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CHEMOSELECTIVE DEBEZYLATION OF THE *N*-1-PHENYLETHYL GROUP IN 2-OXAZOLIDINONES BY THE ANISOLE–METHANESULFONIC ACID SYSTEM

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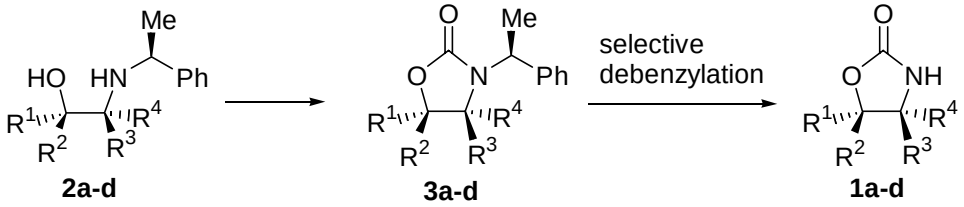
Abstract - The chemoselective removal of *N*-1-phenylethyl group in 2-oxazolidinones by the anisole–methanesulfonic acid system was investigated. Optically active 4,5-*cis*- and 4,5-*trans*-diphenyl-2-oxazolidinones (**1a–d**) were easily synthesized from *dl*-stilbene oxides (*trans*- and *cis*-**7a)** using this debenzylation.

INTRODUCTION

Optically active 4,5-diphenyl-2-oxazolidinones (**1a–d**) have various utilities;[1] for example, (4*S*,5*R*)- and (4*R*,5*S*)-4,5-diphenyl-2-oxazolidinones (**1a** and **1b**) are used as chiral auxiliaries[2] and nucleophilic reagents[3] for asymmetric reactions. Some compounds derived from (4*R*,5*R*)-4,5-diphenyl-2-oxazolidinone (**1d**) have intracellular phospholipase A_2 inhibitor activites.[4] In general, the oxazolidinones (**1a** and **1b**) are synthesized from optically active *erythro*-2-amino-1,2-diphenylethanols,[5,2f,2k,2l] which are prepared by fractional crystallization[6] or asymmetric synthesis.[7] Chromatographic separation of some diastereomers derived from a mixture of **1a** and **1b** has been also achieved successfully.[8] On the other hand, Juaristi and co-workers have reported that the amino alcohols (**2a** and **2b**) are easily prepared by the reaction of *cis*-stilbene oxide and (*S*)-(–)-1-phenylethylamine following fractional crystallization.[9] We thought that **2a** and **2b** would be precursors for the synthesis of **1a** and **1b** *via* *N*-(1'-phenylethyl)-2-oxazolidinones (**3**) (Scheme 1). The selective debenzylation of **2a** and **2b** leading to respective (1*R*,2*S*)- and (1*S*,2*R*)-2-amino-1,2-diphenylethanols requires four steps.[9b] In order to develop a more convenient



a $R^1 = R^4 = H$, $R^2 = R^3 = Ph$; **b** $R^1 = R^4 = Ph$, $R^2 = R^3 = H$;
c $R^1 = R^3 = Ph$, $R^2 = R^4 = H$; **d** $R^1 = R^3 = H$, $R^2 = R^4 = Ph$;

Scheme 1

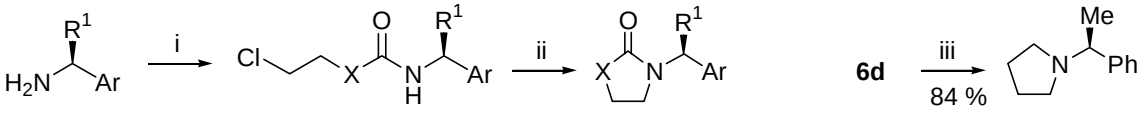
method for the synthesis of **1** from **2**, the selective debenzylation of **3** was required, because **3a–d** have three different benzylic parts; one is the *N*-1-phenylethyl group and the others are the 4- and 5-positions of the oxazolidinone rings.

In our previous paper, we disclosed the cationic debenzylation of the *N*-1-phenylethyl group and the *N*-1-(1-naphthyl)ethyl group in 2-oxazolidinone derivatives by the anisole–methanesulfonic acid system.[10] In these cases, we observed that the *N*-1-(1'-naphthyl)ethyl group was more reactive than the *N*-1-phenylethyl group; however, we did not confirm the generality of this debenzylation. Here, we report the generality of the debenzylation of *N*-(1'-phenylethyl)-2-oxazolidinone derivatives by the anisole–methanesulfonic acid system. Using this chemoseletive debenzylation, we achieved the three-step synthesis of optically active 4,5-*cis*- and 4,5-*trans*-diphenyl-2-oxazolidinones (**1a–d**) from *dl*-*trans*- and *cis*-stilbene oxide (*trans*-**8a** and *cis*-**8a**) *via* **2a–d**.[11] The debenzylation of **3e–g** and the stabilities of phenyl- and diphenyl-2-oxazolidinone rings under these reaction conditions were also examined.

RESULTS AND DISCUSSION

To confirm the reactivity of debenzylation using the anisole-methanesulfonic acid system, we examined at first the reaction of the materials possessing only one *N*-benzyl part; the materials were three 2-oxazolidinones (**6a–c**), one 2-pyrrolidinone (**6d**), and one pyrrolidine (**6e**). The 2-oxazolidinones (**6a–c**) were synthesized by the cyclization of carbamates (**5a–c**) derived from benzylamines (**4a–c**) and 2-chloroethyl chloroformate (Table 1). The 2-pyrrolidinone (**6d**) was also prepared by cyclization of amide (**5d**) derived from **4a** and 4-chlorobutyryl chloride. The pyrrolidine (**6e**) was afforded from **6d** by reduction with lithium aluminum hydride.

