Kinetic Resolution of Isoxazolidines by a Pd−BINAP Complex

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Asymmetric decomposition of isoxazolidine derivatives under catalysis by optically active palladium(II) complexes was examined. When racemic ethyl *cis*-2,5-dimethyl-5-phenylisoxazolidine-3-carboxylate (*cis*-**1a**) was treated with a catalytic amount of $[Pd(MeCN)_2\{(S)\text{-TolBINAP}\}](BF_4)_2$ in CH_2Cl_2 for 60 h, optically active substrate was recovered with 99% *ee* and in 48% yield. The highest selectivity was achieved on treatment of racemic ethyl *trans*-2,4-dimethyl-5,5-diphenylisoxazolidine-3-carboxylate, to give the optically active substrate in 74% yield with 35% *ee*. The k_f/k_s value of this reaction reaches as high as 732. For this decomposition, each substrate should have both a methyl group on the 2-position and an alkoxycarbonyl group on the 3-position of the isoxazolidine ring. The enantioselectivities of the recovered substrates were influenced not only by the other substituent groups on the 4- and 5-positions but also by the geometrical structures of the substrates.

Introduction

The 1,3-dipolar cycloaddition reaction is a very useful method for the synthesis of five-membered heterocycles.[1] Isoxazolidines obtained from 1,3-dipolar cycloaddition reactions between nitrones and olefins are important for the preparation of natural products such as 3-amino alcohols and alkaloids.[2] Recently, in order to obtain optically active isoxazolidines, asymmetric 1,3-dipolar cycloaddition reactions catalyzed by chiral Lewis acids have been reported.[3]

In our laboratory, asymmetric 1,3-dipolar cycloaddition reactions between nitrones and olefins in the presence of palladium(II) complexes have been investigated.[4] During the course of this study, it was found that optically active isoxazolidines could be formed by the kinetic resolution of some racemic isoxazolidines under catalysis by chiral palladium(II) complexes.

Kinetic resolution is one of the most popular methods for the preparation of chiral materials. Enzymes are frequently used for this purpose, and show good selectivity for the resolution of alcohols.[5] Artificial catalysts have now attracted attention for kinetic resolution,[6] and have successfully been applied for the epoxidation of allylic alcohols,[7a] the ring-opening of epoxides,[7b] polymerization,[7c] the carbonyl-ene reaction,[7d] zirconocene-catalyzed alkylation,[7e] and isomerization.[7f] New catalysts for kinetic resolution are still desired for the production of new kinds of optically active materials. We wish to describe here the kinetic resolution of isoxazolidines by palladium complexes.

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Results and Discussion

Reactions were typically performed as follows: Ethyl *cis*-2,5-dimethyl-5-phenylisoxazolidine-3-carboxylate (*cis*-**1a**, 0.4 mmol), solvent (2 mL), and catalyst (0.04 mmol) were placed in a Schlenk tube and the mixture was stirred at room temperature for a suitable time, determined by TLC. The reaction mixture was then concentrated and separated by column chromatography (see Exp. Sect.). Analysis of recovered substrate *cis*-**1a** by chiral HPLC gave the enantiomeric excess. In kinetic resolution, the enantiomeric excesses were also affected by conversion of the substrate, and so the k_f/k_s value was used to estimate the selectivity of the reaction. The k_f/k_s value is defined as the rate of the more rapidly reacting isomer/the rate of the more slowly reacting isomer.[8] The k_f/k_s value of the reaction is actually calculated by the following Equation:

$k_f/k_s = \ln\{Re(1 - ee)\}/\ln\{Re(1 + ee)\}$ [Re = (% of the recovered substrate)/100; *ee* = (% *ee* of the recovered substrate)/100]

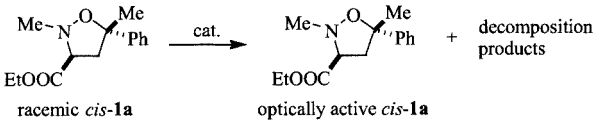
The catalyst was first examined for this decomposition (Table 1). Substrate *cis*-**1a** gradually decomposed in the presence of a catalytic amount of $PdCl_2(PhCN)_2$ (Scheme 1, Table 1, Entry 1), but the addition of BINAP to this complex did not catalyze the decomposition. On the other hand, cationic species prepared in situ from $[Pd(CH_3CN)_4][BF_4]_2$ (**2**) and (*S*)-BINAP showed catalytic activity for this decomposition, resulting in a 52% recovered yield of *cis*-**1a** with

Table 1. Kinetic resolution of isoxazolidine *cis*-**1a** under catalysis by transition metal complexes

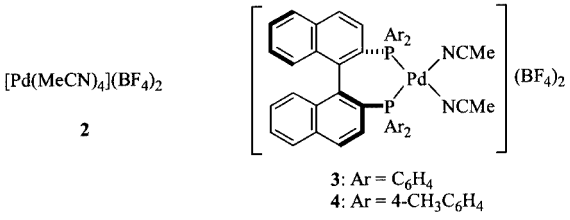
Entry[a]	Catalyst	Time [h]	Recovered *cis*-**1a** (%)[b]	*ee* (%)[c]	k_f/k_s
1	$PdCl_2(PhCN)_2$	114	80	–	–
2[d]	$PdCl_2(PhCN)_2$ + (*S*)-BINAP	48	99	0	–
3	**2** + (*S*)-BINAP	45	52	57	7
4	**3**	45	48	78	14
5	**4**	40	55	76	62
5[e]	**4**	24	54	70	21
6	$Ru(OTf)_2$\{(*S*)-BINAP\}	45	37	5	1
7	$[Rh(C_8H_{12})_2]BF_4$ + (*S*)-BINAP	45	36	0	–

[a] Reaction conditions: *cis*-**1a** (0.4 mmol) and catalyst (10 mol %) were dissolved in CH_2Cl_2 (2 mL), and the resulting mixture was then stirred at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC (Daicel Chiralcel OJ-R). [d] 0.6 mmol scale. [e] Reflux.

57% *ee* after 45 h. The k_f/k_s value of this reaction is 7. Interestingly, [Pd\{(*S*)-BINAP\}$(CH_3CN)_2$][BF_4]$_2$ (**3**, 10 mol % to substrate), which was prepared separately, was used as a catalyst to give a k_f/k_s value of 14. The reaction was very sluggish when amounts of the catalyst smaller than 10 mol % were used. Higher reaction temperature resulted for similar conversions in shorter reaction times but with lower selectivity. [$Ru(OTf)_2$\{(*S*)-BINAP\}] and [$Rh(C_8H_{12})_2$]BF_4 + (*S*)-BINAP showed good catalytic activities but almost no stereoselectivities (Table 1). Consequently, [Pd\{(*S*)-TolBINAP\}$(CH_3CN)_2$][BF_4]$_2$ (Scheme 2; **4**, 10 mol % to substrate) showed the best selectivity for this reaction at room temperature.



Scheme 1



Scheme 2

On treatment with [Pd\{(*S*)-TolBINAP\}$(MeCN)_2$]$(BF_4)_2$ (**4**) in CH_2Cl_2 (2 mL) for 40 h, the substrate was recovered with 76% *ee* and in 55% yield. The k_f/k_s value of this reaction is 62. This showed that the stereoselectivity of this reaction is greatly affected by the chiral ligand. Various chiral phosphorus bidentate ligands were therefore examined as catalysts, prepared in situ by mixing of $[Pd(CH_3CN)_4](BF_4)_2$ (**2**) and a ligand. Results are listed in Table 2. In the case of TolBINAP, the k_f/k_s value of this reaction is 13. This is still lower than the reaction in the presence of pre-prepared complex **4**, the same as in the case of BINAP. Other chiral diphosphanes tested showed selectivities as low as 4 (k_f/k_s value) (Table 2, Entries 2−13). These results showed that TolBINAP is extremely effective for this reaction.

Solvent effects on this decomposition were next examined (Table 3). CH_2Cl_2, $CHCl_3$, and THF displayed almost identical solvent effects, while CH_3CN gave lower stereoselectivity. It is thought that there is competition between a chiral ligand and CH_3CN to coordinate to the palladium metal center.

