Pergamon

Tetrahedron 54 (1998) 2697–2708

TETRAHEDRON

Asymmetric Synthesis of Optically Active 2,3-Diarylsuccinic Acids by Oxidative Homocoupling of Chiral 3-(Arylacetyl)-2-oxazolidones

Naoki Kise,* Kimikage Kumada, Yuichi Terao and Nasuo Ueda

Department of Biotechnology, Faculty of Engineering, Tottori University, Tottori 680, Japan

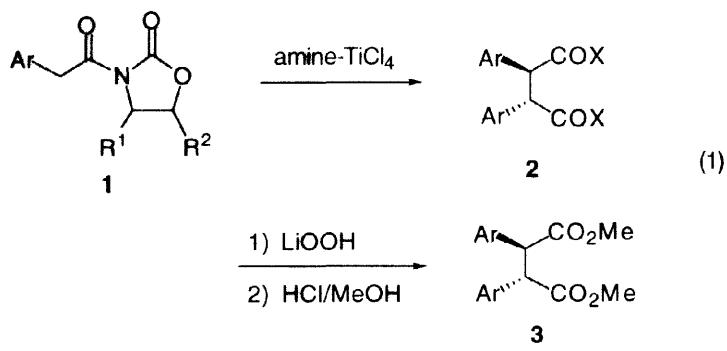
Received 17 December 1997; accepted 12 January 1998

Abstract Oxidative homocoupling of chiral 3-(arylacetyl)-2-oxazolidones **1** was achieved by treatment with DABCO-$TiCl_4$ or DMAP-$TiCl_4$ and afforded the corresponding dimers stereospecifically. The reaction of (4*S*)- and (4*R*)-substituted **1** gave (*S,S*)- and (*R,R*)-dimers respectively. The obtained dimers were easily transformed to the corresponding 2,3-diaryl succinic acids. This reaction therefore provides a useful method for the synthesis of optically pure 2,3-diarylsuccinic acids. The oxidative coupling was not inhibited by para substitution of an electron donating group on the aryl group. A para-substituted electron withdrawing group and an ortho-substituent, however, hindered the coupling.

INTRODUCTION

Oxidative homocoupling of enolate anions of esters is a useful reaction for the synthesis of 2,3-disubstituted succinic acids.[1] Diastereoselectivity in the homocoupling reactions has been studied and improved with Et_3N-$TiCl_4$ as oxidizing agent (dl-selectivity 99%)[2] or by using carboxylic acid dianions[3a] or thioamide α-anions[3b] instead of ester enolate anions (dl-selectivity ~92%). Optically active 2,3-disubstituted succinic acids are useful intermediates in the synthesis of chiral compounds as exemplified by the recent use of optically active 2,3-diphenylsuccinic acid as a chiral source for the preparation of optically active crown ethers[4a] and diphosphine ligands.[4b] In these cases, optically pure 2,3-diphenylsuccinic acid was obtained by optical resolution.[5] Recently, we and others have reported stereoselective oxidative coupling of chiral carboxylic acid derivatives. Intermolecular coupling of chiral oxazolidine[6a] and imidazolidone[6b] derivatives of aliphatic carboxylic acids and intramolecular coupling of chiral imidazolidone[6b] and imidazolidinone[6c] derivatives of aliphatic dicarboxylic acids with LDA-I_2 or LDA-Cu^{II} have been reported. We have also reported that oxidative homocoupling of chiral 3-(phenylacetyl)-2-oxazolidones took place stereospecifically by treatment with amine-$TiCl_4$.[7] Among them, only our method affords optically active 2,3-diphenylsuccinic acid. We wish to report herein that the oxidative homocoupling of chiral 3-(arylacetyl)-2-oxazolidones **1** with amine-$TiCl_4$ is a useful method for the synthesis of a variety of enantiomerically pure 2,3-diarylsuccinic acids (eq 1). We also studied the scope and limitation of this reaction.