Table 1 Preparation of the 2-oxazolidinones (**6a–c**), the 2-pyrrolidinone (**6d**), and the pyrrolidine (**6e**)[a]



4a-c **5a-d** **6a-d** **6e**

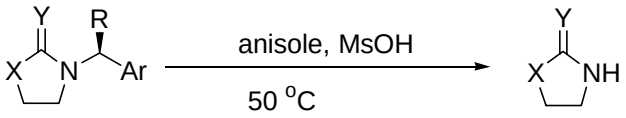
Starting materials	Ar	R^1	X	Products **5**	Yield (%)	Products **6**	Yield (%)
4a	Ph	Me	O	**5a**	99	**6a**	85
4b	Ph	H	O	**5b**	99	**6b**	87
4c	4-MeOPh	H	O	**5c**	93	**6c**	79
4a	Ph	Me	CH_2	**5d**	100	**6d**	91

[a]Reagents and conditions: (i) 2-Chloroethyl chloroformate (X; O) or 4-chlorobutyryl chloride (X; CH_2), Et_3N, THF, 0 °C; (ii) NaH, THF, reflux; (iii) $LiAlH_4$, Et_2O, 0 °C to rt.

The results of the debenzylation are summarized in Table 2. The *N*-1-phenylethyl group in the 2-oxazolidinone (**6a**) was removed clearly to give the 2-oxazolidinone (**7a**) (Entry 1 in Table 2). However, the debenzylation of the *N*-benzyl group in the 2-oxazolidinone (**6b**) and of the

N-1-phenylethyl groups in the 2-pyrrolidinone (**6e**) and the pyrrolidine (**6e**) did not occur under these reaction conditions and the starting materials (**6b**, **6d**, and **6e**) were recovered quantitatively (Entries 2–4). The *N*-(4-methoxyphenyl)methyl group could be removed by this method as easily as the *N*-1-phenylethyl group (Entry 5).

Table 2 Debenzylation of the 2-oxazolidinones (**6a–c**), the pyrrolidinone (**6e**), and the pyrrolidine (**6f**)[a]



6a-e **7a-c**

	N-Benzyl compounds					Reaction	Products	
Entry	**6**	Ar	R	X	Y	time (h)	**7**	Yield (%)[b]
1	**6a**	Ph	Me	O	O	3	**7a**	75
2	**6b**	Ph	H	O	O	6	**7a**	0[c]
3	**6d**	Ph	Me	CH_2	O	3	**7b**	0[c]
4	**6e**	Ph	Me	CH_2	H, H	3	**7c**	0[c]
5	**6c**	4-MeOPh	H	O	O	6	**7a**	56

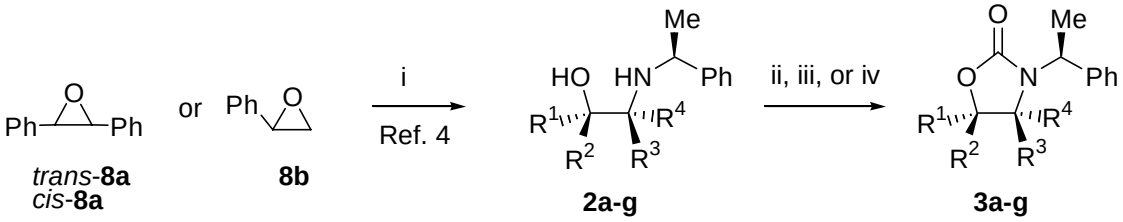
[a]Every mixture of the *N*-bezyl compounds (**6a–e)** and methanesulfonic acid (10 equiv) in anisole (5 equiv) was stirred at 50 °C. [b]Spectrum of the product (**7a**) was good agreement with that of purchased material (**7a**) (Tokyo Kasei). [c]No reaction.

It is worthy to note the dramatic difference of the reactivity between the *N*-1-phenylethyl group and the *N*-benzyl group under these reaction conditions (Entries 1 and 2 in Table 2). The reactivity of this reaction should depend on the stability of the benzylic cation.[10]

The results in Table 2 indicate that the anisole-methanesulfonic acid system was an efficient reagent for the removal of the *N*-1-phenylethyl group in 2-oxazolidinones. Next, we studied the selective debenzylation of the *N*-1-phenylethyl group in 2-oxazolidinones possessing additional phenyl group(s) at the 4- and/or 5-position. The 4,5-diphenyl-2-oxazolidinones (**3a–d**) were synthesized from *dl-trans*- or *cis*-stilbene oxide (**8a** or **8b**) and (*S*)-(–)-1-phenylethylamine (**4a**)[9] following the cyclization of **2a–c** using triphosgene or *N*,*N*'-disuccinimidyl carbonate (DSC) (Table 3). A mixture of amino alcohols (**2e–g**) was prepared from *dl*-styrene oxide (**8b**) and separated by silica gel column chromatography. The mixture (**2e** and **2f**) was treated with DSC to afford 5- and 4-phenyl-2-oxazolidinones (**3e** and **3f**). The diastereomixture of oxazolidinones (**3g**) prepared from **2g** was unable to separate with silica gel column chromatography and this mixture was used at the next reaction without separation.

The results of the debenzylation of **3a–g** are summarized in Table 4. The selective debenzylation of 4,5-diphenyl-*N*-(1'-phenylethyl)-2-oxazolidinones (**3a–d**) using the anisole–methanesulfonic acid system gave desired optically active 4,5-diphenyl-2-oxazolidinones (**1a–d)** in moderate yield, respectively (Entries 1–4 in Table 4). The oxazolidinones (**1a–d)** were optically pure (>99 %ee, checked with HPLC)

Table 3 Preparation of the 4,5-diphenyl-, 5-phenyl-, and 4-phenyl-2-oxazolidinones (**3a–d**, **3e–f**, and **3g**)[a]

