 and 10.3 Hz, 1 H, C*H*NO), 4.06 (d, *J* = 13.2 Hz, 1 H of C*H*$_2$Ph), 4.20 (dq, *J* = 7.0 and 10.3 Hz, 1 H, CH_3C*H*CO), 4.28 (d, *J* = 13.2 Hz, 1 H of C*H*HPh), 4.81 (dq, *J* = 6.6 and 7.6 Hz, 1 H , CH_3C*H*N), 5.61 (d, *J* = 7.6 Hz, 1 H, C*H*Ph), 7.05–7.55 (m, 13 H), 7.88 (s 1 H), 7.90 (s, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 9.6, 14.4, 14.9, 41.1, 55.0, 59.7, 62.6, 78.6, 126.0, 127.5, 128.0, 128.3, 128.6, 128.7, 129.3, 129.4, 129.9, 132.6, 133.9, 136.1, 152.8, 164.9, 176.0; HRMS (FAB) calcd for $C_{29}H_{31}N_2O_5$ ($M+H^+$) 487.2233, found 487.2158.

(4*S*)-3-[(2*R*,3*S*)-3-(*N*-Benzoyloxy-*N*-methylamino)-2-methyl-3-phenylpropanoyl]-4-(1-methylethyl)-2-oxazolidinone (68a): mp 131.5–132.0 °C (ethyl acetate—hexane); $[\alpha]^{33}_D$ +78.12° (*c* 1.18, MeOH); IR (Nujol) 1770 (CON), 1736 (OCO), 1711 (NCOO), 1265, 1201 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.95 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$CHCO), 0.98 (d, *J* = 7.3 Hz, 3 H C*H*$_3$CH), 1.01 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CH), 2.54 (dqq, *J* = 3.7, 7.1, and 7.1 Hz, 1 H, $(CH_3)_2$C*H*), 2.68 (s, 3 H, C*H*$_3$N), 4.22 (m, 2 H C*H*$_2$O), 4.43 (d, *J* = 10.7 Hz, 1 H, PhC*H*), 4.47 (ddd, *J* = 3.9, 3.9, and 5.7 Hz, 1 H, CHC*H*N), 4.80, (dq, *J* = 6.8, and 10.8 Hz, 1 H, CH_3C*H*CO), 7.34–7.48 (m, 1 H, Ph), 7.50–7.57 (m, 1 H, Ph), 7,92–7.98 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.8, 15.6, 18.4, 28.7, 38.8, 43.5, 59.0, 63.2, 74.3, 128.1, 128.2, 128.32, 128.33, 129.5, 130.5, 132.8, 134.1, 153.8 (CH_2*C*ON), 164.5 (N*C*OO), 175.5 (O*C*OPh); HRMS (FAB) calcd for $C_{24}H_{29}N_2O_5$ ($M+H^+$) 425.2076, found 425.2090.

(4*S*)-3-[(2*R*,3*R*)-3-(*N*-Benzoyloxy-*N*-methylamino)-2-methyl-3-phenylpropanoyl]-4-(1-methylethyl)-2-oxazolidinone (68b): mp 151.0–152.0 °C (ethyl acetate—hexane); $[\alpha]^{30}_D$ –69.0° (*c* 1.17, MeOH); IR (Nujol) 1773 (CON), 1732 (OCO), 1707 (NCOO), 1255, 1066, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.25 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$CHCH), 0.62 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHCH), 1.49 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHCO), 1.63 (dqq, *J* = 3.0, 6.8, and 6.8 Hz, 1 H, $(CH_3)_2$C*H*), 2.72 (s, 3 H, C*H*$_3$N), 4.05 (dd, *J* = 2.7 and 8.8 Hz, 1 H, *H*CHO), 4.14 (dd, *J* = 8.3 and 8.3 Hz, 1 H, *H*CHO), 4.20 (d, *J* = 11.5 Hz, 1 H, PhC*H*), 4.25 (ddd, *J* = 2.9, 2.9, and 8.3 Hz, 1 H, $(CH_3)_2$CHC*H*), 4.96 (dq, *J* = 4.2 and 6.6 Hz, 1 H, CH_3C*H*CO), 7.27–7.63 (m, 8 H of Ph), 8.02–8.10 (m, 2 H of Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.0, 16.1, 17.6, 28.1, 40.0, 43.6, 58.2, 62.8, 74.0, 128.2, 128.6, 129.3, 129.4, 130.3, 133.1, 135.7, 153.5 (CH_2*C*ON), 165.2 (N*C*OO), 175.1 (O*C*OPh); HRMS (FAB) calcd for $C_{24}H_{29}N_2O_5$ ($M+H^+$) 425.2076, found 425.2067.

(4*S*)-3-{(2*R*)-2-[(2*R*)-*N*-Benzoyloxypiperidin-2-yl]propanoyl}-4-(1-methylethyl)-2-oxazolidinone (69a): IR (neat) 1777 (NCO), 1736 (COO), 1701 (NCOO), 1452, 1300,

1248, 1207, 1180, 1121, 1090, 1067, 1026, 1005, 754, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.89 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH_3), 0.93 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH_3), 1.16 (d, *J* = 6.8 Hz, 3 H, $COCHCH_3$), 1.20–1.96 (m, 6 H, $(CH_2)_3$), 2.23–2.42 (m, 1 H, $CH(CH_3)_2$), 2.74–2.93 (m, 1 H, $NCHHCH_2$), 3.39 (ddd, *J* = 3.2, 4.9, and 8.1 Hz, 1 H, $NCHCH_2$), 3.62–3.69 (m, 1 H, $NCHHCH_2$), 4.21 (dd, *J* = 3.7 and 9.0 Hz, 1 H, $NCHCHHO$), 4.26 (dd, *J* = 9.0 and 9.0 Hz, 1 H, $NCHCHHO$), 4.51 (dt, *J* = 3.7 and 9.0 Hz, 1 H, $NCHCH_2O$), 7.26–7.59 (m, 4 H, Ph), 8.08–8.26 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.3 and 17.9 ($CH(CH_3)_2$), 23.4 ($NCHCH_2CH_2CH_2$), 28.2 ($CH(CH_3)_2$), 39.7 ($COCHCH_3$), 58.2 ($NCHCH_2O$), 62.9 ($NCHCH_2O$), 66.0 ($NCHCH_2CH_2$), 126.7 (Ph), 128.3 (Ph), 129.3 (Ph) ,129.3 (Ph), 129.7 (Ph), 132.8 (Ph), 153.3 (NCO), 164.7 (OCON), 175.9 (CO_2); HRMS (FAB) calcd for $C_{21}H_{29}N_2O_5$ ($M+H^+$) 389.2076, found 389.2050.

(4*S*)-3-{(2*R*)-2-[(2*S*)-*N*-Benzoyloxypiperidin-2-yl]propanoyl}-4-(1-methylethyl)-2-oxazolidinone (69b): IR (neat) 1777 (NCO), 1740 (COO), 1701 (NCOO), 1451, 1387, 1373, 1304, 1265, 756, 709 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.84 (d, *J* = 6.4 Hz, 3 H, CH_3CHCH_3), 0.72 (d, *J* = 6.2 Hz, 3 H, CH_3CHCH_3), 1.26 (d, *J* = 6.4 Hz, 3 H, $CHCH_3$), 1.38–1.97 (m, 7 H, $NCH_2CH_2CH_2CH$, $CH(CH_3)2$), 2.82–3.04 (m, 1 H, $NCHH$), 3.22 (ddd, J = 3.4, 6.4, and 10.4 Hz, 1 H, $NCHCHCH_3$), 3.63–3.73 (m, 1 H, $NCHH$), 3.98–4.14 (m, 1 H, $NCHCHCH_3$), 4.12–4.24 (m, 2 H, $NCHCH_2O$), 4.34–4.42 (m, 1 H, $NCHCH_2O$), 7.36–7.58 (m, 3 H, Ph), 7.93–8.05 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.5, 18.0, 23.8, 24.5, 28.2, 41.1, 56.6, 58.7, 62.8, 76.5, 77.0, 77.5, 128.0, 128.1, 128.4, 129.4, 129.5, 132.6, 153.8, 264.9, 175.4; HRMS (FAB) calcd for $C_{21}H_{29}N_2O_5$ ($M+H^+$) 389.2076, found 389.2094.

(4*R*,5*S*)-3-{(2*S*)-2-[((2*S*)-*N*-Benzoyloxypiperidin-2-yl)propanoyl]}-4-methyl-5-phenyl-2-oxazolidinone: mp 57–60 °C (ethyl acetate—hexane); $[\alpha]^{20}_D$ +104.5° (*c* 1.01, $CHCl_3$); IR (KBr) 3036, 2944, 1780, 1738, 1699, 1452, 1370, 1244, 1198, 1088, 1067, 1026, 709 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.88 (d, *J* = 6.3 Hz, 3 H, CH_3CHN), 1.20 (d, *J* = 7.1 Hz, 3 H, $NCOCHCH_3$), 1.50–1.96 (m, 6 H, $CH_2CH_2CH_2$), 2.89 (br t, *J* = 11.0 Hz, 1 H, $NCHH$), 3.41 (ddd, *J* = 2.9, 5.9, and 11.2 Hz, 1 H, $NCHCH_2$), 3.64 (br t, *J* = 11.0 Hz, 1 H, $NCHH$), 4.32 (quint, *J* = 6.4 Hz, 1 H, $NCOCHCH_3$), 4.80 (dq, *J* = 6.6 and 7.6 Hz, 1 H, $NCHCHPh$), 5.62 (d, *J* = 7.6 Hz, 1 H, CHO), 7.25–7.62 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.6, 18.4, 23.5, 25.3, 27.0, 39.7, 54.7, 54.9, 57.5, 65.9, 78.7, 125.7, 127.4, 128.4, 128.4, 128.6, 128.7, 129.6, 129.7, 130.3, 132.8, 133.6, 133.7, 152.4 (CH_2CON), 164.8 ($NCOO$), 174.8 (OCO); Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.78; H, 6.47; N, 6.42. Found: C, 68.51; H, 6.51; N, 6.12.

(4*R*,5*S*)-3-{(2*S*)-2-[((1*S*)-*N*-Benzoyloxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propanoyl]}-4-methyl-5-phenyl-2-oxazolidinone (70a): mp 75–78 °C (ethyl acetate—hexane); $[\alpha]^{22}_D$ –14.7° (*c* 0.791, $CHCl_3$); IR (KBr) 2969, 1775, 1742, 1699, 1452, 1368, 1344, 1258, 1240, 1223, 1198, 1063, 1024, 708 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 1.02 (d, *J* = 6.6 Hz, 3 H, CH_3CHN), 1.25 (d, *J* = 6.8 Hz, 3 H, $NCOCHCH_3$), 2.28 (ddd, *J* = 2.2, 5.9, and 17.1 Hz, 1 H, HCH), 3.13 (ddd, *J* = 6.3, 9.3, and 17.1 Hz, 1 H, HCH), 3.62 (ddd, *J* = 2.2, 6.6, and 14.6 Hz, 1 H, HCH), 3.91 (ddd, *J* = 6.1,

11.0, and 14.6 Hz, 1 H, *H*CH), 4.35 (dq, *J* = 10.5 and 7.8 Hz, 1 H, NCOC*H*CH_3), 4.74 (d, *J* = 10.5 Hz, 1 H, NC*H*Ar), 4.89 (quint, *J* = 6.7 Hz, 1 H, NC*H*CHPh), 5.67 (d, *J* = 7.3 Hz, 1 H, C*H*O), 7.15–7.85 (m, 12 H, Ar), 7.75–7.85 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.4, 16.1, 23.6, 41.7, 47.2, 55.2, 67.4, 78.9, 125.3, 125.8, 127.2, 128.2, 128.4, 128.6, 128.7, 128.9, 129.2, 129.3, 129.6, 132.6, 132.7, 133.5, 134.0, 153.2 (CH_2*C*ON), 164.0 (N*C*OO), 175.3 (O*C*O); Anal. Calcd for $C_{29}H_{28}N_2O_5$: C, 71.88; H, 5.82 N, 5.78. found: C, 71.88; H, 5.90; N, 5.92.

Preparation of Methyl 3-(*N*-Benzoyloxy-*N*-benzylamino)-3-phenylpropanoate (28), (4*S*)-3-[(2*R*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-4-(1-methylethyl)-2-oxazolidinone (35a), (4*S*)-3-[(2*R*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropanoyl]-(1-methylethyl)-2-oxazolidinone (35b), (4*S*)-3-[(2*R*)-2-((1*R*)-*N*-benzoyloxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propanoyl]-4-(1-methylethyl)-2-oxazolidinone (71a), and (4*S*)-3-[(2*R*)-2-((1*S*)-*N*-benzoyloxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propanoyl]-4-(1-methylethyl)-2-oxazolidinone (71b). See, Ohtake's doctoral thesis.

Hydrolysis of β-Amino Acid Derivatives 35a and 35b and Transformation to β-Amino Acids (–)-38a and (+)-38b. The determination of the configurations of **35a** and **35b** by derivation to (–)-**37a** and (+)-**37b**, β-amino acids (–)-**38a** and (+)-**38b**, and α-phenylpropylamines (–)-**40**, (+)-**40**, and (–)-**41**, see Ohtake's doctoral thesis.

Preparation of (2*S*,3*R*)-3-(Benzyloxycarbonylamino)-2-methyl-3-phenylpropanoic Acid ((+)-38a). β-Amino acid (+)-**38a** was prepared as shown below.

(4*R*,5*S*)-3-[(2*S*,3*R*)-3-(*N*-Benzyloxycarbonylamino)-2-methyl-3-phenylpropanoyl]-4-methyl-5-phenyl-2-oxazolidinone. To a solution of **45a** (1.02 g, 1.85 mmol) in acetic acid (20 mL) was added zinc powder (3.1 g), and the mixture was stirred at 60 °C for 8 h. The mixture was filtered through Celite and the cake was washed with methanol (40 mL), and the filtrate was evaporated. To the residue, sat. $NaHCO_3$ (10 mL) and ethyl acetate (10 mL) were added, and filtered again through Celite and the cake was washed with ethyl acetate (30 m). The organic layer was separated and dried over Na_2SO_4. Evaporation followed by column chromatography on silica gel (5—40% ethyl acetate in hexane) gave the titled product as a foam (344 mg, 43%) and (5*S*,6*R*)-1-benzyl-5,6-dihydro-5-methyl-6-phenyluracil as a colorless solid (240 mg, 44%). **(4*R*,5*S*)-3-[(2*S*,3*R*)-3-(*N*-Benzyloxycarbonylamino)-2-methyl-3-phenylpropanoyl]-4-methyl-5-phenyl-2-oxazolidinone:** IR (Nujol) 2930, 1780, 1700, 1458, 1377 cm^{-1}; 1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.93 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$), 1.00 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$), 2.17 (br, 1 H, N*H*), 3.37 (d, *J* = 13.4 Hz, 1 H, C*H*HPh), 3.14 (d, *J* = 13.2 Hz, 1 H, C*H*HPh), 3.69 (d, *J* = 10.2 Hz, 1 H, NC*H*Ph), 4.28 (dq, *J* = 10.5 and 6.6 Hz, 1 H, COC*H*Me), 4.82 (quint, *J* = 6.8 Hz, 1 H, NC*H*Me), 5.66 (d, *J* = 6.1 Hz, 1 H, OC*H*Ph), 7.10–7.46 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.3, 15.3, 43.2, 50.8, 55.5, 67.1, 78.9, 125.7, 126.6, 127.5, 127.7, 128.0, 128.2, 128.5, 128.6, 128.7, 133.4, 140.3, 141.7, 153.8, 176.4; HRMS (EI) calcd for $C_{27}H_{29}N_2O_3$ (M^+) 429.2178, found

429.2144. **(5*S*,6*R*)-1-Benzyl-5,6-dihydro-5-methyl-6-phenyluracil:** mp 182–188 °C (diethyl ether); $[\alpha]^{24}_D$ –2.87° (*c* 1.18, $CHCl_3$); IR (KBr) 3200, 3050, 1700, 1471, 1270, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 1.16 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$), 2.76 (dq, *J* = 3.2 and 7.1 Hz, 1 H, C*H*Me), 3.65 (d, *J* = 14.9 Hz, 1 H, C*H*HPh), 4.14 (d, *J* = 3.2 Hz, 1 H, C*H*Ph), 5.47 (d, *J* = 14.6 Hz, 1 H, C*H*HPh), 7.30–7.40 (m, 10 H, Ph), 8.61 (br, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 16.3, 43.3, 48.6, 61.8, 126.2, 127.9, 128.5, 128.6, 128.8, 129.2, 136.2, 137.9, 152.8, 172.1; mp 135.0–137.5 °C; HRMS (EI) calcd for $C_{18}H_{18}N_2O_2$ (M^+) 294.1368, found 294.1351.

(2*S*,3*R*)-3-Benzylamino-2-methyl-3-phenylpropanoic Acid ((+)-48). (4*R*,5*S*)-3-[(2*S*,3*R*)-3-(*N*-Benzyloxycarbonylamino)-2-methyl-3-phenylpropanoyl]-4-methyl-5-phenyl-2-oxazolidinone (380 mg, 0.887 mg) thus obtained above, was dissolved in THF—H_2O (3 : 1, 12 mL), and to the solution was added $LiOH{\cdot}H_2O$ (186 mg, 4.43 mmol) with ice cooling. The mixture was stirred at room temperature for 7 days, and extracted with Et_2O (20 mL x 1 and 10 mL x 2). The organic layer was dried over Na_2SO_4, which gave recovered oxazolidinone (132 mg, 84%) after purified by column chromatography on silica gel (10–60% ethyl acetate in hexane). The water phase was acidified with acetic acid (0.45 mL), and extracted with ethyl acetate (20 mL x 1 and 10 mL x 2). Dried over Na_2SO_4, removal of the solvent gave (+)-**48** (170 mg, 59%) as a colorless solid. The analytical sample was obtained by the titration of the solid with diethyl ether (142 mg): mp 146.0–147.0 °C (diethyl ether); $[\alpha]^{24}_D$ +55.9° (*c* 1.09, MeOH); IR (KBr) 3450, 1645, 16012, 1601, 1458, 1394, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.95 (d, *J* = 7.3 Hz, 3 H, C*H*$_3$), 2.91 (dq, *J* = 11.0 and 7.3 Hz, 1 H, C*H*Me), 3.51 (d, *J* = 13.5 Hz, 1 H, C*H*HPh), 3.77 (d, *J* = 11.0 Hz, 1 H, C*H*Ph), 4.19 (d, *J* = 13.7 Hz, 1 H, C*H*HPh), 7.26–7.46 (m, 10 H, Ph), 9.78 (br, 2 H, N*H* and CO_2H); ^{13}C NMR (CD_3OD, 68 MHz, 35 °C) δ 15.3, 43.9, 48.2, 64.0, 128.4, 128.5, 128.7, 128.8, 129.2, 133.3, 135.8, 178.8; HRMS (CI) calcd for $C_{17}H_{20}NO_2$ ($M+H^+$) 270.1494, found 270.1467.

(2*S*,3*R*)-3-(Benzyloxycarbonylamino)-2-methyl-3-phenylpropanoic Acid ((+)-38a). (+)-**48** (118 mg, 0.438 mmol) was hydrogenated in methanol (4 mL) in the presence of 10% Pd/C (50% wet, 120 mg) and acetic acid (0.05 mL) at atmospheric pressure at room temperature for 1 h. After filtration of the catalyst and removal of the solvent, to the residue were added THF (2 mL), H_2O (2 mL), K_2CO_3 (194 mg, 1.4 mmol), and ZCl (0.075 mL, 0.53 mmol), then, the mixture was stirred for 1 h. After evaporation, H_2O (5 mL) were added, and extracted with Et_2O (20 mL). Dried over $MgSO_4$, the solution was concentrated under reduced pressure. Purification of the oil residue by column chromatography on silica gel (10 mL, 20—30% ethyl acetate in hexane) gave (+)-**38a** (118 mg, 86%) as a colorless solid. The analytical sample was obtained by the titration with diisopropyl ether: mp 135.0–137.5 °C (diisopropyl ether); $[\alpha]^{23}_D$ +22.2 ° (*c* 1.03, $CHCl_3$) ($[\alpha]^{28}_D$ –21.6 ° (*c* 1.02, $CHCl_3$) for (–)-**38a**); IR (Nujol) 3349, 1692, 1530, 1464, 1291, 1250, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 55 °C) δ 1.02–1.30 (m, 3 H, C*H*$_3$), 2.84–3.02 (m, 1 H, C*H*Me), 4.81–4.98 (m, 1 H, C*H*Ph), 5.06 (s, 2 H, C*H*$_2$Ph), 6.30 (br s, 1 H, N*H*), 7.17–7.36 (m, 10 H, Ph), 9.60 (br s, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$, 68 MHz, 55 °C) δ 15.5, 44.8, 57.0, 67.0, 126.3, 127.5, 128.1, 128.4, 128.5, 128.7, 136.2, 140.2, 156.2,

179.7; ^{1}H NMR (CD_3OD, 270 MHz, 55 °C) δ 1.10 (d, J = 7.1 Hz, 3 H, CH_3), 2.86 (dq, J = 8.6 and 7.1 Hz, C*H*Me), 4.79 (d, J = 8.8 Hz, C*H*N), 4.99 (d, J = 12.7 Hz, 1 H, C*H*HPh), 5.05 (d, J = 12.5 Hz, 1 H, C*H*HPh), 7.18–7.33 (m, 10 H, Ph); ^{13}C NMR (CD_3OD, 68 MHz, 35 °C) δ 15.7, 46.3, 59.1, 67.4, 128.1, 128.4, 128.5, 128.8, 129.3, 129.4, 138.1, 142.0, 157.9, 178.2; HRMS (FAB) calcd for $C_{18}H_{20}NO_4$ ($M+H^+$) 314.1392, found 314.1369.

Preparation of (2*S* ,3*S*)-3-(Benzyloxycarbonylamino)-2-methyl-3-phenylpropanoic Acid ((–)-38b). β-Amino acid (–)-**38b** was prepared from **47b** as shown below.

(2*S*)-3-[(2*S*,3*S*)-3-(*N*-Benzyloxycarbonylamino)-2-methyl-3-phenylpropanoyl]-2-*tert*-butyl-1-carbomethoxy-2,3-dihydro-4(1*H*)pyrimidinone (49). β-Amino acid derivative **47b** (400 mg, 0.685 mmol) was dissolved in methanol (5 mL) and 2 M HCl (1.0 mL). After addition of 10% Pd/C (50% wet, 146 mg), hydrogenation was carried out at room temperature at atmospheric pressure for 4 h. The reaction mixture was filtered, and the solvent was removed by evaporation, then the oil residue was dissolved in ethyl acetate—water (3 : 1, 4.0 mL). To the solution were added sodium bicarbonate (800 mg) and ZCl (0.147 mL, 1.03 mmol), and the reaction mixture was stirred for 1.5 h at room temperature. After extracted with ethyl acetate (20 mL), washed with brine, and dried over $MgSO_4$, the solvent was removed under reduced pressure, and the oil residue was purified by column chromatography on silica gel (40 mL, ethyl acetate in hexane) to afford **49** (311 mg, 89%) as a waxy solid: $[\alpha]^{24}_D$ +94.9° (*c* 1.16, $CHCl_3$); IR (KBr) 3350, 1728, 1694, 11332, 1314, 1294, 1223, 1177, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 0.73 (s, , 9 H, *t*-Bu), 1.06 (d, J = 6.8 Hz, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 4.23 (quint, J = 6.4 Hz, 1 H, C*H*Me), 5.01 (d, J = 12.5 Hz, 1 H, C*H*HPh), 5.07 (d, J = 12.2 Hz, 1 H, C*H*HPh), 5.35 (d, J = 7.8 Hz, 1 H, C*H*Ph), 5.45 (br, 1 H, C*H*-*t*-Bu), 6.80 (br, 1 H), 7.17–7.37 (m, 9 H), 7.43–7.50 (m, 2 H), 7.62 (br d, J = 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 12.7, 26.4, 40.1, 45.2, 54.2, 66.7, 68.7, 104.7, 126.9, 127.2, 128.0, 128.1, 128.4, 136.5, 139.6, 141.0, 152.5, 155.8, 164.0, 174.6.

(2*S*,3*S*)-3-(Benzyloxycarbonylamino)-2-methyl-3-phenylpropanoic Acid ((–)-38b). To a solution of **49** (351 mg, 0.692 mmol) in THF—H_2O (3.0 mL : 1.0 mL) were added 30% H_2O_2 (0.565 mL, 5.54 mmol) and LiOH•H_2O (58 mg, 1.38 mmol) at 0 °C.[31,40] After stirring at room temperature for 0.5 h, $NaHSO_3$ (633 mg) was added. The mixture was extracted with ethyl acetate (20 mL x 3), and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent and purification by column chromatography on SiO_2 (20 mL, ethyl acetate) gave 2-*tert*-butyl-1-carbomethoxy-2,3-dihydro-4(1*H*)pyrimidinone (132 mg, 90%) as a colorless solid and (–)-**38b** (204 mg, 94%) as a colorless solid. Further, (–)-**38b** was recrystallized from $CHCl_3$ to give a colorless crystal (67 mg): mp 169.0–171.0 °C ($CHCl_3$); $[\alpha]^{31}_D$ –36.7° (*c* 1.10, MeOH) ($[\alpha]^{31}_D$ +36.1° (*c* 0.97, MeOH) for (+)-**38b**); IR (Nujol) 3358 (NH), 1692, 1532, 1287, 1258, 1019 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 55 °C) δ 1.16 (d, J = 7.1 Hz, 3 H, CH_3CHCO), 2.96 (quint, J = 7.1 Hz, 1 H, C*H*CO), 5.01–5.13 (m, 3 H, C*H*Ph and CH_2Ph), 5.67 (br s, 2 H, CO_2H and N*H*), 7.20–7.36 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 55 °C) δ 13.1, 44.8, 57.2, 67.1,

126.9, 127.8, 128.0, 128.1, 128.5, 128.6, 136.4, 139.6, 156.1, 178.0; ^{1}H NMR (CD_3OD, 270 MHz, 35 °C) δ 1.21 (d, J = 7.1 Hz, 3 H, C*H*$_3$), 2.88 (dq, J = 8.8 and 7.1 Hz, 1 H, C*H*Me), 4.90 (d, J = 8.8 Hz, C*H*N), 5.01 (d, J = 12.4 Hz, 1 H, C*H*HPh), 5.08 (d, J = 12.4 Hz, 1 H, C*H*HPh), 7.12–7.38 (m, 10 H, Ph); ^{13}C NMR (CD_3OD, 68 MHz, 35 °C) δ 15.4, 47.6, 59.5, 68.4, 129.0, 129.2, 129.5, 129.7, 130.1, 130.2, 139.1, 143.3, 159.2, 178.4; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.69; H, 6.09; N, 4.45.

Preparation of (4*S*)-3-[(2*R*)-2-{(2*R*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}-propanoyl]-4-(1-methylethyl)-2-oxazolidinone (58): To a solution of a diasteromeric mixture of **51** (1.80 g, 4.82 mmol) in methanol (16 mL) and acetic acid (1.4 mL) was added 10% Pd/C (1.80 g), then, hydrogenation was carried out at room temperature and atmospheric pressure for 12 h. The reaction mixture was filtered, and the solvent was removed by evaporation, then the oil residue was dissolved in THF—H_2O (1 : 1, 50 mL). To the solution were added K_2CO_3 (2.00 g, 14.5 mmol) and ZCl (1.03 mL, 7.23 mmol), and the mixture was stirred for 0.5 h at room temperature. After extracted with ethyl acetate (50 mL), washed with brine (30 mL x 2), and dried over $MgSO_4$, the solvent was removed under reduced pressure, and the oil residue was purified by column chromatography on silica gel (70 mL, 10% ethyl acetate in hexane) to afford **58** (1.46 g, 82%) as a colorless oil which was a single diastereomer: $[\alpha]^{25}_D$ +43.0° (*c* 1.32, MeOH); IR (neat) 2967, 1781 (CON), 1699 (NCOO), 1455, 1410, 1385, 1364, 1302, 1231, 1206, 1103, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 55 °C) δ 0.81 (d, J = 7.1 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.87 (d, J = 7.1 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.08 (d, J = 6.6 Hz, 3 H, NCOCHC*H*$_3$), 1.70–2.05 (m, 4 H, C*H*$_2$C*H*$_2$), 2.20–2.40 (m, 1 H, C*H*(CH$_3$)$_2$), 3.28–3.42 (m, 1 H, NC*H*H), 3.50–3.66 (m, 1 H, NC*H*H), 4.14 (dd, J = 3.7 and 9.0 Hz, 1 H, *H*CHO), 4.19 (dd, J = 9.0 and 9.0 Hz, 1 H, *H*CHO), 4.25–4.46 (m, 3 H, NC*H*CH$_2$, NCOC*H*CH$_3$, C*H*CH$_2$O), 5.10 (s, 2 H, C*H*$_2$Ph), 7.22–7.42 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 55 °C) δ 12.5 (CH*C*H$_3$), 14.4 and 17.9 (CH(*C*H$_3$)$_2$), 23.7 and 27.8 ((*C*H$_2$)$_2$), 28.2 (*C*H(CH$_3$)$_2$), 40.2 (*C*HCH$_3$), 47.1 (*C*H$_2$N), 58.6 (N*C*HCH$_2$O), 59.2 (*C*HN), 62.9 (NCH*C*H$_2$O), 66.7 (*C*H$_2$Ph), 127.7, 128.3, 136.9, 153.5 (N*C*OO), 155.1 (N*C*OO), 174.9 (O*C*N); HRMS (FAB) calcd for $C_{20}H_{27}N_2O_5$ ($M+H^+$) 389.2076, found 389.2058.