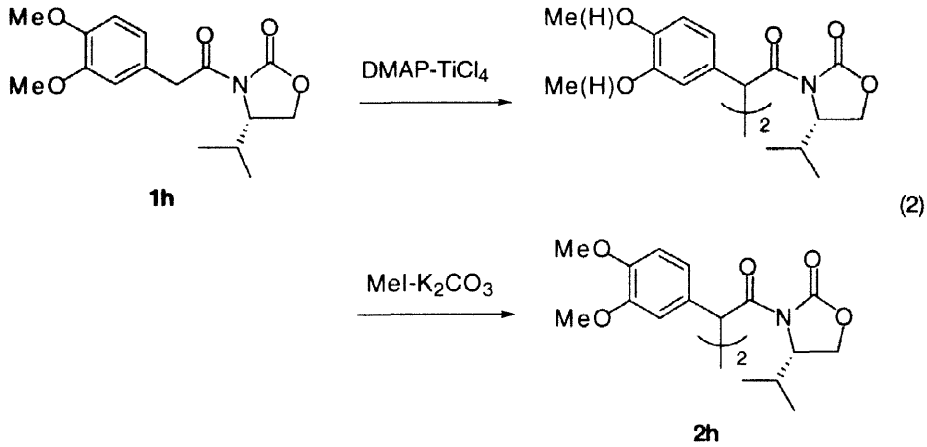
0040-4020/98/$19.00
PII: S0040-4020(98)00049-0



1 2 3 (1)

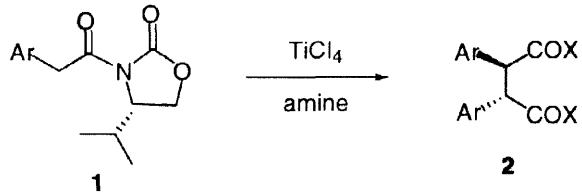
RESULTS AND DISCUSSION

In our preliminary report,[7] we have found that a combination of amine-$TiCl_4$ was most effective for stereospecific dimerization of (*S*)-4-isopropyl-3-(phenylacetyl)-2-oxazolidones **1a** and, in particular, DABCO or DMAP (4-dimethylaminopyridine) was the choice of amine. Therefore, we attempted the oxidative coupling of several (*S*)-3-(arylacetyl)-4-isopropyl-2-oxazolidones **1b-g** using DABCO or DMAP as an amine. The reactions were carried out with 2.5 equiv of $TiCl_4$ and 2 equiv of an amine in dichloromethane at room temperature. The results are summarized in Table 1. In all cases, the dimers **2** were formed stereospecifically[8] and assigned to be (*S,S*) by conversion to dimethyl esters **3** (*vide infra*). A para-substituted electron-donating group (OMe, Cl) did not inhibit the coupling (runs 3-6), whereas a para-substituted electron-withdrawing group (CF_3) disturbed it completely (runs 7 and 8). Steric hindrance caused by ortho-substitution of chloro group also inhibited the homocoupling (runs 9 and 10). In these cases, α-chlorinated and α-hydroxylated products were obtained as by-products. The reaction of 1-naphthyl derivative gave the dimer in poor yields (runs 11 and 12), whereas that of 2-naphthyl one resulted in good yields (runs 13 and 14). The oxidative coupling of (*S*)-3-(3,4-dimethoxyphenylacetyl)-4-isopropyl-2-oxazolidone **1h** gave the dimer **2h** in good yields after methylation, since the dimer was partially demethylated (runs 15 and 16) (eq 2).