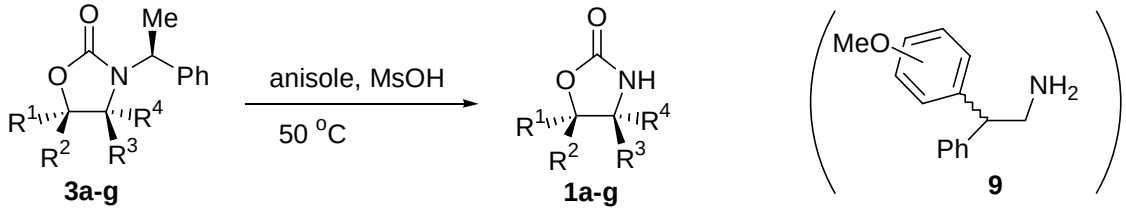


trans-**8a** *cis*-**8a** **8b** **2a-g** **3a-g**

Starting materials	R^1	R^2	R^3	R^4	Products **2**	Yield (%)	Reaction conditions[a]	Products **3**	Yield (%)
trans-**8a**	H	Ph	Ph	H	**2a**[b]	42	ii	**3a**	73
	Ph	H	H	Ph	**2b**[b]	52[c]	iii	**3b**	36[d]
cis-**8a**	Ph	H	Ph	H	**2c**	33	iii	**3c**	78
	H	Ph	H	Ph	**2d**	42	iii	**3d**	70
8b	Ph	H	H	H	**2e**[e]	63[f]	iv	**3e**	46
	H	Ph	H	H	**2f**[e]	63[f]	iv	**3f**	39
	H	H	(Ph and H)[g]		**2g**[e,g]	26[g]	iv	**3g**	61[h]

[a]Reagents and conditions: (i) (*S*)-(–)-1-Phenylethylamine (**4a**), $LiClO_4$, MeCN, reflux; (ii) Triphosgene, K_2CO_3, toluene, H_2O, rt; (iii) DSC, Et_3N, MeCN, rt; (iv) DSC, Et_3N, CH_3CN, reflux. [b]See ref. 4. [c]**2b**:**2a** = 96:4. [d]**3b**:**3a** = 90:10. Pure **3b** was given after recrystallization. [e]See ref. 4a. [f]A mixture of **2e** and **2f** was give in 63 % yield. [g]Mixture of diastereomers. [h](4*R*)-**3g**:(4*S*)-**3g** = 55:45.

Table 4 Debenzylation of *N*-(1'-phenylethyl)-2-oxazolidinones (**3a–g**)[a]



3a-g **1a-g** **9**

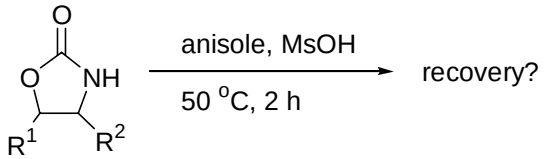
Entry	*N*-(1'-Phenylethyl)-2-oxazolidinones **3**	R^1	R^2	R^3	R^4	Reaction Time (h)	Products **1**	Yield (%)
1	**3a**	Ph	H	H	Ph	1.5	**1a**	76
2	**3b**	H	Ph	Ph	H	1.5	**1b**	75
3	**3c**	Ph	H	Ph	H	2	**1c**	35[b]
4	**3d**	H	Ph	H	Ph	2	**1d**	35[c]
5	**3e**	Ph	H	H	H	2	**1e**	0[d]
6	**3f**	H	Ph	H	H	2	**1f**	0[e]
7	**3g**	H	H	(Ph and H)[f]		3	**1g**[b]	73

[a]The reaction conditions; See Table 3, footnote *a*. [b]The starting material (**3c**) was recovered in 58 %. [c]The starting material (**3d**) was recovered in 52 % yield. [d]The amine (**9**) was formed (checked with ^{1}H-NMR). [e]The amine (**9**) was formed in 73 % yield. [f]Mixture of stereoisomers; (4*R*)-**3g**:(4*S*)-**3g** = 55:45.

and diastereomerically pure (checked with ^{1}H-NMR). A three-step synthesis of four optically active 4,5-diphenyl-2-oxazolidinones (**1a–d**) from *dl-trans*- and *cis*-stilbene oxide (*trans*- and *cis*-**8a**) was easily achieved by this debenzylation. The 4-phenyl-2-oxazolidinone (**1g**) was also obtained from **3g** (Entry 7 in Table 4); however, the 5-phenyl-2-oxazolidinones (**1e** and **1f**) were not obtained from **3e** and **3f** by these reaction conditions (Entries 5 and 6). Instead of the 2-oxazolidinone (**1f**), a mixture of 2-(*p*-methoxyphenyl)- and 2-(*o*-methoxyphenyl)-2-phenylethylamines (**9**) was obtained from **3f**. In the case of **3e**, the same product (**9**) was formed (checked with ^{1}H-NMR). Other reaction conditions using anisole and methanesulfonic acid, such as the dilution of the reaction mixture with toluene and/or reactions at room temperature, were also examined; however, **1e** and **1f** were not obtained.

To examine the stabilities of phenyl- and diphenyl-2-oxazolidinones (**1b**, **1c**, and **1e–g**) and *cis*-4-methyl-5-phenyl-2-oxazolidinone (**10**), we treated these oxazolidinones with anisole and methanesulfonic acid at 50 ^{o}C (Table 5). The 4-phenyl-2-oxazolidinone (**1g**) was stable (100 % recovery, Entry 1); however, the 5-phenyl-2-oxazolidinones (**1e** and **1f**) were unstable (completely decomposed) under these reaction conditions (Entry 2). On the other hand, *cis*-4-methyl-5-phenyl-2-oxazolidinone (**10**) and both *cis*- and *trans*-4,5-diphenyl-2-oxazolidinones (**1b** and **1c**) were recovered in 64–84 % yield from these reaction mixtures (Entries 3–5). The results show that the stability of the 5-phenyl-2-oxazolidinone rings under this cationic reaction depends on the substituents (such as methyl and phenyl groups) on their 4-positions.

Table 5 Stability of the phenyl-substituted 2-oxazolidinone rings



	Oxazolidinones				
Entry	Materials	R^1	R^2	*cis*/*trans*	Recovery (%)[a]
1	**1g**	H	Ph	-	100
2	**1e–f**[b,c]	Ph	H	-	0
3	**10**[c]	Ph	Me	*cis*	64
4	**1b**	Ph	Ph	*cis*	84
5	**1c**	Ph	Ph	*trans*	75

[a]All recovered yields were calculated from integration in the 400 MHz ^{1}H-NMR spectra of the crude material compared to the internal standard (triphenylmethane). [b]The oxazolidinones (**1e–f**); a racemic mixture. [c]The 2-oxazolidinones (**1e–f** and **10**) were prepared from corresponding amino alcohols and 1,1'-carbonyldiimidazole (CDI).