Preparation of (2*R*)-2-{(2*R*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}propanoic Acid ((+)-59) and Methyl (2*R*)-2-{(2*R*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}propanoate ((+)-60). To a solution of **58** (5.20 g, 13.4 mmol) in THF—H_2O (160 mL : 53 mL) were added 30% H_2O_2 (6.61 mL, 67.1 mmol) and LiOH•H_2O (1.13 g, 26.8 mmol) at 0 °C. After stirring at room temperature for 1 h, the solvent was evaporated and diluted with water (60 mL). The solution was washed with CH_2Cl_2 (40 mL x 6), which gave recovered oxazolidinone. The aqueous layer was acidified with 6 M HCl at pH 1 and extracted with CH_2Cl_2 (50 mL x 3). The combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The resulted colorless oil of (+)-**59** was dissolved in DMF (7.5 mL). To the solution were added CH_3I (1.29 mL, 20.7 mmol) and K_2CO_3 (2.20 g, 15.9 mmol), and the mixture was stirred at room temperature for 18 h. To the mixture were added hexane—ethyl acetate (1 : 1, 20 mL) and washed with water (10 mL x 1, 6 mL

x 2) and brine. The organic layer was dried over $MgSO_4$. Removal of the solvent and purification by column chromatography on silica gel (150 mL, 10—40% ethyl acetate in hexane) gave (+)-**60** (3.17 g, 81%) as a colorless oil. (+)-**59:** $[\alpha]^{25}_D$ +26.3° (*c* 1.45, MeOH); IR (neat) 3400 (OH), 1730 (COO), 1703 (NCOO), 1420, 1360, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 55 °C) δ 1.04 (d, *J* = 7.2 Hz, 3 H, $CHCH_3$), 1.70–2.10 (m, 4 H, $(CH_2)_2$), 3.20–3.42 (m, 1 H, $CHCH_3$), 3.50–3.66 (m, 1 H), 4.28–4.38 (m, 1 H), 5.13 (s, 2 H, CH_2Ph), 7.22–7.38 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 55 °C) δ 9.9, 23.8, 27.0, 41.3, 47.3, 58.4, 66.8, 127.6, 127.7, 128.3, 136.7, 154.9 (NCOO), 179.0 (COO); HRMS (FAB) calcd for $C_{15}H_{20}NO_4$ ($M+H^+$) 278.1392, found 278.1401. (+)-**60:** $[\alpha]^{22}_D$ +11.6° (*c* 0.92, MeOH); IR (neat) 2978, 2951, 1734 (COO), 1703 (NCOO), 1414, 1360, 1339, 1206, 1103, 754, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 55 °C) δ 1.04 (d, 3 H, *J* = 7.2 Hz, $CHCH_3$), 1.72–2.04 (m, 4 H, $(CH_2)_2$), 3.10–3.40 (m, 1 H, $CHCH_3$), 3.26–3.42 (m, 1 H), 3.52–3.66 (m, 1 H), 3.62 (s, 3 H, CO_2CH_3), 4.22–4.32 (m, 1 H), 5.13 (s, 2 H, CH_2Ph), 7.26–7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 55 °C) δ 10.5, 24.0, 27.2, 41.0, 47.4, 51.5, 58.8, 66.8, 127.8, 127.9, 128.4, 137.0, 154.9, 175.0; HRMS (FAB) calcd for $C_{16}H_{22}NO_4$ ($M+H^+$) 292.1549, found 292.1535.

Preparation of (2*R*)-2-{(2*R*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}propanol ((+)-61). To a solution of (+)-**60** (252 mg, 0.865 mmol) in toluene (5 mL) was added dropwise a 1.0 M DIBAL-H in hexane (2.60 mL, 2.60 mmol) at –78 °C, and the mixture was stirred at 0 °C for 30 min. The mixture was poured into ethyl acetate—H_2O (1 : 1, 20 mL), and the precipitate was dissolved by addition of 6 N HCl (2.0 mL). The organic layer was separated, washed with brine (20 mL), sat. $NaHCO_3$ (20 mL), and brine (20 mL x 2), and dried over $MgSO_4$. Removal of the solvent followed by purification by column chromatography on silica gel (35 mL, 15—20% ethyl acetate in hexane) gave (+)-**61** as a colorless oil (152 mg, 67%): $[\alpha]^{23}_D$ +31.7 (*c* 0.89, MeOH); IR (neat) 3450 (OH), 2967, 2880, 1678 (NCOO), 1455, 1418, 1358, 1337, 1101, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 1.03 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.38–1.53 (m, 1 H, $CHCH_3$), 1.75–2.05 (m, 4 H, $(CH_2)_2$), 3.24–3.74 (m, 4 H), 3.80–3.95 (m, 1 H), 3.95–4.18 (br s, 1 H, OH), 5.14 (d, *J* = 12.0 Hz, 1 H, *H*CHPh), 5.17 (d, *J* = 12.0 Hz, 1 H, *H*CHPh), 7.28–7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 14.7, 23.5, 28.6, 38.9, 46.3, 59.6, 64.0, 67.1, 127.7, 128.0, 128.4, 136.6, 156.9; HRMS (EI) calcd for $C_{15}H_{21}NO_3$ (M^+) 263.1521, found 263.1503.

Methyl (2*S*)-2-{(2*S*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}propanoate ((–)-60). β-Amino ester (–)-**60** was prepared by the similar method for (+)-**60** as shown below.

Preparation of (4*R*)-3-[(2*S*)-2-{(2*S*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}-propanoyl]-4-benzyl-2-oxazolidinone (62). Catalytic hydrogenation of **53a** (7.42 g, 17.6 mol) in the presence of 10% Pd/C (4.7 g), followed by protection by ZCl gave **62** (6.70 g, 87%) as a colorless crystal: mp 86.0–87.0 °C (ethyl acetate—hexane); $[\alpha]^{24}_D$ –7.4° (*c* 1.04, $CHCl_3$); IR (neat) 2974, 1773, 1701, 1411, 1096, 919, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 1.13 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.76–2.09 (m, 4 H, CH_2CH_2), 2.42 (br, 1 H, C*H*HPh), 3.19–3.71 (m, 3 H, CH_2N and C*H*HPh), 4.03 (dd, *J* = 3.4 and 9.0 Hz, 1 H,

OC*H*HCH), 4.09 (dd, J = 8.0 and 9.0 Hz, 1 H, OC*H*HCH), 4.28 (m, 2 H, C*H*Me and C*H*N), 4.61 (ddt, J = 8.0, 14.0, and 3.4 Hz, 1 H, C*H*CH_2Ph), 5.08 (d, J = 12.0 Hz, 1 H, C*H*HPh), 5.15 (d, J = 12.0 Hz, 1 H, C*H*HPh), 7.11–7.52 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 13.0, 23.8, 28.3, 38.0, 40.5, 47.1, 55.6, 59.7, 66.1, 66.7, 127.1, 127.6, 127.8, 128.4, 128.8, 129.4, 135.9, 137.2, 153.1, 155.1, 175.1; HRMS (FAB) calcd for $C_{25}H_{29}N_2O_5$ (M+H$^+$) 437.2076, found 437.2086; Anal. Calcd for $C_{25}H_{28}H_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.65; H, 6.51; N, 6.50.

Preparation of Methyl (2*S*)-2-{(2*S*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}propanoate ((–)-60). Hydrolysis of **62** (6.69 g, 15.3 mmol) by LiOH—30% H_2O_2, followed by treatment with diazomethane in ether gave (–)-**60** (4.50 g, 99%) as a colorless oil: $[\alpha]^{24}_D$ –14.3° (*c* 0.98, MeOH).

The Reactions of Chiral *N*-Acyloxyiminium Species Prepared from Nitrones with Acetylmandelyl Chloride (21).

Preparation of Acetylmandelyl Chloride (21). Optically active acyl chloride **21** was prepared by reported procedure.[24] (*R*)-**21**: bp 110–112 °C/3.5 mmHg; $[\alpha]^{25}_D$ –184.6° (*c* 2.94, $CHCl_3$) (lit.[24c] bp 80–81 °C/0.1 mmHg; $[\alpha]^{27}_D$ +186±1° (*c* 3.20, $CHCl_3$) for the *S* isomer). (*S*)-**21**: bp 76–78 °C/0.7 mmHg; $[\alpha]^{21}_D$ +182.8° (*c* 3.31, $CHCl_3$).

Preparation of Methyl *N*-(2*S*)-2-Acetoxyphenylacetoxy-*N*-benzyl-3-amino-3-phenylpropanoate (74). The β-amino acid derivative **74** was prepared by the similar procedure for the general procedure for the reaction with the boron enolate by using ketene silyl acetal **27** instead of the boron enolate. A diasteromeric mixture of **74** (1 : 1): IR (neat) 3064, 1780, 1740, 1695, 1498, 1456, 1437, 1373, 1230, 1051, 738, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 2.13 and 2.15 (s, 3 H, C*H*$_3$), 2.63 (dd, J = 8.8 and 15.6 Hz, 1 H, one of C*H*H), 2.84 (dd, J = 8.8 and 15.6 Hz, 1 H, one of C*H*H), 2.91–3.05 (m, 1 H, two of C*H*H), 3.53 and 3.54 (s, 3 H, C*H*$_3$), 3.60 (d, J = 13.9 Hz, 1 H, one of C*H*HPh), 3.75 (s, 2 H, two of C*H*HPh), 3.89 (d, J = 13.6 Hz, 1 H, one of C*H*HPh), 4.38–4.51 (m, 2 H, two of C*H*N), 5.79 (s, 1 H, one of C*H*CO), 5.80 (s, 1 H, one of C*H*CO), 6.96–7.44 (m, 30 H, Ph).

Preparation of {*N*-[(2*R*)-2-Acetyoxyphenylacetoxy]-*N*-benzylamino-2-methyl-3-phenylpropanoyl}-2-oxazolidinone (76). The β-amino acid derivative **76** was prepared according to the general procedure of the reaction of *N*-acyloxyiminium ion with the enolate. Here is shown a *syn* isomer of **76** (*syn* : *anti* = 91 : 9): IR (Nujol) 1778, 1740, 1696, 1380, 1231, 1220, 1046, 760, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37 (d, J = 6.6 Hz, 3 H, C*H*$_3$), 3.42 (ddd, J = 6.4, 9.3, and 11.0, 1 H, C*H*HN), 3.65 (d, J = 12.9 Hz, 1 H, PhC*H*H), 3.71 (ddd, J = 7.3, 9.3, and 11.0, 1 H, C*H*HN), 3.99–4.09 (m, 1 H, C*H*HO), 4.03 (d, J = 12.9 Hz, 1 H, PhC*H*H), 4.09 (d, J = 10.8 Hz, 1 H, PhC*H*N), 4.20 (dt, J = 6.4 and 8.8 Hz, 1 H, C*H*HO), 4.35 (dq, J = 11.0 and 6.8 Hz, 1 H, CH_3C*H*), 5.89 (s, 1 H, PhC*H*CO), 7.16–7.48 (m, 15 H, Ph) ; ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.7, 20.6, 40.4, 42.4, 59.3, 61.6, 69.8, 73.8, 127.6, 127.9, 128.0, 128.1, 128.4, 129.0, 129.1, 129.2, 130.1, 133.7,

135.5, 135.6, 152.5, 167.2, 170.0, 175.1; Anal. Calcd for $C_{30}H_{30}N_2O_7$: C, 67.91; H, 5.70; N, 5.28. Found: C, 67.62: H, 5.76; N, 5.38.

Preparation of *N*-{(2*R*)-2-Acetoxyphenylacetoxy}-*N*-benzyl-1-phenyl-3-buten-1-ylamine (77). To a solution of *N*-acyloxyiminium ion (0.50 mmol) prepared from nitrone **24** (106 mg, 0.50 mmol) and (*R*)-**21** (0.091 mL, 0.50 mmol) *in situ*, and 4-Å molecular sieves (100 mg) in CH_2Cl_2 (1.5 mL) was added $TiCl_4$ (0.06 mL, 0.55 mmol) at –78 °C, and the mixture was stirred at 0 °C for 0.5 h. After cooling at –78 °C again, to the mixture was allyltrimethylsilane (0.0.119 mL, 0.75 mmol) was added, then the mixture was stirred at 0 °C for 1 h. To the mixture were added hexane (5 mL), sat. $NaHCO_3$ (5 mL), and 10 M KF (5 mL), and the mixture was stirred at room temperature for 0.5 h. The mixture was filtered through Celite and the cake was washed with ethyl acetate (20 mL). The organic layer was separated, washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL), and dried over $MgSO_4$. After filtration and removal of the solvent, $CHCl_2CHCl_2$ (45.4 mg, 0.270 mmol) was added as an internal standard, and the yield and the diastereomeric ratio were determined by ^1H NMR analysis. The product was purified by column chromatography on silica gel (ethyl acetate in hexane) to give **77** (71% yield, 64% de) as a diasteromeric mixture: IR (neat) 3065, 1773, 1750, 1497, 1454, 1373, 1235, 1142, 1050, 750, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 2.13 (s, 3 H, CH_3), 3.58–3.96 (m, 3 H, PhCH_2, PhC*H*), 4.79–4.93 (m, 2 H, CH_2=CH), 5.46–5.64 (m, 1 H, C*H*=CH_2), 5.81 (s, 1 H, C*H*OAc of major isomer), 5.82 (s, 1 H, C*H*OAc of minor isomer), 7.08–7.38 (m, 15 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 20.6, 37.7, 59.8, 70.9, 73.6, 116.8, 127–129 (Ph), 133.5, 134.8, 135.7, 137.9, 167.2, 170.0; HRMS (FAB) calcd for $C_{27}H_{28}O_4N$ ($M+H^+$) 430.2019, found: 430.2006.

The Reactions of the Chiral *N*-Acyloxyiminium Ions with Chiral Enolate Were Also Done According to the General Procedures. The results were shown in text.

(4*R*,5*S*)-3-{(2*S*)-2-{(2*S*)-*N*-[(2*R*)-2-Acetoxyphenylacetoxy]pyrrolidin-2-yl}propanoyl}-4-methyl-5-phenyl-2-oxazolidinone (78a): IR (KBr) 2976, 1784, 1761, 1703, 1456, 1346, 1228, 1149, 766, 704 cm^{-1} ; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.85 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$CHN), 1.15 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHCO), 1.44–2.21 (m, 4 H, C*H*$_2$C*H*$_2$), 2.18 (s, 3 H, C*H*$_3$CO), 3.06 (ddd, *J* = 7.3, 7.5, and 13.0 Hz, 1 H, C*H*HN), 3.14–3.30 (m, 1 H, CH*H*N), 3.54 (q, *J* = 8.4 Hz, 1 H, NC*H*CH$_2$), 4.01 (br, 1 H, CH$_3$C*H*CO), 4.73 (dq, *J* = 7.0 and 6.7 Hz, 1 H, C*H*CHPh), 5.62 (d, *J* = 7.6 Hz, 1 H, PhC*H*CH), 5.93 (s, 1 H, C*H*O$_2$CCH$_3$), 7.02–7.54 (m, 10 H , Ph); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 14.3, 20.7, 22.2, 25.8, 39.2, 54.9, 57.7, 70.8, 73.6, 78.8, 125.9, 127.5, 128.5, 128.6, 128.7, 129.0, 133.6, 133.8, 152.7(CH$_2$*C*ON), 166.9 (N*C*OO), 170.0 (CH$_3$*C*O$_2$), 174.9 (O*C*O); HRMS (FAB) calcd for $C_{27}H_{31}N_2O_7$ ($M+H^+$) 495.2131, found 495.2136.

(4*R*,5*S*)-3-{(2*S*)-2-{(2*S*)-*N*-[(2*S*)-2-Acetoxyphenylacetoxy]pyrrolidin-2-yl}propanoyl}-4-methyl-5-phenyl-2-oxazolidinone (78b): IR (Nujol) 1780, 1745, 1701, 1350, 1237, 1042, 763, 728, 700 cm^{-1} ; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.84 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHN), 1.19 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHCO), 1.48–2.04 (m, 4 H, C*H*$_2$C*H*$_2$), 2.15 (s, 3 H, C*H*$_3$CO), 2.89 (ddd, *J* = 6.6, 6.8, and 12.7 Hz, 1 H, C*H*HN), 3.28 (ddd, *J* = 6.4, 7.0

and 12.2 Hz, 1 H, CH*H*N), 3.67 (q, J = 8.2 Hz, 1 H, NC*H*CH_2), 3.96 (dq, J = 8.2 and 7.0 Hz, 1 H, CH_3C*H*CO), 4.75 (dq, J = 6.8 and 6.6 Hz, 1 H, C*H*CHPh), 5.61 (d, J = 6.8 Hz, 1 H, PhC*H*CH), 5.91 (s, 1 H, C*H*O_2CCH_3), 7.20–7.54 (m, 10 H , Ph); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 14.3, 20.6, 22.1, 25.3, 39.7, 54.9, 57.1, 70.4, 73.8, 78.8, 125.8, 127.7, 128.5, 128.6, 128.7, 129.1, 133.6, 133.9, 152.6(CH_2*C*ON), 166.8 (N*C*OO), 170.0 (CH_3*C*O), 174.8 (O*C*O); HRMS (FAB) Calcd for $C_{27}H_{31}N_2O_7$ ($M+H^+$) 495.2131, found 495.2119.

Preparation of (4*R*,5*S*)-3-[(2*S*)-2-{(2*S*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}propanoyl]-4-methyl-5-phenyl-2-oxazolidinone (79): The β-amino acid derivative **78** (4.35 g, 8.8 mmol) was dissolved in methanol (30 mL) and 4 M hydrochloric acid (20 mL). Zinc powder (11.68 g, 176 mmol) was added to the solution and the mixture was stirred at 60 °C for 0.5 h. The mixture was cooled to room temperature and filtered. After removal of the solvent, the oil residue was dissolved in THF—H_2O (1 : 1, 45 mL). To the solution were added K_2CO_3 (2.00 g, 14.5 mmol) to adjust pH to 8 and ZCl (2.51 mL, 17.6 mmol), and the mixture was stirred at room temperature for 2 h. After extracted with ethyl acetate (50 mL), washed with brine (30 mL x 2), and dried over $MgSO_4$, the solvent was removed under reduced pressure and the oil residue was purified by column chromatography on silica gel (200 mL, 15—20% ethyl acetate in hexane) to afford **79** (3.40 g, 7.78 mmol, 88%) as a colorless oil: $[\alpha]^{24}_D$ +21.1° (*c* 1.01, CH_2Cl_2); IR (neat) 1779, 1705, 1499, 1456, 1410, 1200, 1148, 1030, 988, 959, 767, 736, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 50 °C) δ 0.81 (d, J = 6.6 Hz, 3 H, C*H*$_3$), 1.15 (br s, 3 H, C*H*$_3$), 1.74–2.08 (m, 4 H, CH_2CH_2), 3.28–3.70 (m, 2 H), 4.20–4.39 (m, 2 H), 4.77 (quint, J = 6.6 Hz, 1 H, CH_3C*H*CO), 5.08 (br, 2 H, C*H*$_2$Ph), 5.61 (d, J = 7.4 Hz, 1 H, PhC*H*O) 7.12–7.54 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 50 °C) δ 14.4, 23.8, 28.2, 40.5, 47.2, 47.3, 54.9, 66.7, 77.2, 78.8, 125.8, 127.8, 127.9, 128.4, 128.6, 128.7, 133.7, 137.1, 152.2, 155.1, 174.9; HRMS(FAB) calcd for $C_{25}H_{29}N_2O_5$ ($M+H^+$) 437.2076, found 437.2075.

Asymmetric Synthesis of 8-Methylindolizidine Alkaloids.

Preparation of (2*S*)-2-{(2*S*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}propanol ((–)-61). The β-amino acid derivative **79** (273 mg, 0.63 mmol) was dissolved in THF—H_2O (2 : 1, 10.5 mL) and cooled at 0 °C. To the solution $NaBH_4$ (95 mg, 2.5 mmol) was added and the mixture was stirred at 5 °C for 15 h. To the mixture was added 1.6 M aqueous NaH_2PO_4 dropwise. After removal of THF, the mixture was extracted with ethyl acetate (25 mL), washed with brine (15 mL x 2) and dried over $MgSO_4$. After filtration and removal of the solvent, the oil residue was purified by column chromatography on silica gel (25 mL, 30—50% ethyl acetate in hexane) to afford (–)-**61** (146 mg, 88%) as a colorless oil along with 97 mg (82%) of the recovered chiral auxiliary. (–)-**61:** $[\alpha]^{23}_D$ –37.3° (*c* 1.43, MeOH); IR (neat) 3424 (OH), 2969, 2880, 1678 (NCOO), 1455, 1416, 1358, 1339, 1101, 769 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz, 50 °C) δ 1.03 (d, J = 7.0 Hz, 3 H, C*H*$_3$), 1.49 (br, 1 H, C*H*CH_3), 1.75–1.98 (m, 4 H, (CH_2)$_2$), 3.24–3.47 (m, 2 H), 3.47–3.71 (m, 2 H), 3.72–3.95 (m, 2 H), 5.14 (d, J = 12.0 Hz, 1 H, *H*CHPh), 5.17 (d, J = 12.0 Hz, 1 H, *H*CHPh), 7.28–7.38 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 50 °C) δ 14.7,

23.6, 28.6, 39.0, 46.3, 59.6, 64.0, 67.2, 127.8, 128.0, 128.5, 136.7, 157.0; HRMS(EI) calcd for $C_{15}H_{21}NO_3$ (M^+) 263.1521, found 263.1494.

Preparation of (2*S*)-1-Bromo-2-{(2*S*)-*N*-benzyloxycarbonylpyrrolidin-2-yl}propane ((–)-80). Amino alcohol (–)-**61** (396.7 mg, 1.50 mmol) was dissolved in THF (8 mL) under argon and cooled to 0 °C. To the solution PPh_3 (590 mg, 2.25 mmol) and CBr_4 (746 mg, 2.25 mmol) was added and the reaction mixture was warmed up to room temperature. The solution was stirred for 10 min then sat. $NaHCO_3$ (3 mL) added. The mixture was extracted with ethyl acetate (20 mL), washed with brine (10 mL x 2) and dried over $MgSO_4$. After filtration and removal of the solvent, the oil residue was purified by column chromatography on silica gel (50 mL, 15% ethyl acetate in hexane) to afford (–)-**80** (471 mg, 96%) as a colorless oil: $[\alpha]^{25}_D$ –39.4° (*c* 1.26, $CHCl_3$); IR (neat) 2970, 1699, 1499, 1456, 1410, 1356, 1103, 770, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 55 °C) δ 0.97 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.73–1.98 (m, 4 H, $(CH_2)_2$), 2.38 (septet, *J* = 6.6 Hz, 1 H, CH_3CH), 3.12–3,45 (m, 3 H), 3.53–3.70 (m, 1 H), 3.93–4.04 (m, 1 H), 5.11 (d, *J* = 12.5 Hz, 1 H of CH_2Ph), 5.15 (d, *J* = 12.5 Hz, CHHPh), 7.15–7.42 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 55 °C) δ 14.4, 24.0, 26.9, 37.3, 38.8, 46.9, 60.8, 66.9, 127.8, 127.9, 128.5, 137.0, 155.4; HRMS (FAB) calcd for $C_{15}H_{20}NO_2Br$ ($M+H^+$) 325.0677, found 325.0707.

Preparation of Diethyl (2*R*)-2-{(2*S*)-*N*-Benzyloxycarbonylpyrrolidin–2-yl}propylmalonate ((–)-81): A solution of diethyl malonate (8.95 mL, 58.9 mmol) in DME (20 mL) was added to the suspension of NaH (53.6 mmol, secured from 2.14 g of 60% mineral oil dispersion through hexane washing) in DME (20 mL). A solution of (–)-**80** (1.75 g, 5.36 mmol) in DME (20 mL) was added dropwise over 20 min and the mixture was stirred at 60 °C for 20 h. Ethereal acetic acid was added to neutralize the excess sodiomalonate and the mixture was extracted with ethyl acetate (100 mL) and washed with brine (40 mL x 2). Dried over $MgSO_4$ and the solvent was removed. The oil residue was purified by column chromatography on silica gel (400 mL, 10—20% ethyl acetate in hexane) to afford (–)-**81** (1.87 g, 86%) as a colorless oil: $[\alpha]^{23}_D$ –13.6° (*c* 1.71, $CHCl_3$); IR (neat) 2995, 1751, 1732, 1701, 1410, 1030, 769, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 50 °C) δ 0.81 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.16–1.29 (m, 6 H, CH_2CH_3), 1.62–2.29 (m, 7 H), 3.23–3.34 (m, 1 H), 3.39 (br t, *J* = 6.4 Hz, 1 H, $CH(CO_2)_2$), 3.61 (br, 1 H), 3.86 (br q, *J* = 5.0 Hz, 1 H, CHN), 4.02–4.27 (m, 4 H, CH_2CH_3), 5.12 (s, 2 H, CH_2Ph), 7.26–7.37 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 50 °C) δ 13.8, 14.0, 24.1, 26.2, 32.7, 33.5, 39.9, 47.3, 50.5, 61.2, 61.3, 62.7, 66.6, 127.7, 128.4, 137.2, 155.2, 169.3, 169.6; HRMS (FAB) calcd for $C_{22}H_{32}NO_6$ ($M+H^+$) 406.2230, found 406.2196.

Preparation of Ethyl (4*R*)-4-{(2*S*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl}pentanoate ((–)-82): Diester (–)-**81** (1.85 g, 4.6 mmol) was dissolved in DMSO (25 mL), and NaCl (539 mg, 9.22 mmol) and water (0.33 mL, 18.44 mmol) were added to the solution. The mixture was stirred under argon at 170 °C for 10 h. To the mixture was added water (40 mL). The mixture was extracted with ethyl acetate—diethyl ether (3 : 1, 100 mL), washed with brine (40 mL x 2) and dried over $MgSO_4$. After filtration and removal of the solvent, the oil residue was purified by column chromatography on silica

gel (200 mL, 15% ethyl acetate in hexane) to afford (–)-**82** (1.22 g, 3.65 mmol, 80%) as a pale yellow oil: $[\alpha]^{25}_D$ –26.9° (*c* 1.05, $CHCl_3$); IR (neat) 2973, 1732, 1703, 1456, 1412, 1183, 1100, 1028, 770, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 50 °C) δ 0.79 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.23 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.34–1.52 (m, 1 H), 1.57–1.93 (m, 5 H), 1.93–2.49 (m, 3 H), 3.23–3.36 (m, 1 H), 3.62 (br, 1 H), 3.79–3.91 (m, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 5.10 (d, *J* = 12.5 Hz, CHHPh), 5.15 (d, *J* = 12.5 Hz, CHHPh), 7.24–7.39 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 68 MHz, 50 °C) δ 13.7, 14.2, 24.2, 25.9, 29.0, 32.6, 34.7, 47.2, 60.2, 61.5, 66.7, 127.7, 127.8, 128.4, 137.2, 155.2, 173.6; HRMS (FAB) calcd for $C_{19}H_{28}NO_4$ ($M+H^+$) 334.2019, found 334.2000.

Preparation of (2*S*)-1-Benzyloxycarbonyl-2-[(2*R*)-5,5-dimethoxypent-2-yl]pyrrolidine ((–)-83): Ester (–)-**82** (157.2 mg, 0.47 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled to –78 °C under argon. To the solution was added dropwise DIBAL-H (1.0 M in hexane, 0.54 mmol). The mixture was stirred for 30 min at same temperature. The reaction was quenched by Na_2SO_4•10 H_2O and diluted with hexane. The mixture was filtered and evaporated. The oil residue was dissolved in methanol (12 mL) and TsOH•H_2O (catalytic amount) was added, then the mixture was refluxed for 3 h. After addition of sat. $NaHCO_3$ (10 mL), the mixture was extracted with ether (25 mL), and the combined extracts were washed with brine and dried over $MgSO_4$. After filtration and removal of the solvent, the oil residue was purified by column chromatography on silica gel (20 mL, 20% ethyl acetate in hexane) to afford (–)-**83** (101 mg, 0.30 mmol, 64%) as a colorless oil: $[\alpha]^{22}_D$ –26.7° (*c* 1.39, CHCl3); IR (neat) 2955, 1699, 1408, 1190, 1100, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50 °C) δ 0.78 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.05–2.30 (m, 9 H), 3.29 (s, 6 H, OCH_3), 3.15–3.38 (m, 1 H), 3.62 (br, 1 H), 3.86 (m, 1 H), 4.30 (br, 1 H), 5.10 (d, *J* = 12.5 Hz, 1 H, HCHPh), 5.15 (d, *J* = 12.5 Hz, 1 H, HCHPh), 7.26–7.38 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 50 °C) δ 13.8, 24.2, 25.7, 28.7, 30.7, 34.5, 47.3, 52.7, 61.8, 66.5, 104.8, 127.7, 128.0, 128.4, 137.2, 155.2.

Preparation of (2*S*)-2-[(2*R*)-5,5-Dimethoxypent-2-yl]pyrrolidine ((+)-84).[26a] Acetal (–)-**83** (490 mg, 1.46 mmol) was hydrogenated in methanol (8 mL) in the presence of 10% Pd/C (160 mg) at room temperature and atmospheric pressure for 1.5 h. Filtration followed by removal of the solvent gave (+)-**84** (252.6 mg, 1.25 mmol, 86%): $[\alpha]^{23}_D$ +7.8° (*c* 1.12 CH_2Cl_2), (lit.[26a] $[\alpha]_D$ +7.4° (*c* 1.1 CH_2Cl_2)); IR (neat) 3347, 2957, 1460, 1383, 1192, 1127, 1059 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ0.88 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.08-1-88 (m, 10 H), 2.74 (m, 1 H), 2.82 (m, 1 H), 2.99 (m, 1 H), 3.31 (s, 6 H, OCH_3), 4.33 (t, *J* = 5.5 Hz, 1 H, $CH(OCH_3)_2$); ^{13}C NMR (68 MHz, $CDCl_3$, 50 °C) δ 16.2, 25.5, 29.3, 29.4, 30.1, 38.5, 46.8, 52.7, 64.4, 105.1; HRMS(EI) calcd for $C_{11}H_{23}NO_2$ (M^+) 201.1729, found 201.1735.

Preparation of (5*R*,8*R*,8a*R*)-(–)-5-Cyano-8-methylindolizidine ((–)-23).[26a] Amino acetal (+)-**84** (240 mg, 1.19 mmol) was dissolved in CH_2Cl_2—H_2O (1 : 1, 30 mL), and KCN (932 mg, 14.3 mmol) was added, then the pH was adjusted to 3 with conc. HCl. The mixture was stirred for 10 h. After basification with 2 M NaOH, the mixture was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered and evaporated to afford (–)-**23** as a colorless oil (191 mg, containing another diastereomer in

7%, 98%): $[\alpha]^{24}_D$ –25.8° (*c* 1.64, CH_2Cl_2), (lit.[26a] $[\alpha]_D$ –18.8° (*c* 1, CH_2Cl_2)); IR (neat) 2953, 2224, 1460, 1167 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 50 °C) δ 0.92 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.20–1.47 (m, 3 H), 1.61–2.06 (m, 7 H), 2.49 (q, *J* = 8.8 Hz, 1 H, C_3-*H*), 2.95 (dt, *J* = 3.0 and 8.5 Hz, C_3-*H*), 4.03 (t, *J* = 3.4 Hz, 1 H, C_5-*H*); ^{13}C NMR (68 MHz, $CDCl_3$, 50 °C) δ 18.3, 20.3, 28.7, 28.9, 29.4, 36.7, 51.3, 51.4, 64.8, 116.6; HRMS (EI) calcd for $C_{10}H_{16}N_2$ (M^+) 164.1313, found, 164.1288.