Interestingly, the stereoselectivity was strongly affected by the amount of the solvent. When the reaction of substrate *cis*-**1a** (0.4 mmol) in the presence of **4** in CH_2Cl_2 was performed in various quantities of solvent, more concentrated solutions were found to accelerate the reaction, but to give lower selectivities. A k_f/k_s value of 19 was obtained from the reaction in CH_2Cl_2 (1 mL) for 24 h (45% recovered yield), while the same reaction with the substrate **1a** in CH_2Cl_2 (4 mL) for 40 h afforded *cis*-**1a** with a k_f/k_s value of 245 and in 52% yield. In a mixture of CH_2Cl_2 (4 mL) and hexane (4 mL) as the solvent, *cis*-**1a** was recovered after 100 h with 69% *ee* − which means a k_f/k_s value of 585 − and in 59% yield.

The stereoselectivity of this reaction was strongly influenced by the substituents on the isoxazolidine ring (Scheme 3, Table 4). Compound *cis*-**1a** was stereoselectively decomposed with a k_f/k_s value of 62, while its isomer *trans*-**1a** was decomposed with low selectivity, showing a k_f/k_s value of 2. As far as the substituent R^1 on the nitrogen atom was concerned, the best choice for this reaction was the methyl substituent, and the bulkier benzyl derivatives *cis*- and *trans*-**1b** were not decomposed at all. The substituent R^2 on C-3 was very important for this reaction. When R^2 was phenyl, the decomposition reaction scarcely proceeded. With an alkoxycarbonyl substituent as R^2, the ethoxycarbonyl and isopropoxycarbonyl moieties provided good selectivity, but the presence of the benzyloxycarbonyl substituent decreased the selectivity. For R^3, R^4, and R^5, several substitution patterns were examined. Among the substrates, *trans*-**1i**, with a methyl group as R^3 and phenyl groups as R^4 and R^5, was decomposed most efficiently, giving the product with a k_f/k_s value of 732.

^{1}H NMR experiments showed that four kinds of decomposition products were observed on treatment of *cis*-**1a** in this manner. These were acetophenone (**5**), ethyl 2-oxopro-

Table 2. Ligand effect on kinetic resolution of *cis*-**1a** under catalysis by Pd complexes

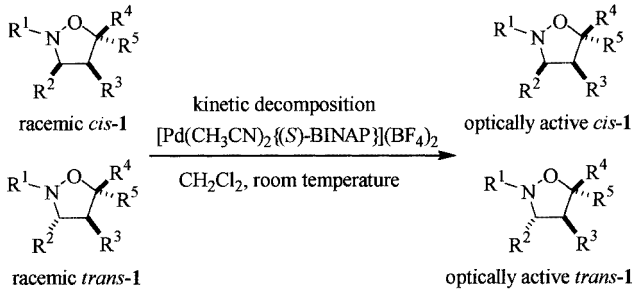
Entry[a]	Ligand	Time [h]	Recovered *cis*-**1a** (%)[b]	*ee* (%)[c]	k_f/k_s
1	(*S*)-TolBINAP	70	59	53	13
2	(*R*,*R*)-DIOP	70	59	0	–
3	(*R*,*R*)-MOD-DIOP	70	56	24	2
4[d]	(*R*)-PROPHOS	70	38	0	–
5	(*R*,*R*)-CHIRAPHOS	70	32	0	–
6	(*R*,*R*)-NORPHOS	40	61	0	–
7	(*S*,*S*)-BDPP	40	44	10	1
8	(*R*,*R*)-Me-DUPHOS	40	29	7	1
9	(*R*,*R*)-Me-BPE	20	52	0	–
10	(*R*,*R*)-Et-BPE	20	63	0	–
11	(*S*,*S*)-BPPM	70	71	0	–
12	(*S*,*S*)-BCPM	70	71	16	3
13	(*S*,*R*)-BPPFA	70	58	37	4

[a] Reaction conditions: **2** (0.04 mmol) and ligand (0.042 mmol) were dissolved in CH_2Cl_2 (0.5 mL) and CH_3CN (0.5 mL), and the solvent was then removed under vacuum for 1 h. Catalyst (0.04 mmol) and *cis*-**1** (0.4 mmol) were dissolved in CH_2Cl_2 (4 mL), and the resulting mixture was then stirred at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC (Daicel Chiralcel OJ-R). [d] Suspension.

Table 3. Effect of concentration on asymmetric decomposition of *cis*-**1a** under catalysis by Pd complexes

Entry[a]	Cat.	Solvent (mL)	Time [h]	Recovered *cis*-**1a** (%)[b]	*ee* (%)[c]	k_f/k_s
1	**3**	CH_2Cl_2 (2)	45	48	78	14
2	**3**	CH_2Cl_2 (4)	70	52	75	22
3	**3**	$CHCl_3$ (4)	70	53	74	24
4	**3**	THF (4)	70	71	47	23
5	**3**	CH_3CN (4)	70	61	46	10
6	**3**	CH_2Cl_2 (2) + C_6H_{14} (2)	70	61	59	45
7	**4**	CH_2Cl_2 (1)	24	45	89	19
8	**4**	CH_2Cl_2 (2)	40	55	76	62
9	**4**	CH_2Cl_2 (3)	60	48	99	116
10	**4**	CH_2Cl_2 (4)	70	52	90	245
11	**4**	CH_2Cl_2 (4) + C_6H_{14} (4)	100	59	69	585

[a] A mixture of *cis*-**1a** (0.4 mmol) and catalyst (0.04 mmol) in solvent was stirred at room temperature for an appropriate time. [b] Isolated yield. [c] Determined by chiral HPLC (Daicel Chiralcel OJ-R).



	R^1	R^2	R^3	R^4	R^5
1a	Me	CO_2Et	H	Ph	Me
1b	Bn	CO_2Et	H	Ph	Me
1c	Me	Ph	H	Ph	Me
1d	Me	CO_2iPr	H	Ph	Me
1e	Me	CO_2Bn	H	Ph	Me
1f	Me	CO_2Et	H	Ph	Ph
1g	Me	CO_2Et	H	Ph	H
1h	Me	CO_2Et	H	Bu	H
1i	Me	CO_2Et	Me	Ph	Ph

Scheme 3

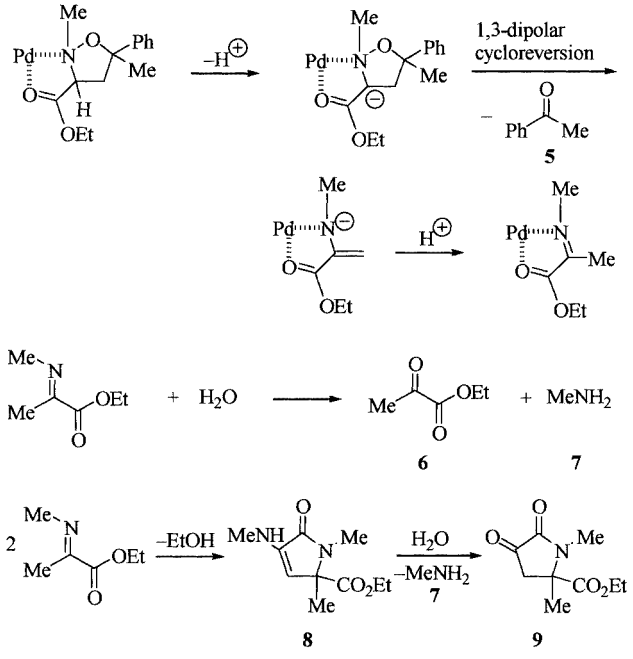
panoate (**6**), methylamine (**7**), and **9**. They are considered to be formed by the mechanism shown in Scheme 4. At first, *cis*-**1a** coordinates to the cationic palladium center. Deprotonation at C-3 of the isoxazolidine ring, 1,3-dipolar cycloreversion, and protonation give acetophenone (**5**) and ethyl 2-(methylimino)propanoate. This imine is hydrolyzed to ethyl 2-oxopropanoate (**6**) and methylamine (**7**) by small amounts of water, which is difficult to remove from the reaction mixture. An alternative pathway is that the dimerization of imine and hydrolysis could provide **9** and **7**. In this mechanism, the bidentate coordination of the substrate to the palladium center is important. This coordination increases the acidity of the proton at C-3 in the isoxazolidine ring, and the bidentate coordination produces greater steric hindrance in the intermediate, decomposition by bidentate coordination therefore occurring smoothly.