In conclusion, we confirmed that the debenzylation using the anisole–methanesulfonic acid system was a useful method for the debenzylation of *N*-(1-phenylethyl)-2-oxazolidinone derivatives. A three-step synthesis of four optically active 4,5-diphenyl-2-oxazolidinones (**1a–d**) from *dl-trans*- and *cis*-stilbene oxide (*trans*- and *cis*-**8a**) was achieved easily by this debenzylation.[18]

EXPERIMENTAL

Melting points were measured with Yanaco MP-3 apparatus and uncorrected. Optical rotations were determined on a JASCO DIP-140 polarimeter. IR spectra were recorded on a Hitachi 215 spectrophotometer. ^{1}H-NMR spectra were obtained with a JEOL JNM-GX400 (400 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard and *J* values are given in Hz. MS and HR-MS were taken on a JEOL JMS-DX302 spectrometer. Column chromatography was performed with Merck silica gel 60 (230–400 mesh). Sodium hydride (*ca*. 60 % oil suspension) was washed with hexane just before use.

2-Chloroethyl (*S*)-*N*-(1-phenylethyl)carbamate (5a). After a mixture of (*S*)-(–)-1-phenylethylamine (**4a**) (1.43 g, 10 mmol) and triethylamine (1.02 g, 10 mmol) in THF (20 mL) was cooled to 0 ^{o}C, 2-chloroethyl chloroformate (1.43 g, 10 mmol) was added dropwise to the mixture. The resulting mixture was stirred for 30 min at 0 ^{o}C, poured into saturated aqueous ammonium chloride, and extracted with ethyl acetate. The extracts were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford **5a** as colorless solid (2.26 g, 99 %). White needles, mp 57–58.5 ^{o}C (hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.49 (3 H, d, *J* = 7.0, Me), 3.65 (2 H, t, *J* = 5.2, $ClCH_2$), 4.29 (2 H, m, OCH_2), 4.83 (1 H, m, ArC*H*), 5.07 (1 H, br, NH), 7.23–7.37 (5 H, m, Ar). IR ($CHCl_3$) cm^{-1}: 1720 (C=O). MS (EI) *m/z*: 227 (M^+). $[\alpha]_D^{27}$ –59.2^o (*c* 1.0, $CHCl_3$). *Anal*. Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.03; H, 6.20; N, 6.15. Found: C, 58.15; H, 6.06; N, 6.16.

2-Chloroethyl *N*-benzylcarbamate (5b). According to the synthetic procedure of **5a**, the carbamate (**5b**) was prepared from benzyl amine (**4b**) and 2-chloroethyl chloroformate (99 %). White plates, mp 44–46 ^{o}C (hexane). ^{1}H-NMR ($CDCl_3$) δ: 3.69 (2 H, d, *J* = 5.7, $ClCH_2$), 4.35 (2 H, d, *J* = 5.7, OCH_2), 4.38 (2 H, d, *J* = 6.2, ArC*H*$_2$), 5.10 (1 H, br s, NH), 7.37–7.27 (5 H, m, Ar). IR ($CHCl_3$) cm^{-1}: 1725 (C=O). HR-MS *m/z*: 213.0563 (Calcd for $C_{10}H_{12}NO_2Cl$: 213.0558). MS (EI) *m/z*: 213 (M^+).

2-Chloroethyl *N*-(4-methoxyphenyl)methylcarbamate (5c). According to the synthetic procedure of **5a**, the carbamate (**5c**) was prepared from (4-methoxyphenyl)methylamine (**4c**) and 2-chloroethyl chloroformate (93 %). White needles, mp 69–70 ^{o}C (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ: 3.68 (2 H, d, *J* = 5.5, $ClCH_2$), 3.80 (3 H, s, Me), 4.31 (2 H, d, *J* = 5.9, ArC*H*$_2$), 4.34 (2 H, d, *J* = 5.5, OCH_2), 5.05 (1 H, br s, NH), 6.87 (2 H, d, *J* = 8.6, Ar), 7.22 (2 H, d, *J* = 8.6, Ar). IR ($CHCl_3$) cm^{-1}: 1720 (C=O). HR-MS *m/z*: 243.0663 (Calcd for $C_{11}H_{14}NO_2Cl$: 243.0663). MS (EI) *m/z*: 243 (M^+).

(*S*)-*N*-(1-Phenylethyl)-4-chlorobutyrylamide (5d). According to the synthetic procedure of **5a**, the amide (**5d**) was prepared from (*S*)-(–)-1-phenylethylamine (**4a**) and 4-chlorobutyryl chloride (100 %). Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (3 H, d, *J* = 7.1, Me), 2.11 (2 H, quint, *J* = 6.6, C*H*$_2$CH$_2$Cl), 2.31–2.42 (2 H, m, $COCH_2$), 3.54–3.63 (2 H, m, $ClCH_2$), 5.13 (1 H, quint, *J* = 7.1 PhC*H*), 5.79 (1 H, br s, NH), 7.25–7.36 (5 H, m, Ar). IR ($CHCl_3$) cm^{-1}: 1640 (C=O). HR-MS *m/z*: 225.0917 (Calcd for $C_{12}H_{16}NOCl$: 225.0922). MS (EI) *m/z*: 225 (M^+). $[\alpha]_D^{26}$ –84.0^o (*c* 1.2, $CHCl_3$).

Preparation of the 2-oxazolidinones (6a–c) and the pyrrolidinone (6d).