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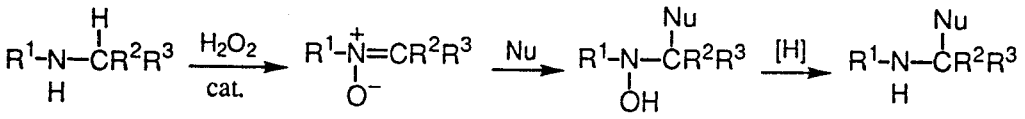
Chapter 4 Chiral Lewis Acid-Catalyzed Asymmetric Addition of Ketene Silyl Acetals to Nitrones

Introduction

Development of asymmetric reactions has enabled the synthesis of various optically active compounds with high optical purity. The catalytic asymmetric reactions have developed rapidly, in which a small amount of chiral auxiliaries can induce asymmetry in large quantity.[1] Acid and base catalysts are widely used to accelerate organic reactions, and in last few years remarkable progress of chiral Lewis acid-catalyzed reactions has been observed. Chiral Lewis acids are used for Diels-Alder reaction,[2] aldol reaction,[3] ene reaction,[4] silylcyanation,[5] Sharpless epoxidation[6] and so on.[7] Lewis acids-catalyzed reactions of nitrogen containing substrates such as imines are difficult because of its basicity,[8,9] although transition metal catalyzed-asymmetric reactions such as hydrogenation[10] and isomerization[11] succeeded in some cases. Therefore, the catalytic asymmetric reactions of nitrogen containing substrates are challenging approaches to the synthesis of optically active amino compounds.[12]

Nitrones are highly valuable synthetic intermediates.[13] Murahashi *et al.* have already established the convenient synthetic method of nitrones **2** by the catalytic oxidation of secondary amines **1** with hydrogen peroxide in the presence of a catalyst such as sodium tungstate,[14a,d,e] selenium dioxide,[14b] and flavinium perchlorate (eq 1).[14c] The addition of



(1)

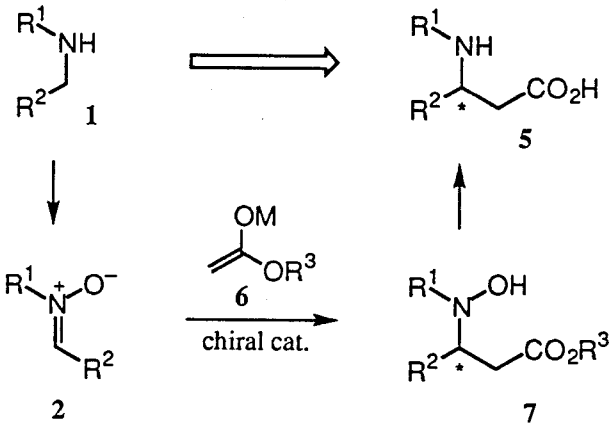
1 **2** **3** **4**

nucleophiles such as Grignard reagents, organolithiums, potassium cyanide, and metal hydrides to nitrones gives α-substituted hydroxylamines **3** easily.[15] Furthermore, hydroxylamines **3** thus obtained are converted into the corresponding amines **4** easily by catalytic hydrogenation[16a] and reduction with Zn/H^+ [16b] or $TiCl_3$.[16c] Therefore, in this system α-substituted hydroxylamines **3** and amines **4** are prepared from secondary amines **1** conveniently. The asymmetric synthesis has been performed by using chiral methyl *p*-tolyl α-sulfinyl carbanion as a nucleophile,[17] although previously only chiral nitrones have been employed.[18] Furthermore, the chiral ruthenium complex-catalyzed asymmetric hydrosilylation was reported by Murahashi *et al.*[19] Quite recently, Ukaji and Inomata *et al.* reported the enantioselective addition of Grignard reagents and diethyl zinc using chiral amino alcohol as an external chiral auxiliary,[20] whereas the catalytic asymmetric carbon-carbon bond formation of nitrones has never been reported.

β-Amino acids are present in various natural products and show significant bacteriological and fungicidal properties.[21] In addition they are useful starting materials for synthesis of β-lactam antibiotics[22] and other nitrogen containing biologically active compounds.[23] From these view points, asymmetric synthesis of β-amino acids attracts considerable interest.[24]

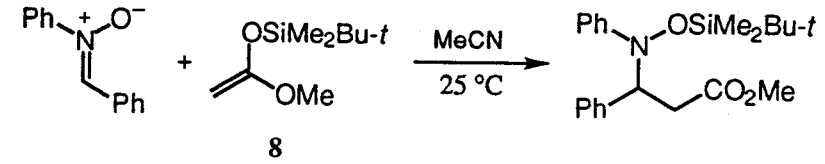
The reaction of nitrones **2** with enolates **6** will provide a convenient method for the synthesis of β-amino acids **5** from secondary amines **1** (Scheme 1). However, the reactivity of soft nucleophiles such as enolates **6** toward nitrones **2** is usually low in comparison with that of hard nucleophiles. Therefore, the reaction of nitrones with soft nucleophiles must be activated somehow.[25,26] In Chapter 3, the activation of nitrones with acyl halides to form *N*-acyloxyiminium species is described, in which the asymmetric synthesis of amino compounds by using chiral enolates or chiral acyl chlorides are described. Another possibility of the activation of nitrones will be performed by using Lewis acids. In this chapter, the activation of nitrones by using chiral Lewis acid catalysts such as titanium, boron, and zinc Lewis acids is described. The catalytic asymmetric addition of enolates to nitrones by using chiral catalysts opens a new and efficient approach to the synthesis of optically active β-amino acids **5** (Scheme 1).

Scheme 1

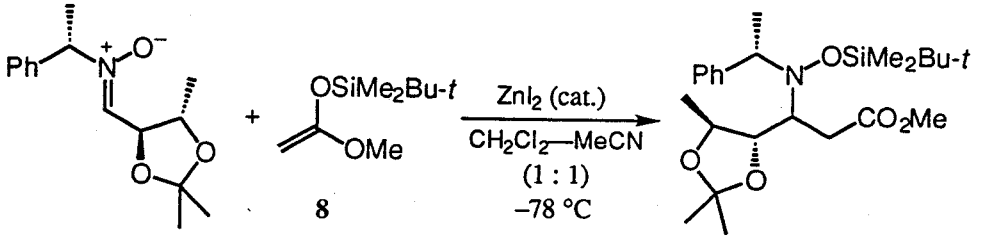


Results and Discussion

The Catalysis of Lewis Acids for the Addition of Ketene Silyl Acetals to Nitrones. The reaction of nitrones with ketene silyl acetals[27] has been reported to proceed at 25 °C in polar solvents such as acetonitrile, dimethylformamide, and tetrahydrofuran (THF) (eq 2).[28] The asymmetric reaction of chiral nitrones in the presence of zinc iodide in a mixed solvent of dichloromethane—acetonitrile (1 : 1) was also reported by Kita *et al.* (eq 3).[29] Murahashi *et al.* have found that the reaction of achiral nitrones with chiral ketene silyl acetals proceeded in the presence of 10 mol% of zinc iodide in dichloromethane at –78 °C to give β-amino acid derivatives with high diastereoselectivity (eq 4).[30]



8 (2)



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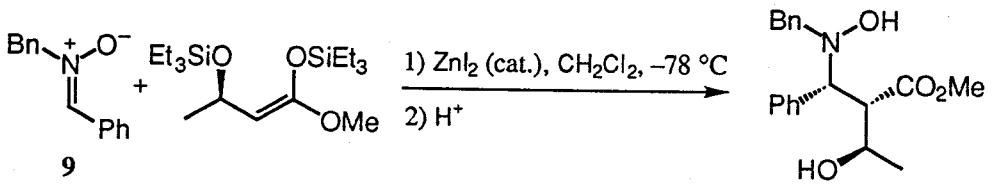
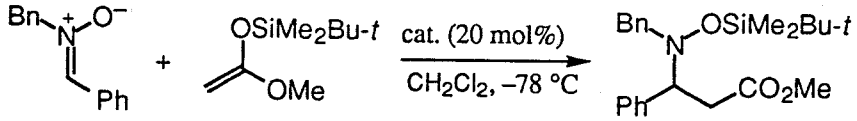


9 (4)

First, the catalytic reaction of nitrone **9** with ketene silyl acetal **8** was examined in the presence of various Lewis acids in dichloromethane (eq 5). The results are summarized in Table 1. The reaction proceeded at –78 °C for 3 h in the presence of 20 mol% of zinc iodide to give methyl 3-(*N*-*t*-butyldimethylsiloxy-*N*-benzylamino)-3-phenylpropanoate (**10**) in 96% isolated yield (entry 2), although in the absence of the catalyst the reaction



9 **8** **10** (5)

didn't proceed (entry 1). Trimethylsilyl trifluorometanesulfonate (TMSOTf) is also a good catalyst (entry 3), which was used for the reactions of nitrones with allylsilanes or silyl enol ethers.[31] Chiral boron[32] and titanium[33] complexes are powerful Lewis acids and progress in various types of catalysts for aldol reaction, ene reaction, Diels-Alder reaction and so on, because in alkoxides the B-O and Ti-O bond length is shorter than other metal alkoxides. While in the presence of boron tribromide or trimethyl borate, the β-phenylalanine derivative **10** was not obtained (entries 4 and 6), it was found that triphenyl borate can promote the reaction efficiently at –78 °C to give **10** in 93% yield (entry 5). Similar influence of ligands was observed in titanium Lewis acids; although $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$ didn't promote the reaction (entries 7 and 10), in the presence of $Ti(OPh)_4$ prepared by the reaction of $Ti(O\text{-}i\text{-}Pr)_4$ with 4 equiv of phenol *in situ*, the reaction proceeded smoothly at –78 °C to give the adduct **10** in 85% yield (entry 9). These results are due to Lewis acidity of catalysts (*vide infra*). Other metals including late-transition metals were examined as a catalyst. Ferric chloride was found as an efficient catalyst (entry 16). Further, magnesium bromide, copper(I) chloride, and cobalt(II) chloride are

good catalysts (entries 11, 14, and 18). Tris(triphenylphosphine)ruthenium(II) chloride which was a good catalyst for hydrosilylation of nitrones,[34] didn't promote the reaction of nitrone **9** with ketene silyl acetal **8** (entry 22), although this catalyst could have opened a new methodology in the reaction of nitrones with carbon nucleophiles using chiral phosphine ligands.

Table 1. The Effect of Catalysts for the Addition of Ketene Silyl Acetal **8** to Nitrone **9**[a]

entry	cat. (20 mol%)	condition	yield,[b] %
1	none	–78 °C (3 h), 0 °C (3 h)	0
2	ZnI_2	–78 °C (3 h)	96
3	TMSOTf	–78 °C (3 h)	58[d]
4	BBr_3	–78→10 °C (8 h)	0
5	$B(OPh)_3$	–78 °C (3 h)	93
6	$B(OMe)_3$	–78 °C (3 h)	0
7	$TiCl_4$	–78 °C (3 h), –15 °C (3 h)	0
8	$TiCl_2(O\text{-}i\text{-}Pr)_2$	–78 °C (3 h)	8
9	$Ti(OPh)_4$[c]	–78 °C (3 h)	85
10	$Ti(O\text{-}i\text{-}Pr)_4$	–78 °C (3 h), –15 °C (3 h)	trace
11	$MgBr_2$	–78 °C (3 h), –15 °C (3 h)	50
12	$AlCl_3$	–78→10 °C (8 h)	0[g]
13	CuCl	–78 °C (3 h), –15 °C (3 h)	36
14	$CuCl_2$	–78 °C (3 h), –15 °C (3 h)	69
15	$MnCl_2$	–78 °C (3 h), –15 °C (3 h)	0
16	$FeCl_3$	–65 °C (2 h)	85
17	$RuCl_2(PPh_3)_3$	–78 °C→rt (24 h)	0
18	$CoCl_2$	–78 °C (3 h), –15 °C (3 h)	43
19	$NiBr_2$	–78 °C (3 h), –15 °C (3 h)	19

[a]The reaction of nitrone **9** (0.50 mmol) with ketene silyl acetal **8** (0.60 mmol) was carried out in the presense of a Lewis acid catalyst (20 mol%) in CH_2Cl_2 (1.5 mL) at –78 °C under argon. [b]Isolated yield. [c]Prepared *in situ* by the reaction of $Ti(O\text{-}i\text{-}Pr)_4$ with PhOH (4 eq) in the presense of 4-Å MS at room temperature for 30 min under argon. [d]In addition desilylated hydroxylamine was obtained in 36%. [e]The cyclyc product 5-isoxazolidinone was obtained in 30% yield.

The Lewis acidity can be controlled by choosing ligands. The relative acidity of boron Lewis acids has been determined by the ^{13}C NMR analysis of complexes with pyridine in the following order: $BF_3 > C_6H_4O_2BOPh > B(OPh)_3 > BPh_3 > BEt_3$.[35] Trimethyl borate is not acidic enough to allow the formation of the complex with pyridine. The activation ability of Lewis acids as catalysts is influenced by the Lewis acidity.

The interactions of nitrone **9** with Lewis acids can be detected as down field shifts observed by ^{13}C NMR analysis. The ^{13}C NMR of a mixture of nitrone **9** (0.10 mmol) and Lewis acids (0.10 mmol) in chloroform-*d* (0.60 mL) was measured at 35 °C, and the differences ($\Delta\delta$) of the chemical shift (δ) of the α carbon between free nitrone **9** and its complex with Lewis acids are shown in Table 2. The difference of 3.1 ppm between free

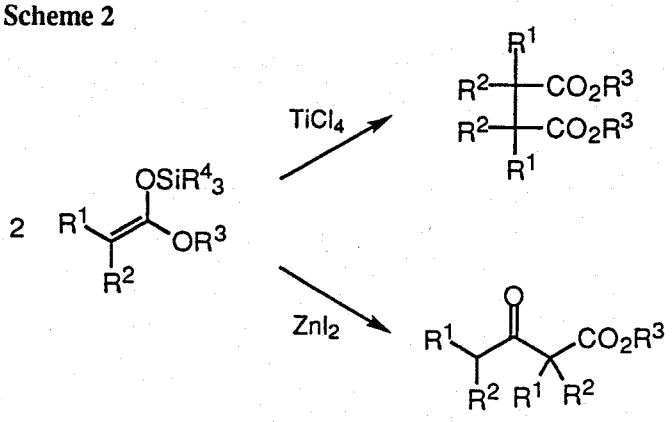
nitrone **9** and its complex with triphenyl borate which is an efficient catalyst, was observed (entry 5), while no difference was observed in the presence of trimethyl borate (entry 6). In the presence of boron tribromide, nitrone **9** was decomposed, thus the ^{1}H and ^{13}C NMR spectra showed several benzylic peaks (entry 4). The interaction with titanium was also measured. The very strong interaction ($\Delta\delta$ = 15.2 ppm) of nitrone **9** with $TiCl_4$ was observed (entry 7), while the NMR spectrum of the mixture with Ti(O-*i*-Pr)$_4$ didn't show any differences (entry 9). In the presence of $Ti(OPh)_4$, $\Delta\delta$ of 1.6 ppm was observed (entry 8). Zinc iodide and *t*-butyldimethylsilyl trifluoromethanesulfonate which are efficient catalysts, showed the differences of the chemical shifts in 11.5 and 3.2 ppm, respectively (entries 2 and 3). The range of differences of the chemical shifts in these Lewis acids is from 1.6 to 11.5 ppm. When the differences of the chemical shifts are in this range, the Lewis acid-catalyzed reaction of nitrone **9** with ketene silyl acetal **8** should proceed. Titanium(IV) chloride showed the strongest interaction with nitrone **9**, but the adduct **10** was not obtained. This is due to the fact that ketene silyl acetals react themselves in the presence of $TiCl_4$ to give the coupling products (Scheme 2).[36] Other Lewis acids such as zinc iodide, triphenyl borate, and $Ti(OPh)_4$ also promote the oxidative coupling reaction or Claisen condensation of ketene silyl acetals at room temperature, but the reactions proceed more slowly than the $TiCl_4$-promoted reaction. The addition of ketene silyl acetals to nitrones competes against the coupling reaction of ketene silyl acetals themselves in the presence of Lewis acids. It was found that the reactions in the presence of suitable Lewis acids such as triphenyl borate, $Ti(OPh)_4$, and zinc iodide, gives the corresponding β-amino acid derivatives exclusively. Further, boron and titanium Lewis acid catalysts which have suitable acidity can be designed by replacing ligands with phenols.

Table 2. Complexation of Nitrone **9** with Lewis Acids[a]

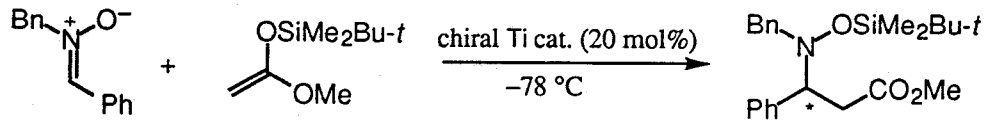
entry	Lewis acid	δ of α-C, ppm	$\Delta\delta^b$
1	none	134.0	—
2	ZnI_2	145.5	11.5
3	*t*-$BuMe_2SiOSO_2CF_3$	137.2	3.2
4	BBr_3	decomp	—
5	$B(OPh)_3$	137.1	3.1
6	$B(OMe)_3$	134.1	0.1
7	$TiCl_4$	149.2	15.2
8	$Ti(OPh)_4$[c]	135.6	1.6
9	Ti(O-*i*-Pr)$_4$	134.1	0.1

[a]The ^{13}C NMR (68 MHz) of a mixture of nitrone **9** (0.10 mmol) and Lewis acid (0.10 mmol) in $CDCl_3$ (0.60 mL) was measured at 35 °C. [b]$\Delta\delta$ = (δ of α-C of **9**) – (δ of α-C of complex of **9** with Lewis acids). [c]Prepared *in situ* from Ti(O-*i*-Pr)$_4$ and PhOH (4 eq) in the presense of 4-Å MS under argon.

Scheme 2



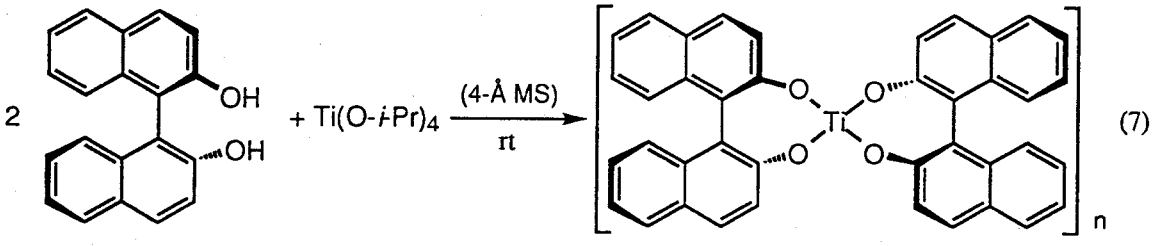
Enantioselective Addition of Ketene Silyl Acetals to Nitrones Catalyzed by Chiral Titanium Complexes. It was found that the reaction of nitrones with nucleophiles can be activated by the titanium Lewis acids modified by phenol. Chiral titanium complexes are known to be powerful Lewis acid catalysts for asymmetric synthesis.[33] 1,1'-Bi-2-naphthol (BINOL) (**11**) is one of the most efficient chiral ligands.[37] The complex prepared from Ti(O-*i*-Pr)$_4$ and **11** is expected to have the suitable acidity for the reaction of nitrones with ketene silyl acetals. The catalytic asymmetric reaction of nitrone **9** with ketene silyl acetal **8** was examined in the presence of 20 mol% of the chiral titanium complexes (eq 6).



(6)

9 **8** **10**

First, a catalyst was prepared from Ti(O-*i*-Pr)$_4$ and (*R*)-**11** in the ratio of 1 : 2, whose structure was assumed as a spirotitanate (*R*)-**12** (eq 7). More recently, this catalyst was used for the catalytic asymmetric allylation of aldehydes by Keck *et al.*[38]



(7)

(*R*)-**11** (*R*)-**12**

To a mixture of (*R*)-**11** (0.12 mmol) and 4-Å molecular sieves (0.1 g) in dichloromethane (1.0 mL) was added Ti(O-*i*-Pr)$_4$ (0.060 mmol) at room temperature under argon, and the mixture was stirred at room temperature for 1 h to become dark brown. After cooling to –78 °C, to the resultant mixture were added nitrone **9** and ketene silyl

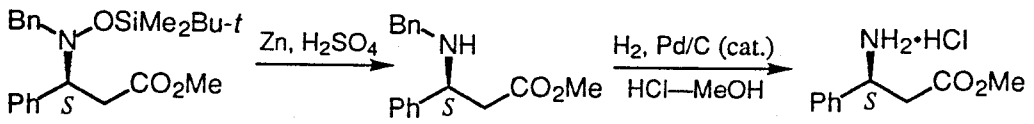
acetal **8**, successively, and the reaction was allowed to proceed at –78 °C. The β-phenylalanine derivative (–)-**10** was isolated in 79% yield with the optical rotation of $[\alpha]^{23}_D$ –6.7° (*c* 1.44, $CHCl_3$) (21% ee). The solvent effect toward the present reaction was examined as summarized in Table 3. When toluene was employed, the enantiomeric excess was 35% (entry 1). Furthermore, the enantiomeric excess was 48% in a mixed solvent of toluene—petroleum ether (P.E.) (1 : 1), and this is the best result among the solvents examined.

Table 3. The Effect of Solvents to the Enantioselective Addition of Ketene silyl Acetal **8** to Nitrone **9** Catalyzed by (*R*)-**12**[a]

entry	solvent	time, h	yield,[b] %	% ee[c]
1	toluene	6	78	35[e]
2	toluene—P.E. (1:1)	18	77	48
3	toluene—P.E. (1:1)[d]	9	78	40
4	CH_2Cl_2	2	79	21
5	THF	22	22	19[e]
6	Et_2O	24	78	45
7	EtCN	22	62	4[e]

[a]The catalyst (*R*)-**12** was prepared *in situ* by the reaction of (*R*)-**11** (0.12 mmol) with $Ti(O\text{-}i\text{-}Pr)_4$ (0.060 mmol, 20 mol%) in the presence of 4-Å MS in a solvent (1.0 mL) at room temperature for 1 h under argon. The reaction of nitrone **9** (0.30 mmol) with **8** (0.36 mmol) was carried out at –78 °C. [b]Isolated yield. [c]Determined by HPLC analysis (Daicel CHIRALCEL OD) after converted to amino ester **13**. In all cases the *S* isomer was obtained. [d]4-Å MS was not used. [e]Determined by the optical rotation based on $[\alpha]_D$ 27° (*c* 1, $CHCl_3$) as the maximum.

The adduct (–)-**10** (48% ee) was converted into amino ester (–)-**13** by reduction with Zn/H^+ in methanol, and the enantiomeric excess was determined to be 48% by the HPLC analysis using chiral column (Daicel CHIRALCEL OD, 10% isopropyl alcohol in hexane, 0.5 mL/min). Furthermore, catalytic hydrogenation of (–)-**13** in the presence of hydrochloric acid gave β-amino ester hydrochloride (+)-**14**, and the absolute configuration was determined to be *S* in comparison with the sign of the optical rotation ($[\alpha]^{25}_D$ +3.7° (*c* 2.06, MeOH), lit.[39] $[\alpha]^{20}_D$ +7.8° (*c* 2, MeOH) for the *S* isomer) (eq 8). The β-phenylalanine structure is an important fragment of spermidine and taxine alkaloids.[40]



(–)-**10** (–)-**13** (+)-**14** (8)

The solvation parameters such as the donor and acceptor ability are considered as the controlling factor of this solvent effect. For example, the donor ability influences the reactivity, thus, the reaction was retarded in THF which has the large donor number. The

acceptor number influences the enantioselectivity. The solvents which have the large acceptor number such as dichloromethane and propionitrile, reduced the enantioselectivity. On the other hand, in the solvent which have the small acceptor number such as diethyl ether and toluene, the eantioselectivity increases. The mixed solvent of toluene and P.E. has the smaller acceptor ability, therefore relatively high enantioselectivity is observed. Furthermore, the molecular interaction such as π-staking between toluene and nitrone and/or the BINOL moiety may influence the enantioselectivity.[41] The similar tendency of the solvent effect has been also observed in the chiral titanium complex-catalyzed Diels-Alder reaction reported by Narasaka *et al.*[42]

Next, various chiral ligands (L*) were examined as summarized in Table 4. The catalytic activity of a complex prepared from (*R*)-**11** and Ti(O-*i*-Pr)$_4$ in the ratio of 1 : 1, was lower than that of the 2 : 1 complex, and the enantioselectivity was also low (18% ee) (entry 1). A catalyst prepared from $TiCl_2$(O-*i*-Pr)$_2$ which was used for ene reaction with high level enantioselectivity,[43] showed good catalytic activity, but it gave low enantioselectivity (entries 3 and 4). The substituents of **11** were examined for the steric and electronic effects. A catalyst prepared from 3,3'-diphenyl-BINOL **15**[44,45] did not show the catalysis at –78 °C, though the reaction proceeded at –50 °C, and the enantiomeric excess was only 7% ee (entry 5). On the other hand, the use of 6,6'-disubstituted BINOL **16**[46,47] and **17** increased the catalytic activity, thus the reactions finished within 2 h, but the enantioselectivity was reduced slightly (entries 6 and 7). Chiral diol ligands such as 1,2-diol **18** and 1,4-diol **19** were also employed, but both the catalytic activity and the enantioselectivity became low (entries 8 and 9). The decrease of Lewis acidity seems to cause the descent of catalytic activity.

The structure of the complex prepared from **15** and Ti(O-*i*-Pr)$_4$ is assumed as shown in Figure 1. It seems to be too hindered around the coordination site. Even if nitrones coordinate to the titanium, both sides of the enantiofaces of nitrones are shielded by phenyl and naphthyl groups of **15**; therefore, the addition of nucleophiles may be retarded.

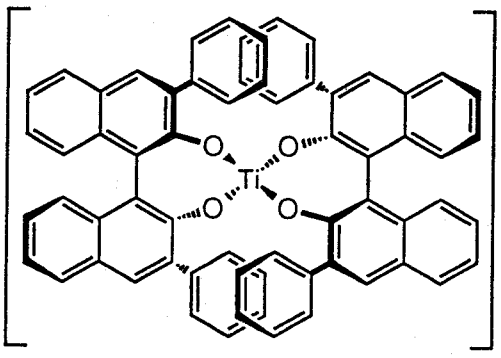


Figure 1. The assumed structure of the complex prepared from (*R*)-**15** and Ti(O-*i*-Pr)$_4$ in the ratio of 2 : 1.

Table 4. The Effect of Chiral Ligands to the Titanium-Catalyzed Addition of Ketene Silyl Acetal **8** to Nitrone **9**[a]

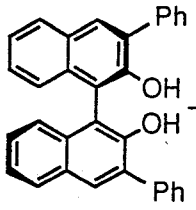
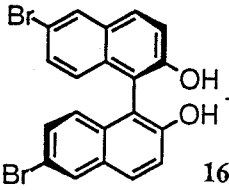
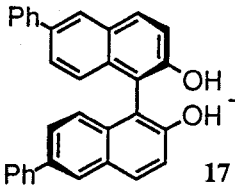
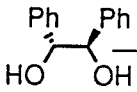
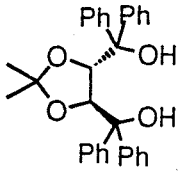
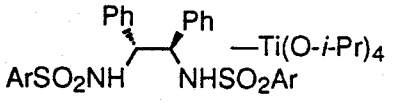
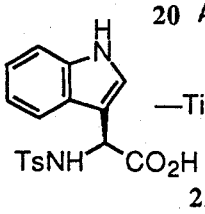
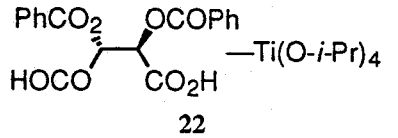
entry	cat. (20 mol%)	L* : Ti	condition	yield,[b] %	% ee (config)[c]
1	(*R*)-BINOL **11**—Ti(O-*i*-Pr)$_4$	1 : 1	–78 °C, 48 h	70	18 (*S*)
2	(*R*)-**11**—Ti(O-*i*-Pr)$_4$	2 : 1	–78 °C, 18 h	78	48 (*S*)[d]
3	(*R*)-**11**—TiCl$_2$(O-*i*-Pr)$_2$	1 : 1	–78 °C, 7 h	90	4 (*S*)
4	(*R*)-**11**—TiCl$_2$(O-*i*-Pr)$_2$	2 : 1	–78 °C, 7 h	90	19 (*S*)
5	 —Ti(O-*i*-Pr)$_4$ **15**	2 : 1	–78— –50 °C, 92 h	99	7 (*S*)
6	 —Ti(O-*i*-Pr)$_4$ **16**	2 : 1	–78 °C, 1 h	83	41 (*S*)
7	 —Ti(O-*i*-Pr)$_4$ **17**	2 : 1	–78 °C, 2 h	82	33 (*S*)
8	 —Ti(O-*i*-Pr)$_4$ **18**	2 : 1	–78— –50 °C, 92 h	47	6 (*R*)
9	 —Ti(O-*i*-Pr)$_4$ **19**	2 : 1	0 °C, 2 h	46	1 (*R*)

Table 4. (continued)

entry	cat. (20 mol%)	L* : Ti	condition	yield,[b] %	% ee (config)[c]
10	 **20** Ar = *p*-ClC_6H_4-	2 : 1	–78—rt	trace	—
11	 **21**	2 : 1	–78—–20 °C, 45 h	87	1 (*R*)
12	 **22**	2 : 1	–78—rt	0	—

[a]The catalyst was prepared *in situ* by the reaction of a chiral ligand with Ti(O-*i*-Pr)$_4$ (0.060 mmol, 20 mol%) in the presence of 4-Å MS in toluene (0.50 mL) at room temperature for 1 h under argon. The reaction of nitrone **9** (0.30 mmol) with **8** (0.36 mmol) was carried out in toluene—P.E. (1 : 1, 1.0 mL). [b]Isolated yield. [c]Determined by the optical rotation based on $[\alpha]_D$ 27° (*c* 1, $CHCl_3$) as the maximum. [d]Determinided by HPLC analysis (Daicel CHIRALCEL OD) after converted into amino ester **13**.