From the above considerations, the intermediates of this decomposition were proposed as follows (Scheme 5): Compound (3*R*,5*S*)-*cis*-**1a** can coordinate to [Pd−(*S*)-TolBINAP] in a bidentate fashion and the decomposition then occurs. On the other hand, the opposite isomer can hardly coordinate to the metal center in a bidentate fashion, due

Table 4. Kinetic resolution of **1** with Pd−TolBINAP

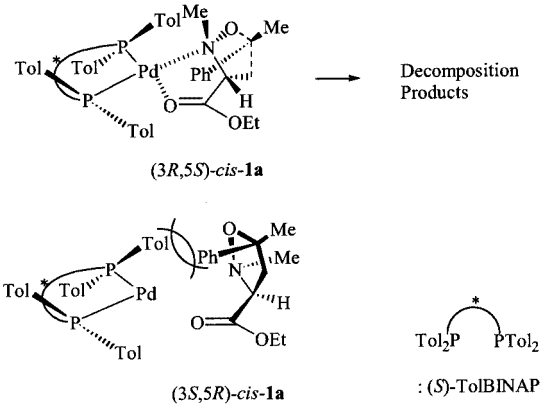
Entry[a]	Substrate	Time [h]	Yield (%)[b]	*ee* (%)[c]	k_f/k_s
1	*cis*-**1a**	40	55	76	62
2	*trans*-**1a**	48	54	17	2
3[d]	*trans*-**1a**	48	34	42	2
4[d] [e]	*cis*-**1b**	48	100	0	–
5[d]	*trans*-**1b**	48	100	0	–
6[d]	*cis*-**1c**	48	94	0	–
7[d]	*trans*-**1c**	48	97	0	–
8	*cis*-**1d**	48	45	99	49
9	*trans*-**1d**	48	44	16	1
10	*cis*-**1e**	48	66	40	12
11	*trans*-**1e**	48	80	11	3
12	**1f**	41	50	75	16
13[d]	**1f**	48	46	81	13
14	*cis*-**1g**	45	66	18	2
15[d]	*cis*-**1g**	48	35	35	2
16	*trans*-**1g**	48	53	36	3
17	*cis*-**1h**	48	80	5	2
18[d]	*cis*-**1h**	48	69	10	2
19	*trans*-**1h**	72	70	0	–
20	*cis*-**1i**	48	100	0	–
21	*trans*-**1i**	45	74	35	732

[a] Reaction conditions: ratio of substrate (mmol)/catalyst (mmol)/solvent (mL) 10:1:50 (see Exp. Sect.). Typically, substrate (0.4 mmol) and catalyst **4** (0.04 mmol) were dissolved in CH_2Cl_2 (2 mL), and the resulting mixture was then stirred at room temperature for the appropriate reaction time. [b] Isolated yield. [c] Determined by chiral HPLC (Daicel Chiralcel OJ-R or OD-H). [d] Reflux. [e] $CHCl_3$ (2.5 mL) was used as the solvent.



Scheme 4

to steric hindrance. Consequently, (3*S*,5*R*)-*cis*-**1a** may even survive the contact with the palladium catalyst.



Scheme 5

Conclusion

For this decomposition, a substrate should have both a methyl group on the 2-position and an alkoxycarbonyl group on the 3-position of the isoxazolidine ring. The enantioselectivities of the recovered substrates were influenced not only by the substituent groups on the 4- and 5-positions, but also by the geometrical structures of the substrates. The concentration of the solution significantly affects the stereoselectivity. This method offers a convenient method for the preparation of optically active isoxazolidines, as this class of isoxazolidine is easily formed in racemic form merely by mixing of the corresponding nitrones and olefins. Further application of this kinetic decomposition is now underway.

Experimental Section

General: ^{1}H NMR spectra were measured with a JEOL JNM-A400 (400 MHz) spectrometer with tetramethylsilane as the internal standard. IR spectra were measured with a Shimadzu IR-408 instrument. Optical rotations were recorded with a Horiba SEPA-200 spectrophotometer. Liquid chromatographic analyses were conducted with Shimadzu LC-10A (Daicel Chiralcel OJ-R, 0.15 m, 0.5 mL/min, 200 kgf/cm^2, UV 220 nm) and/or Hitachi L-7100 (Daicel Chiralcel OD-H, 0.25 m, 0.3 or 0.5 mL/min, UV 220 nm) machines. FAB-MS (HRMS) spectra were measured with a JEOL JMS-700 spectrometer with PEG-200 as a calibration standard. X-ray analysis was conducted with a Rigaku Rasa-7R system (AFC-7R for data collection and the teXsan program (see below) for data analysis). Melting points were measured with a Yanaco Model MP and are uncorrected. All solvents were dried by standard methods and distilled under argon. Commercially available compounds were used without further purification. *N*-(2-Ethoxy-2-oxoethylidene)methylamine *N*-oxide,[9] *N*-(2-ethoxy-2-oxoethylidene)benzylamine *N*-oxide,[9] *N*-(benzylidene)methylamine *N*-oxide,[10] *N*-(2-isopropoxy-2-oxoethylidene)methylamine *N*-oxide,[9] *N*-(2-benzyloxy-2-oxoethylidene)methylamine *N*-oxide,[9] 1,1-diphenylpropene,[11] [Pd{(*S*)-BINAP}$(CH_3CN)_2$]$(BF_4)_2$ (**3**),[4c] [Ru{(*S*)-BINAP}$(OTf)_2$],[12] and [Pd{(*S*)-TolBINAP}$(CH_3CN)_2$]$(BF_4)_2$ (**4**)[4c] were prepared by literature methods. Isoxazolidines **1a**−**1i** were prepared by treatment of the corresponding *N*-(alkylidene)methylamine *N*-oxides with the corresponding olefins.

The ratios of *cis* and *trans* isomers were determined by ^{1}H NMR, and the resulting mixtures were subjected to column chromatography to isolate the *cis* and *trans* isomers described below. All new solid compounds were analyzed by elemental analyses, while all new liquid samples were analyzed by high-resolution mass spectrometry (FAB, in *m*-nitrobenzyl alcohol as a matrix), because of some differences in elemental analyses. In the case of the faster running isomer of **1a** on TLC (silica gel), the amidation compound **1j** was prepared and analyzed by single-crystal X-ray structure determination to reveal the orientation of the 5-phenyl and 3-carboxamide moieties to be *cis*. Other relative stereochemistries of isoxazolidines were determined by comparison of their ^{1}H NMR spectra with that of **1a**. The absolute configurations of the products have not be determined yet. We consider that the stereochemistry of (+)-*cis*-**1a** may be (3*S*,5*R*) according to Scheme 5.

Preparation of Ethyl 2,5-Dimethyl-5-phenylisoxazolidine-3-carboxylate (1a): *N*-(2-Ethoxy-2-oxoethylidene)methylamine *N*-oxide (0.66 g, 5.0 mmol), α-methylstyrene (1.18 g, 10.0 mmol), and chloroform (10 mL) were placed in a 50-mL flask and the mixture was then heated at reflux for 72 h. After removal of the solvent, the mixture was analyzed by ^{1}H NMR (ratio of *cis*/*trans* = 50:50). The residue was purified by column chromatography (chloroform/ethyl acetate, 20:1). **Isomer *cis*-1a:** 0.63 g, 51% yield, yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.58 (s, 3 H, 5-Me), 2.71 (dd, *J* = 8.4, 12.0 Hz, 1 H, 4-*H*H), 2.88 (s, 3 H, *N*-Me), 2.95 (dd, *J* = 8.4, 12.0 Hz, 1 H, 4-H*H*), 3.48 (t, *J* = 8.4 Hz, 1 H, 3-H), 4.08 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 7.18−7.22 (m, 1 H, Ph), 7.30−7.34 (m, 2 H, Ph), 7.44−7.47 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 13.9, 30.0, 45.4, 46.9, 61.1, 70.4, 82.3, 124.6, 126.5, 128.1, 147.3, 169.7 ppm. IR (NaCl): ṽ = 2950, 2850, 1730, 1590, 1485, 1440, 1365, 1335, 1270, 1190, 1075, 1065, 1025, 960, 925, 890, 860, 760, 700 cm^{-1}. HRMS (FAB$^+$): $C_{14}H_{20}NO_3$ [M + H]$^+$: calcd. 250.1444; found 250.1449. **Isomer *trans*-1a:** 0.38 g, 31% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.66 (s, 3 H, 5-Me), 2.77−2.86 (m, 2 H, 4-H_2), 2.84 (s, 3 H, *N*-Me), 3.46 (t, *J* = 7.6 Hz, 1 H, 3-H), 4.24 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 7.23−7.28 (m, 1 H, Ph), 7.32−7.36 (m, 2 H, Ph), 7.43−7.45 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 14.0, 29.4, 45.1, 46.4, 61.1, 69.5, 82.8, 124.6, 126.7, 128.1, 146.8, 170.2 ppm. IR (NaCl): ṽ = 2950, 2850, 1735, 1595, 1490, 1440, 1365, 1340, 1265, 1190, 1090, 1065, 1025, 955, 895, 860, 760, 700 cm^{-1}. HRMS (FAB$^+$): $C_{14}H_{20}NO_3$ [M + H]$^+$: calcd.250.1444, found 250.1449.