Typical procedure for preparation of the oxazolidinones (6a–c) and the pyrrolidinone (6e). A suspension of sodium hydride (202 mg, 8.43 mmol) in THF (17 mL) was added carefully to a mixture of carbamate (**5a**) (1.92 g, 8.43 mmol) in THF (17 mL) at rt. The resulting mixture was refluxed for 6 h, poured into saturated aqueous ammonium chloride, and extracted with ethyl acetate. The extracts were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane:ethyl acetate = 1:1) to give **6a** as colorless oil (1.38 g, 85 %). The oxazolidinones (**6b**) (87 %) and **6c** (79 %) were also given according to this procedure. In the case of the pyrrolidinone (**6d**), the residue after work up was distilled under reduced pressure (Kugel rohr, ~180 ^{o}C/0.4 Torr) to give **6d** (91 %).

(*S*)-*N*-(1'-Phenylethyl)-2-oxazolidinone (6a). The spectrum data were good agreement with the reported data.[12] A colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (3 H, d, *J* = 7.0, Me), 3.16 (1 H, ddd, *J* = 9.2, 8.4, 6.6, NC*H*H), 3.50 (1 H, ddd, *J* = 9.2, 8.4, 7.0, NCH*H*), 4.23 (1 H, ddd, *J* = 9.2, 8.8, 6.6, OC*H*H), 4.31 (1 H, ddd, *J* = 9.2, 8.8, 7.0, OCH*H*), 5.23 (1 H, d, *J* = 7.0, ArC*H*), 7.29–7.38 (5 H, m, Ar). IR (neat) cm^{-1}: 1730 (C=O). HR-MS *m/z*: 191.0942 (Calcd for $C_{11}H_{13}NO_2$: 191.0947). MS (EI) *m/z*: 191 (M^+). $[\alpha]_D^{27}$ –103.9^{o} (*c* 1.0, $CHCl_3$) [for the *R*-isomer; lit.,[12] $[\alpha]_D$ +95.6^{o} (*c* 0.66, $CHCl_3$)].

***N*-Benzyl-2-oxazolidinone (6b).** The spectrum data were good agreement with the reported data.[13]

***N*-(4-Methoxyphenyl)methyl-2-oxazolidinone (6c).** White plates, mp 73–74.5 ^{o}C (ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ: 3.40 (2 H, t, *J* = 8.1, NCH_2), 3.81 (3 H, s, Me), 4.29 (2 H, t, *J* = 8.1, OCH_2), 4.37 (2 H, s, ArCH_2), 6.88 (2 H, d, *J* = 8.6, Ar), 7.25 (2 H, d, *J* = 8.6, Ar). IR ($CHCl_3$) cm^{-1}: 1745 (C=O). HR-MS *m/z*: 207.0893 (Calcd for: $C_{11}H_{13}NO_3$: 207.0896). MS (EI) *m/z*: 207 (M^+).

(*S*)-*N*-(1'-Phenylethyl)-2-pyrrolidinone (6d). Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (3 H, d, *J* = 7.1, Me), 1.84–2.03 (2 H, m, NCH_2CH_2), 2.39–2.44 (2 H, m, $COCH_2$), 2.98 (1 H, ddd, *J* = 9.6, 8.5, 5.4, NC*H*H), 3.32 (1 H, ddd, *J* = 9.5, 8.3, 6.1, NCH*H*), 5.39 (1 H, q, *J* = 7.1, PhC*H*), 7.25–7.37 (5 H, m). IR (neat) cm^{-1}: 1680 (C=O). HR-MS *m/z*: 189.1148 (Calcd for $C_{12}H_{15}NO$: 189.1155). MS (EI) *m/z*: 189 (M^+). $[\alpha]_D^{28}$ –206.7^{o} (*c* 1.1, $CHCl_3$).

(*S*)-*N*-(1'-Phenylethyl)pyrrolidine (6e). Lithium aluminum hydride (454 mg, 12.0 mmol) was added portionwise to a mixture of the 2-pyrrolidinone (**6d**) (1.13 g, 5.97 mmol) in ether (12 mL) at 0 ^{o}C. The resulting mixture was stirred overnight at rt. After the reaction mixture was cooled to 0 ^{o}C, H_2O (0.5 mL) in THF, 15 % aqueous sodium hydroxide and H_2O (1.5 mL) were added subsequently. The mixture was stirred for 1 h at rt and filtered. The filtrate was concentrated *in vacuo* and distilled under reduced pressure (Kugel rohr, ~75 ^{o}C/0.4 Torr) to give **6e** (878 mg, 84 %). Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3 H, d, *J* = 6.6, Me), 1.76 (4 H, m, NCH_2CH_2 x 2), 2.37 (2 H, m, NC*H*H x 2), 2.54 (2 H, m, NCH*H* x 2), 3.17 (1 H, q, *J* = 6.6, PhC*H*), 7.20–7.34 (5 H, m, Ar). IR (neat) cm^{-1}: 2960, 2770. HR-MS *m/z*: 175.1366 (Calcd for $C_{12}H_{17}N$: 175.1362). MS (EI) *m/z*: 175 (M^+). $[\alpha]_D^{26}$ –61.9^{o} (*c* 2.0, $CHCl_3$).

Preparation of the amino alcohols (2a–g) from the epoxides

(1*R*,2*S*,1'*S*)- And (1*S*,2*R*,1'*S*)-2-(1'-phenylethyl)amino-1,2-diphenylethanol (2a and 2b). This procedure was according to the reported method[9] except work up. (S)-(–)-1-Phenylethylamine (**4a**) (6.06

g, 50 mmol) was added to a mixture of lithium perchlorate (5.32 g, 50 mmol) and *trans*-stilbene oxide (*trans*-**8a**) (9.81 g, 50 mmol) in acetonitrile (50 mL). The resulting mixture was refluxed for 27 h. The mixture was cooled to rt overnight without stirring. After the mixture was stirred for about 5 min, crystallized **2a** was collected with a suction funnel and washed with acetonitrile (*ca*. 10 mL) to give **2a** (6.74 g, 42 %). The ^{1}H-NMR spectral data of **2a** were good agreement with the reported data.[9] This material (**2a**) was diastereomerically pure and used at the next reaction without any further purification. The filtrate was poured into water (100 mL), and extracted with ethyl acetate three times. The extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to give viscous oil. The oil was distilled (Kugel rohr, ~195 ^{o}C/0.2 Torr) to give a mixture of **2b** and **2a** (96:4, 8.24 g, 52 %) as a colorless oil. This mixture was used at the next reaction without any further purification.