In the reaction employed the catalyst prepared from 6,6'-disubstituted BINOL **16** or **17** with Ti(O-*i*-Pr)$_4$, the catalytic activity increased. This is due to both higher Lewis acidity by electron-withdrawing groups of BINOL derivatives and slightly loose chiral environments. The chiral environment created by the spirotitanate complexes constituted by BINOL derivatives and titanium in the ratio of 2 : 1, is C_2 symmetry as schematically illustrated in Figure 2. Since titanium complexes can make the tetragonal bipyramidal structures, there are two possible coordination sites. When it is assumed that the four Ti-O bonds locate at the equatorial positions, the two coordination sites exist at the axial positions. In the complex, each naphthyl group of two BINOL moieties exists above the plane of the titanate and will construct a cavity (Figure 2). These naphthyl groups look

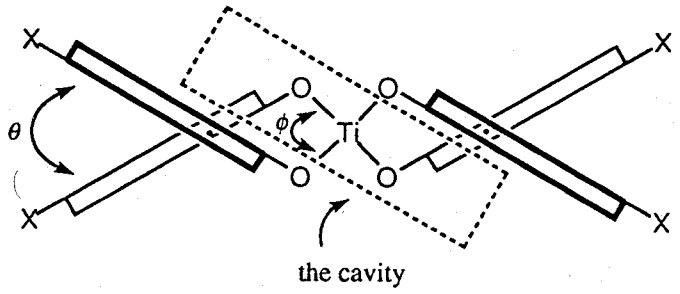
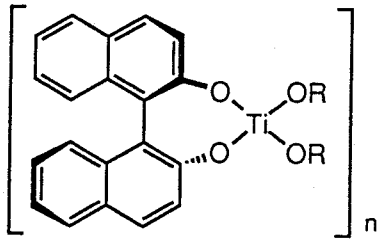


Figure 2. The assumed structure of the complex prepared from (*R*)-BINOL derivatives and Ti(O-*i*-Pr)$_4$ in the ratio of 2 : 1. ◘ indicates to orient in the up side of the titanate. □ is in the down side.

like walls. Nitrones should coordinate to the titanium along the walls in which one enantioface of nitrones must be shielded by one of the naphthyl skeletons. The enantioselectivity seems to be influenced by the bond angles ϕ of O-Ti-O, which will be determined by the dihedral angles θ of BINOL moieties (Figure 2). For example, the 6,6'-dibromo-BINOL moiety (X = Br) has the larger dihedral angle θ than BINOL itself because of the dipolar repulsion between the two brominated binaphtyl rings,[47] and the 6,6'-diphenyl-BINOL moiety (X = Ph) also has the larger θ because of the steric repulsion of two phenyl groups to make the ϕ larger. The results shown in Table 4 indicates that the smaller bond angle ϕ seems to render the enantioselectivity high, because the cavity becomes smaller.

Phenol derivatives are the most suitable ligands for the catalysis of the reaction of nitrones with ketene silyl acetals. The replacement of one of two BINOL moieties of the catalyst (*R*)-**12** with two isopropoxides ((*R*)-**23a** (R = *i*-Pr)) make not only the catalytic activity but also the enantioselectivity low (Table 4). Thus, these ligands of the catalysts influence the enantioselectivity so much, because the shape of the cavity (Figure 2) is changed by replacement of these ligands. The effect of these ligands (RO-) to the complex (*R*)-**23** was examined as shown in Table 5.



(*R*)-**23**

The catalyst (*R*)-**23** was prepared *in situ* as follows; first, Ti(O-*i*-Pr)$_4$ was added to a solution of 1 equiv of (*R*)-BINOL in toluene in the presence of 4-Å molecular sieves under argon, and the mixture was stirred at room temperature for 30 min. Then, phenol derivatives (2 equiv as a hydroxy group) was added, and the mixture was further stirred for 30 min. Replacement with 2,2'-biphenol raised the catalytic activity, although the enantioselectivity was lower (entry 2). When catechol was used, the enantiomeric excess was only 3% because one of the walls shown in Figure 2 disappears in the complex (entry 3). Phenols such as phenol, *p*-fluorophenol, *p*- and *m*-cresol lowered both the catalytic activity and the enantioselectivity (entries 4–7), but *o*-substituted phenols gave higher enantioselectivity. Especially when *o*-cresol was used, the enantiomeric excess was 59% (entry 8). 1-Naphthol which will make the large wall in the complex, was the best additional ligand examined to give the β-phenylalanine derivative **10** in 95% yield with 62% ee (entry 13).

It is known that 4-Å molecular sieves plays an important role of a catalyst for ligand exchange for the preparation of titanium catalysts.[6,42,43] In the absence of 4-Å molecular sieves both of the catalytic activity and the enantioselectivity of the complex prepared

Table 5. The Effect of Phenol Derivatives to the Catalyst (*R*)-**23** for the Addition of Ketene Silyl Acetal **8** to Nitrone **9**[a]

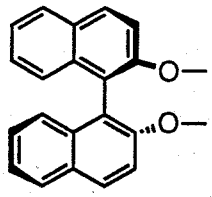
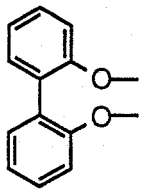
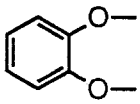
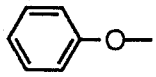
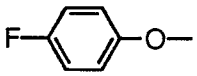
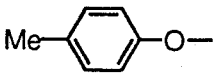
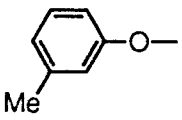
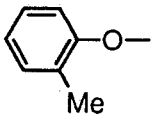
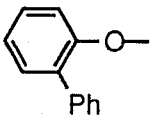
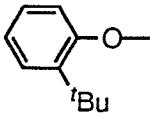
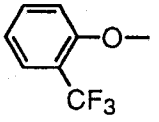
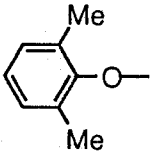
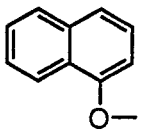
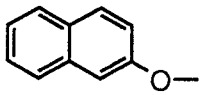
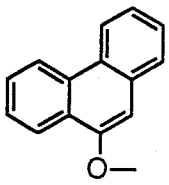
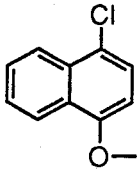
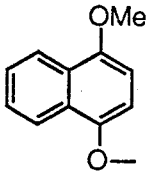
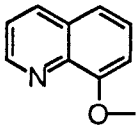
entry	RO–	time, h	yield,[b] %	% ee[c]
1		18	77	48[f]
2		4	99	32
3		48	84	3
4		30	99	40
5		30	58	8
6		48	87	14
7		48	99	33
8		48	85	59[f]
9		30	99	49
10		48	79	33
11		48	38	35
12		18	99	50

Table 5. (continued)

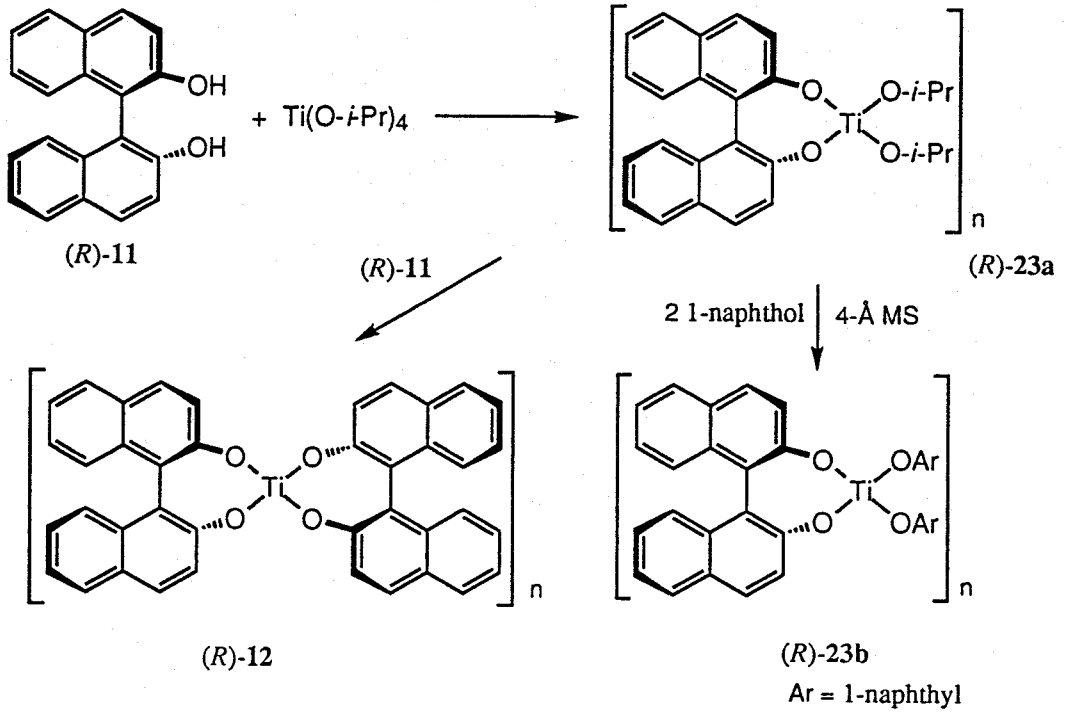
entry	RO–	time, h	yield,[b] %	% ee[c]
13		24	95	62[f]
14[d]		48	63	13
15[e]		24	73	27
16		24	96	18
17		24	99	21
18		48	76	6
19		48	88	6
20		(–78 °C—rt)	0	—

[a]The catalyst was prepared *in situ* as follows; a mixture of (*R*)-**11** (0.060 mmol, 20 mol%) and Ti(O-*i*-Pr)$_4$ (0.060 mmol, 20 mol%) in the presence of 4-Å MS (0.1 g) in toluene (0.50 mL) was stirred at room temperature for 30 min under argon, then to the resultant mixture phenol derivative (0.12 mmol) was added, and the mixture was stirred for 30 min. The reaction of nitrone **9** (0.30 mmol) with **8** (0.36 mmol) was carried out in toluene—P.E. (1 : 1, 1.0 mL) at –78 °C. [b]Isolated yield. [c]Determined by the optical rotation based on $[\alpha]_D$ 27° (*c* 1, $CHCl_3$) as the maximum. The absolute configuration of **10** was *S* in all cases. [d]4-Å MS was not used. [e]One equiv of 1-naphthol to titanium was used. [f]Determinided by HPLC analysis (Daicel CHIRALCEL OD) after converted into amino ester **13**.

from Ti(O-*i*-Pr)$_4$, (*R*)-**11**, and 1-naphthol (1 : 1 : 2), decreased, and the complex gave the similar result which was obtained by the reaction using (*R*)-**23a** (R = *i*-Pr) as a catalyst (entry 14). When an equivalent of 1-naphthol was employed, the enantioselectivity also became low (entry 15). The above results indicate that the exchange with 1-naphthol does not occur in the absence of 4-Å molecular sieves, and 2 equiv of 1-naphthol is necessary. Although the complex (*R*)-**12** could be formed in the absence of 4-Å molecular sieves from Ti(O-*i*-Pr)$_4$ and 2 equiv of (*R*)-**11** (Table 3, entries 2 and 3), 4-Å molecular sieves is

necessary to exchange the isopropoxides of (*R*)-**23a** for 1-naphthols, to give the complex (*R*)-**23b** (Scheme 3).

Scheme 3



The ^{1}H and ^{13}C NMR analysis of the titanium complex (*R*)-**23b** prepared *in situ* was carried out in chloroform-*d*. Isopropoxides of Ti(O-*i*-Pr)$_4$ were exchanged for BINOL **11** and 1-naphthol, although liberated isopropyl alcohols were not free completely. Thus, there is the interaction between (*R*)-**23b** and isopropyl alcohol. The effect of the preparative methods of chiral titanium catalysts are shown in Table 6.

The catalyst prepared from Ti(OEt)$_4$ showed low catalytic activity and low enantioselectivity (28% yield with 17% ee) (entry 1). Further, when the catalyst prepared from Ti(O-*n*-Bu)$_4$ was used, the enantioselectivity was reversed (9 % ee for the *R* isomer of the β-phenylalanine derivative **10**) (entry 2). On the other hand, after the usual preparation of the catalyst (*R*)-**23b**, the solvent was evaporated *in vacuo* then added again, the catalytic activity increased. However, the enantiomeric excess was reduced to 44% (entry 4). When Ti(O-*t*-Bu)$_4$ was used, the catalytic activity also raised, but the enantiomeric excess was lowered to 39% (entry 5).

The complex prepared from $TiCl_4$ under the similar condition showed good catalytic activity, but the enantiomeric excess was quite low (entry 7). Hydrogen chloride generated by the exchange of ligands was trapped with *i*-Pr$_2$EtN or *n*-butyllithium, but no activity was shown (entries 8 and 9). Addition of isopropyl alcohol to the complex prepared from $TiCl_4$, (*R*)-**11**, and 1-naphthol (1 : 1 : 2) improved the enantioselectivity slightly to 16% ee in comparison with the catalyst in the absence of isopropyl alcohol (entry 10).

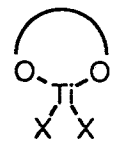
Table 6. The Effect of the Preparative Methods of Chiral Titanium Catalysts[a]

entry	cat. (20 mol%)	time, h	yield,[b] %	% ee (config)[c]
1	(*R*)-BINOL—$Ti(OEt)_4$—1-naphthol (1 : 1 : 2)	48	28	17 (*S*)
2	(*R*)-BINOL—$Ti(O\text{-}n\text{-}Bu)_4$—1-naphthol (1 : 1 : 2)	48	82	9 (*R*)
3	(*R*)-BINOL—$Ti(O\text{-}i\text{-}Pr)_4$—1-naphthol (1 : 1 : 2)	24	95	62 (*S*)[e]
4	(*R*)-BINOL—$Ti(O\text{-}i\text{-}Pr)_4$—1-naphthol (1 : 1 : 2)[d]	4	99	44 (*S*)
5	(*R*)-BINOL—$Ti(O\text{-}t\text{-}Bu)_4$—1-naphthol (1 : 1 : 2)	2	87	39 (*S*)
6	(*R*)-BINOL—$Ti(O\text{-}t\text{-}Bu)_4$ (1 : 1)	48	99	37 (*S*)
7	(*R*)-BINOL—$TiCl_4$—1-naphthol (1 : 1 : 2)	24	99	9 (*S*)
8	(*R*)-BINOL—$TiCl_4$—1-naphthol—$i\text{-}Pr_2NEt$ (1 : 1 : 2 : 4)	48	trace	—
9	(*R*)-BINOL—$TiCl_4$—1-naphthol—*n*-BuLi (1 : 1 : 2 : 4)	24	0	—
10	(*R*)-BINOL—$TiCl_4$—1-naphthol—*i*-PrOH (1 : 1 : 2 : 4)	24	93	16 (*S*)

[a]The catalyst was prepared *in situ* as follows; a mixture of TiX_4 (0.060 mmol) and (*R*)-**11** (0.060 mmol) in the presence of 4-Å MS in toluene (0.50 mL) was sttirred at room temperature for 30 min under argon, then 1-naphthol (0.12 mmol) was added to the resultant mixture, and the mixture was stirred further for 30 min (entries 1–5 and 7). In entries 8–10, above procedure was carried out in the presence of $i\text{-}Pr_2EtN$, *n*-BuLi, or *i*-PrOH (0.24 mmol, rspectively). The reaction of nitrone **9** (0.30 mmol) with ketene silyl acetal **8** (0.36 mmol) was carried out in toluene—P.E. (1 : 1) at –78 °C. [b]Isolated yield. [c]Determined by the optical rotation based on $[\alpha]_D$ 27° (*c* 1, $CHCl_3$) as the maximum. [d]After removal of toluene, the mixed solvent was added again. [e]Determined by HPLC analysis (Daicel CHIRALCEL OD) after converted to amino ester **13**.

These results indicate that the anion parts of starting titanium reagents are important. The bulky ligands such as *t*-butyl alcohol seem to accelerate the reaction. It is known that titanium alkoxides are aggregated,[48] and the X-ray structures of the complexes prepared from $Ti(O\text{-}i\text{-}Pr)_4$ and BINOL derivatives in the ratio of 1 : 1, were reported as described in Chart 1.[33c,49] More sterically hindered ligands favor fewer bridging. Thus, the titanium complex **24** containing a 3,3'-$(t\text{-}BuMe_2)_2$BINOL moiety has a monomeric structure, **25** containing a 3,3'-Me_2BINOL moiety has a dimeric structure, and **23a** containing a BINOL moiety has a trimeric structure. The present titanium complex (*R*)-**23b** prepared by the reaction of the complex (*R*)-**23a** with 1-naphthol (Scheme 3) should be sterically more hindered. Therefore, **23b** seems to have the dimeric or monomeric structure. Further, the complex (*R*)-**23b** interacts with isopropyl alcohols which influences the enantioselectivity

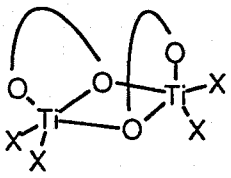
Chart 1



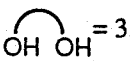
24

= 3,3'-(*t*-BuMe$_2$Si)$_2$BINOL

X = O-*i*-Pr

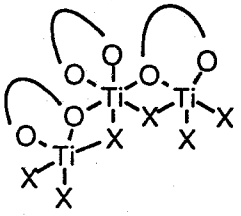


25

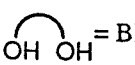


= 3,3'-Me$_2$BINOL

X = O-*i*-Pr, Cl



23a

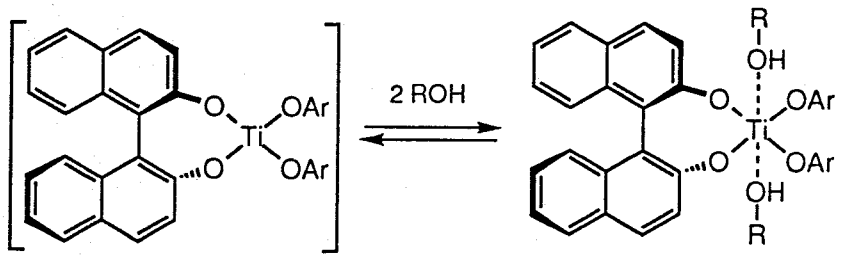


= BINOL

X = O-*i*-Pr

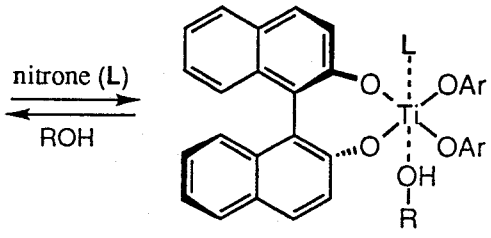
strongly as shown in Table 6. Therefore, the complex (*R*)-**23b** should have the monomeric structure coordinated by isopropyl alcohols as the structure (*R*)-**26a** (Scheme 4). Because each naphthyl group of the BINOL moiety and each 1-naphthol moiety were equivalent by NMR analysis, each Ti-O bond was considered to be located at the equatorial positions. Nitrones should coordinate to the complex **26** by exchange for the coordinated alcohol to give the complex (*R*)-**27**. The rate of the ligand exchange at this stage will be faster in the case of *t*-butyl alcohol in comparison with isopropyl alcohol. Thus, there exists fast ligand exchange in the bulky complex due to steric hindrance to coordinate.[50] Therefore, the complex (*R*)-**26b** coordinated by *t*-butyl alcohol, shows the higher catalytic activity.

Scheme 4



(*R*)-**23b**
Ar = 1-naphthyl

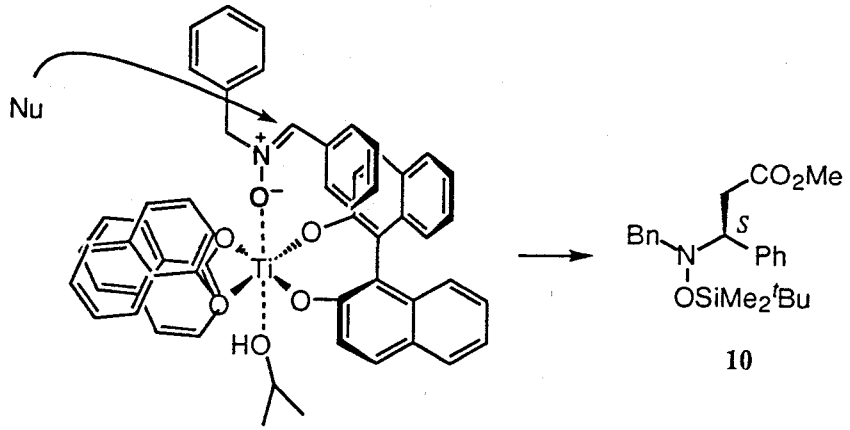
(*R*)-**26**
26a; R = *i*-Pr
26b; R = *t*-Bu



(*R*)-**27**
27a; R = *i*-Pr
27b; R = *t*-Bu

The transition model of the reaction of nitrone **9** with ketene silyl acetal **8** under the catalysis of the titanium complex (*R*)-**23b** was rationalized by assuming Scheme 5. Judging from the product configuration, the chiral catalyst (*R*)-**23b** should shield the *re* face of nitrone **9** on its coordination, and the selective approach of nucleophiles to the *si* face should occur. It can be considered that the catalyst is divided into two parts; (a) the part which shields one face of the C-N double bond of the nitrone and (b) the part which restricts the orientation of the nitrone on the titanium. The BINOL moiety is considered to correspond to the part (a), while the 1-naphthol moiety corresponds to the part (b) in the complex (*R*)-**23b** in connection with the complex (*R*)-**11** shown in Figure 2. The geometry of nitrone **9** is *Z*, which was determined by the NOE experiment; therefore, the benzylidene moiety of nitrone **9** will orient toward the BINOL moiety because of the steric repulsion with the 1-naphthol moiety. In the complex the BINOL moiety shields the *re* face of nitrone **9**. Attractive interaction[51] caused by the π interaction between the C-N double bond and/or the phenyl group of nitrone **9** and the naphthyl group of the BINOL moiety can be considered. Then, ketene silyl acetal **8** (Nu) attacks to the *si* face of nitrone **9** to give the *S* isomer **10**.

Scheme 5

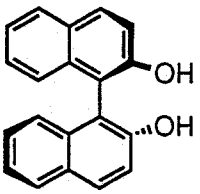
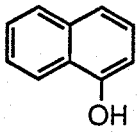
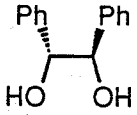
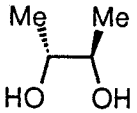
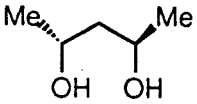
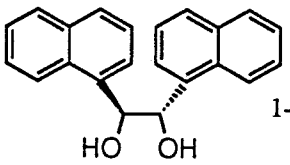
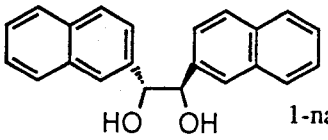


10

In order to orient nitrones more rigidly, the combinations of various ligands including bidentate chiral 1,2-diols were examined. The results are summarized in Table 7.

Interesting results were observed by the combinations of **11** and hydrobenzoin (**18**) or other chiral diols as the starting alcohol for the preparation of the catalysts with Ti(O-*i*-Pr)$_4$. First, the combination of ligands **11** and **18** showed the good catalytic activity, while the combination with 2,3-butanediol (**28**) or 2,4-pentanediol (**29**) showed quite low catalytic activity (entries 4 and 5). The catalytic activity can be explained by the steric hindrance of the titanium complexes formed. Second, from the aspect of the enantiofacial differentiation of nitrone **9**, the catalyst (*R*)-(*R*,*R*)-**32** prepared from (*R*)-**11**, (*R*,*R*)-**18**, and Ti(O-*i*-Pr)$_4$ gave the *S* isomer **10** with 39% ee, while (*S*)-(*R*,*R*)-**32** prepared from (*S*)-**11**, (*R*,*R*)-**18**, and Ti(O-*i*-Pr)$_4$ also gave the *S* isomer with 12% ee (entries 2 and 3). These observations show that the enantioselective differentiation appears to be induced by the

Table 7. The Combinations of Ligands toward the Titanium Catalysts for the Addition of Ketene Silyl Acetal **8** to Nitrone **9**[a]

entry	the combination of ligands A and B		time, h	yield,[b] %	% ee (config)[c]
1	 (*R*)-**11**	 1-naphthol (2 eq)	24	95	62 (*S*)[e]
2	(*R*)-**11**	 (*R*,*R*)-**18**	48	62	30 (*S*)
3	(*S*)-**11**	(*R*,*R*)-**18**	48	52	12 (*S*)
4	(*R*)-**11**	 (*R*,*R*)-**28**	24[d]	trace	—
5	(*R*)-**11**	 (*R*,*R*)-**29**	24[d]	trace	—
6	(*R*,*R*)-**18**	1-naphthol (2 eq)	24	52	12 (*S*)
7	 (*S*,*S*)-**30**	1-naphthol (2 eq)	24	62	2
8	 (*R*,*R*)-**31**	1-naphthol (2 eq)	24	57	12 (*R*)

[a]The catalyst was prepared *in situ* as follows; a mixture of a ligand **A** (0.060 mmol, 20 mol%) and Ti(O-*i*-Pr)$_4$ (0.060 mmol, 20 mol%) in the presence of 4-Å MS (0.1 g) in toluene (0.50 mL) was stirred at room temperature for 30 min under argon, then to the resultant mixture a ligand **B** (0.12 mmol as a hydroxy group) was added, and the mixture was stirred further for 30 min. The reaction of nitrone **9** (0.30 mmol) with **8** (0.36 mmol) was carried out in toluene—P.E. (1 : 1, 1.0 mL) at –78 °C. [b]Isolated yield. [c]Determined by the optical rotation based on $[\alpha]_D$ 27° (*c* 1, $CHCl_3$) as the maximum. [d]The reaction was carried out at 0 °C. [e]Determinided by HPLC analysis (Daicel CHIRALCEL OD) after converted into amino ester **13**.

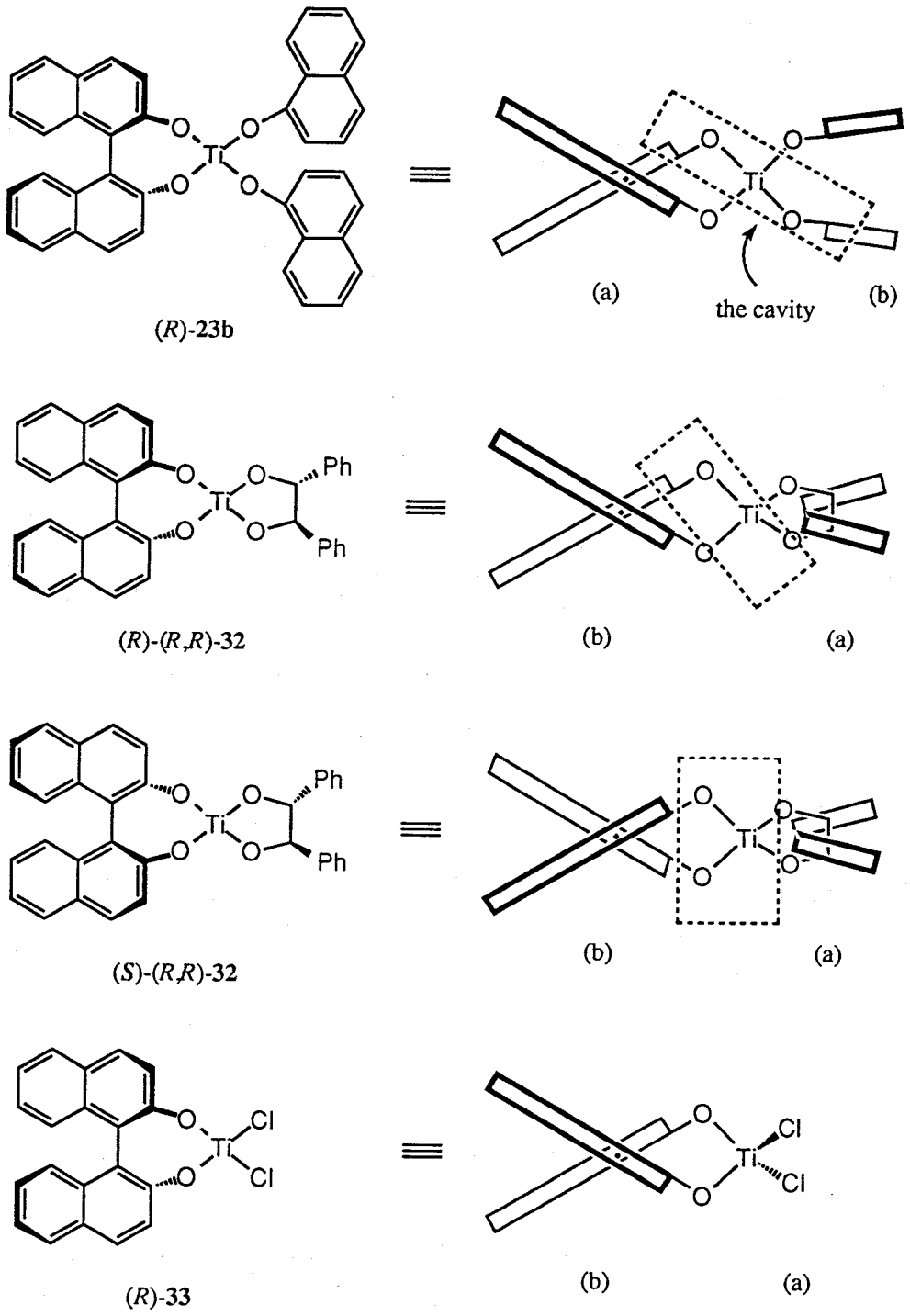


Figure 3. The Models of the catalysts. (a) The part of shielding the enantioface of nitrone. (b) The part of restricting the orientation of nitrone. ■ indicats to orient in the up side of the titanate, and □ is in down side.

(*R*,*R*)-**18** moiety not by the BINOL moiety. The combinations of chiral diols such as (*R*,*R*)-**18**, (*S*,*S*)-1-hydronaphtoin (**30**), or (*R*,*R*)-2-hydronaphtoin (**31**) and 1-naphthol with Ti(O-*i*-Pr)$_4$, lead to complicate understanding of the asymmetric induction. When (*R*,*R*)-**18** was employed with 1-naphthol as the starting alcohol for the preparation of the catalyst with Ti(O-*i*-Pr)$_4$, the *S* isomer **10** was obtained in 12% ee, while by use of (*R*,*R*)-**31**, the *R* isomer **10** was obtained in 12% ee (entries 6 and 8). These results may indicate that the enantiofacial differentiation of nitrones is induced by different ways.