Preparation of Ethyl 2-Benzyl-5-methyl-5-phenylisoxazolidine-3-carboxylate (1b): *N*-(2-Ethoxyethylidene-2-oxo)benzylamine *N*-oxide (0.21 g, 1.0 mmol), α-methylstyrene (0.59 g, 5.0 mmol), and chloroform (5 mL) were placed in a 50-mL flask, and the mixture was allowed to react at reflux temperature for 48 h. After removal of the solvent, the mixture was analyzed by ^{1}H NMR (*cis*/*trans* ratio = 52:48). The relative stereochemistry was determined by ^{1}H NMR and comparison with **1a**. The products were isolated by column chromatography (hexane/ethyl acetate, 10:1). **Isomer *cis*-1b:** 0.161 g, 50% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.12 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.52 (s, 3 H, 5-Me), 2.64 (dd, *J* = 8.0, 12.0 Hz, 1 H, 4-*H*H), 2.93 (dd, *J* = 8.0, 12.0 Hz, 1 H, 4-H*H*), 3.68 (t, *J* = 8.0 Hz, 1 H, 3-H), 3.94−4.07 (m, 2 H, CH_2CH_3), 4.05 (d, *J* = 12.8 Hz, 1 H, *N*−C*H*HPh), 4.31 (d, *J* = 12.8 Hz, 1 H, *N*−CH*H*Ph), 7.17−7.19 (m, 1 H, Ph), 7.23−7.36 (m, 7 H, Ph), 7.45 (d, *J* = 7.6 Hz, 2 H, Ph) ppm. ^{13}C NMR: δ = 13.9, 30.0, 46.5, 61.0, 61.8, 67.3, 82.4, 124.8, 126.4, 127.3, 127.9, 128.0, 129.3, 136.8, 147.3, 169.9 ppm. IR (NaCl): ṽ = 2950, 1735, 1595, 1485, 1440, 1365, 1270, 1185, 1065, 1025, 970, 925, 855, 755, 730, 695 cm^{-1}. HRMS (FAB$^+$): $C_{20}H_{24}NO_3$ [M + H]$^+$: calcd. 326.1757; found 326.1777. **Isomer *trans*-1b:** 0.04 g, 12% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.63 (s, 3 H, 5-Me), 2.81 (dd, *J* = 6.8, 12.4 Hz, 1 H, 4-*H*H), 2.87 (dd, *J* = 8.0, 12.4 Hz, 1 H, 4-H*H*), 3.68 (dd, *J* = 6.8, 8.0 Hz, 1 H, 3-H), 4.00 (d, *J* = 13.6 Hz, 1 H, *N*−C*H*HPh), 4.08−4.18 (m, 2 H, CH_2CH_3), 4.16 (d, *J* = 13.6 Hz, 1 H, *N*−CH*H*Ph), 7.22−7.28 (m, 2 H, Ph), 7.29−7.34 (m, 4 H, Ph), 7.38−7.41 (m, 4 H, Ph) ppm. ^{13}C NMR: δ = 14.1, 29.7, 45.6, 61.2, 61.9, 67.0, 83.6, 124.8, 126.8, 127.3, 128.1, 129.2, 136.6, 147.1, 170.7 ppm. IR (NaCl): ṽ = 2950, 1735, 1595, 1485, 1440, 1365, 1335, 1265, 1185, 1090, 1060, 1040, 1025, 885, 760, 730, 695 cm^{-1}. HRMS (FAB$^+$): $C_{20}H_{24}NO_3$ [M + H]$^+$: calcd. 326.1757; found 326.1757.

Preparation of 2,5-Dimethyl-3,5-diphenylisoxazolidine (1c):[13] *N*-Benzylidenemethylamine *N*-oxide (0.54 g, 4.0 mmol), α-methylstyrene (0.71 g, 6.0 mmol), and toluene (8 mL) were placed in a 50-mL flask and the mixture was then heated to reflux for 51 h. After removal of the solvent, the mixture was analyzed by ^{1}H NMR (ratio of *cis*/*trans* = 48:52). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 10:1). **Isomer *cis*-1c:** 0.23 g, 23% yield, white solid. M.p. 60.0−61.0 °C. ^{1}H NMR ($CDCl_3$): δ = 1.62 (s, 3 H, 5-Me), 2.63 (s, 3 H, *N*-Me), 2.70 (dd, *J* = 10.0, 12.4 Hz, 1 H, 4-*H*H), 2.82 (dd, *J* = 8.0, 12.4 Hz, 1 H, 4-H*H*), 3.69 (dd, *J* = 8.0, 10.0 Hz, 1 H, 3-H), 7.18−7.27 (m, 6 H, Ph), 7.34−7.38 (t, *J* = 7.2 Hz, 2 H, Ph), 7.51 (d, *J* = 8.0 Hz, 2 H, Ph) ppm. ^{13}C NMR: δ = 30.3, 43.2, 54.1, 74.6, 81.8, 124.7, 126.3, 127.8, 127.9, 128.2, 128.5, 138.7, 149.1 ppm. IR (KBr): ṽ = 3025, 2950, 2800, 1590, 1485, 1440, 1420, 1390, 1355, 1300, 1285, 1270, 1210, 1140, 1105, 1090, 1080, 1020, 940, 910, 880, 845, 790, 755, 700 cm^{-1}. **Isomer *trans*-1c:** 0.21 g, 21% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.77 (s, 3 H, 5-Me), 2.56 (dd, *J* = 10.4, 12.4 Hz, 1 H, 4-*H*H), 2.69 (s, 3 H, *N*-Me), 2.85 (dd, *J* = 7.6, 12.4 Hz, 1 H, 4-H*H*), 3.62 (dd, *J* = 7.6, 10.4 Hz, 1 H, 3-H), 7.21−7.29 (m, 2 H, Ph), 7.31−7.39 (m, 6 H, Ph), 7.50−7.52 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 30.1, 43.4, 54.2, 73.3, 82.1, 124.9, 126.7, 127.6, 127.8, 128.1, 128.6, 138.7, 147.3 ppm. IR (NaCl): ṽ = 3000, 2950, 2800, 1595, 1490, 1440, 1390, 1360, 1290, 1200, 1150, 1115, 1080, 1060, 1020, 965, 910, 885, 840, 755, 695 cm^{-1}.

Preparation of Isopropyl 2,5-Dimethyl-5-phenylisoxazolidine-3-carboxylate (1d): *N*-(2-Isopropyloxy-2-oxoethylidene)methylamine *N*-oxide (0.73 g, 5.0 mmol), α-methylstyrene (1.18 g, 10.0 mmol), and chloroform (10 mL) were placed in a 50-mL flask. The mixture was heated at reflux for 72 h. After removal of the solvent, the mixture was analyzed by ^{1}H NMR (ratio of *cis*/*trans* = 51:49). The relative stereochemistry was determined by ^{1}H NMR and comparison with **1a**. The residue was purified by column chromatography (silica gel, chloroform/ethyl acetate, 20:1). **Isomer *cis*-1d:** 0.55 g, 42% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.15 [d, *J* = 6.4 Hz, 3 H, $CH(CH_3)_2$], 1.17 [d, *J* = 6.4 Hz, 3 H, $CH(CH_3)_2$], 1.57 (s, 3 H, 5-Me), 2.69 (dd, *J* = 8.0, 12.0 Hz, 1 H, 4-*H*H), 2.88 (s, 3 H, *N*-Me), 2.92 (dd, *J* = 8.0, 12.0 Hz, 1 H, 4-H*H*), 3.44 (t, *J* = 8.0 Hz, 1 H, 3-H), 4.95 [sept, *J* = 6.4 Hz, 1 H, $CH(CH_3)_2$], 7.18−7.22 (m, 1 H, Ph), 7.30−7.33 (m, 2 H, Ph), 7.45−7.47 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 21.6, 30.1, 45.4, 47.0, 68.7, 70.5, 82.3, 124.7, 126.5, 128.1, 147.4, 169.2 ppm. IR (NaCl): ṽ = 2950, 2850, 1730, 1590, 1485, 1440, 1365, 1270, 1200, 1140, 1100, 1075, 1065, 1025, 995, 930, 900, 840, 820, 760, 700 cm^{-1}. HRMS (FAB$^+$): $C_{15}H_{22}NO_3$ [M + H]$^+$: calcd. 264.1601; found 264.1618. **Isomer *trans*-1d:** 0.29 g, 22% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.278 (d, *J* = 6.4 Hz, 3 H, $CHCH_3CH_3$), 1.282 (d, *J* = 6.4 Hz, 3 H, $CHCH_3CH_3$), 1.65 (s, 3 H, 5-Me), 2.74−2.84 (m, 2 H, 4-H_2), 2.84 (s, 3 H, *N*-Me), 3.42 (t, *J* = 7.6 Hz, 1 H, 3-H), 5.10 [sept, *J* = 6.4 Hz, 1 H, $CH(CH_3)_2$], 7.22−7.27 (m, 1 H, Ph), 7.32−7.36 (m, 2