(1*S*,2*S*,1'*S*)- and (1*R*,2*R*,1'*S*)-2-(1'-Phenylethyl)amino-1,2-diphenylethanol (2c and 2d). This procedure was according to the reported method.[9] (*S*)-(–)-1-Phenylethylamine (**4a**) (0.703 g, 5.8 mmol) was added to a mixture of lithium perchlorate (0.617 g, 5.8 mmol) and *cis*-stilbene oxide (*cis*-**8a**) (1.14 g, 5.8 mmol) in acetonitrile (5.8 mL). The resulting mixture was refluxed for 22 h. After being cooled to rt, water (20 mL) was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate (50 mL, three times). The organic extracts were combined, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane:ethyl acetate = 4:1) to give **2c** (0.775 g, 42 %) and **2d** (0.605 g, 33 %).

2c: a pale yellow oil. ^{1}H-NMR (neat) δ: 1.37 (3 H, d, *J* = 6.6, Me), 3.64 (1 H, q, *J* = 6.4, PhC*H*Me), 3.73 (1 H, d, *J* = 8.4, NCH), 4.54 (1 H, d, *J* = 8.4, OCH), 6.93–6.96 (2 H, m, Ar), 7.07–7.10 (2 H, m, Ar), 7.16–7.18 (8 H, m), 7.21–7.37 (3 H, m, Ar). IR ($CHCl_3$) cm^{-1}: 1740 (C=O). MS (positive FAB) *m/z*: 318 $(M + 1)^+$. $[\alpha]_D^{30}$ –66.1^o (*c* 1.0, $CHCl_3$). *Anal*. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.27; H, 7.41; N, 4.18.

2d: a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3 H, d, *J* = 6.6, Me), 3.36 (1 H, d, *J* = 8.4, NCH), 3.60 (1 H, q, *J* = 6.6, PhC*H*Me), 4.56 (1 H, d, *J* = 8.4, OCH), 6.90–6.95 (4 H, m, Ar), 7.04–7.10 (3 H, m, Ar), 7.19–7.35 (8 H, m). IR (neat) cm^{-1}: 1730 (C=O). MS (positive FAB) *m/z*: 318 $(M + 1)^+$. $[\alpha]_D^{30}$ –112.8^o (*c* 1.0, $CHCl_3$). *Anal*. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.07; H, 7.49; N, 4.26.

A mixture of (1*S*, 1'*S*)-, and (1*R*,1'*S*)-2-(1'-phenylethyl)amino-1-phenylethanols (2e and 2f) and a mixture of (2*S*,1'*S*)- and (2*R*,1'*S*)-2-(1'-phenylethyl)amino-2-phenylethanols (mixture 2g). These mixtures were prepared from *dl*-styrene oxide (**8b**) and (*S*)-(–)-phenylethylamine according to the reported method[9a] (**2e**–**f**; 63 %, **2g**; 26 %). These mixtures were used at the next reactions without any further purification.

Preparation of the oxazolidinones from the amino alcohols.

(4*S*,5*R*,1'*S*)-*N*-(1'-Phenylethyl)-4,5-diphenyl-2-oxazolidinone (3a). Triphosgene (1.16 g, 3.69 mmol) was added to a two-phase mixture of the amino alcohol (**2a**) (3.04 g, 9.56 mmol) in toluene (100 mL) and potassium carbonate (1.81 g, 13.1 mmol) in water (42 mL) with vigorously stirring at rt. After the mixture was vigorously stirred for 9 h at rt, the organic layer was separated and washed with once with water, twice with 10% hydrochloric acid, once with water, and once with saturated aqueous sodium

chloride. The organic layer was dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane:ethyl acetate = 7:3) to give the oxazolidinone (**3a**) (2.41 g, 73%). White needles, mp 154–156 °C (ethyl acetate). ^{1}H-NMR ($CDCl_3$)[14] δ: 1.22 (3 H, d, *J* = 7.3, Me), 4.57 (1 H, d, *J* = 8.1, NCH), 5.35 (1 H, q, *J* = 7.3, PhC*H*Me), 5.67 (1 H, d, *J* = 8.3, OCH), 6.93–6.96 (2 H, m, Ph), 7.02–7.26 (7 H, m, Ph), 7.30–7.42 (6 H, m, Ph). IR ($CHCl_3$) cm^{-1}: 1740 (C=O). MS (EI) *m/z*: 343 $(M + 1)^+$. $[\alpha]_D^{30}$ +19.1° (*c* 1.0, $CHCl_3$). *Anal*. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.08; H, 6.16; N, 3.89.

Typical procedure for preparation of the oxazolidinones (3b–g).

DSC (1.66 g, 6.47 mmol) was added to a mixture of the amino alcohol (**2b**) (2.06 g, containing 4 % of **2a**, 6.47 mmol) and triethylamine (0.655 g, 6.47 mmol) in acetonitrile (16 mL) at rt. After being stirred for 24 h, the reaction mixture was poured into aqueous saturated ammonium chloride and extracted with ethyl acetate. The organic layer was separated, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane:ethyl acetate = 7:3) to give a white solid (0.799 g, 36 %, **3b**:**3a** = 90:10). The oxazolidinones (**3c**) (78 %), **3d** (70 %), **3e** (46 %), **3f** (39 %), and **3g** (61 %) were also given from **2c**, **2d**, the mixture (**2e** and **2f**), and the mixture (**2g**). In the case of **2g**, another solvent (hexane:ethyl acetate = 1:1) was used for silica gel column chlromatography.