In Figure 3, the models of these catalysts are illustrated schematically. There are two parts in these catalysts as shown before; (a) the part which shields the enantioface and (b) the part which restricts the orientation. In the complex (*R*)-**23b**, the BINOL moiety seems to correspond to the part (a), and the 1-naphthol moiety corresponds to the part (b). One naphthyl group of the BINOL moiety is placed in the up side of the plane which is constructed by four Ti-O bonds at the equatorial positions, and the other naphthyl group is in the down side. Two 1-naphthol moieties are also placed in the up side and in the down side, respectively. Thus, there is the cavity constructed between the two naphthyl groups. These naphthyl groups look like the walls. The complex (*R*)-**23b** constructs the similar chiral environment to that of the complex (*R*)-**12** shown in Figure 2. Nitrone **9** seems to be packed in the cavity along the walls and is shielded with the *re* face on its coordination as shown in Scheme 5. Therefore, nucleophiles approach to the *si* face of nitrone **9**. In the complexes (*R*)-(*R*,*R*)-**32** and (*S*)-(*R*,*R*)-**32**, a reversal of these parts (a) and (b) seems to take place, because in these complexes the phenyl groups of the hydrobenzoin moiety place closer to the coordination site of the titanium than the BINOL moiety. Therefore, stereochemistry seems to be induced by the hydrobenzoin moiety. On the other hand, Mikami and Nakai insist that in the catalyst **33** prepared from TiCl$_2$(O-*i*-Pr)$_2$ and **11**, the BINOL moiety restricts the conformation of the complex, and the chloride ligands restrict the enantiofacial differentiation in the ene reaction of glyoxylates which are the bidentate substrates.[43]

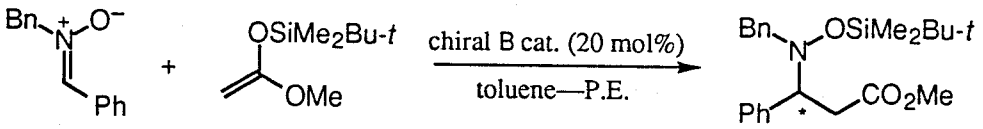
The reactions of nitrones which have some substituents with ketene silyl acetal **8** were examined in the presence of the catalyst (*R*)-**23b** to give *N*-siloxy-β-amino esters, and the results are summarized in Table 8. The reaction of *N*-benzylidenemethylamine *N*-oxide (**34**) gave the similar enantiomeric excess (60% ee) to the reaction of nitrone **9** (entry 1), while the reaction of *N*-ethylidenebenzylamine *N*-oxide (**35**) gave only 6% ee (entry 2). These results support the attractive interaction caused by the π interaction between nitrone and the ligand of the catalyst, and the interaction is obstructed by the methyl group of **35**. Further, the reaction of *N*-(4-fluorophenylmethylidene)benzylamine *N*-oxide (**36**), which has electron-withdrawing group, gave the best result of 66% ee (entry 3). The reaction of *N*-(4-methoxyphenylmethylidene)benzylamine *N*-oxide (**37**) gave the lower enantioselectivity (entry 4). Nitrones **38** and **39** which have naphthyl groups also gave the lower enanthioselectivity (entries 5 and 6). Although the absolute configurations of the β-amino acid derivatives obtained were not determined, the transition model shown in Scheme 5 indicates that the *S* isomer should be obtained.

Table 8. The Reactions of (Z)-Nitrones $R^1N^+(O^-)=CHR^2$ with Ketene Silyl Acetal **8**[a]

entry	R^1	R^2	time, h	yield,[b] %	% ee[c]
1	Me	Ph	24	52	60
2	Bn	Me	24	61	6
3	Bn	4-FC_6H_4	48	65	66
4	Bn	4-$MeOC_6H_4$	48	28	37
5	Bn	1-naphthyl	48	92	3
6	Bn	2-naphthyl	48	52	35

[a]The reaction of nitrone (0.50 mmol) with ketene silyl acetal **8** (0.60 mmol) was carried out in toluene—P.E. (1 : 1, 3.0 mL) at –78 °C under argon in the presence of 20 mol% of the catalyst (*R*)-**23b**. [b]Isolated yield. [c]Determined by HPLC analysis after converted to the corresponding amino esters.

Enantioselective Addition of Ketene Silyl Acetals to Nitrones Catalyzed by Chiral Borates. The catalytic activity of boron Lewis acids is also influenced by ligands. Triphenyl borate is a good catalyst for the reaction of nitrones with ketene silyl acetals. Thus, phenoxides are suitable ligands. First, the reaction of nitrone **9** with ketene silyl acetal **8** was examined in the presence of the boron Lewis acids bearing the (*R*)-BINOL moiety as a chiral ligand (eq 9), and the results are summarized in Table 9.

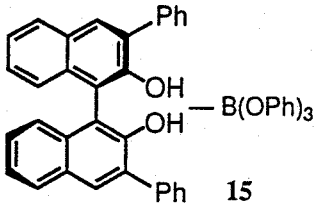


9 **8** **10** (9)

The boron Lewis acid (20 mol%) prepared *in situ* by the reaction of (*R*)-**11** with triphenyl borate in the ratio of 1 : 1 at room temperature,[9] promoted the reaction of nitrone **9** with ketene silyl acetal **8** in toluene—petroleum ether (P.E.) (1 : 1) at –78 °C to give the β-phenylalanine derivative **10** in 84% with 5% ee (entry 1). The catalyst prepared from BH_3•THF also gave low enantioselectivity (1% ee) (entry 2). In the presence of the catalyst prepared from (*R*)-**11** and BH_3•SMe_2 in the ratio of 2 : 1,[9a] 26% enantiomeric excess was obtained (entry 3).

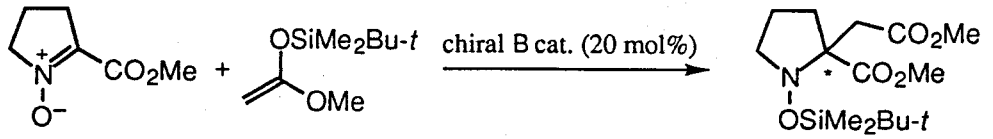
The reaction of other nitrones with ketene silyl acetal **8** was examined, and the reaction of nitrone **40** was found to give proline derivative **41** with the moderate enantioselectivity (eq 10). In this reaction the chiral construction of the quaternary carbon is done, and the asymmetric creation of the quaternary carbon attracts considerable attention.[52] Further, asymmetric synthesis of α-alkylated α-amino acids has been also

Table 9. Chiral Boron Lewis Acids-Catalyzed Addition of Ketene Silyl Acetal **8** to Nitrone **9**[a]

entry	cat. (20 mol%)	L*:B	condition	yield,[b] %	% ee (config)[c]
1	(*R*)-BINOL—$B(OPh)_3$	1:1	–78 °C, 2 h	84	5 (*S*)
2	(*R*)-BINOL—BH_3•THF	1:1	0 °C, 3 h	94	1 (*S*)
3	(*R*)-BINOL—BH_3•SMe_2	2:1	–78 °C, 48 h	99	26 (*S*)
4	 **15**	3:2	–78 °C, 24 h	95	4 (*R*)

[a]The catalyst was prepared *in situ* by the reaction of BX_3 (0.060 mmol, 20 mol%) with (*R*)-**11** in toluene (0.50 mL) at room temperature (entries 1, 2, and 4) or at 100 °C (entry 3) for 1 h under argon. The reaction of nitrone **9** (0.30 mmol) with ketene silyl acetal **8** (0.36 mmol) was carried out in toluene—P.E. (1 : 1, 1.0 mL). [b]Isolated yield. [c]Determined by the optically rotation based on $[\alpha]_D$ 27° (*c* 1, $CHCl_3$) as the maximun.

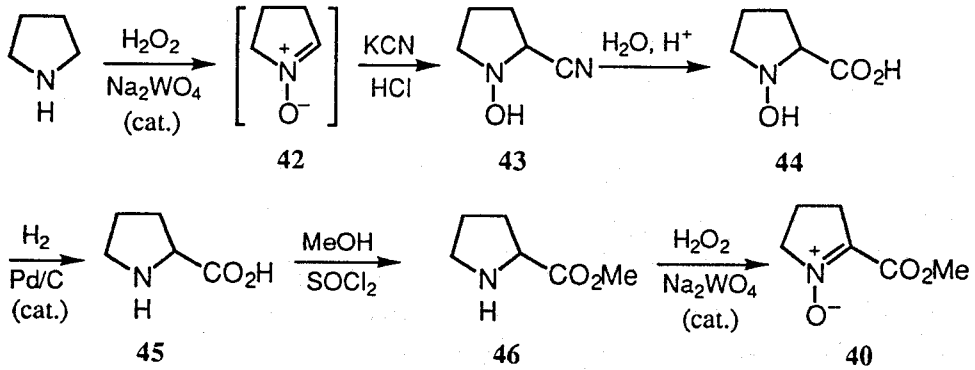
interested.[53] The similar structure of **41** has been utilized for the spiro-bicyclic systems such as a type II β-turn peptidomimic[54] and the total synthesis of brevianamide B which was isolated from *Penicillium brevicompactum*.[55]



40 **8** **41** (10)

Here one can prepare racemic proline (**45**) *via* the catalytic oxidation of pyrrolidine as shown in Scheme 6.[15b] Thus, 2-cyano-1-hydroxypyrrolidine (**43**) is readily prepared by the oxidation of pyrrolidine with hydrogen peroxide in the presence of sodium tungstate as a catalyst in water to give nitrone **42** which is treated in the same flask with potassium cyanide and hydrochloric acid. Hydrolysis of **43** under the acidic condition gives 1-hydoxyproline (**44**). Catalytic hydrogenation of **44** over Pd/C gives **45**. Esterification of **45** upon treatment with thionyl chloride in methanol, followed by catalytic oxidation afford nitrone **40**.[15a]

Scheme 6



42 **43** **44**

45 **46** **40**

The reaction of the nitrone **40** with ketene silyl acetal **8** in the presence of 20 mol% of a chiral boron catalyst was carried out at first as follows; to a mixture of (*R*)-**11** (0.060 mmol) and 4-Å molecular sieves (0.1 g) in a solvent (1.0 mL) was added BH_3•THF (1.0 M in THF, 0.060 mL) at room temperature, and the mixture was stirred for 1 h. After cooling to –78 °C, nitrone **40** (0.30 mmol) and ketene silyl acetal **8** (0.36 mmol) were added subsequently to the resultant solution. The results are summarized in Table 10. Similar tendency of the solvent effect was observed in comparison with that of the chiral titanate-catalyzed reaction. When a mixed solvent of toluene and P.E. was used, the reaction gave the adduct (–)-**41** in 73% yield, and the enantiomeric excess was 46% (entry 2).

Table 10. The Effect of Solvents toward the Addition of Ketene Silyl Acetal **8** to Nitrone **36** Catalyzed by the Boron Lewis Acid Prepared from (*R*)-**11** and BH_3•THF (1 : 1)[a]

entry	solvent	time, h	yield,[b] %	% ee[c]
1	toluene	2	99	36
2	toluene—P.E. (1:1)	1	73	46
3	CH_2Cl_2	2	99	19
4	THF	1.5	99	32
5	Et_2O	1.5	79	44
6	EtCN	2	99	4

[a]The ctalyst was prepared *in situ* by the reaction of (*R*)-**11** (0.060 mmol) with BH_3•THF (1.0 M in THF, 0.060 mL) in the presence of 4-Å MS in a solvent (1.0 mL) under argon at room temperature for 1 h, then the reaction of nitrone **40** (0.30 mmol) with **8** (0.36 mmol) was carried out at –78 °C. [b]Isolated yield. [c]Determined by the ^1H NMR analysis using Eu(hfc)$_3$. In all cases the *S* isomer was obtained.

Next, the combinations of various chiral ligands (L*) and boron reagents were examined. The results are summarized in Table 11. By changing the ratio of (*R*)-**11** and BH_3•THF to 3 : 2, where all hydrogens of BH_3•THF were exchanged for **11**, the enantiomeric excess was reduced to 28% (entry 2). By changing a boron reagent to triphenyl borate, the significant change was not observed (entries 3 and 4). The combinations of (*R*)-3,3'-diphenyl-BINOL **15** and BH_3•THF in the ratios of 1 : 1 and 3 : 2 didn't show significant changes (entries 6 and 7), while the use of triphenyl borate instead of BH_3•THF reversed the enantioselectivity (entries 8 and 9). It is considered that the environment of the coordination site of the catalyst is changed because of the steric effect of both the phenyl group of the moiety of **15** and liberated phenol which seems to interact with the resultant complex. Chiral diols showed efficiency in the borate catalysts in contrast to the corresponding titanium complexes. Although the boron Lewis acid prepared from (*R*,*R*)-hydrobenzoin (**18**) and BH_3•THF in the ratio of 1 : 1, showed no catalytic activity, the 3 : 2 complex catalyzed the reaction at –78 °C, to give **41** in quantitative yield with 6% ee (entries 10 and 11). Further, in the presence of the catalyst prepared from (*R*,*R*)-**18** and triphenyl borate in the ratios of 1 : 1 and 3 : 2, (*R*)-**41** was obtained in 78% and 97% yields with 48% and 58% ee, respectively (entries 12 and 13).

Table 11. The Effect of Chiral Ligands to Boron-Catalyzed Addition of Ketene Silyl Acetal **8** to Nitrone **40**[a]

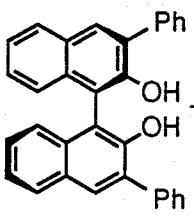
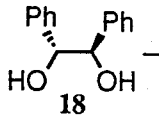
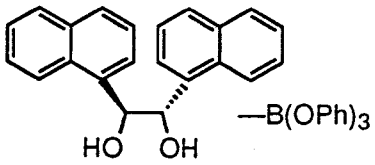
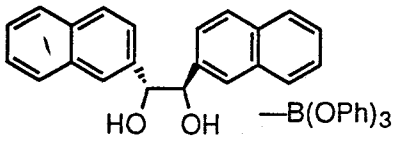
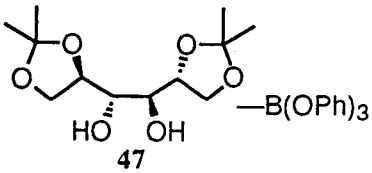
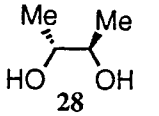
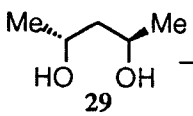
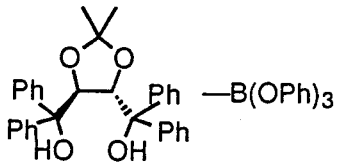
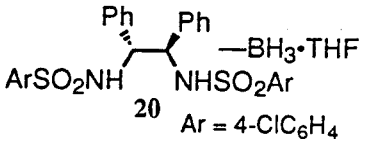
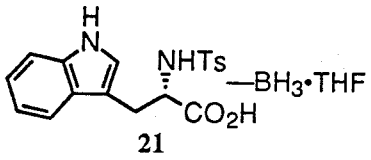
entry	cat. (20 mol%)	L* : B	time, h	yield,[b] %	% ee (config)[c]
1	(*R*)-BINOL **11**—BH_3•THF	1 : 1	2	73	46 (*S*)
2	(*R*)-**11**—BH_3•THF	3 : 2	2	99	28 (*S*)
3	(*R*)-**11**—$B(OPh)_3$	1 : 1	2	82	44 (*S*)
4	(*R*)-**11**—$B(OPh)_3$	3 : 2	2	67	38 (*S*)
6	 —BH_3•THF	1 : 1	6	95	44 (*S*)
7		3 : 2	2	21	26 (*S*)
8	(*R*)-**15**—$B(OPh)_3$	1 : 1	2	99	8 (*R*)
9	(*R*)-**15**—$B(OPh)_3$	3 : 2	2	99	11 (*R*)
10	 —BH_3•THF	1 : 1	20[d]	trace	—
11	**18**	3 : 2	2	99	6 (*R*)
12	(*R*,*R*)-**18**—$B(OPh)_3$	1 : 1	2	78	48 (*R*)
13	(*R*,*R*)-**18**—$B(OPh)_3$	3 : 2	2	97	58 (*R*)
14		1 : 1	2	99	10 (*S*)
15	**30**	3 : 2	24	85	12 (*S*)
16		1 : 1	2	92	3 (*S*)
17	**31**	3 : 2	2	99	26 (*R*)
18	 **47**	3 : 2	2	92	22 (*R*)
19		1 : 1	2	44	7 (*R*)
20	**28**	3 : 2	24[d]	trace	—
21		1 : 1	2	94	1 (*S*)
22	**29**	3 : 2	24[d]	trace	—

Table11. (continued)

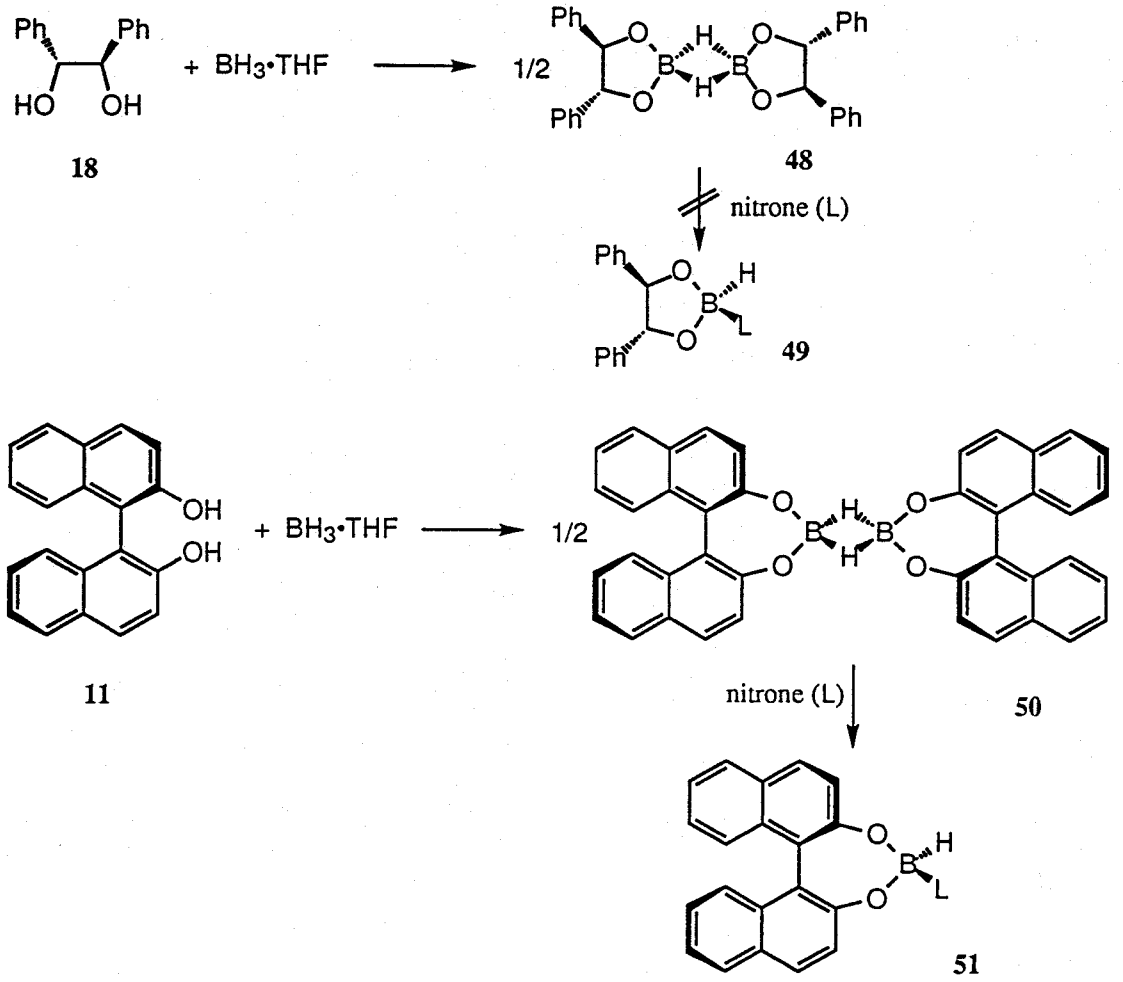
entry	cat. (20 mol%)	L* : B	time, h	yield,[b] %	% ee (config)[c]
23	 **19**	1 : 1	2	85	2 (*R*)
24		3 : 2	2	42	6 (*R*)
25	 **20** Ar = 4-ClC$_6$H$_4$	1 : 1	24[d]	trace	—
26		3 : 2	3	99	0
27	**20**—B(OPh)$_3$	3 : 2	2	99	0
28	 **21**	1 : 1	3	78[e]	4 (*R*)

[a]The catalyst was prepared *in situ* by the reaction of BX_3 (0.060 mmol, 20 mol%) with a chiral ligand in the presence of 4-Å MS in toluene (0.50 mL) at 50 °C for 1 h under argon instead of entries 1, 2, and 11. The reaction of nitrone **40** (0.30 mmol) with **8** (0.36 mmol) was carried out in toluene—P.E. (1 : 1, 1.0 mL). [b]Isolated yield. [c]Determined by the ^{1}H NMR analysis using Eu(hfc)$_3$. [d]Temperature was raised up to room temperature. [e]The reaction was carried out in CH_2Cl_2.

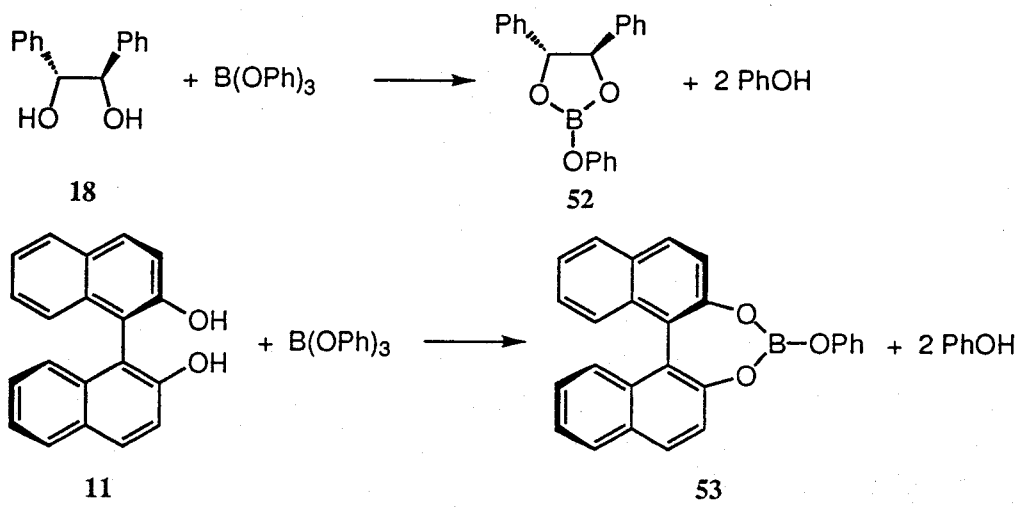
The product from **18** and BH_3•THF (1 : 1) is considered to have the structure **48**, which has no catalytic activity (Scheme 7). The reaction of **11** with BH_3•THF (1 : 1) gives the product **50**, which shows the catalytic activity. The product from **18** and BH_3•THF in the ratio of 3 : 2 showed the efficient catalytic activity, although trimethyl borate did not catalyze the reaction (Table 1, entry 11). From above results, one should consider ligand acceleration in addition to Lewis acidity as observed in the titanate-catalyzed reaction (*vide supra*).[50] Thus, the more hindered chiral ligands give more active catalysts in the present boron Lewis acids. Fast ligand exchange with another ligand (L) such as nitrones exists at the boron-site in the bulky borane compounds, because the compound **50** is hindered more than **48** (Scheme 7).

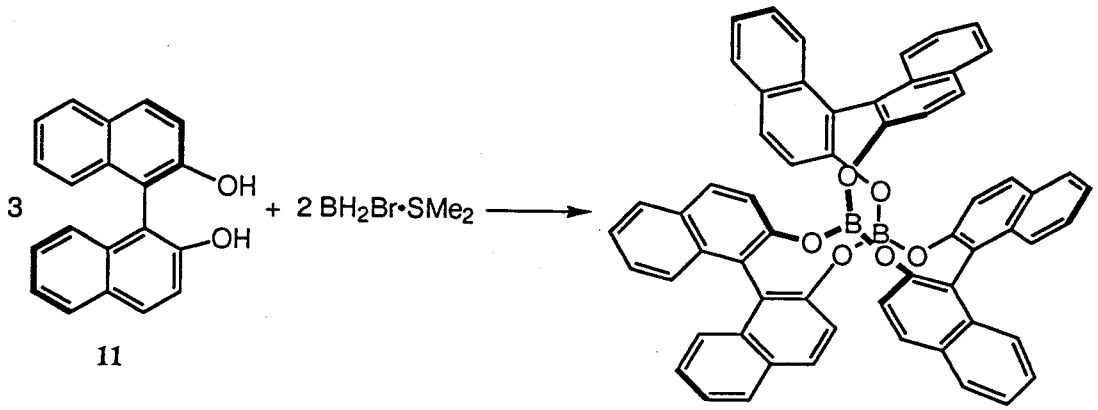
The catalyst prepared from **18** and triphenyl borate in the ratio of 3 : 2 gave higher enantioselectivity in comparison with that of the 1 : 1 complex. The structure of the 1 : 1 complex may have the structure **52** in which the boron is chelated by the moiety of **18** (Scheme 8). But the structure is not necessarily correct (*vide infra*). The structure **53** of the product from **11** and triphenyl borate (1 : 1) is illustrated in Scheme 8, and the complex has been used as a chiral promoter for hetero Diels-Alder reaction and addition of ketene silyl acetals to chiral imines.[9] The product from **11** and BH_2Br•SMe_2 (3 : 2), whose X-ray structure is established, can be used as a catalyst for Diels-Alder reaction.[56] This complex has a bimetallic structure **54** bridged by three BINOL moieties (eq 11). What is the structure of the product from **18** and triphenyl borate (3 : 2)?

Scheme 7



Scheme 8

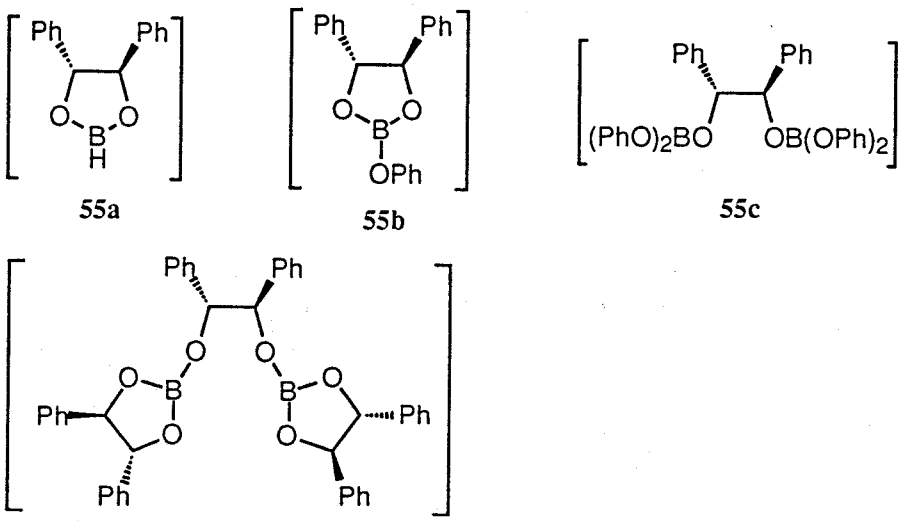




11 54 (11)

The ^{1}H NMR analysis of the products prepared *in situ* from **18** and triphenyl borate (3 : 2) in chloroform-*d* at 50 °C, was carried out, and the spectrum is shown in Figure 4 (a). This spectrum (a) indicates that many species are generated. Therefore, the conditions which generate a single species, were examined. The reaction of **18** (0.090 mmol) with BH_3•SMe_2 (0.060 mmol) which is handled easier than BH_3•THF, in chloroform-*d* (1.0 mL) was carried out at 60 °C for 1 h under argon, and the ^{1}H NMR spectrum is shown in Figure 4 (b). Surprisingly the product **55a** was formed as shown in Cart 2, and the diol **18** remained free in 0.5 equiv. Then, to the solution of **55a** prepared from **18** (0.060 mmol) and BH_3•SMe_2 (0.060 mmol) in chloroform-*d* (1.0 mL) was added phenol (0.18 mmol), and the solution was stirred further for 1 h to give the product **55b** (Figure 4 (c)). The 1 : 2 complex **55c** was obtained by the reaction of **18** (0.060 mmol) and triphenyl borate (0.12 mmol) at room temperature for 1 h (Figure 4 (d)). The trial to isolate **55b** as a crystal failed to give another product shown in Figure 4 (e), whose structure is shown as **55d** tentatively. The catalyst prepared from **18** and triphenyl borate in the ratio of 3 : 2 was found to contain these complexes **55b–55c** as a mixture in comparison with the spectra.