H, Ph), 7.43−7.45 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 21.7, 29.5, 45.2, 46.7, 68.8, 69.7, 82.9, 124.7, 126.8, 128.2, 146.9, 169.8 ppm. IR (NaCl): ṽ = 2950, 2850, 1730, 1595, 1490, 1440, 1370, 1270, 1190, 1140, 1100, 1065, 1025, 960, 930, 905, 830, 760, 700 cm^{-1}. HRMS (FAB$^+$): $C_{15}H_{22}NO_3$ [M + H]$^+$: calcd. 264.1601; found 264.1576.

Preparation of Benzyl 2,5-Dimethyl-5-phenylisoxazolidine-3-carboxylate (1e): *N*-(2-Benzyloxy-2-oxoethylidene)methylamine *N*-oxide (1.93 g, 10.0 mmol), α-methylstyrene (2.36 g, 20.0 mmol), and chloroform (20 mL) were placed in a 50-mL flask and the mixture was heated at reflux for 70 h. After removal of the solvent, the mixture was analyzed by ^{1}H NMR (ratio of *cis*/*trans* = 51:49). The relative stereochemistry was determined by ^{1}H NMR and comparison with **1a**. The residue was purified by column chromatography (silica gel, chloroform/ethyl acetate, 20:1). **Isomer *cis*-1e:** 1.15 g, 37% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.57 (s, 3 H, 5-Me), 2.71 (dd, *J* = 8.4, 12.0 Hz, 1 H, 4-*H*H), 2.88 (s, 3 H, *N*-Me), 2.96 (dd, *J* = 8.4, 12.0 Hz, 1 H, 4-H*H*), 3.52 (t, *J* = 8.4 Hz, 1 H, 3-H), 5.04 (d, *J* = 12.4 Hz, 1 H, C*H*HPh), 5.07 (d, *J* = 12.4 Hz, 1 H, CH*H*Ph), 7.19−7.25 (m, 3 H, Ph), 7.29−7.35 (m, 5 H, Ph), 7.43−7.46 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 29.8, 45.2, 46.8, 66.6, 70.2, 82.3, 124.6, 126.4, 128.0, 128.1, 128.2, 128.4, 135.3, 147.2, 169.4 ppm. IR (NaCl): ṽ = 3000, 2950, 2850, 1740, 1600, 1490, 1440, 1370, 1345, 1270, 1180, 1080, 1070, 1025, 1010, 940, 905, 845, 755, 700 cm^{-1}. HRMS (FAB$^+$): $C_{19}H_{22}NO_3$ [M + H]$^+$: calcd. 312.1601; found 312.1606. **Isomer *trans*-1e:** 1.14 g, 36% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.66 (s, 3 H, 5-Me), 2.77−2.87 (m, 2 H, 4-H), 2.84 (s, 3 H, *N*-Me), 3.52 (t, *J* = 8.0 Hz, 1 H, 3-H), 5.20 (d, *J* = 12.4 Hz, 1 H, C*H*HPh), 5.23 (d, *J* = 12.4 Hz, 1 H, CH*H*Ph), 7.22−7.26 (m, 1 H, Ph), 7.31−7.38 (m, 7 H, Ph), 7.41−7.44 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 29.4, 45.1, 46.5, 66.8, 69.5, 82.9, 124.6, 126.8, 128.1, 128.2, 128.3, 128.5, 135.4, 146.8, 170.0 ppm. IR (NaCl): ṽ = 3000, 2950, 2850, 1735, 1600, 1490, 1445, 1365, 1345, 1265, 1180, 1080, 1065, 1025, 960, 900, 840, 755, 700 cm^{-1}. HRMS (FAB$^+$): $C_{19}H_{22}NO_3$ [M + H]$^+$: calcd. 312.1601; found 312.1606.

Preparation of Ethyl 2-Methyl-5,5-diphenylisoxazolidine-3-carboxylate (1f): *N*-(2-Ethoxy-2-oxoethylidene)methylamine *N*-oxide (1.31 g, 10.0 mmol), 1,1-diphenylethylene (3.61 g, 20.0 mmol), and chloroform (20 mL) were placed in a 50-mL flask and the mixture was heated at reflux for 72 h. The residue was purified by column chromatography (silica gel, C_6H_{14}/ethyl acetate, 3:1). **Compound 1f:** 2.95 g, 95% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.91 (s, 3 H, *N*-Me), 3.25 (dd, *J* = 8.0, 12.8 Hz, 1 H, 4-*H*H), 3.37 (dd, *J* = 8.0, 12.8 Hz, 1 H, 4-H*H*), 3.62 (t, *J* = 8.0 Hz, 1 H, 3-H), 4.12 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 7.18−7.24 (m, 2 H, Ph), 7.27−7.32 (m, 4 H, Ph), 7.40−7.42 (m, 2 H, Ph), 7.45−7.47 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 13.8, 45.7, 46.0, 61.1, 69.9, 86.3, 125.8, 125.9, 126.7, 127.0, 127.9, 128.0, 145.0 145.1, 169.6 ppm. IR (NaCl): ṽ = 2950, 1730, 1590, 1485, 1440, 1365, 1265, 1190, 1110, 1040, 910, 860, 745, 695 cm^{-1}. HRMS (FAB$^+$): $C_{19}H_{22}NO_3$ [M + H]$^+$: calcd. 312.1601; found 312.1625.

Preparation of Ethyl 2-Methyl-5-phenylisoxazolidine-3-carboxylate (1g): *N*-(2-Ethoxy-2-oxoethylidene)methylamine *N*-oxide (0.66 g, 5.0 mmol), styrene (1.04 g, 10.0 mmol), and chloroform (10 mL) were placed in a 50-mL flask and the mixture was stirred at room temperature for 43 h. After removal of the solvent, the mixture was analyzed by ^{1}H NMR (ratio of *cis*/*trans* = 91:9). The relative stereochemistry was determined by ^{1}H NMR and comparison with **1a**. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 2:1). **Isomer *cis*-1g:** 0.46 g, 39% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.32 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.48 (ddd, *J* = 8.0, 9.6, 12.4 Hz, 1 H, 4-*H*H), 2.87−2.94 (m, 1 H, 4-H*H*), 2.90 (s, 3 H, *N*-Me), 3.50 (dd, *J* = 7.2, 9.6 Hz, 1 H, 3-H), 4.25 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 5.12 (t, *J* = 8.0 Hz, 1 H, 5-H), 7.27−7.39 (m, 5 H, Ph) ppm. ^{13}C NMR: δ = 14.0, 41.0, 45.2, 61.2, 69.6, 78.9, 126.4, 127.9, 128.3, 139.2, 170.2 ppm. IR (NaCl): ṽ = 2950, 1735, 1485, 1440, 1365, 1340, 1260, 1195, 1110, 1040, 945, 860, 750, 695 cm^{-1}. HRMS (FAB$^+$): $C_{13}H_{18}NO_3$ [M + H]$^+$: calcd. 236.1287; found 236.1289. **Isomer *trans*-1g:** 0.027 g, 2%, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.61 (ddd, *J* = 6.4, 8.0, 12.8 Hz, 1 H, 4-*H*H), 2.88 (s, 3 H, *N*-Me), 3.00 (dt, *J* = 8.0, 12.8 Hz, 1 H, 4-H*H*), 3.68 (dd, *J* = 6.4, 8.0 Hz, 1 H, 3-H), 4.23 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 5.23 (t, *J* = 8.0 Hz, 1 H, 5-H), 7.26−7.30 (m, 1 H, Ph), 7.32−7.37 (m, 2 H, Ph), 7.43−7.44 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 14.1, 41.2, 45.3, 61.4, 69.6, 78.1, 126.7, 127.9, 128.4, 139.8, 170.9 ppm. IR (NaCl): ṽ = 2950, 1730, 1485, 1445, 1365, 1340, 1265, 1195, 1105, 1030, 905, 860, 755, 700 cm^{-1}. HRMS (FAB$^+$): $C_{13}H_{18}NO_3$ [M + H]$^+$: calcd. 236.1287; found 236.1295.