(4*R*,5*S*,1'*S*)-*N*-(1'-Phenylethyl)-4,5-diphenyl-2-oxazolidinone (3b). The mixture (**3b**:**3a** = 90:10, 0.785 g) was recrysatallized from a mixed solvent (cyclohexane:ethyl acetate = 7:3, 14 mL) to give the oxazolidinone (**3b**) (0.418 g). White plates, mp 164–166 °C (solvent, see above). ^{1}H-NMR ($CDCl_3$)[14] δ: 1.84 (3 H, d, *J* = 7.2, Me), 4.51 (1 H, q, *J* = 7.2, PhC*H*Me), 4.92 (1 H, d, *J* = 8.4, PhC*H*N), 5.73 (1 H, d, *J* = 8.4, PhC*H*O), 6.70–6.73 (2 H, m, Ph), 6.91–7.06 (8 H, m, Ph), 7.18–7.38 (5 H, m, Ph). IR ($CHCl_3$) cm^{-1}: 1740 (C=O). HR-MS *m/z*: 343.1572 (Calcd for $C_{23}H_{21}NO_2$: 343.1573). MS (EI) *m/z*: 343 (M^+). $[\alpha]_D^{30}$ –36.9° (*c* 1.0, $CHCl_3$).

(4*S*,5*S*,1'*S*)-*N*-(1'-Phenylethyl)-4,5-diphenyl-2-oxazolidinone (3c). A pale yellow oil. ^{1}H-NMR ($CDCl_3$)[14] δ: 1.21 (3 H, d, *J* = 7.3, Me), 4.11 (1 H, d, *J* = 6.2, NCH), 5.19 (1 H, d, *J* = 7.3, OCH), 5.32 (1 H, q, *J* = 7.3, PhC*H*Me), 7.01–7.04 (2 H, m, Ph), 7.16–7.21 (4 H, m, Ph), 7.24–7.29 (6 H, m, Ph), 7.36–7.40 (3 H, m, Ph). IR (neat) cm^{-1}: 1750 (C=O). MS (EI) *m/z*: 343 $(M + 1)^+$. $[\alpha]_D^{30}$ –105.2° (*c* 1.0, $CHCl_3$). *Anal*. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.09; H, 6.27; N, 3.89.

(4*R*,5*R*,1'*S*)-*N*-(1'-Phenylethyl)-4,5-diphenyl-2-oxazolidinone (3d). White plates, mp 109–112 °C (ethyl acetate). ^{1}H-NMR ($CDCl_3$)[14] δ: 1.75 (3 H, d, *J* = 7.3, Me), 4.46 (1 H, d, *J* = 7.3, NCH), 4.55 (1 H, q, *J* = 7.3, PhC*H*Me), 5.20 (1 H, d, *J* = 7.3, OCH), 7.10–7.16 (6 H, m, Ph), 7.25–7.34 (9 H, m, Ph). IR ($CHCl_3$) cm^{-1}: 1742 (C=O). MS (EI) *m/z*: 343 $(M + 1)^+$. $[\alpha]_D^{30}$ +3.81° (*c* 1.0, $CHCl_3$). *Anal*. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.15; H, 6.26; N, 4.01.

(5*S*,1'*S*)-*N*-(1'-Phenylethyl)-5-phenyl-2-oxazolidinone (3e).[15] White amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (3 H, d, *J* = 7.2, Me), 3.03 (1 H, dd, *J* = 8.8, 7.5, NC*H*H), 3.83 (1 H, t, *J* = 8.8, NCH*H*), 5.29 (1 H, q, *J* = 7.2, PhC*H*Me), 5.45 (1 H, t, *J* = 8.2, OC*H*), 7.19–7.32 (10 H, m, Ph). IR ($CHCl_3$) cm^{-1}: 1730 (C=O). MS (EI) *m/z* 267 (M^+). $[\alpha]_D^{27}$ –93.9° (*c* 1.1, $CHCl_3$). *Anal*. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.06; H, 6.44; N, 5.26.

(5*R*,1'*S*)-*N*-(1'-Phenylethyl)-5-phenyl-2-oxazolidinone (3f).[15] White amorphous solid. ^{1}H-NMR

($CDCl_3$) δ: 1.56 (3 H, d, *J* = 7.2, Me), 3.37 (1 H, dd, *J* = 8.6, 7.5, NC*H*H), 3.52 (1 H, t, *J* = 8.6, NCH*H*), 5.29 (1 H, q, *J* = 7.2, PhC*H*Me), 5.39 (1 H, t, *J* = 8.2, OC*H*), 7.31–7.42 (10 H, m, Ph). IR ($CHCl_3$) cm^{-1}: 1740 (C=O). MS (EI) *m/z* 267 (M^+). $[\alpha]_D^{27}$ +21.1° (*c* 1.1, $CHCl_3$). *Anal*. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.09; H, 6.44; N, 5.16.

A mixture of (4*R*,1'*S*)- and (4*S*,1'*S*)-*N*-(1'-phenylethyl)-4-phenyl-2-oxazolidinones [3g, (4*R*)-3g:(4*S*)-3g = 55:45].[14] Characteristic signals of ^{1}H-NMR ($CDCl_3$) spectrum; (4*R*)-**3g**,[14,15] δ: 1.75 (3 H, d, *J* = 7.3, Me), 4.06 (1 H, dd, *J* = 8.5, 7.6, NC*H*CH_2), 4.48 (1 H, q, *J* = 7.3, PhC*H*Me), 4.52 (1 H, t, *J* = 8.2, OC*H*H), 4.71 (1 H, dd, *J* = 8.8, 7.6, OCH*H*). (4*S*)-**3g**,[14,15] δ: 1.16 (3 H, d, *J* = 7.3, Me), 4.09 (1 H, dd, *J* = 8.5, 5.9, NC*H*CH_2), 4.33 (1 H, dd, *J* = 9.0, 6.1, OC*H*H), 4.44 (1 H, t, *J* = 8.5, OCH*H*), 5.27 (1 H, q, *J* = 7.3, PhC*H*Me). IR ($CHCl_3$) cm^{-1}: 1740 (C=O). MS (EI) *m/z* 267 (M^+).