Chart 2



55a **55b** **55c**

55d

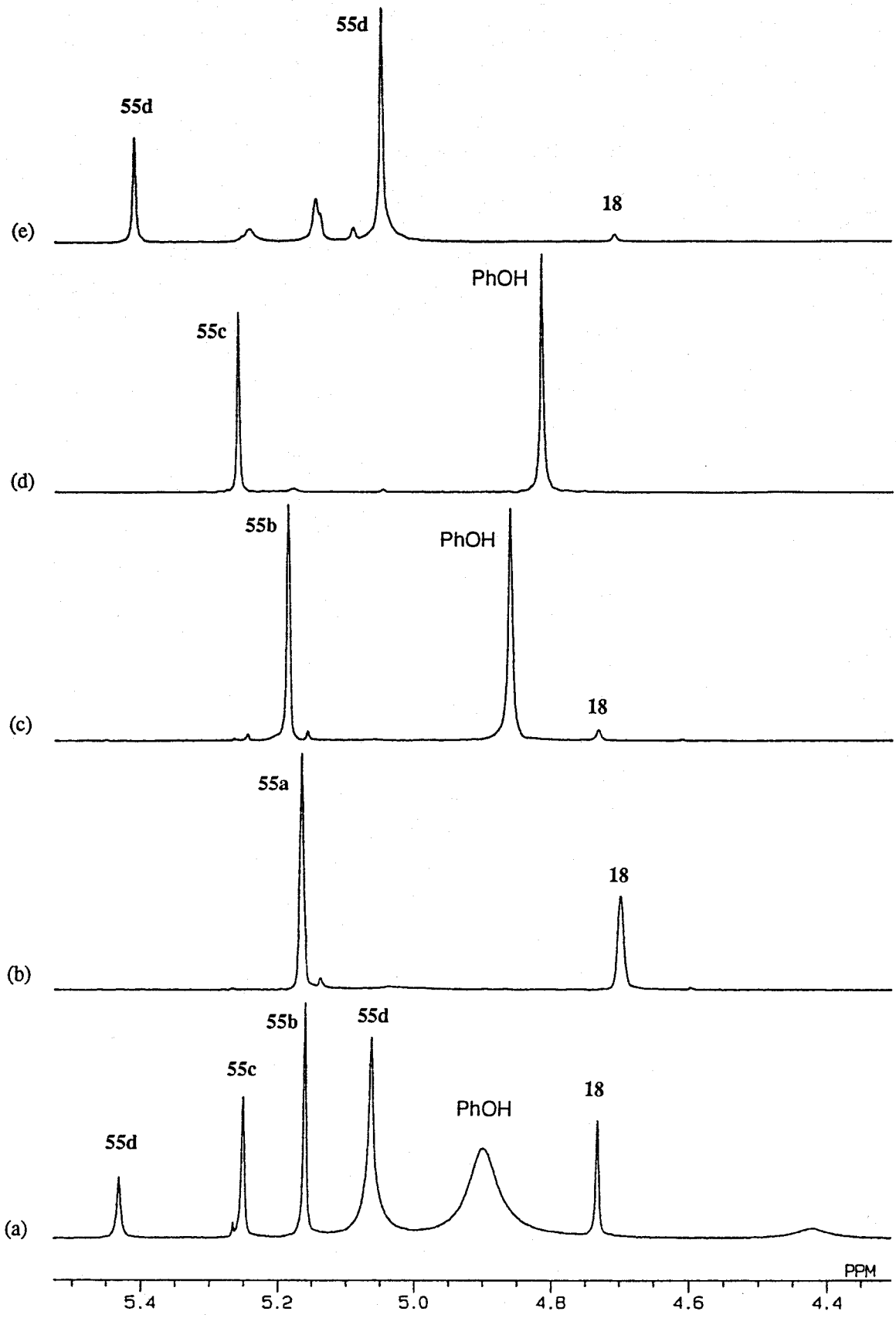


Figure 4. The ^{1}H NMR spectra of the products prepared from **18** and boron reagents were measured in $CDCl_3$ at 35 °C under argon. (a) The products prepared *in situ* from **18** (0.090 mmol) and triphenyl borate (0.060 mmol); (b) **55a**, (c) **55b**, (d) **55c**, (e) **55d**. The procedures for the preparation of these compounds were shown in text and the structures are shown in Chart 2.

The resultant these compounds **55a–55d** were used as a catalyst for the reaction of nitrone **40** with ketene silyl acetal **8**, and the results are summarized in Table 12. The compound **55a** didn't show the catalytic activity (entry 1), while in the presence of the catalyst **55b**, the proline derivative (*R*)-**41** was obtained in 96% yield, and the enantiomeric excess was 61% (entry 2). The compound **55c** also showed the catalytic activity, but the enantiomeric excess was only 5% (entry 3). Both of the catalytic activity and the enantioselectivity of the compound **55d** were low (entry 4). These results indicate that the most effective species is the compound **55b** in the products prepared from **18** and triphenyl borate in the ratio of 3 : 2.

Table 12. Enantioselective Addition of Ketene Silyl Acetal **8** to Nitrone **40** Catalyzed by the Boron Compound **55**[a]

entry	cat. (20 mol%)	time, h	yield,[b] %	% ee[c]
1	**55a**	24	trace	—
2	**55b**	2	96	61
3	**55c**	2	95	5
4	**55d**	72[d]	97	22

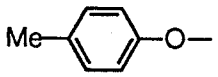
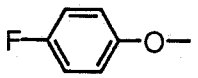
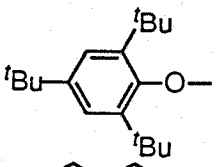
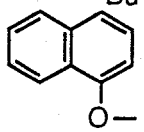
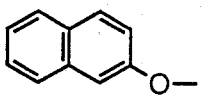
[a]The catalysts were prepared *in situ* in toluene, and the procedures were shown in text. The reaction of **40** (0.30 mmol) with **8** (0.36 mmol) was carried out in the presence of 20 mol% of a catalyst in toluene—P.E. (1 : 1, 1.0 mL) at –78°C. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis using Eu(hfc)$_3$. The *R* isomer was obtained. [d]The reaction temperature was raised up to room temperature.

Next, the effect of phenol derivatives in place of phenol for the complex **55b** was examined. The results are summarized in Table 13. Phenol is the best additional ligand among those examined toward the catalyst prepared from **18** and BH_3•SMe_2.

The enantiofacial differentiation of nitrone **40** by the catalyst **55b** is rationalized by assuming Scheme 9. Nitrone **40** was activated by the coordination of the compound **55b** to the oxygen of the nitrone. The ^{13}C NMR study of complexation of nitrone **40** with triphenyl borate showed that the chemical shift (δ) of the C-2 of **40** increased from 133.6 to 135.2, whereas the shift of the carbonyl did not change in a mixture of **40** (0.10 mmol) and triphenyl borate (0.10 mmol) in chloroform-*d* at 35 °C. Thus, nitrone **40** coordinates to the boron by only one oxygen of **40**, because borate have only one coordination site. Judging from the product configuration, the catalyst **55b** should shield the *si* face of **40**, and the selective approach of nucleophiles to the *re* face should occur. The ester function of **40** will orient in the side of the hydrobenzoin moiety because of steric repulsion with the phenol moiety. Then, the *si* face of **40** is shielded by one of the phenyl groups of the hydrobenzoin moiety. Attractive interaction between the ester group of **40** and the phenyl group of the hydrobenzoin moiety can be assumed.[51] Thus, nucleophiles such as **8** attack to the *re* face to give the *R* isomer.

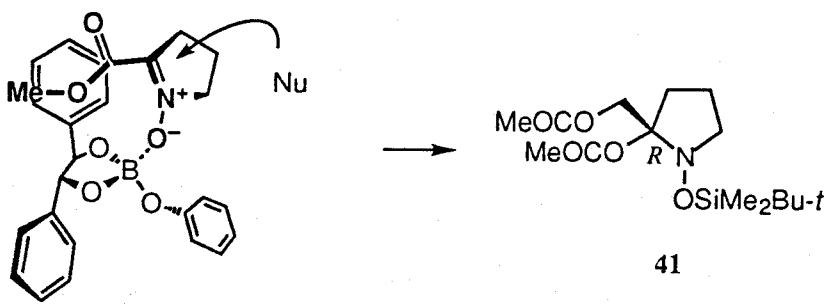
Diol **18**, which is the best chiral ligand among those examined, can be prepared by the osmium-catalyzed asymmetric dihydroxylation of *trans*-stilbene (see Chapter 2).[57]

Table 13. The Effect of Phenol Derivatives to the Catalyst Prepared from (*R*,*R*)-**18** and BH_3•SMe_2 for the Reaction of Nitrone **40** with Ketene Silyl Acetal **8**[a]

entry	ArO-	time, h	yield,[b] %	ee,[c] %
1	H	24	trace	—
2	PhO-	2	96	61
3	PhO- (3 eq)	2	99	60
4		2	90	49
5		2	94	41
6		24	86	2
7		19	96	45
8		4	91	53
9	MeO-	17	0	—
10	$PhCO_2$–	21	0	—

[a]The catalyst was prepared *in situ* as follows; to a solution of (*R*,*R*)-**18** (0.060 mmol) in toluene (0.50 mL) was added BH_3•SMe_2 (0.060 mmol), and the solution was stirred at 50 °C for 1 h under argon. Then, to the resultant solution was added phenol derivative (0.060 mmol), and the solution was sitrred for 1 h. The reaction of **40** (0.30 mmol) with **8** (0.36 mmol) was carried out in toluene—P.E. (1 : 1, 1.0 mL) at –78 °C. [b]Isolated yield. [c]Determined by ^1H NMR analysis using Eu(hfc)$_3$. In all cases the *R* isomer **40** was obtained.

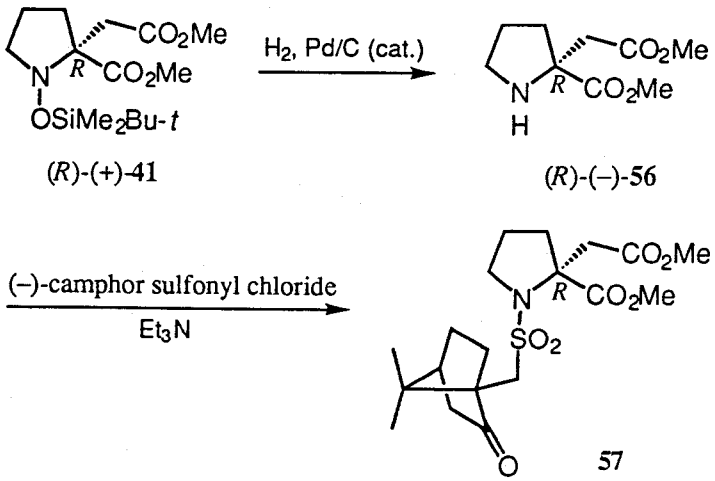
Scheme 9



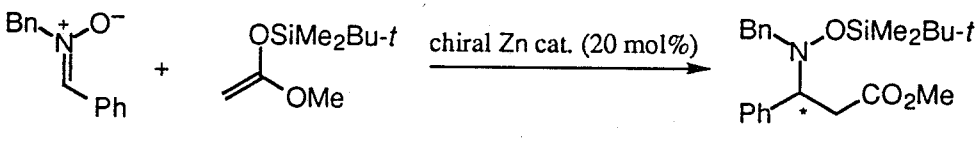
41

The absolute configuration of the proline derivative (+)-**41** was determined by the X-ray analysis after converted to sulfonamide **57** as shown in Scheme 10. Catalytic hydrogenation of (+)-**41** (55% ee) gave amino ester (–)-**56** which was treated with (–)-camphorsulfonyl chloride and triethylamine to give the sulfonamide **57** as a diastereomeric mixture (57% de). The single diastereomer **57** could be obtained by recrystallization from diethyl ether. The X-ray diffraction of **57** showed that the absolute configuration of **57** is *R* (Figure 5). Thus, the configuration of (+)-**41** is *R*.

Scheme 10

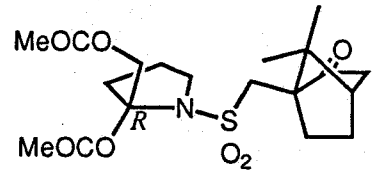


Chiral Zinc-Catalyzed Addition of Ketene Silyl Acetals to Nitrones. Zinc iodide is an efficient catalyst for the reaction of nitrone **9** with ketene silyl acetal **8**. By the modification of diethyl zinc with methanol, acetic acid, or *t*-butyl mercaptan, the adduct **10** was not obtained. However, as seen in the cases of titanium and boron catalysts, sterically hindered ligands may improve the activity of the zinc catalysts. The reaction of nitrone **9** with **8** was examined in the presence of 20 mol% of chiral zinc catalysts (eq 12).



9 **8** **10** (12)

The zinc reagent **58**, which has been used for asymmetric intramolecular ene reaction,[58] was prepared by the reaction of dialkyl zinc with **11** (eq 13) The reaction of nitrone **9** with ketene silyl acetal **8** did not occur in the presence of 20 mol% of **58**. The zinc complex **59**, which was prepared *in situ* from diethyl zinc and (*R*,*R*)-**20** by the similar manner (eq 14), was used as a chiral catalyst. The β-phenylalanine derivative **10** was obtained in quantitative yield by the reaction in toluene at 0 °C, however the enantiomeric excess was 2%. This is due to the free rotation of the coordinated nitrone **9** to zinc because of the lack of the part which restricts orientation of nitrone on **59** (*vide supra*). In order to



57

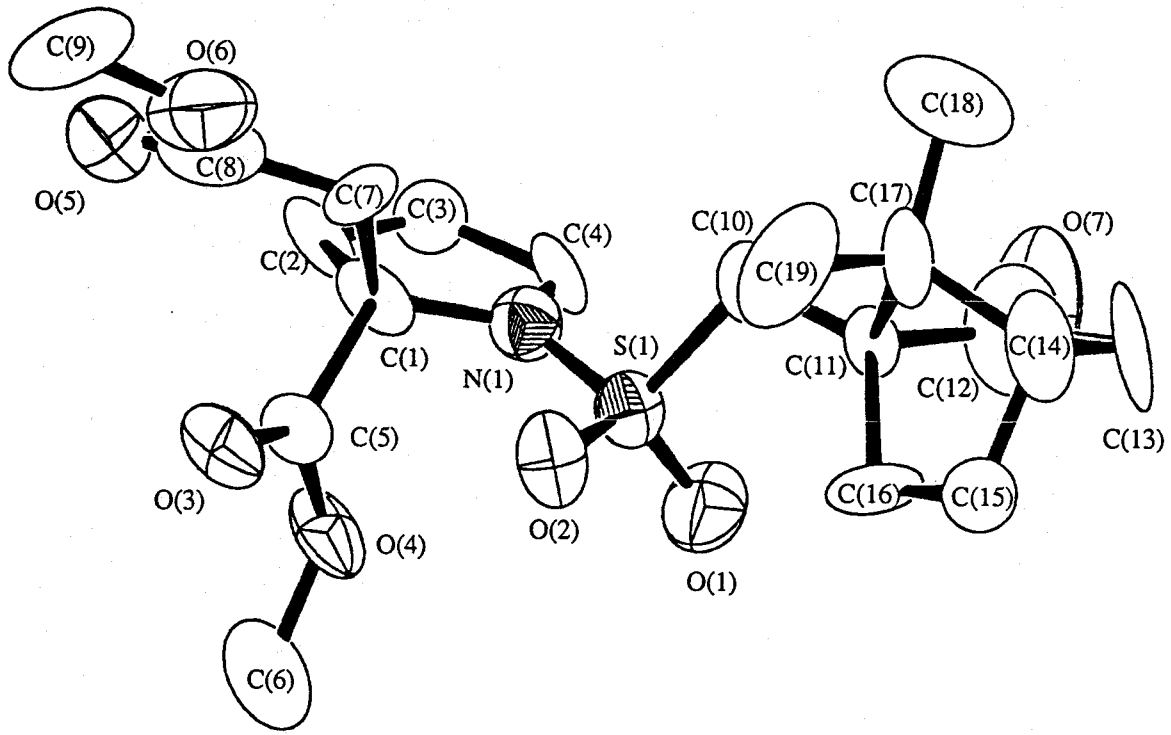
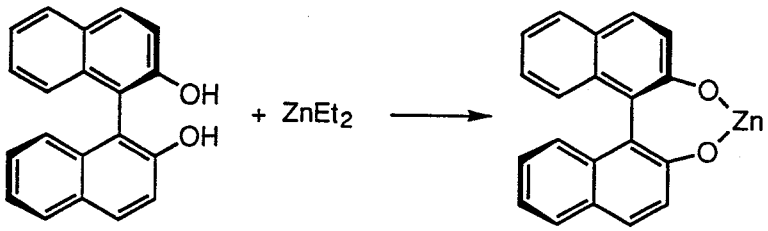
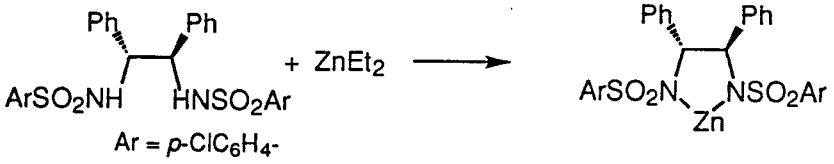


Figure 5. ORTEP drawing of **57**.



(13)

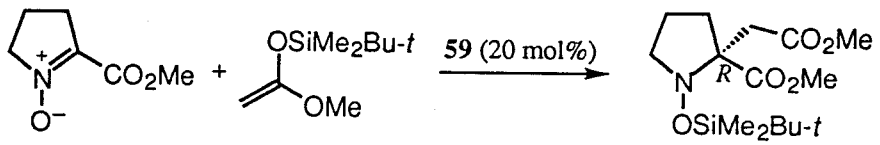
11 58



(14)

20 59

fix the conformation of nitrones by chelation to zinc, bidentate nitrones were examined. Nitrone **40** will chelate to the chiral zinc complex **59** with both the nitrone oxygen and the carbonyl oxygen. Rigidity gained by the chelation should improve the enantioselectivity. The reaction of nitrone **40** with ketene silyl acetal **8** in the presence of 20 mol% of the chiral zinc catalyst **59** at 0 °C gave the proline derivative **41** in 88% yield with 13% ee (*R*) (eq 15).

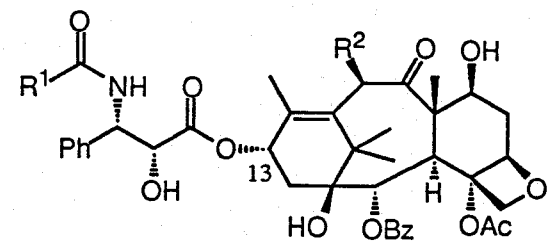


(15)

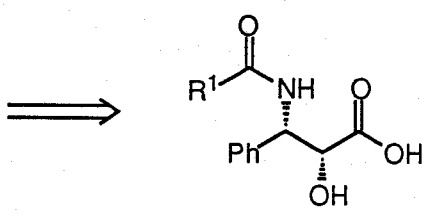
40 **8** (*R*)-(+)-**41**

Asymmetric Synthesis of β-Amino-α-Hydroxy Acids. β-Amino-α-hydroxy acids are becoming increasingly important in the view of the synthesis of biologically active compounds. Taxol isolated from the bark of the Pacific Yew (*Taxus brevifolia*), exhibits strong antitumour/antileukaemic activity and is currently considered a major lead in cancer chemotherapy (Scheme 11).[59] The synthesis of 3-phenylisoserine derivatives **60** which is the C-13 side chain unit of taxol, have become of major interest in recent years particularly with respect to the total synthesis and semi-synthetic approach to taxol,[59,60] because the C-13 side chain is crucial for the strong antitumor activity of taxol. Extraction of the fresh leaves of *Taxus baccata* yields 10-deacetylbaccatin III up to 1 g/kg, which lacks the C-13 side chain, although taxol is obtained in only 0.1—0.2 g/kg from the bark of the Pacific Yew. Further, the unnatural compound taxotere which has the *t*-butoxycarbonyl group instead of the benzoyl group on the amino group at the C-13 side chain and the hydroxy group instead of the acetoxy group at the C-10, seems to have antitumor activity superior to taxol with better bioavailability.[61]

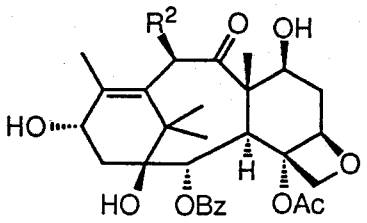
Scheme 11



Taxol; R^1 = Ph, R^2 = OAc
Taxotere; R^1 = *t*-BuO, R^2 = OH



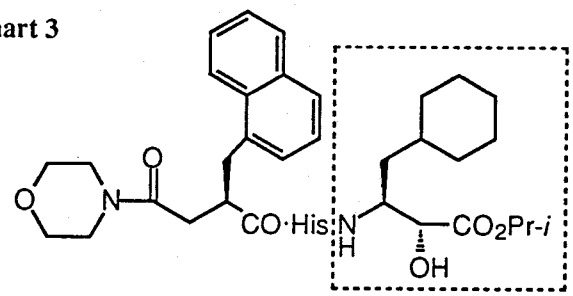
60



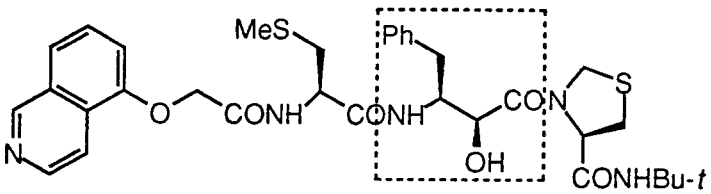
10-deacetylbaccatin III; R^2 = OH

Other important compounds containing β-amino-α-hydroxy acids are illustrated by the classes of enzyme inhibitors. For example, pseudopeptidic protease inhibitors, both designed and naturally containing, derive their efficacy from the ability of the β-amino-α-hydroxy acid motif to act as a transition state mimic of peptide hydrolysis.[21] KRI-1314 and KNI-272 are such designed protease inhibitors of renin and HIV-1 protease, respectively (Chart 3).[62]

Chart 3



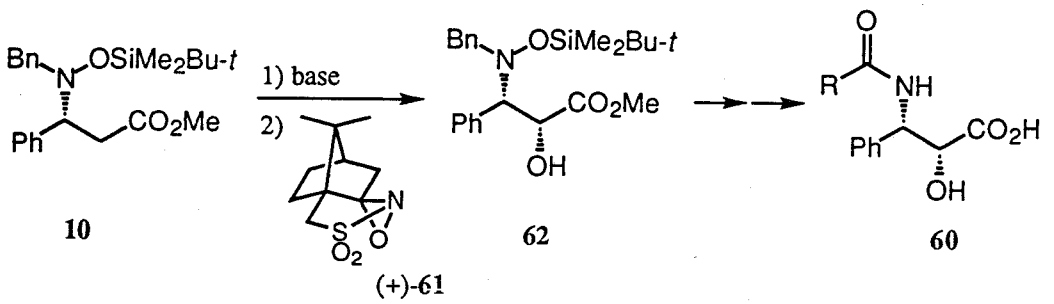
KRI-1314



KNI-272

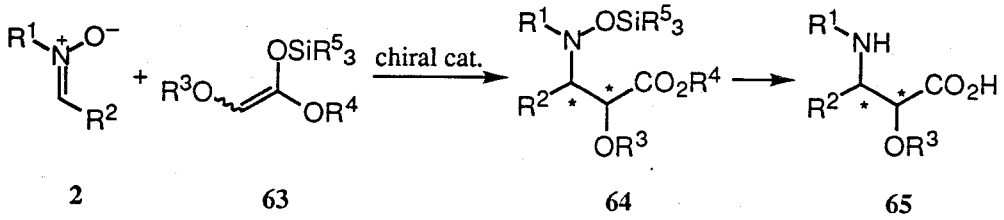
In the recent advance in the synthesis of β-amino acids, access to β-amino acids with α-substitution is developed rapidly. Several have been involved in the stereoselective reaction of enolates of β-amino acid derivatives to produce α-substituted β-amino acids. α-Hydroxylations of the β-phenylalanine derivatives have been performed *via* the oxidation of the corresponding enolates by F. A. Davis[63] and S. G. Davies,[64] independently. The optically active β-phenylalanine derivative **10** can be synthesized by

the chiral titanate-catalyzed reaction of nitrone **9** with ketene silyl acetal **8**. Then, a hydroxy group will be introduced at the α position of **10** by the above method (eq 16). Further, the β-phenylalanine derivative **10** will be transformed to other α-substituted β-phenylalanine derivatives, since the introduction of other groups such as fluoride[65] and many alkyl groups[66] at the α position of β-amino acid derivatives were reported.



(16)

The reaction of nitrones **2** with ketene silyl acetals **63** will give β-amino-α-hydroxy acid derivatives **64**, which provides a more efficient approach to β-amino-α-hydroxy acids **65** (eq 17). There are the problems of both the enantioselectivity and the

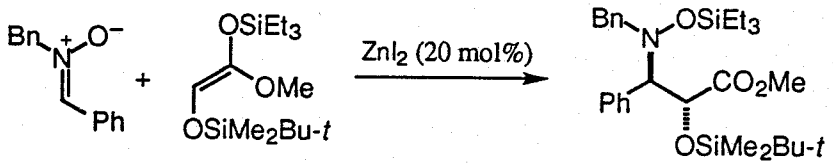


(17)

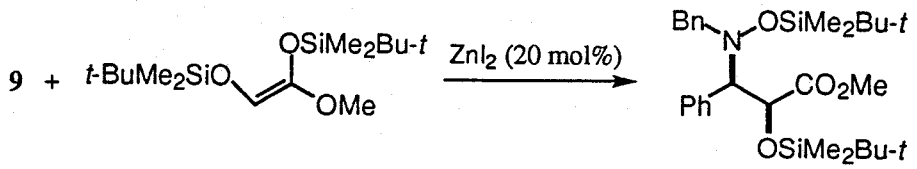
diastereoselectivity in the reaction with substituted ketene silyl acetals. First, the reaction of nitrone **9** with ketene silyl acetals (*E*)-**66** and (*Z*)-**68**[67] was examined (Scheme 12). The reaction in the presence of 20 mol% of zinc iodide in dichloromethane did not occur at –78 °C, and proceeded slowly around 0 °C. The reaction at room temperature gave the β-amino-α-hydroxy acid derivatives in quantitative yield. The addition of (*E*)-ketene silyl acetal **66** gave an *anti* isomer **67** in the ratio of *anti*/*syn* = 76 : 24, while the addition of (*Z*)-**68** gave a *syn* isomer **69** in the ratio of *anti*/*syn* = 35 : 65. The adduct **69** could be converted into *N*-benzoyl-3-phenylisoserine methyl ester (**70**) as a mixture of *anti* and *syn* isomers. However, the reaction of nitrone **9** with ketene silyl acetals (*E*)-**66** and (*Z*)-**68** did not occur in the presence of the chiral titanate (*R*)-**23b**. The attempt to the asymmetric addition of these ketene silyl acetals is now in progress.

Catalytic asymmetric reaction of nitrones with ketene silyl acetals was performed by using the chiral titanium, boron, and zinc Lewis acids up to 66% ee, and this is the first catalytic asymmetric carbon-carbon bond formation of nitrones. Further, it is expected to apply these catalysts to other asymmetric reactions.[68–70]

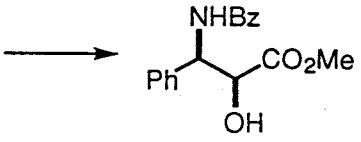
Scheme 12



9 (*E*)-66 67 (*anti*/*syn* = 76 : 14)



(Z)-68 69 (*anti*/*syn* = 35 : 65)



70

Experimental Section

General. All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 polarimeter. IR spectra were recorded on a Shimadzu FTIR 4100 spectrometer. NMR spectra were obtained on a JEOL JNM-GSX-270 (^{1}H, 270 MHz, ^{13}C 68 MHz) spectrometer; chemical shifts (δ) were expressed in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; quint; quintet; m, multiplet; br, broad. Coupling constants (*J*) are reported in hertz. HPLC analyses were performed on a JASCO TRI ROTAR-VI system with a JASCO MULTI 340 UV detector by using a 250 mm x 4.6 mm analytical column packed with Daicel CHIRALCEL OD, OD-H, or CHIRALPACK AD. Elemental analyses were carried out on a Yanagimoto Model MT-3 CHN corder. Mass spectra were obtained on a JEOL JMS-DX303 mass spectrometer. Analytical TLC was performed on E. Merck silica gel 60 F254 (Art. 5714) or E. Merck DC-Fertigplatten RP-18F245S (Art. 15685). Flash chromatography was carried out on E. Merck silica gel 60 (230–400 mesh). X-Ray analysis was performed on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation and a 12kW rotating anode generator.

Materials. *p*-Fluorobezaldehyde, *p*-anisaldehyde, 1-naphthaldehyde, 2-naphthaldehyde, *t*-butyl mercaptan, benzyl chloroformate, *p*-chlorobenzenesulfonyl chloride, *p*-toluenesulfonyl chloride, L-camphorsulfonyl chloride, L-tryptophan, *N*,*N*-

dimethylaminopyrridine, phenol, catechol, *o*-cresol, *m*-cresol, *p*-cresol, 4-fluorophenol, 4-chlorophenol, 2-phenylphenol, 2-*t*-butylphenol, 2,2'-dihydroxybiphenyl, 2,6-dimethyphenol, 2,4,6-tri-*t*-butylphenol, 1-naphthol, 2-naphthol, 9-phenanthrol (Aldrich Chem. Co.), 2-α,α,α-trifluoromethylphenol, 4-chloro-1-naphthol, 4-methoxy-1-naphthol, 8-hydroxyquinoline, benzoic acid, zinc powder (Aldrich Chem. Co.), zinc iodide, trimethylsilyl trifluoromethanesulfonate, *t*-butyldimethylsilyl trifluoromethanesulfonate, magnesium bromide, aluminum chloride, copper(I) chloride, copper(II) chloride, manganese(II) chloride, ferric chloride, tris(triphenylphosphine)ruthenium(II) chloride, cobalt(II) chloride, nickel(II) bromide, boron tribromide, borane-dihydorofuran complex (BH_3•THF) (1.0 M in THF), borane-dimethyl sulfide (BH_3•SMe_2) complex, triphenyl borate, trimethyl borate, diethylzinc (1.0 M in hexane), and 10% palladium on charcoal were commercially available and used without further purification. Triethylamine, titanium(IV) chloride, titanium(IV) isopropoxide, toluene, petroleum ether (P.E.), tetrahydrofuran (THF), diethyl ether, and propionitrile were commercially available and distilled before use. Dichloromethane (Hayashi Pure Chemical Industry Ltd.) and chloroform-*d* commercially available and dried over 4-Å molecular sieves. 4-Å Molecular sieves is commercially available and dried over P_2O_5 at 120 °C *in vacuo* before use. Ketene silyl acetal **8**[71], (*E*)-**66**[67], and (*Z*)-**68**[67] were prepared by reported procedures.

Preparation of Nitrones. *N*-Benzylidenebenzylamine *N*-oxide (**9**) and methyl 1-pyrroline-2-carboxylate *N*-oxide (**40**) was prepared by the catalytic oxidation of the corresponding secondary amines with 30% hydrogen peroxide in the presence of sodium tungstate dihydrate (4 mol%).[14,15] Preparation of *N*-benzylidenemethylamine *N*-oxide (**34**) and *N*-ethylidenebenzylamine *N*-oxide (**35**) were described in Chapter 3. *N*-(4-Fluorophenylmethylidene)benzylamine *N*-oxide (**36**), *N*-(4-methoxyphenylmethylidene)benzylamine *N*-oxide (**37**), *N*-(1-naphthylmethylidene)benzylamine *N*-oxide (**38**), and *N*-(2-naphthylmethylidene)benzylamine *N*-oxide (**39**) were prepared by the condensation of *N*-benzylhydroxylamine with the corresponding aldehydes.

***N*-(4-Fluorophenylmethylidene)benzylamine *N*-Oxide (36).** Nitrone **36** was prepared by the condensation of *p*-fluorobenzaldehyde with *N*-benzylhydroxylamine: R_f 0.31 (SiO_2, hexane—ethyl acetate = 3 : 2); mp 109.0–110.0 °C; IR (KBr) 1599, 1576, 1503, 1450, 1231, 1148, 856, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 5.02 (s, 2 H, C*H*$_2$), 7.05 (tt, *J* = 2.0 and 8.8 Hz, 2 H, Ar), 7.35–7.50 (m, 6 H, Ar), 8.20–8.29 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 71.1, 115.4 (d, *J* = 22 Hz), 126.8 (*d*, J = 3 Hz), 128.9, 129.0, 129.1, 130.7 (d, *J* = 8 Hz), 132.9 (*C*=N), 133.1, 165.1 (d, *J* = 252 Hz); HRMS (EI) calcd for $C_{14}H_{12}NOF$ (M^+) 229.0903, found 229.0914.