Preparation of Ethyl 5-Butyl-2-methylisoxazolidine-3-carboxylate (1h): *N*-(2-Ethoxy-2-oxoethylidene)methylamine *N*-oxide (0.66 g, 5.0 mmol), 1-hexene (0.84 g, 10.0 mmol), and chloroform (10 mL) were placed in a 50-mL flask, and stirred for 43 h at room temperature. After removal of the solvent, the mixture was analyzed by ^{1}H NMR (ratio of *cis*/*trans* = 83:17). The relative stereochemistry was determined by ^{1}H NMR and comparison with **1a**. Products were isolated by column chromatography (silica gel, hexane/ethyl acetate, 2:1). **Isomer *cis*-1h:** 0.82 g, 76% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.90 [t, *J* = 7.2 Hz, 3 H, $CH_2(CH_2)_2CH_3$], 1.28−1.41 [m, 4 H, $CH_2(CH_2)_2CH_3$], 1.30 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.47−1.55 [m, 1 H, C*H*H$(CH_2)_2CH_3$], 1.60−1.66 [m, 1 H, CH*H*$(CH_2)_2CH_3$], 2.10 (ddd, *J* = 7.6, 9.6, 12.0 Hz, 1 H, 4-*H*H), 2.55 (dt, *J* = 6.4, 12.0 Hz, 1 H, 4-H*H*), 2.79 (s, 3 H, *N*-Me), 3.26 (dd, *J* = 6.4, 9.6 Hz, 1 H, 3-H), 4.07 (quint, *J* = 7.6 Hz, 1 H, 5-H), 4.22 (q, *J* = 7.2 Hz, 2 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR: δ = 13.4, 13.6, 22.1, 27.7, 33.2, 38.5, 44.5, 60.5, 68.8, 76.7, 169.9 ppm. IR (NaCl): ṽ = 2925, 2850, 1740, 1450, 1365, 1335, 1265, 1190, 1115, 1040, 900, 860, 750 cm^{-1}. HRMS (FAB$^+$): $C_{11}H_{22}NO_3$ [M + H]$^+$: calcd. 216.1601; found 216.1610. **Isomer *trans*-1h:** 0.12 g, 11% yield, light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.90 [t, *J* = 7.2 Hz, 3 H, $CH_2(CH_2)_2CH_3$], 1.25−1.41 [m, 4 H, $CH_2(CH_2)_2CH_3$], 1.30 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.51−1.55 [m, 1 H, C*H*H$(CH_2)_2CH_3$], 1.66−1.73 [m, 1 H, CH*H*$(CH_2)_2CH_3$], 2.20 (dt, *J* = 6.4, 12.8 Hz, 1 H, 4-*H*H), 2.66 (ddd, *J* = 7.6, 8.4, 12.8 Hz, 1 H, 4-H*H*), 2.75 (s, 3 H, *N*-Me), 3.49 (dd, *J* = 6.4, 7.6 Hz, 1 H, 3-H), 4.18−4.24 (m, 1 H, 5-H), 4.22 (q, *J* = 7.2 Hz, 2 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR: δ = 13.9, 14.0, 22.5, 28.3, 33.9, 38.1, 45.1, 61.2, 69.1, 76.5, 171.1 ppm. IR (NaCl): ṽ = 2925, 2850, 1735, 1450, 1365, 1340, 1260, 1185, 1115, 1035, 855 cm^{-1}. HRMS (FAB$^+$): $C_{11}H_{22}NO_3$ [M + H]$^+$: calcd. 216.1601; found 216.1610.

Preparation of Ethyl 2,4-Dimethyl-5,5-diphenylisoxazolidine-3-carboxylate (1i): *N*-(2-Ethoxy-2-oxoethylidene)methylamine *N*-oxide (0.66 g, 5.0 mmol), 1,1-diphenylpropene (1.94 g, 10.0 mmol), and chloroform (10 mL) were placed in a 50-mL flask and the mixture was heated at reflux for 70 h. After removal of the solvent, the mixture was analyzed by ^{1}H NMR (ratio of *cis*/*trans* = 58:42). The relative stereochemistry was determined by ^{1}H NMR and comparison with **1a**. The residue was purified by column chromatography (silica gel, chloroform/ethyl acetate, 20:1). **Isomer *cis*-1i:** 0.67 g, 41% yield, colorless crystals (hexane). M.p. 51.3−52.0. ^{1}H NMR ($CDCl_3$): δ = 0.89 (d, *J* = 7.2 Hz, 3 H, 4-Me), 1.25 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.94 (s, 3 H, *N*-Me), 3.21 (d, *J* = 8.8 Hz, 1 H, 3-

H), 3.71 (dq, J = 7.2, 8.8 Hz, 1 H, 4-H), 4.18 (q, J = 7.2 Hz, 2 H, CH_2CH$_3$), 7.17−7.28 (m, 6 H, Ph), 7.32−7.37 (m, 2 H, Ph), 7.50−7.52 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 13.7, 16.5, 44.3, 50.3, 60.8, 77.5, 88.0, 126.2, 126.6, 126.7, 126.9, 127.3, 127.7, 141.6, 146.0, 169.0 ppm. IR (KBr): ṽ = 3050, 2950, 2850, 1715, 1590, 1485, 1440, 1370, 1360, 1345, 1315, 1285, 1250, 1220, 1120, 1090, 1080, 1025, 1005, 970, 950, 905, 860, 840, 780, 755, 700 cm^{-1}. $C_{20}H_{23}NO_3$ (325.41): calcd. C 73.82, H 7.12, N 4.30; found C 74.02, H 7.22, N 4.21. **Isomer *trans*-1i:** 0.49 g, 30% yield, colorless crystals (hexane). M.p. 76.7−78.5. ^{1}H NMR ($CDCl_3$): δ = 0.86 (d, J = 6.8 Hz, 3 H, 4-Me), 1.29 (t, J = 7.2 Hz, 3 H, CH$_2$CH_3), 2.80 (s, 3 H, *N*-Me), 3.74−3.80 (m, 2 H, 3-H and 4-H), 4.21 (dq, J = 7.2, 10.8 Hz, 1 H, CHHCH$_3$), 4.26 (dq, J = 7.2, 10.8 Hz, 1 H, CHHCH$_3$), 7.12−7.16 (m, 1 H, Ph), 7.21−7.27 (m, 3 H, Ph), 7.33−7.37 (m, 4 H, Ph), 7.62−7.65 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 12.6, 13.9, 46.3, 47.1, 60.6, 73.3, 89.3, 125.6, 125.8, 126.2, 126.9, 127.5, 128.0, 141.8, 146.5, 168.8 ppm. IR (KBr): ṽ = 3050 cm^{-1}, 2950, 2825, 1740, 1590, 1485, 1440, 1360, 1335, 1270, 1195, 1140, 1110, 1090, 1060, 1025, 1000, 960, 930, 900, 860, 770, 745, 700 cm^{-1}. $C_{20}H_{23}NO_3$ (325.41): calcd. C 73.82, H 7.12, N 4.30; found C 73.86, H 7.10, N 4.20.