Debenzylation using the anisole–methansulfonic acid system.[10]

Typical procedure for debenzylation by anisole–methanesulfonic acid. Methanesulfonic acid (5.89 g, 61.3 mmol) was added to a mixture of the oxazolidinone (**3a**) (2.10 g, 6.13 mmol) and anisole (3.31 g, 30.6 mmol), and the resulting mixture was stirred for 1.5 h (reaction times for the other substrates, see Tables 3–5) at 50 °C (bath temperature). After being to cool to rt, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo*. The residue was suspended with hexane, and the suspension was filtered to give solid. The solid was chromatographed on silica gel (ethyl acetate) to give the oxazolidinone **1a** as white solid (1.10 g, 75 %). The other results are shown in Tables 2 and 4.

(4*S*,5*R*)-4,5-Diphenyl-2-oxazolidinone (1a). $[\alpha]_D^{27}$ –58.4° (*c* 0.91, MeOH).

(4*R*,5*S*)-4,5-Diphenyl-2-oxazolidinone (1b). $[\alpha]_D^{28}$ +61.6° (*c* 1.0, MeOH) {lit.,[2k] $[\alpha]_D^{20}$ +60.6° (*c* 0.858, MeOH)}. The spectrum data were good agreement with the reported data.[2k]

(4*S*,5*S*)-4,5-Diphenyl-2-oxazolidinone (1c). $[\alpha]_D^{28}$ –58.7° (*c* 1.0, $CHCl_3$) {lit.,[16] $[\alpha]_D^{22}$ –52.1° (c 0.9, $CHCl_3$)}. The spectrum data were good agreement with the reported data.[11c]

(4*R*,5*R*)-4,5-Diphenyl-2-oxazolidinone (1d). $[\alpha]_D^{22}$ +59.2° (*c* 1.0, $CHCl_3$).[17]

Determination of the optical purity.

HPLC analysis of 1a and **1b.** Column, Daisel Chiralpak AD (25 cm x 0.46 cm ϕ); eluent, hexane:2-propanol = 4:1; flow-rate, 0.5 mL/min; detection, UV (254 nm); retention time, **1a**: 14.7 min, **1b**: 16.7 min.

HPLC analysis of 1c and **1d.** Column, Daisel Chiralcel OD (25 cm x 0.46 cm ϕ); eluent, hexane:2-propanol = 4:1; flow-rate, 0.5 mL/min; detection, UV (254 nm); retention time, **1c**: 22.7 min, **1d**: 26.3 min.

A mixture of 2-(*p*-methoxyphenyl)- and 2-(*o*-methoxyphenyl)-2-phenylethylamines (9, *p*-form:*o*-form = 7:3). Characteristic signals of ^{1}H-NMR ($CDCl_3$) spectrum; *p*-form, δ: 3.45 (2 H, d-like m, NCH_2), 3.73 (3 H, s, Me), 4.39 (1 H, t, *J* = 8.0, PhC*H*); *o*-form, 3.49 (1 H, overlapped with signals of

p-form, NC*H*H), 3.57 (1 H, dd, *J* = 12.0, 8.0, NCH*H*), 3.77 (3 H, s, Me), 4.71 (1 H, t, *J* = 8.0, PhC*H*). MS (EI) *m/z* 227 (M^+).

(*RS*)-4-Phenyl-2-oxazolidinone (1g). The ^{1}H-NMR spectrum was identical with that of a purchased (*R*)-form [(*R*)-**1g**] (Aldrich).

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14. We found characteristic chemical shifts on the ^{1}H-NMR spectrum of 4-phenyl-*N*-(1'-phenylethyl)-2-oxazolidinones [**3a–d**, (4*R*)-**3g,** and (4*S*)-**3g**]. The δ values of the methyl group and the benzylic proton in *N*-(1'-phenylethyl)-2-oxazolidinone (**6a**) are 1.59 and 5.23 ppm, respectively, and these δ values are regarded as standard values (Table 6). (4*R*,1'*S*)-Type oxazolidinones [**3b**, **3d**, and (4*R*)-**3g**] reveled the following shift values; the methyl groups, 1.84, 1.75, and 1.75 ppm (low fields compared to **6a**); the benzylic protons, 4.51, 4.55, and 4.48 ppm (high fields compared to **6a**). On the other hand, (4*S*,1'*S*)-type oxazolidinones [**3a**, **3c**, and (4*S*)-**3g**] showed the following δ values; the methyl group, 1.22, 1.21, and 1.16 ppm (high fields compared to **6a**); the benzylic protons, 5.35, 5.32, and 5.27 ppm (low fields compared to **6a**).

Table 6 ^{1}H-NMR Shift values of *N*-1-phenylethyl groups on 4-phenyl-2-oxazolidinones (**3a–d** and **3g**)

	Standard	(4*R*,1'*S*)-Type oxazolidinones			(4*S*,1'*S*)-Type oxazolidinones		
Protons	**6a**	**3b**	**3d**	(4*R*)-**3g**	**3a**	**3c**	(4*S*)-**3g**
Me	1.59	1.84	1.75	1.75	1.22	1.21	1.16
PhC*H*	5.23	4.51	4.55	4.48	5.35	5.32	5.27

15. To determine the stereochemistry of **3e**, **3f**, (4*R*)-**3g**, and (4*S*)-**3g**, we synthesized **3e** and (4*R*)-**3g** from (*S*)-(–)-styrene oxide (Aldrich) and (*S*)-(–)-1-phenylethylamine (**4a**).
16. J. N. Stefanovsky, S. L. Spassov, B. J. Kurtev, M. Balla, and L. Ötvös, *Chem. Ber*., 1969, **102**, 717.
17. For further evidence of the stereochemistry of oxazolidinone (**1d**), we synthesized **1d** according to the referrence[11a] and measured its specific rotation {$[\alpha]_D^{27}$ = +60.3^o (c = 1.0, $CHCl_3$)}.
18. Recently (*R*)-4-iodomethyl-2-oxazolidinone was prepared from (4*R*,1'*S*)-*N*-(1'-phenylethyl)-4-iodomethyl-2-oxazolidinone by debenzylation using anisole and methanesulfonic acid in toluene. See: D. K. Pyun, C. H. Lee, H.-J. Ha, C. S. Park, J.-W. Chang, and W. K. Lee, *Org. Lett.*, 2001, **3**, 4197.