***N*-(4-Methoxyphenylmethylidene)benzylamine *N*-Oxide (37).** Nitrone **37** was prepared by the condensation of *p*-anisaldehyde with *N*-benzylhydroxylamine: R_f 0.15 (SiO_2, hexane—ethyl acetate = 3 : 2); mp 100.0–100.5 °C; IR (KBr) 1603, 1566, 1509, 1458, 1254, 1173, 1148, 1026, 843, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 3.81 (s, 3 H, C*H*$_3$), 5.00 (s, 2 H, C*H*$_2$), 6.89 (dt, *J* = 9.0 and 2.0 Hz, 2 H, C*H*), 7.31 (s, 1 H, C*H*=N), 7.34–7.50 (m, 5 H, Ar), 8.20 (dt, *J* = 9.0 and 2.0 Hz, 2 H, Ar); ^{13}C NMR ($CDCl_3$,

68 MHz, 35 °C) δ 55.2, 70.7, 113.7, 123.5, 128.8, 128.9, 129.1, 130.5, 133.5, 133.7 (*C*=N), 161.0.

***N*-(1-Naphthylmethylidene)benzylamine *N*-Oxide (38).** Nitrone **38** was prepared by the condensation 1-naphthaldehyde with *N*-benzylhydroxylamine: R_f 0.29 (SiO_2, hexane—ethyl acetate = 3 : 2); mp 114.0–115.0 °C; IR (KBr) 1566, 1506, 1458, 1339, 1146, 939, 789, 770, 139, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 5.18 (s, 2 H, CH_2), 7.35–7.56 (m, 8 H, Ar), 7.80–7.89 (m, 3 H, Ar), 8.16 (s, 1 H, C*H*=N), 9.51 (d, *J* = 7.6 Hz, 1 H, Ar); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 72.0, 121.1, 125.4, 125.7, 125.8, 126.7, 129.0, 129.2, 129.3, 129.8 (*C*=N), 130.6, 130.8, 133.4.

***N*-(2-Naphthylmethylidene)benzylamine *N*-Oxide (39).** Nitrone **39** was prepared by the condensation 2-naphthaldehyde with *N*-benzylhydroxylamine: R_f 0.31 (SiO_2, hexane—ethyl acetate = 3 : 2); mp 114.0–114.5 °C; IR (KBr) 1575, 1453, 1354, 1161, 903, 866, 829, 733, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz, 35 °C) δ 5.07 (s, 2 H, CH_2), 7.32–7.53 (m, 8 H, Ar), 7.74–7.90 (m, 4 H, Ar), 9.20 (s, 1 H, C*H*=N); ^{13}C NMR ($CDCl_3$, 68 MHz, 35 °C) δ 71.2, 125.8, 126.4, 127.2, 127.4, 127.6, 127.8, 128.5, 128.9, 129.1, 129.2, 133.1, 133.3, 134.1 (*C*=N).

Preparation of Chiral Ligands. (*R*)-And (*S*)-1,1'-bi-2-naphthol (BINOL) (**11**) was commercially available and its derivatives (*R*)-3,3'-Diphenyl-BINOL **15**[44] and (*R*)-6,6'-dibromo-BINOL **16**[46] were prepared by reported procedures. (*R*,*R*)-Hydrobenzoin (**18**), (*S*,*S*)-1-hydronaphtoin (**30**), and (*R*,*R*)-2-hydronaphtoin (**31**) were prepared by the osmium tetroxide-catalyzed asymmetric dihydroxylation of *trans*-olefins.[57] Preparation of (*R*,*R*)-**18** was shown in Chapter 2. *trans*-1,2-Di(1-naphthyl)ethene and *tans*-1,2-di(2-naphthyl)ethene were obtained by reported procedure.[72] (*S*,*S*)-α,α,α',α'-Tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (**19**) was prepared by reported procedure.[50] Other chiral diols such as (*R*,*R*)-1,2-butanediol (**28**), (*R*,*R*)-2,4-pentanediol (**29**), and 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**47**) were commercially available. Dibenzoyl-D-tartaric acid (**22**) was also commercially available, and dried *in vacuo* over P_2O_5 before use.

(–)-(*R*)-6,6'-Diphenyl-1,1'-bi-2-naphthol•CH_2Cl_2 (17). BINOL derivative (*R*)-**17** was prepared by the coupling[44] of (*R*)-**16** (1.33 g, 3.0 mmol) with phenylmagnesium bromide (17 mmol) in the presence of bis(triphenylphosphine)nickel(II) chloride (98 mg, 0.8 mol%) in THF (33 mL) at 50 °C to give (–)-**17** (1.14 g). Recrystallization from CH_2Cl_2—hexane to give (–)-**17** as an yellow crystal containing 1 equiv of CH_2Cl_2: R_f 0.53 (SiO_2, hexane—ethyl acetate = 3 : 1); mp 120–124 °C (CH_2Cl_2—hexane); $[\alpha]^{22}_D$ –220.0° (*c* 1.06, $CHCl_3$); IR (KBr) 3500, 1595, 1492, 1220, 1170, 1147, 759, 699 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 5.07 (s, 2 H, O*H*), 5.28 (s, 2 H, CH_2Cl_2), 7.23–7.50 (m, 10 H, Ar), 7.58 (dd, *J* = 1.7 and 8.5 Hz, 2 H, Ar), 7.63–7.70 (m, 4 H, Ar), 8.03 (d, *J* = 8.8 Hz, 2 H, Ar), 8.10 (d, *J* = 1.7 Hz, 2 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 53.4, 110.8, 118.3, 124.8, 126.4, 127.2, 127.2, 127.3, 128.9, 129.8, 131.8, 132.6, 137.0, 140.8, 152.9.

Preparation of (*S*,*S*)-(–)-1,2-Di(1-naphthyl)-1,2-ethanediol (30).[73a] Diol **30** was prepared by Sharpless catalytic asymmetric dihydroxylation:[57] To a mixture of hydroquinine 4-chlorobenzoate (0.39 g, 0.80 mmol), $K_3Fe(CN)_6$ (20 g, 60 mmol), K_2CO_3

(8.3 g, 60 mmol), and $CH_3SO_2NH_2$ (1.9 g, 20 mmol) in *t*-BuOH—H_2O (1 : 1, 200 mL) was added a solution of OsO_4 in toluene (0.2 M, 0.4 mL, 0.08 mmol). The resulting yellow solution was cooled to 0 °C, and *trans*-1,2-di(1-naphthyl)ethene[72] (5.6 g, 20 mmol) was then added. The mixture was stirred at 0 °C for 43 h, and further stirred at 5 °C for 42 h. To this mixture was added Na_2SO_3 (2.8 g), and the resulting mixture was stirred at room temperature for 0.5 h. The mixture was extracted with ethyl acetate (300 mL), washed with 2 M KOH (100 mL), and dried over $MgSO_4$. Concentration and column chromatography on silica gel (200 mL, ethyl acetate—hexane) afforded a colorless solid **30**. The ee of **30** was determined to be 97% by the HPLC analysis using CHIRALCEL OB (5% EtOH in hexane, 2.0 mL/min). Furthermore, **30** was recrystallized from ethyl acetate, though the obtained colorless crystal had low optical purity. The concentrated mother liquid was purified by column chromatography to give optically pure diol **30** (4.8 g, 76% yield, >99% ee) as a colorless solid: R_f 0.21 (SiO_2, hexane—ethyl acetate = 3 : 1); mp 149.0–150.0 °C (mp of a racemic sample was 184–185 °C); $[\alpha]^{24}_D$ –57.6° (*c* 1.01, THF) (lit.[73a] $[\alpha]^{24}_D$ +48° (*c* 0.86, THF) for the *R,R* isomer); IR (KBr) 3345, 1063, 800, 775 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 2.96 (s, 2 H, O*H*), 5.78 (s, 2 H, CH_2), 7.23–7.42 (m, 6 H, Ar), 7.65–7.77 (m, 6 H, Ar), 7.87 (d, *J* = 8.8 Hz, 2 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 74.5, 123.0, 124.8, 125.1, 125.3, 125.8, 128.6, 128.7, 130.9, 133.7, 136.1.

Preparation of (*R,R*)-(+)-1,2-Di(2-naphthyl)-1,2-ethanediol (31).[73] Diol **31** was also prepared by Sharpless catalytic asymmetric dihydroxylation:[57] AD-mix-β (Aldrich) was employed to give **31** in 92% yield and **31** could be purified by crystallization from DMSO—$CHCl_3$ as a colorless crystal: R_f 0.17 (SiO_2, hexane—ethyl acetate = 3 : 1); mp 248.0–250.0 °C (hydrate) (lit.[73b] 237–238 °C); $[\alpha]^{21}_D$ +217.3° (*c* 0.988, THF) (lit.[73b] $[\alpha]^{23}_D$ +212° (*c* 1.04, THF), for the *R,R* isomer); IR (KBr) 3345, 1600, 1410, 1364, 1121, 1073, 1034, 862, 832, 781, 762, 743, 740 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6, 35 °C) δ 3.30 (s, 2 H, O*H*), 4.88–4.96 (m, 2 H, H_2O), 5.47–5.54 (m, 2 H, CH_2), 7.29–7.45 (m, 6 H, Ar), 7.66–7.84 (m, 8 H, Ar); ^{13}C NMR (68 MHz, DMSO-d_6, 35 °C) δ 77.4, 125.3, 125.5, 125.6, 125.7, 126.5, 127.3, 127.5, 132.1, 132.4, 140.1.

Preparation of (*R,R*)-*N,N'*-Di(4-chlorobenzenesulfonyl)-1,2-diphenylethylenediamine (20). To a mixture of (*R,R*)-1,2-diphenylethylenediamine[74] (mp 83.5–84.0 °C, $[\alpha]^{22}_D$ +104.9° (*c* 0.982, MeOH) (2.24 g, 10.6 mmol) and *p*-chlorobenzenesulfonyl chloride (4.45 g, 21.1 mmol) in CH_2Cl_2 (20 mL) were added *N,N*-dimethlylaminopyrridine (0.13 g, 1.0 mmol) and triethylamine (4.4 mL, 32 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. To the reaction mixture was added 2 M HCl (20 mL) at 0 °C. The mixture was filtered, separated, then washed with 2 M HCl (50 mL). The solid obtained was crystallized from acetone to give (*R,R*)-**20** (5.32 g, 88%) as a colorless crystal: R_f 0.70 (SiO_2, $CHCl_3$—MeOH = 9 :1); mp 264.0–265.0 °C (acetone); $[\alpha]^{22}_D$ +113.7° (*c* 0.839, DMSO); IR (KBr) 3387, 1588, 1476, 1456, 1433, 1358, 1343, 1161, 1084, 936, 752, 702, 625, 554 cm^{-1}; 1H NMR (270 MHz, DMSO-d_6, 35 °C) δ 4.54 (ddd, *J* = 5.7, 7.1, and 9.3 Hz, 2 H, C*H*), 6.79–6.95 (m, 10 H), 7.17–7.24 (m, 4 H), 7.28–7.30 (m, 4 H), 8.42–8.53 (m, 2 H, N*H*); ^{13}C NMR (68 MHz, DMSO-d_6, 35 °C) δ 62.3, 126.6, 127.3, 127.4, 127.8, 128.3, 136.3, 137.4, 140.0; Anal. Calcd for

$C_{26}H_{22}N_2S_2O_4Cl_2$: C, 55.62; H, 3.95; N, 4.99; S,11.42; Cl, 12.60. found: C, 55.82; H, 4.00; N, 4.82; S, 11.59; Cl, 12.93.

Preparation of *N*-(*p*-Tolylsulfonyl)-L-tryptophan (21).[51a] To a mixture of L-tryptophan (2.0 g, 9.8 mmol), THF (1 mL), and H_2O (10 mL) were added triehtylamine (3.4 mL, 24 mmol), followed by *p*-toluelesulfonyl chloride (2.0 g, 11 mmol) with ice cooling. After stirred at room temperature for 3 h, to the mixture was added 2 M HCl (10 mL) to pH 9. It was extracted with ethyl acetate (50 mL x 2) and the extracts were dried over Na_2SO_4. The crude product obtained was crystallized from $CHCl_3$ (150 mL) to give **21** as a crystal (2.5 g, 70%): mp 157.0–159.0 °C ($CHCl_3$); $[\alpha]^{26}_D$ –40.5° (*c* 1.18, EtOH); IR (KBr) 3300, 1761, 1412, 1356, 1213, 1161, 1088, 739, 561 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6, 35 °C) δ 2.31 (s, 1 H, CH_3), 2.86 (dd, *J* = 6.8 and 14.4 Hz, 1 H, C*H*H), 3.06 (dd, *J* = 6.6 and 14.4 Hz, 1 H, C*H*H), 3.32 (br, 1 H, N*H*), 3.90 (q, *J* = 7.2 Hz, 1 H, $CHCO_2H$), 6.88–7.52 (m, 9 H, Ar), 8.07 (d, *J* = 7.5 Hz, 1 H, N*H*), 10.7 (br, 1 H, CO_2H); ^{13}C NMR (68 MHz, DMSO-d_6, 35 °C) δ 20.9, 28.2, 56.5, 108.8, 111.3, 117.7, 118.2, 120.7, 123.8, 126.2, 126.8, 129.0, 136.0, 138.0, 142.1, 172.2 (CO_2H).

Preparation of Titanium(IV) *tert*-Butoxide. Titanium(IV) *t*-butoxide was prepared by the similar procedure for other titanium(IV) alkoxides.[75] Thus, in the three-necked round bottom flask equipped with a distillation set and a magnetic stirrer bar, Ti(O-*i*-Pr)$_4$ (5.86 mL, 20.0 mmol) was placed. To the mixture, *t*-BuOH (3.8 mL, 40 mmol) was added and from this mixture *i*-PrOH was distilled off at 110 °C. This operation was performed for four times. Then, the residue was distilled to give Ti(O-*t*-Bu)$_4$ (4.74 g, 70%) (52–55 °C/0.6 mmHg).

General Procedure for the Reactions of Nitrones with Ketene Silyl Acetals Catalyzed by the Titanium Complex Prepared from Ti(O-*i*-Pr)$_4$—(*R*)-BINOL—1-Naphthol (1 : 1 : 2) (23b). A magnetic stirrer bar, activated 4-Å MS (100 mg), and (*R*)-BINOL **11** (17.2 mg, 0.060 mmol) were placed in a reaction test tube filled with argon and capped with a septum rubber equipped with a balloon filled with argon. To the vessel were added toluene (0.50 mL) and Ti(O-*i*-Pr)$_4$ (0.018 mL, 0.060 mmol), and the mixture was stirred at room temperature for 0.5 h. To this solution, 1-naphthol (17.3 mg, 0.12 mmol) was added and the solution was stirred further for 0.5 h. After cooling at –78 °C, to the resultant mixture were added nitrone (0.30 mmol), petroleum ether (0.50 mL), and ketene silyl acetal **8** (0.075 mL, 0.36 mmol) successively. After stirring this solution at –78 °C, the product was directly isolated by column chromatography on silica gel (60 mL, 5% ethyl acetate in hexane) to give a colorless oil of *N*-silyloxy-β-amino ester. The obtained *N*-silyloxy-β-amino ester was dissolved in MeOH (3.0 mL), and to this solution were added conc H_2SO_4 (0.5 mL) and Zn powder (350 mg). The mixture was stirred at 60 °C for 2 h, then sat. $NaHCO_3$ (5 mL) was added. The reaction mixture was filtered through Celite and the cake was washed with ethyl acetate (20 mL). After separation, the organic layer was washed with brine (5 mL), and dried over Na_2SO_4. After concentration the product was purified by column chromatography on silica gel (20 mL, 20% ethyl acetate in hexane) to give β-amino ester as a colorless oil.

General Procedure for the Reaction of Nitrones with Ketene Silyl Acetals Catalyzed by Chiral Borate 55b. (*R*,*R*)-Hydrobenzoin (**18**) (17.2 mg, 0.060 mmol)) were placed in a reaction test tube filled with argon and capped with a septum rubber equipped with a balloon filled with argon. To the vessel were added toluene (0.5 mL) and BH_3•SMe_2 (0.0060 mL, 0.060 mmol), and the mixture was stirred at 60 °C for 1.0 h. To this solution, phenol (5.6 mg, 0.060 mmol) was added and the solution was stirred further at 60 °C for 1 h. After cooling at –78 °C, to the resultant mixture were added nitrone (0.30 mmol), petroleum ether (0.50 mL), followed by, ketene silyl acetal **8** (0.075 mL, 0.36 mmol). The reaction mixture was stirred. The product was directly isolated by column chromatography on silica gel (ethyl acetate in hexane).

General Procedure for the Reaction of Nitrones and Ketene Silyl Acetal 8 Catalyzed by Chiral Zinc Complex 59. A magnetic stirrer bar and bissulfonamide (*R*,*R*)-**20** (56 mg, 0.10 mmol) were placed in a reaction vessel filled with argon and capped with a septum rubber. To the vessel were added toluene (1.5 mL) and a solution of diethylzinc in hexane (0.050 mmol) at room temperature and the solution was stirred for 0.5 h. To the resultant solution was added nitrone (0.50 mmol) at room temperature, and after cooling at –78 °C, to the solution was added ketene silyl acetal **8** (0.114 mL, 0.55 mmol). The reaction mixture was stirred. The product was directly purified by column chromatography on silica gel (ethyl acetate in hexane).

(*S*)-(–)-Methyl 3-(*N*-*tert*-Butyldimethylsiloxy-*N*-benzylamino)-3-phenylpropanoate (10). β-Amino ester (*S*)-(–)-**10** was obtained in 95% yield by the (*R*)-**23b**-catalyzed reaction of nitrone **9** with **8** as a colorless oil: R_f 0.40 (SiO_2, hexane—ethyl acetate = 5 : 1); $[\alpha]^{23}_D$ –15.7° (*c* 1.02, $CHCl_3$) for 62% ee; IR (neat) 2953, 2897, 2857, 1744, 1256, 837, 781, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ –0.14 (br, 6 H, C*H*$_3$Si), 0.89 (s, 9 H, C*H*$_3$), 2.82 (dd, *J* = 8.8 and 14.1 Hz, 1 H, C*H*HCO), 3.20 (dd, *J* = 5.6 and 14.9 Hz, 1 H, C*H*HCO), 3.50 (d, *J* = 13.4 Hz, 1 H, C*H*HPh), 3.57 (s, 3 H, C*H*$_3$O), 3.77 (br, 1 H, C*H*HPh), 4.40 (dd, *J* = 6.1 and 8.8 Hz, 1 H, C*H*Ph), 7.17–7.38 (m, 10 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ –4.9, 17.9, 25.8, 26.2, 51.5, 59.8, 61.7, 127.2, 127.7, 128.0, 128.1, 129.4, 129.9, 137.5, 138.2, 172.2; HRMS (FAB) calcd for $C_{23}H_{33}NO_3Si$ (M^+) 399.2230, found 399.2236.

(*S*)-(–)-Methyl 3-(Benzylamino)-3-phenylpropanoate (13). Amino ester (*S*)-(–)-**13** was obtained by the reduction of (*S*)-(–)-**10** (88% yield based on nitrone **9**) as a colorless oil. The enantiomeric excess was determined by HPLC analysis using Daicel CHIRALCEL OD (10% isopropyl alcohol in hexane, 1 mL/min) to be 62% ee: R_f 0.56 (SiO_2, hexane—ethyl acetate = 3 : 2); $[\alpha]^{23}_D$ –16.9° (*c* 1.07, MeOH) for 62% ee; IR (neat) 3350, 1736, 1495, 1455, 1437, 1200, 1167, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.95 (br, 1 H, N*H*), 2.62 (dd, *J* = 5.4 and 15.6 Hz, 1 H, C*H*HCO), 2.73 (dd, *J* = 8.6 and 15.4 Hz, 1 H, C*H*HCO), 3.54 (d, *J* = 13.2 Hz, 1 H, C*H*HPh), 3.63 (s, 3 H, C*H*$_3$O), 3.66 (d, *J* = 13.2 Hz, 1 H, C*H*HPh), 4.11 (dd, *J* = 5.4 and 8.5 Hz, 1 H, C*H*Ph), 7.18–7.36 (m, 10 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 42.9, 51.3, 51.5, 58.8, 126.8, 127.1, 127.5,

128.1, 128.3, 128.6, 140.3, 142.6, 172.2; HRMS (EI) calcd for $C_{17}H_{20}NO_2$ (M^+) 270.1494, found 270.1496.

(+)-Methyl 3-(*N*-*tert*-Butyldimethylsiloxy-*N*-methylamino)-3-phenylpropanoate. A title compound was obtained by the (*R*)-**23b**-catalyzed reaction of nitrone **34** with **8** in 62% yield as a colorless oil: R_f 0.61 (SiO_2, hexane—ethyl acetate = 5 : 1); $[\alpha]^{28}_D$ +15.7° (*c* 1.11, $CHCl_3$) for 60% ee; IR (neat) 2932, 1742, 1256, 837, 781 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 0.14 (s, 6 H, C*H*$_3$), 0.91, (s, 9 H, *t*-Bu), 2.34 (s, 3 H, C*H*$_3$), 2.63 (br, 1 H), 3.38 (dd, *J* = 5.9 and 15.1 Hz, 1 H, C*H*HCO), 3.46 (s, 3 H, C*H*$_3$), 4,03 (br, 1 H, C*H*Ph), 7.20–7.37 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ –5.0, 17.9, 25.7, 26.1, 37.2, 51.4, 58.0, 58.7, 127.2, 128.1, 129.9, 138.0, 172.9.

(–)-Methyl 3-(*N*-Methylamino)-3-phenylpropanoate. A title compound was obtained by the reduction of (+)-methyl 3-(*N*-*tert*-butyldimethylsiloxy-*N*-methylamino)-3-phenylpropanoate (51% yield based on nitrone **34**). The enantiomeric excess was determined by HPLC analysis using Daicel CHIRALCEL OD-H (10% isopropyl alcohol in hexane, 0.5 mL/min) to be 60% ee: R_f 0.09 (SiO_2, hexane—ethyl acetate = 3 : 2); $[\alpha]^{27}_D$ –3.3° (*c* 0.96, $CHCl_3$) for 60% ee; IR (neat) 3320, 2953, 1734, 1437, 1171, 1138, cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ1.85 (br, 1 H, N*H*), 2.27 (s, 3 H, C*H*$_3$), 2.61 (dd, *J* = 5.6 and 15.6 Hz, 1 H, C*H*HCO), 2.72 (dd, *J* = 8.3 and 15.6 Hz, 1 H, C*H*HCO), 3.64 (s, 3 H, C*H*$_3$), 3.96 (dd, *J* = 5.4 and 8.3 Hz, 1 H, C*H*Ph), 7.20–7.39 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 34.3, 42.5, 51.6, 61.5, 127.0, 127.4, 128.6, 142.4, 172.3; HRMS (EI) calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1085.

(–)-Methyl 3-(*N*-*tert*-Butyldimethylsiloxy-*N*-benzylamino)butanoate. A title compound was obtained by the (*R*)-**23b**-catalyzed reaction of nitrone **34** with **8** in 52% yield as a colorless oil: R_f 0.66 (SiO_2, hexane—ethyl acetate = 5 : 1); $[\alpha]^{28}_D$ –1.1° (*c* 1.37, $CHCl_3$) for 6% ee; IR (neat) 2959, 1746, 1256, 837 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ –0.15 (br, 6 H, C*H*$_3$), 0.84, (s, 9 H, *t*-Bu), 1.15 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$), 2.30 (dd, *J* = 8.3 and 14.7 Hz, 1 H, C*H*HCO), 2.78 (brd, *J* = 9.0 Hz, 1 H, C*H*HCO), 3.41 (dq, *J* = 14.4 and 6.6 Hz, 1 H, C*H*Me), 3.66 (s, 3 H, C*H*$_3$), 3.75 (br, 2 H, C*H*$_2$Ph), 7.18–7.35 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ –4.7, 17.8, 26.1, 39.5, 46.1, 51.4, 71.2, 127.7, 128.2, 128.7, 129.5, 172.1.

Methyl 3-(Benzylamino)butanoate. A title compound was obtained by the reduction of (–)-methyl 3-(*N*-*tert*-butyldimethylsiloxy-*N*-benzylamino)butanoate (36% yield based on nitrone **34**). The enantiomeric excess was determined by HPLC analysis using Daicel CHIRALCEL OD-H (10% isopropyl alcohol in hexane, 0.5 mL/min) to be 6% ee: R_f 0.21 (SiO_2, hexane—ethyl acetate = 3 : 2); IR (neat) 3300, 2955, 1734, 1437, 1294, 1251 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.16 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$), 1.26 (br, 1 H, N*H*), 2.38 (dd, *J* = 6.1 and 15.4 Hz, 1 H, C*H*HCO), 2.50 (dd, *J* = 6.6 and 15.1Hz, 1 H, C*H*HCO), 3.16 (sextet, *J* = 6.6 Hz, 1 H, C*H*Me), 3.67 (s, 3 H, C*H*$_3$), 3.75 (d, *J* = 12.9 Hz, 1 H, C*H*HPh), 3.85 (d, *J* = 12.9 Hz, 1 H, C*H*HPh), 7.18–7.36 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 20.5, 41.5, 49.7, 51.2, 51.4, 126.9, 128.1, 128.4, 140.4, 172.7; HRMS (EI) calcd for $C_{12}H_{17}NO_2$ (M^+) 207.1259, found 207.1274.

(−)-Methyl 3-(*N*-*tert*-Butyldimethylsiloxy-*N*-benzylamino)-3-(4'-fluorophenyl)propanoate. A title compound was obtained by the (*R*)-**23b**-catalyzed reaction of nitrone **36** with **8** in 65% yield as a colorless oil: R_f 0.51 (SiO_2, hexane—ethyl acetate = 5 : 1); $[\alpha]^{26}_D$ −14.2° (*c* 1.07, $CHCl_3$) for 66% ee; IR (neat) 2953, 1744, 1510, 1256, 1225, 1161, 837 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ −0.11 (br, 3 H, C*H*$_3$), 0.10 (br, 3 H, C*H*$_3$), 0.83, (s, 9 H, *t*-Bu), 2.79 (dd, *J* = 9.0 and 15.1 Hz, 1 H, C*H*HCO), 3.15 (dd, *J* = 5.9 and 15.1Hz, 1 H, C*H*HCO), 3.48 (d, *J* = 13.4 Hz, 1 H, C*H*HPh), 3.56 (s, 3 H, C*H*$_3$), 3.78 (d, *J* = 13.4 Hz, 1 H, C*H*HPh), 4.34 (dd, *J* = 6.1 and 9.0 Hz, 1 H, C*H*Ar), 6.96–7.06 (m, 2 H, Ar), 7.16–7.35 (m, 7 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ −4.9, −4.6, 17.9, 26.2, 36.2, 51.5, 60.0, 64.5, 114.8 (d, *J* = 21 Hz), 127.4, 128.2, 129.4, 131.0, 137.2, 162.3 (d, *J* = 246 Hz), 172.0; HRMS (FAB) calcd for $C_{23}H_{32}NO_3F$ (M^+) 417.2136, found 417.2159.

(−)-Methyl 3-(Benzylamino)-3-(4'-fluorophenyl)propanoate. A title compound was obtained by the reduction of (−)-methyl 3-(*N*-*tert*-butyldimethylsiloxy-*N*-benzylamino)-3-(4'-fluorophenyl)propanoate (48% yield based on nitrone **36**). The enantiomeric excess was determined by HPLC analysis using Daicel CHIRALCEL OD-H (2% isopropyl alcohol in hexane, 0.5 mL/min) to be 66% ee: R_f 0.16 (SiO_2, hexane—ethyl acetate = 5 : 1); $[\alpha]^{27}_D$ −25.1° (*c* 1.04, MeOH) for 66% ee; IR (neat) 3320, 1736, 1510, 1223 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.99 (br, 1 H, N*H*), 2.58 (dd, *J* = 5.4 and 15.6 Hz, 1 H, C*H*HCO), 2.70 (dd, *J* = 8.3 and 15.6 Hz, 1 H, C*H*HCO), 3.52 (d, *J* = 13.2 Hz, 1 H, C*H*HPh), 3.62 (s, 3 H, C*H*$_3$), 3.63 (d, *J* = 13.2 Hz, 1 H, C*H*HPh), 4.10 (dd, *J* = 5.4 and 8.3 Hz, 1 H, C*H*Ar), 6.98–7.08 (m, 2 H, Ar), 7.18–7.36 (m, 7 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 42.9, 51.3, 51.6, 58.2, 115.3 (d, *J* = 21 Hz), 126.9, 128.0, 128.3, 128.7 (d, *J* = 8 Hz), 138.2, 140.1, 162.0 (d, *J* = 245 Hz), 172.0; HRMS (FAB) calcd for $C_{17}H_{19}NO_2F$ ($M+H^+$) 288.1400, found 288.1377.

(−)-Methyl 3-(*N*-*tert*-Butyldimethylsiloxy-*N*-benzylamino)-3-(4'-methoxyphenyl)propanoate. A title compound was obtained by the (*R*)-**23b**-catalyzed reaction of nitrone **37** with **8** in 28% yield as a colorless oil: R_f 0.37 (SiO_2, hexane—ethyl acetate = 5 : 1); $[\alpha]^{26}_D$ −13.9° (*c* 1.07, $CHCl_3$) for 37% ee; IR (neat) 2955, 1744, 1514, 1251, 837 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ −0.13 (br, 3 H, C*H*$_3$), 0.06 (br, 3 H, C*H*$_3$), 0.89, (s, 9 H, *t*-Bu), 2.79 (dd, *J* = 9.3 and 15.1 Hz, 1 H, C*H*HCO), 3.15 (dd, *J* = 5.9 and 15.1Hz, 1 H, C*H*HCO), 3.49 (d, *J* = 12.0 Hz, 1 H, C*H*HPh), 3.57 (s, 3 H, C*H*$_3$), 3.76 (br, 1 H, C*H*HPh), 3.80 (s, 3 H, C*H*$_3$), 4.34 (dd, *J* = 6.1 and 9.0 Hz, 1 H, C*H*Ar), 6.83–6.90 (m, 2 H, Ar), 7.17–7.32 (m, 7 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ −4.5, 17.9, 26.2, 45.4, 51.4, 55.2, 59.6, 64.8, 113.3, 127.2, 128.0, 129.9, 130.5, 137.6, 159.1, 172.2.