Asymmetric Decomposition of Ethyl *cis*-2,5-Dimethyl-5-phenylisoxazolidine-3-carboxylate (*cis*-1a) in the Presence of [Pd{(*S*)-TolBINAP}(CH$_3$CN)$_2$](BF$_4$)$_2$ (4): This is a typical procedure for the decomposition of compounds **1** in the presence of palladium complex. Compound *cis*-**1a** (100 mg, 0.4 mmol) was placed in a 30-mL flask equipped with a reflux condenser, and the mixture was placed under argon. Dichloromethane (3.0 mL) and [Pd(CH$_3$CN)$_2$\{(S)-TolBINAP\}](BF$_4$)$_2$ (42 mg, 0.04 mmol) were introduced, and the mixture was then stirred at room temperature for 60 h. After removal of the solvent, the residue was purified by column chromatography to give the recovered substrate. The enantiomeric excess was determined by HPLC with a chiral column. ***cis*-1a:** 48 mg, 48% yield. $[\alpha]_D^{20}$ = +136.0 (c = 1.0, CHCl$_3$). HPLC (Daicel Chiralcel OJ-R, CH$_3$OH/H$_2$O, 60:40, UV 220 nm, 0.5 mL/min): t_R = 66.4 min (major), t_R = 119.0 min (minor); 99% *ee* (Table 3, Entry 9).

Ethyl *trans*-2,5-Dimethyl-5-phenylisoxazolidine-3-carboxylate (*trans*-1a): Reaction conditions: *trans*-**1a** (200 mg, 0.8 mmol), catalyst **4** (83 mg, 0.08 mmol), CH_2Cl_2 (4 mL), reflux, 48 h; 68 mg, 34% yield. $[\alpha]_D^{20}$ = +17.0 (c = 1.0, CHCl$_3$). HPLC (Daicel Chiralcel OJ-R, CH$_3$OH/H$_2$O, 60:40, UV 220 nm, 0.5 mL/min): t_R = 90.0 min (major), t_R = 140.6 min (minor); 42% *ee* (Table 4, Entry 3).

Ethyl *cis*-2-Benzyl-5-methyl-5-phenylisoxazolidine-3-carboxylate (*cis*-1b): Reaction conditions: *cis*-**1b** (159 mg, 0.49 mmol), catalyst **4** (51 mg, 0.049 mmol), $CHCl_3$ (2.5 mL), reflux, 48 h; 159 mg, 100% yield. HPLC (Daicel Chiralcel OJ-R, CH$_3$OH/H$_2$O, 80:20, UV 220 nm, 0.5 mL/min): t_R = 27.3 min, t_R = 35.5 min; 0% *ee* (Table 4, Entry 4).

Ethyl *trans*-2-Benzyl-5-methyl-5-phenylisoxazolidine-3-carboxylate (*trans*-1b): Reaction conditions: *cis*-**1b** (195 mg, 0.6 mmol), catalyst **4** (63 mg, 0.06 mmol), CH_2Cl_2 (3 mL), reflux, 48 h; 194 mg, 100% yield. HPLC (Daicel Chiralcel OJ-R, CH$_3$OH/H$_2$O, 70:30, UV 220 nm, 0.5 mL/min): t_R = 114.3 min, t_R = 129.8 min; 0% *ee* (Table 4, Entry 5).

***cis*-2,5-Dimethyl-3,5-diphenylisoxazolidine (*cis*-1c):** Reaction conditions: *cis*-**1c** (200 mg, 0.8 mmol), catalyst **4** (83 mg, 0.08 mmol), CH_2Cl_2 (4 mL), reflux, 48 h; 187 mg, 94% yield. HPLC (Daicel Chiralcel OJ-R, CH$_3$OH/H$_2$O, 80:20, UV 220 nm, 0.5 mL/min) t_R = 42.6 min, t_R = 53.1 min; 0% *ee* (Table 4, Entry 6).

***trans*-2,5-Dimethyl-3,5-diphenylisoxazolidine (*trans*-1c):** Reaction conditions: *trans*-**1c** (74 mg, 0.29 mmol), catalyst **4** (30 mg, 0.029 mmol), CH_2Cl_2 (1.5 mL), reflux, 48 h; 72 mg, 97% yield. HPLC (Daicel Chiralcel OJ-R, CH$_3$OH/H$_2$O, 75:25, UV 220 nm, 0.5 mL/min): t_R = 90.8 min, t_R = 107.0 min; 0% *ee* (Table 4, Entry 7).

Isopropyl *cis*-2,5-Dimethyl-5-phenylisoxazolidine-3-carboxylate (*cis*-1d): Reaction conditions: *cis*-**1d** (160 mg, 0.6 mmol), catalyst **4** (63 mg, 0.06 mmol), CH_2Cl_2 (3 mL), room temp., 48 h; 69 mg, 45% yield. $[\alpha]_D^{20}$ = +128.0 (c, = 1.0, CHCl$_3$). HPLC (Daicel Chiralcel OJ-R, CH$_3$OH/H$_2$O, 60:40, UV 220 nm, 0.5 mL/min): t_R = 72.2 min (major), t_R = 99.8 min (minor); 99% *ee* (Table 4, Entry 8).

Isopropyl *trans*-2,5-Dimethyl-5-phenylisoxazolidine-3-carboxylate (*trans*-1d): Reaction conditions: *trans*-**1d** (160 mg, 0.6 mmol), catalyst **4** (63 mg, 0.06 mmol), CH_2Cl_2 (3 mL), room temp., 48 h; 68 mg, 44% yield. $[\alpha]_D^{20}$ = +8.0 (c = 1.0, CHCl$_3$). HPLC (Daicel Chiralcel OJ-R, CH$_3$OH/H$_2$O, 65:35, UV 220 nm, 0.5 mL/min): t_R = 61.0 min (major), t_R = 99.7 min (minor); 16% *ee* (Table 4, Entry 9).

Benzyl *cis*-2,5-Dimethyl-5-phenylisoxazolidine-3-carboxylate (*cis*-1e): Reaction conditions: *cis*-**1e** (190 mg, 0.6 mmol), catalyst **4** (63 mg, 0.06 mmol), CH_2Cl_2 (3 mL), room temp., 48 h; 126 mg, 66% yield. $[\alpha]_D^{20}$ = +50.0 (c = 1.0, CHCl$_3$). HPLC [Daicel Chiralcel OD-H, C$_6$H$_{14}$/(CH$_3$)$_2$CHOH, 99:1, UV 220 nm, 0.5 mL/min]: t_R = 19.1 min (major), t_R = 23.2 min (minor); 40% *ee* (Table 4, Entry 10).

Benzyl *trans*-2,5-Dimethyl-5-phenylisoxazolidine-3-carboxylate (*trans*-1e): Reaction conditions: *trans*-**1e** (120 mg, 0.4 mmol), catalyst **4** (42 mg, 0.04 mmol), CH_2Cl_2 (2 mL), room temp., 48 h; 96 mg, 80% yield. $[\alpha]_D^{20}$ = +5.0 (c = 1.0, CHCl$_3$). HPLC (Daicel Chiralcel OD-H, C$_6$H$_{14}$/CH$_3$CH$_2$OH, 99.5:0.5, 220 nm, 0.5 mL/min): t_R = 19.7 min (major), t_R = 20.8 min (minor); 11% *ee* (Table 4, Entry 11).

Ethyl 2-Methyl-5,5-diphenylisoxazolidine-3-carboxylate (1f): Reaction conditions: **1f** (250 mg, 0.8 mmol), catalyst **4** (83 mg, 0.08 mmol), CH_2Cl_2 (4 mL), reflux, 48 h; 115 mg, 46% yield. $[\alpha]_D^{20}$ = +24.0 (c = 1.0, CHCl$_3$). HPLC (Daicel Chiralcel OJ-R, CH$_3$OH/H$_2$O, 80:20, UV 220 nm, 0.5 mL/min): t_R = 44.5 min (minor), t_R = 60.2 min (major); 81% *ee* (Table 4, Entry 13).

Ethyl *cis*-2-Methyl-5-phenylisoxazolidine-3-carboxylate (*cis*-1g): Reaction conditions: *cis*-**1g** (140 mg, 0.6 mmol), catalyst **4** (63 mg, 0.06 mmol), CH_2Cl_2 (3 mL), reflux, 48 h; 49 mg, 35% yield. $[\alpha]_D^{20}$ = +16.0 (c = 1.0, CHCl$_3$). HPLC [Daicel Chiralcel OD-H, C$_6$H$_{14}$/(CH$_3$)$_2$CHOH, 99:1, UV 220 nm, 0.3 mL/min]: t_R = 43.2 min (major), t_R = 47.7 min (minor); 35% *ee* (Table 4, Entry 15).