(−)-Methyl 3-(Benzylamino)-3-(4'-methoxyphenyl)propanoate. A title compound was obtained by the reduction of (−)-methyl 3-(*N*-*tert*-butyldimethylsiloxy-*N*-benzylamino)-3-(4'-methoxyphenyl)propanoate (22% yield based on nitrone **37**). The enantiomeric excess was determined by HPLC analysis using Daicel CHIRALCEL OD-H (10% isopropyl alcohol in hexane, 0.5 mL/min) to be 37% ee: R_f 0.09 (SiO_2, hexane—ethyl acetate = 5 : 1); $[\alpha]^{27}_D$ −16° (*c* 0.9, MeOH) for 37% ee; IR (neat) 3320, 1736, 1512, 1248 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.90 (br, 1 H, N*H*), 2.59 (dd, *J* = 5.4 and

15.4 Hz, 1 H, C*H*HCO), 2.71 (dd, J = 8.5 and 15.4 Hz, 1 H, C*H*HCO), 3.52 (d, J = 13.2 Hz, 1 H, C*H*HPh), 3.62 (s, 3 H, CH_3), 3.65 (d, J = 14.0 Hz, 1 H, C*H*HPh), 3.80 (s, 3 H, CH_3), 4.06 (dd, J = 5.4 and 8.6 Hz, 1 H, C*H*Ar), 6.85–6.91 (m, 2 H, Ar), 7.18–7.34 (m, 7 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 43.0, 51.2, 51.5, 55.2, 58.2, 114.0, 126.8, 128.1, 128.2, 128.3, 134.5, 140.4, 159.0, 172.2; HRMS (FAB) calcd for $C_{18}H_{22}NO_3$ (M+H$^+$) 300.1600, found 300.1645.

(–)-Methyl 3-(*N*-*tert*-Butyldimethylsiloxy-*N*-benzylamino)-3-(1'-naphthyl)propanoate. A title compound was obtained by the (*R*) **23b**-catalyzed-reaction of nitrone **38** with **8** in 92% yield as a colorless oil: R_f 0.54 (SiO_2, hexane—ethyl acetate = 5 : 1); $[\alpha]^{26}_D$ –3.1° (*c* 1.11, $CHCl_3$) for 3% ee; IR (neat) 2930, 1740, 1255 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$, 35 °C) δ –0.40 (br, 3 H, CH_3), 0.00 (br, 3 H, CH_3), 0.89, (s, 9 H, *t*-Bu), 3.09 (dd, J = 9.3 and 15.1 Hz, 1 H, C*H*HCO), 3.36–3.31 (m, 1 H, C*H*HCO), 3.47 (s, 3 H, CH_3), 3.78 (br, 1 H, C*H*HPh), 3.88 (br, 1 H, C*H*HPh), 5.18 (br, 1 H, C*H*Ar), 7.05–8.03 (m, 12 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ –5.1, –4.3, 18.0, 26.3, 34.5, 51.5, 61.5, 124.6, 124.9, 125.3, 125.5, 126.1, 127.4, 128.0, 128.4, 128.5, 130.2, 132.4, 134.0, 137.1, 172.5.

(+)-Methyl 3-(Benzylamino)-3-(1'-naphthyl)propanoate. A title compound was obtained by the reduction of (–)-methyl 3-(*N*-*tert*-butyldimethylsiloxy-*N*-benzylamino)-3-(1'-naphthyl)propanoate (72% yield based on nitrone **38**). The enantiomeric excess was determined by HPLC analysis using Daicel CHIRALPACK AD (3% isopropyl alcohol in hexane, 0.5 mL/min) to be 3% ee: R_f 0.38 (SiO_2, hexane—ethyl acetate = 3 : 1); $[\alpha]^{27}_D$ +1.8° (*c* 1.21, MeOH) for 3% ee; IR (neat) 3320, 1734, 1437, 1172, 802, 779, 737. 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$, 35 °C) δ 2.16 (br, 1 H, N*H*), 2.77 (dd, J = 8.3 and 15.9 Hz, 1 H, C*H*HCO), 2.83 (dd, J = 5.4 and 15.9 Hz, 1 H, C*H*HCO), 3.61 (d, J = 13.2 Hz, 1 H, C*H*HPh), 3.64 (s, 3 H, CH_3), 3.73 (d, J = 13.2 Hz, 1 H, C*H*HPh), 4.99 (dd, J = 5.1 and 8.1 Hz, 1 H, C*H*Ar), 7.17–7.32 (m, 5 H, Ar), 7.43–7.54 (m, 3 H, Ar), 7.72–7.80 (m, 2 H, Ar), 7.84–7.91 (m, 1 H, Ar), 8.17–8.24 (m, 1 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 42.3, 51.6, 51.7, 54.8, 122.9, 123.8, 125.5, 125.6, 126.0, 126.9, 127.9, 128.1, 128.3, 129.0, 131.4, 134.1, 137.9, 140.4, 172.4; HRMS (FAB) calcd for $C_{21}H_{22}NO_2$ (M+H$^+$) 320.1651, found 320.1615.

(–)-Methyl 3-(*N*-*tert*-Butyldimethylsiloxy-*N*-benzylamino)-3-(2'-naphthyl)propanoate. A title compound was obtained by the (*R*)-**23b**-catalyzed reaction of nitrone **39** with **8** in 52% yield as a colorless oil: R_f 0.71 (SiO_2, hexane—ethyl acetate = 5 : 1); $[\alpha]^{27}_D$ –15.8° (*c* 1.01, $CHCl_3$) for 35% ee; IR (neat) 2859, 1740, 1256 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$, 35 °C) δ –0.13 (br, 3 H, CH_3), 0.14 (br, 3 H, CH_3), 0.91, (s, 9 H, *t*-Bu), 2.95 (dd, J = 9.0 and 15.4 Hz, 1 H, C*H*HCO), 3.29 (dd, J = 5.9 and 15.1 Hz, 1 H, C*H*HCO), 3.54 (d, J = 15.6 Hz, 1 H, C*H*HPh), 3.56 (s, 3 H, CH_3), 3.80 (br, 1 H, C*H*HPh), 4.56 (dd, J = 6.1 and 9.0 Hz, 1 H, C*H*Ar), 7.18–7.32 (m, 5 H, Ar), 7.43–7.59 (m, 3 H, Ar), 7.72–7.86 (m, 4 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ –4.9, –4.7, 18.0, 26.2, 35.9, 51.5, 59.9, 65.6, 125.9, 127.3, 127.5, 127.6, 127.8, 128.1, 128.2, 129.9, 133.0, 133.1, 137.5, 172.2.

(–)-Methyl 3-(Benzylamino)-3-(2'-naphthyl)propanoate. A title compound was obtained by the reduction of (–)-methyl 3-(*N-tert*-butyldimethylsiloxy-*N*-benzylamino)-3-(2'-naphthyl)propanoate (27% yield based on nitrone **39**). The enantiomeric excess was determined by HPLC analysis using Daicel CHIRALPACK AD (5% isopropyl alcohol in hexane, 0.5 mL/min) to be 35% ee: R_f 0.32 (SiO_2, hexane—ethyl acetate = 3 : 1); $[\alpha]^{26}_D$ –11.7° (*c* 0.522, MeOH) for 35% ee; IR (neat) 3340, 1736, 1437, 1169, 748, 740, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 2.13 (br, 1 H, N*H*), 2.70 (dd, *J* = 5.4 and 15.6 Hz, 1 H, C*H*HCO), 2.81 (dd, *J* = 8.5 and 15.6 Hz, 1 H, C*H*HCO), 3.57 (d, *J* = 13.2 Hz, 1 H, C*H*HPh), 3.62 (s, 3 H, CH_3), 3.68 (d, *J* = 13.4 Hz, 1 H, C*H*HPh), 4.28 (dd, *J* = 5.4 and 8.5 Hz, 1 H, C*H*Ar), 7.18–7.34 (m, 5 H, Ar), 7.41–7.54 (m, 3 H, Ar), 7.70–7.87 (m, 4 H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 42.8, 51.4, 51.6, 59.0, 124.9, 125.8, 126.1, 126.2, 126.9, 127.7, 127.8, 128.1, 128.3, 128.5, 133.1, 133.4, 140.0, 140.3, 172.1; HRMS (FAB) calcd for $C_{21}H_{22}NO_2$ ($M+H^+$) 320.1651, found 320.1666.

***N-tert*-Butydimethylsilyloxy-2-methoxycarbonyl-2-(methoxycarbonylmethyl)pyrrolidine (41).** A title compound **41** was obtained by the reaction of nitrone **40** with ketene silyl acetal **8** in the presence of a chiral Lewis acid catalyst (20 mol%), and the enantiomeric excess was determined by the ^1H NMR analysis using chiral shift reagent Eu(hfc)$_3$. The results were shown in text: R_f 0.46 (SiO_2, hexane—ethyl acetate = 5 : 1); $[\alpha]^{25}_D$ +19.1° (c 0.728, $CHCl_3$) for the *R* isomer (61% ee); IR (neat) 2955, 1742, 1437, 1352, 1250, 1205, 1185, 860, 837, 781 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 0.08 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), 0.86 (s, 9 H, CH_3), 1.68–2.03 (m, 3 H), 2.43 (d, *J* = 16.8 Hz, 1 H, C*H*HCO), 2.48–2.68 (m, 1 H), 3.06–3.15 (m, 2 H), 3.24 (d, *J* = 16.6 Hz, 1 H, C*H*HCO), 3.65 (s, 3 H, CH_3O), 3.68 (s, 3 H, CH_3O); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ –4.8, –4.7, 17.5, 19.6, 25.8, 31.6, 40.2 (br), 51.3, 51.4, 56.2, 72.3, 171.8, 172.0; HRMS (FAB) calcd for $C_{15}H_{30}NO_5Si$ ($M+H^+$) 332.1893, found 332.1908.

Determination of the Absolute Configuration of (–)-(*S*)-Methyl 3-(*N-tert*-Butyldimethylsiloxy-*N*-benzylamino)-3-phenylpropanoate (10). To a solution of β-amino ester (–)-**13** (48% ee) (135 mg, 0.5 mL) in MeOH (3.0 mL) were added 2 M HCl (1.0 mL) and 10% Pd/C (50% wet) (107 mg, 0.05 mmol), and this mixture was stirred under hydrogen atmosphere at room temperature for 19 h. After the catalyst was filtered off, the filtrate was concentrated to give hydrochloride **14** (112 mg) as an solid: $[\alpha]^{25}_D$ +3.7° (*c* 2.06, MeOH) (lit.[39] $[\alpha]_D$ +7.8° (*c* 2, MeOH) for the *S* isomer).

(*S*)-(–)-Methyl 3-Amino-3-phenylpropanoate. Hydrochloride **14** was treated with sat. $NaHCO_3$ (5 mL), and was extracted with CH_2Cl_2 (10 mL x 3) and the combined extracts were dried over Na_2SO_4. Evaporation afforded a colorless oil (62 mg, 69%): $[\alpha]^{22}_D$ +0.84° (*c* 1.90, MeOH) for 48% ee; IR (neat) 3645, 2951, 1732, 1439, 1200, 1175, 1020, 764, 702 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.70 (br, 2 H, NH_2), 2.58–2.71 (m, 2 H, CH_2CO), 3.68 (s, 3 H, CH_3), 4.40 (dd, *J* = 6.3 and 7.3 Hz, 1 H, C*H*Ph), 7.21–7.39 (m, 5 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 44.4, 51.5, 52.6, 126.1, 127.3, 128.6, 144.7, 172.4.

Preparation of (–)-(*S*)-Methyl *N*-Benzyloxycarbonyl-3-amino-3-phenylpropanoate. Obtained β-phenylalanine methyl ester was protected by benzyloxycarbonyl (Z) group upon treatment with benzyl chloroformate and $NaHCO_3$ in ethyl acetate—H_2O (4 : 1, 25 mL), and after separation, the obtained oil residue was purified by column chromatography on silica gel (10 mL, 10—20% ethyl acetate in hexane) to give (–)-(*S*)-methyl *N*-benzyloxycarbonyl-3-amino-3-phenylpropanoate (110 mg, 70%). The enantiomeric excess was determined by HPLC analysis using CHIRALCEL OD (5% IPA in hexane, 1 mL/min) to be 49% ee: R_f 0.30 (SiO_2, hexane—ethyl acetate = 3 : 1); $[\alpha]^{22}_D$ –10.5° (*c* 1.17, MeOH) for 49% ee; IR (neat) 3320, 3034, 2953, 1720, 1705, 1530, 1368, 1046 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 2.82 (dd, *J* = 6.1 and 15.7 Hz, 1 H, C*H*HCO), 2.90 (dd, *J* = 6.4 and 15.9 Hz, 1 H, C*H*HCO), 3.59 (s, 3 H, C*H*$_3$O), 5.06 (d, *J* = 12.4 Hz, 1 H, C*H*HPh), 5.12 (d, *J* = 12.2 Hz, 1 H, C*H*HPh), 5.16 (dt, *J* = 8.3 and 6.1 Hz, 1 H, C*H*Ph), 5.72 (br, 1 H, N*H*), 7.21–7.36 (m, 10 H, Ph); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 40.5, 51.7, 66.8, 126.1, 127.6, 128.0, 128.4, 128.7, 136.4, 140.8, 155.6, 171.2.

Determination of the Absolute Configuration of (+)-(*R*)-*N*-*tert*-Butydimethylsilyloxy-2-methoxycarbonyl-2-(methoxycarbonylmethyl)pyrrolidine (41). Amino ester (+)-**41** (55% ee) (212 mg, 0.64 mmol) was dissolved in methanol (5.0 mL) and 4 M HCl (1.0 mL). After addition of 10% Pd/C (50% wet) (68 mg), hydrogenation was carried out at room temperature and atmospheric pressure for 18 h. After the catalyst was filtered off, then the solvent was removed by evaporation. The oil residue was treated with sat. $NaHCO_3$ (10 mL), then extracted with CH_2Cl_2 (15 mL x 6) and dried over Na_2SO_4. Evaporation afforded (–)-(*R*)-2-methoxycarbonyl-2-(methoxycarbonylmethyl)pyrrolidine (**56**) (97 mg, 75%): $[\alpha]^{23}_D$ –38.9° (*c* 1.32, MeOH) for 55% ee; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 1.67–1.91 (m, 3 H), 1.98–2.15 (m, 1 H), 2.58 (d, *J* = 16.1 Hz, 1 H, C*H*HCO), 2.91 (br, 1 H, N*H*), 3.05 (d, *J* = 16.6 Hz, 1 H, C*H*HCO), 2.95–3.21 (m, 2 H, C*H*$_2$N), 3.65 (s, 3 H, C*H*$_3$O), 3.74 (s, 3 H, C*H*$_3$O); ^{13}C NMR (270 MHz, $CDCl_3$, 35 °C) δ 24.8, 36.6, 44.3, 46.8, 51.5, 52.4, 66.2, 171.6, 176.6.

Preparation of Camphorsulfonyl amide 57. Camphorsulfonyl amide **57** was prepared as follows; (–)-**56** (96 mg, 0.477 mmol) and (–)-camphorsulfonyl chloride (264 mg, 1.0 mmol) were dissolved in CH_2Cl_2 (2.0 mL) with ice cooling under argon. To the mixture were added triethylamine (0.22 mL, 1.58 mmol) and *N*,*N*-dimethylaminopyridine (6 mg, 0.05 mmol), then the mixture was stirred at room temperature for 2 weeks. To the resultant mixture was added sat. $NaHCO_3$ (5 mL), and extracted with ethyl acetate (10 mL x 2). The combined extracts were dried over $MgSO_4$. After evaporation, the residue was purified by column chromatography on silica gel (15 mL, 20% ethyl acetate in hexane) to give **57** as a diastereomeric mixture (146 mg, 74%), and the diastereomeric excess was 57% by ^1H NMR analysis. Recrystallization from diethyl ether gave **57** as a single diastereomer: R_f 0.26 (SiO_2, hexane—ethyl acetate = 3 : 2); mp 103.0–104.0 °C (diethyl ether); $[\alpha]^{26}_D$ –4.4° (*c* 0.55, $CHCl_3$); IR (KBr) 1745, 1735, 1371, 1196, 1145 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 35 °C) δ 0.89 (s, 3 H, C*H*$_3$), 1.14 (s, 3 H, C*H*$_3$), 1.39 (ddd, *J* = 4.2, 10.3, and 13.5 Hz, 1 H), 1.53–1.66 (m, 1 H), 1.86–2.17 (m, 5 H), 2.29 (ddd, *J* = 6.1,

7.3, and 13.2 Hz, 1 H), 2.37 (dt, J = 17.6 and 3.7 Hz, 1 H), 2.46–2.59 (m, 1 H), 2.60 (dt, J = 13.2 and 3.6 Hz, 1 H), 3.00 (d, J = 14.9, 1 H, C*H*H), 3.10 (d, J = 15.6 Hz, 1 H, C*H*H), 3.21 (d, J = 15.6 Hz, 1 H, C*H*H), 3.52 (dt, J = 8.8 and 6.6 Hz, 1 H), 3.57 (d, J = 14.9 Hz, 1 H, C*H*H), 3.65–6.75 (m, 1 H), 3.70 (s, 3 H, CH_3), 3.79 (s, 3 H, CH_3); ^{13}C NMR (68 MHz, $CDCl_3$, 35 °C) δ 19.8, 20.2, 23.6, 25.2, 26.9, 37.5, 40.0, 42.6, 42.9, 47.7, 49.4, 49.6, 51.7, 52.8, 58.6, 68.8, 170.9, 173.4, 215.1; HRMS (FAB) calcd for $C_{19}H_{30}NO_7S$ ($M+H^+$) 416.1743, found 416.1750.

X-Ray Structure Analysis of Camphorsulfonyl amide 57. A single crystal of **57** was grown in Diethyl ether. Crystal data, collection parameters, and refinement parameters were summarized in Table 14.[76] Atomic coordinates, anisotropic thermal parameters, bond lengths, and selected bond angles were shown in Table 15, 16, 17, and 18, respectively. Hydrogen atoms were idealized with C-H = 0.95 Å.

Table 14. Crystal Data, Collection Parameters, and Refinement Parameters for **58**

molecular formula	$C_{19}H_{29}NO_7S$
fw	415.50
crystal color, habit	colorless, prismatic
dimensions, mm	0.50 x 0.40 x 0.30
radiation, Å	Mo-Kα (0.71069)
crystal system	monoclinic
lattice type	primitive
lattice parameters	
a, Å	9.726(3)
b, Å	9.271(7)
c, Å	12.003(3)
β, °	95.61(2)
V, Å^3	1077(9)
space group	$P2_1$ (#4)
Z	2
D_{calc}, g/cm^3	1.281
reflections collected	2781
reflections unique	2633
reflections observed	1111
scan width, °	1.84 + 0.30 tan θ
F (000)	444.00
temp, °C	20.0
μ, cm^{-1}	1.88
no. of variables	252
shift/error at final cycle	0.17
ρ_{max}, e^-/Å^3	0.65
ρ_{min}, e^-/Å^3	–0.47
R	0.113
R_w	0.105
goodness of fit	4.60

Table 15. Atomic coordinates and B_{eq} of 58[a]

atom	x	y	z	B_{eq}
S(1)	–0.7836(5)	0.0000	–0.1005(4)	3.7(1)
O(1)	–0.929(1)	–0.020(2)	–0.120(1)	6.0(4)
O(2)	–0.696(1)	–0.121(2)	–0.0892(9)	4.4(3)
O(3)	–0.557(1)	–0.178(2)	0.153(1)	4.6(4)
O(4)	–0.781(1)	–0.128(2)	0.155(1)	5.1(4)
O(5)	–0.379(1)	0.083(2)	0.251(1)	6.3(4)
O(6)	–0.264(2)	0.025(2)	0.107(1)	7.3(5)
O(7)	–0.951(2)	0.209(3)	–0.364(1)	11.2(7)
N(1)	–0.751(1)	0.092(2)	0.007(1)	3.7(4)
C(1)	–0.644(2)	0.060(2)	0.100(2)	3.4(5)
C(2)	–0.681(2)	0.165(2)	0.191(2)	4.8(6)
C(3)	–0.779(3)	0.255(3)	0.147(3)	11(1)
C(4)	–0.837(2)	0.216(2)	0.038(2)	5.3(6)
C(5)	–0.649(2)	–0.095(2)	0.140(1)	3.0(5)
C(6)	–0.808(2)	–0.279(4)	0.185(2)	7.7(8)
C(7)	–0.501(2)	0.081(2)	0.063(2)	5.5(6)
C(8)	–0.382(3)	0.062(3)	0.152(2)	5.8(7)
C(9)	–0.141(3)	0.021(3)	0.178(2)	9.8(9)
C(10)	–0.732(2)	0.109(2)	–0.207(1)	4.5(6)
C(11)	–0.762(2)	0.047(2)	–0.325(1)	2.4(4)
C(12)	–0.866(3)	0.127(3)	–0.397(2)	7.5(9)
C(13)	–0.853(3)	0.084(4)	–0.522(2)	9.0(9)
C(14)	–0.728(2)	0.001(4)	–0.505(2)	6.4(7)
C(15)	–0.775(2)	–0.145(3)	–0.465(1)	6.8(7)
C(16)	–0.804(2)	–0.106(2)	–0.347(2)	6.3(7)
C(17)	–0.642(2)	0.059(3)	–0.402(2)	6.1(7)
C(18)	–0.598(3)	0.218(4)	–0.420(2)	9(1)
C(19)	–0.519(2)	–0.032(4)	–0.360(2)	8.5(8)
H(1)	–0.7013	0.1082	0.2536	6.7320
H(2)	–0.5930	0.2161	0.2160	6.7320
H(3)	–0.8549	0.2516	0.1975	12.6907
H(4)	–0.7476	0.3525	0.1499	12.6907
H(5)	–0.8253	0.2950	–0.0108	5.6924
H(6)	–0.9279	0.1886	0.0369	5.6924
H(7)	–0.9003	–0.2912	0.1900	8.3317
H(8)	–0.7778	–0.3366	0.1241	8.3317

Table 15. (continued)

atom	x	y	z	B_{eq}
H(9)	–0.7523	–0.3015	0.2508	8.3317
H(10)	–0.4816	0.0150	0.0057	6.9126
H(11)	–0.4916	0.1769	0.0365	6.9126
H(12)	–0.1437	–0.0442	0.2374	11.1138
H(13)	–0.0623	–0.0036	0.1370	11.1138
H(14)	–0.1174	0.1166	0.2108	11.1138
H(15)	–0.7765	0.1983	–0.2038	5.7077
H(16)	–0.6347	0.1204	–0.1949	5.7077
H(17)	–0.9315	0.0457	–0.5574	11.7973
H(18)	–0.8346	0.1787	–0.5571	11.7973
H(19)	–0.6852	–0.0097	–0.5710	7.6464
H(20)	–0.8527	–0.1802	–0.5116	8.0843
H(21)	–0.7008	–0.2132	–0.4674	8.0843
H(22)	–0.7557	–0.1713	–0.2943	6.4568
H(23)	–0.9029	–0.1219	–0.3401	6.4568
H(24)	–0.5705	0.2583	–0.3516	10.9019
H(25)	–0.5336	0.2220	–0.4713	10.9019
H(26)	–0.6831	0.2671	–0.4523	10.9019
H(27)	–0.5408	–0.1251	–0.3607	8.9506
H(28)	–0.4460	–0.0136	–0.4119	8.9506
H(29)	–0.4826	0.0051	–0.2898	9.5533

[a] $B_{eq} = (8/3)\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$.

Table 16. Anisotropic Displacement Parameters of 58[a]

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S(1)	0.054(3)	0.052(4)	0.036(3)	0.006(4)	0.011(2)	–0.004(3)
O(1)	0.050(8)	0.12(1)	0.063(9)	–0.02(1)	0.009(7)	0.01(1)
O(2)	0.085(9)	0.045(9)	0.039(8)	0.033(9)	0.008(7)	–0.013(7)
O(3)	0.055(9)	0.039(9)	0.08(1)	0.028(8)	0.011(8)	0.019(8)
O(4)	0.044(9)	0.09(1)	0.064(9)	0.005(9)	0.021(8)	0.044(10)
O(5)	0.08(1)	0.08(1)	0.07(1)	–0.011(10)	–0.001(9)	0 02(1)
O(6)	0.08(1)	0.07(1)	0.13(1)	–0.01(1)	0.00(1)	0.00(1)
O(7)	0.10(1)	0.23(3)	0.09(1)	0 10(2)	0.00(1)	–0 01(2)
N(1)	0.07(1)	0.017(9)	0.05(1)	0.035(9)	0.001(9)	0.034(8)
C(1)	0.05(1)	0.02(1)	0.06(1)	0.03(1)	0.02(1)	0.01(1)
C(2)	0.14(2)	0.01(1)	0.04(1)	0.02(1)	0.00(1)	0.002(10)
C(3)	0.13(3)	0.11(3)	0.18(3)	0.13(2)	–0.06(2)	–0.09(2)
C(4)	0.10(2)	0.05(2)	0.05(1)	0.00(2)	–0.02(1)	0.03(1)
C(5)	0.03(1)	0.04(1)	0.05(1)	0.02(1)	0.015(10)	0.01(1)
C(6)	0.07(2)	0.14(3)	0.09(2)	0.00(2)	0.02(1)	0.06(2)
C(7)	0.08(2)	0.05(1)	0.07(1)	–0.03(1)	–0.03(1)	0.00(1)
C(8)	0.08(2)	0.05(2)	0.09(2)	–0.01(2)	0.03(2)	–0.01(2)
C(9)	0.09(2)	0.09(2)	0.19(3)	–0.03(2)	–0.04(2)	–0.02(2)
C(10)	0.06(1)	0.09(2)	0.02(1)	–0.02(1)	0.009(9)	0.01(1)
C(11)	0.025(9)	0.03(1)	0.04(1)	0.022(9)	0.000(8)	0.003(9)
C(12)	0.09(2)	0.13(3)	0.07(2)	0.04(2)	0.03(2)	–0.01(2)
C(13)	0.14(2)	0.16(3)	0.04(1)	0.01(2)	–0.02(1)	0.06(2)
C(14)	0.07(1)	0.14(3)	0.04(1)	0.01(2)	0.01(1)	0.03(2)
C(15)	0.13(2)	0.13(2)	0.007(10)	–0.04(2)	0.01(1)	–0.04(1)
C(16)	0.10(2)	0.05(2)	0.09(2)	–0.05(2)	–0.01(2)	–0.01(1)
C(17)	0.07(1)	0.12(2)	0.04(1)	–0.01(2)	–0.01(1)	0.04(2)
C(18)	0.16(3)	0.14(3)	0.09(2)	–0.07(2)	0.07(2)	0.03(2)
C(19)	0.07(2)	0.15(3)	0.09(2)	0.01(2)	–0.01(1)	–0.04(2)

[a]The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 17. Bond Lengths (Å) of **58**

atom	atom	distance	atom	atom	distance
S(1)	O(1)	1 42(1)	S(1)	O(2)	1.41(1)
S(1)	N(1)	1 56(2)	S(1)	C(10)	1.74(2)
O(3)	C(5)	1.18(2)	O(4)	C(5)	1.35(2)
O(4)	C(6)	1.47(3)	O(5)	C(8)	1.20(2)
O(6)	C(8)	1.36(2)	O(6)	C(9)	1.41(3)
O(7)	C(12)	1.21(3)	N(1)	C(1)	1 48(2)
N(1)	C(4)	1.48(2)	C(1)	C(2)	1.53(2)
C(1)	C(5)	1.51(2)	C(1)	C(7)	1 52(3)
C(2)	C(3)	1.34(3)	C(3)	C(4)	1.42(3)
C(7)	C(8)	1 51(3)	C(10)	C(11)	1.53(2)
C(11)	C(12)	1 46(3)	C(11)	C(16)	1.50(3)
C(11)	C(17)	1 56(3)	C(12)	C(13)	1.57(3)
C(13)	C(14)	1 44(3)	C(14)	C(15)	1.52(3)
C(14)	C(17)	1 52(3)	C(15)	C(16)	1.51(3)
C(17)	C(18)	1.56(4)	C(17)	C(19)	1.51(3)

Table 18. Bond Angles (°) of **58**

atom	atom	atom	angle	atom	atom	atom	angle
O(1)	S(1)	O(2)	119(1)	O(1)	S(1)	N(1)	109 2(8)
O(1)	S(1)	C(10)	107.9(8)	O(2)	S(1)	N(1)	106 6(7)
O(2)	S(1)	C(10)	108 4(9)	N(1)	S(1)	C(10)	104.0(8)
C(5)	O(4)	C(6)	116(1)	C(8)	O(6)	C(9)	117(2)
S(1)	N(1)	C(1)	125(1)	S(1)	N(1)	C(4)	123(1)
C(1)	N(1)	C(4)	109(1)	N(1)	C(1)	C(2)	102(1)
N(1)	C(1)	C(5)	113(1)	N(1)	C(1)	C(7)	110(1)
C(2)	C(1)	C(5)	111(1)	C(2)	C(1)	C(7)	114(1)
C(5)	C(1)	C(7)	105(1)	C(1)	C(2)	C(3)	108(1)
C(2)	C(3)	C(4)	114(2)	N(1)	C(4)	C(3)	104(1)
O(3)	C(5)	O(4)	123(1)	O(3)	C(5)	C(1)	128(1)
O(4)	C(5)	C(1)	108(1)	C(1)	C(7)	C(8)	116(1)
O(5)	C(8)	0(6)	119(2)	O(5)	C(8)	C(7)	128(2)
O(6)	C(8)	C(7)	111(2)	S(1)	C(10)	C(11)	114(1)
C(10)	C(11)	C(12)	114(1)	C(10)	C(11)	C(16)	123(1)
C(10)	C(11)	C(17)	115(1)	C(12)	C(11)	C(16)	102(1)
C(12)	C(11)	C(17)	97(1)	C(16)	C(11)	C(17)	99(1)
O(7)	C(12)	C(11)	125(2)	O(7)	C(12)	C(13)	125(2)
C(11)	C(12)	C(13)	108(2)	C(12)	C(13)	C(14)	98(1)
C(13)	C(14)	C(15)	104(2)	C(13)	C(14)	C(17)	108(2
C(15)	C(14)	C(17)	102(1)	C(14)	C(15)	C(16)	99(1)
C(11)	C(16)	C(15)	108(1)	C(11)	C(17)	C(14)	94(1)
C(11)	C(17)	C(18)	112(2)	C(11)	C(17)	C(19)	112(1)
C(14)	C(17)	C(18)	110(2)				

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