Ethyl *trans*-2-Methyl-5-phenylisoxazolidine-3-carboxylate (*trans*-1g): Reaction conditions: *trans*-**1g** (95 mg, 0.4 mmol), catalyst **4** (42 mg, 0.04 mmol), CH_2Cl_2 (2 mL), room temp., 48 h; 50 mg, 53% yield. $[\alpha]_D^{20}$ = +16.0 (c = 0.25, CHCl$_3$). HPLC [Daicel Chiralcel OD-H, C$_6$H$_{14}$/(CH$_3$)$_2$CHOH, 90:10, UV 220 nm, 0.3 mL/min]: t_R = 25.1 min (minor), t_R = 80.1 min (major); 36% *ee* (Table 4, Entry 16).

Ethyl *cis*-5-Butyl-2-methylisoxazolidine-3-carboxylate (*cis*-1h): Reaction conditions: *cis*-**1h** (130 mg, 0.6 mmol), catalyst **4** (63 mg, 0.06 mmol), CH_2Cl_2 (3 mL), reflux, 48 h; 89 mg, 69% yield. $[\alpha]_D^{20}$ = +9.0 (c = 1.0, CHCl$_3$). HPLC [Daicel Chiralcel OD-H, C$_6$H$_{14}$/(CH$_3$)$_2$CHOH, 99.5:0.5, UV 220 nm, 0.5 mL/min]: t_R = 11.9 min (minor), t_R = 12.8 min (major); 10% *ee* (Table 4, Entry 18).

Ethyl *trans*-5-Butyl-2-methylisoxazolidine-3-carboxylate (*trans*-1h): Reaction conditions: *trans*-**1h** (86 mg, 0.4 mmol), catalyst **4** (42 mg, 0.04 mmol), CH_2Cl_2 (2 mL), room temp., 72 h; 60 mg, 70% yield. HPLC (Daicel Chiralcel OD-H, C_6H_{14}/CH_3CH_2OH, 99.5:0.5, UV 220 nm, 0.3 mL/min): t_R = 16.8 min, t_R = 17.9 min; 0% *ee* (Table 4, Entry 19).

Ethyl *cis*-2,4-Dimethyl-5,5-diphenylisoxazolidine-3-carboxylate (*cis*-1i): Reaction conditions: *cis*-**1i** (130 mg, 0.4 mmol), catalyst **4** (42 mg, 0.04 mmol), CH_2Cl_2 (2 mL), room temp., 48 h; 129 mg, 100% yield. HPLC [Daicel Chiralcel OD-H, $C_6H_{14}/(CH_3)_2CHOH$, 99.5:0.5, UV 220 nm, 0.5 mL/min]: t_R = 14.3 min, t_R = 15.6 min; 0% *ee* (Table 4, Entry 20).

Ethyl *trans*-2,4-Dimethyl-5,5-diphenylisoxazolidine-3-carboxylate (*trans*-1i): Reaction conditions: *trans*-**1i** (130 mg, 0.4 mmol), catalyst **4** (42 mg, 0.04 mmol), CH_2Cl_2 (2 mL), room temp., 48 h; 96 mg, 74% yield. $[\alpha]_D^{20}$ = −75.0 (*c*, 1.0, $CHCl_3$). HPLC [Daicel Chiralcel OD-H, $C_6H_{14}/(CH_3)_2CHOH$, 99.5:0.5, 220 nm, 0.5 mL/min]: t_R = 27.2 min (major), t_R = 30.4 min (minor); 35% *ee* (Table 4, Entry 21).

Preparation of 2,5-Dimethyl-5-phenylisoxazolidine-3-carboxamide (*cis*-1j): Compound *cis*-**1a** (100 mg, 0.4 mmol), aqueous ammonia (28%, 80 mmol), and dichloromethane (2 mL) were placed in a 100-mL flask and the mixture was stirred for 144 h at room temperature. The organic layer was separated, and the water layer was extracted with dichloromethane. The organic layers were combined, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, chloroform/methanol, 20:1) to give 2,5-dimethyl-5-phenylisoxazolidine-3-carboxamide (*cis*-**1j**): 25 mg, 28% yield, colorless needle (diethyl ether). M.p. 116.0−117.0 °C. ^{1}H NMR ($CDCl_3$): δ = 1.57 (s, 3 H, 5-Me), 2.79 (dd, *J* = 10.4, 12.8 Hz, 1 H, 4-*H*H), 2.84 (s, 3 H, *N*-Me), 2.84−2.89 (m, 1 H, 4-H*H*), 3.40 (dd, *J* = 5.6, 10.4 Hz, 1 H, 3-H), 5.11 (s, 1 H, N*H*H), 6.45 (s, 1 H, NH*H*), 7.20−7.24 (m, 1 H, Ph), 7.30−7.33 (m, 2 H, Ph), 7.41−7.44 (m, 2 H, Ph) ppm. ^{13}C NMR: δ = 29.4, 45.3, 47.2, 71.0, 83.5, 124.8, 126.8, 128.2, 146.3, 173.6 ppm. IR (KBr): $\tilde{\nu}$ = 3390, 3120, 2950, 2850, 1685, 1570, 1480, 1450, 1440, 1390, 1360, 1300, 1270, 1240, 1180, 1160, 1115, 1090, 1070, 1025, 940, 920, 890, 835, 795, 765, 750, 700 cm^{-1}.

X-ray Analysis of *cis*-1j: Suitable crystals were analyzed with a Rigaku AFC-7R machine for collection of reflection data with use of the teXsan[14] program for analysis of the data. Direct method (SIR, 88[15]), isotropic for hydrogen atoms and anisotropic for non-hydrogen atoms, least-squares method for final structure. Figure 1 shows the ORTEP-3 view of *cis*-**1j**. CCDC-186220 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

Ethyl 1,2-Dimethyl-4-(methylamino)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate (8): Red oil. ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.53 (s, 3 H,2-Me), 2.74 (s, 3 H, NH-*Me*), 2.95 (s, 3 H, 1-Me), 4.08−4.27 (m, 3 H, CH_2CH_3 and N*H*), 5.12 (s, 1 H, 3-H) ppm. ^{13}C NMR: δ = 14.1, 20.9, 25.7, 30.5, 61.6, 66.9, 102.0, 141.3, 167.3, 171.6 ppm. IR (NaCl): $\tilde{\nu}$ = 3325, 2950, 2900, 1725, 1690, 1645, 1495, 1415, 1385, 1360, 1235, 1150, 1100, 1015, 855, 770, 730 cm^{-1}. GC-MS: *m*/*z* = 212.

Ethyl 1,2-Dimethyl-4,5-dioxopyrolidine-2-carboxylate (9): Yellow solid. ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 6.8 Hz, 3 H, CH_2CH_3), 1.70 (s, 3 H, 2-Me), 2.54 (d, *J* = 19.2 Hz, 1 H, 3-*H*H), 3.00 (d, *J* = 19.2 Hz, 1 H, 3-H*H*), 3.03 (s, 3 H, *N*-Me), 4.23 (dq, *J* = 6.8, 11.0 Hz, 1 H, C*H*HCH$_3$), 4.24 (dq, *J* = 6.8, 11.0 Hz, 1 H, CH*H*CH$_3$) ppm. ^{13}C NMR: δ = 13.9, 21.8, 27.1, 43.3, 60.9, 62.6, 159.8, 170.8, 195.8 ppm. IR (NaCl): $\tilde{\nu}$ = 2950, 2900, 1765, 1720, 1440, 1385, 1280, 1195, 1175, 1135, 1090, 1010, 935, 855,.775, 725 cm^{-1}. GC-MS (*m*/*z*) = 199.

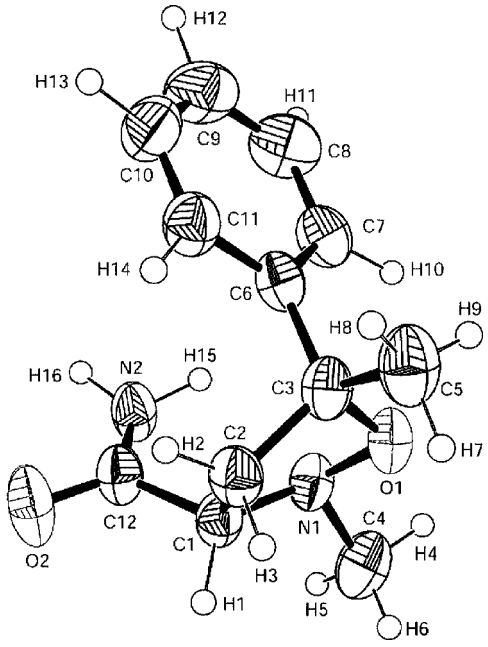


Figure 1. ORTEP view of compound **1j**

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