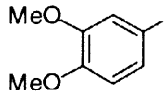


1h 2h (2)

Table 1. Oxidative Coupling of (*S*)-3-(Arylacetyl)-4-isopropyl-2-oxazolidones



1 2

run	1	Ar	amine	%yield of 2[a]
1	**1a**	Ph	DABCO	**2a** 69
2	**1a**		DMAP	**2a** 76
3	**1b**	*p*-$MeOC_6H_4$	DABCO	**2b** 86
4	**1b**		DMAP	**2b** 88
5	**1c**	*p*-ClC_6H_4	DABCO	**2c** 72
6	**1c**		DMAP	**2c** 67
7	**1d**	*p*-$CF_3C_6H_4$	DABCO	**2d** 0[b]
8	**1d**		DMAP	**2d** 0[b]
9	**1e**	*o*-ClC_6H_4	DABCO	**2e** 39[c]
10	**1e**		DMAP	**2e** 17[c]
11	**1f**	1-Naphthyl	DABCO	**2f** 29[d]
12	**1f**		DMAP	**2f** 25[d]
13	**1g**	2-Naphthyl	DABCO	**2g** 85
14	**1g**		DMAP	**2g** 63
15	**1h**		DABCO	**2h** 72[e]
16	**1h**		DMAP	**2h** 84[e]

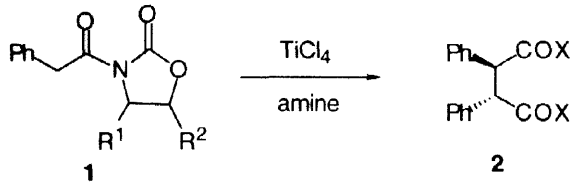
a) Isolated yields of (*S,S*)-**2**. In all cases, small amounts of **1** (<10%) were recovered.
b) Complex mixture was obtained. c) α-Chlorinated and α-hydroxylated products were yielded as by-products. d) Complex mixture was obtained as major product.
e) Partially demethylated. See text.

Next, we tried the reaction of several optically active 3-(phenylacetyl)-2-oxazolidones **1i-l** with substituents other than 4*S*-isopropyl (**1a**). As shown in Table 2, all the dimers were obtained stereospecifically. While (4*S*)-substituted 2-oxazolidones gave (*S,S*)-dimers (runs 1-4), (4*R*)-substituted and (4*R*,5*S*)-disubstituted ones yielded (*R,R*)-dimers (runs 5 and 6). The yields of the dimers depended on the used amine. The high stereoselectivity in this oxidative coupling obviously resulted from the substituent of the oxazolidone ring,

since the reaction of 3-(phenylacetyl)-2-oxazolidone **4** gave a diastereomeric mixture (dl:meso = 65:35) of the corresponding dimer **5** (eq 3).

Oxidative coupling with the combination of amine-$TiCl_4$ was limited to 3-(arylacetyl)-2-oxazolidones **1**. In fact, (*S*)-3-butyryl-4-isopropyl-2-oxazolidone and (*S*)-4-isopropyl-3-(2-phenylpropionyl)-2-oxazolidone were recovered under the same conditions.

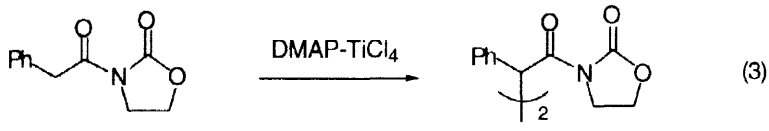
Table 2. Oxidative Coupling of Optically Active 3-(Phenylacetyl)-2-oxazolidones



1 **2**

run	1	R^1	R^2	amine	%yield of **2**[a]	
1	**1i**	*i*-Bu (*S*)	H	DABCO	**2i**	59[b]
2	**1i**			DMAP	**2i**	52[b]
3	**1j**	$PhCH_2$ (*S*)	H	DABCO	**2j**	69[b]
4	**1j**			DMAP	**2j**	37[b]
5	**1k**	Ph (*R*)	H	DABCO	**2k**	56[c]
6	**1k**			DMAP	**2k**	76[c]
7	**1l**	Me (*R*)	Ph (*S*)	DABCO	**2l**	38[c]
8	**1l**			DMAP	**2l**	71[c]

a) Isolated yields. In all cases, small amounts of **1** (<5%) were recovered.
b) (*S,S*)-form. c) (*R,R*)-form.



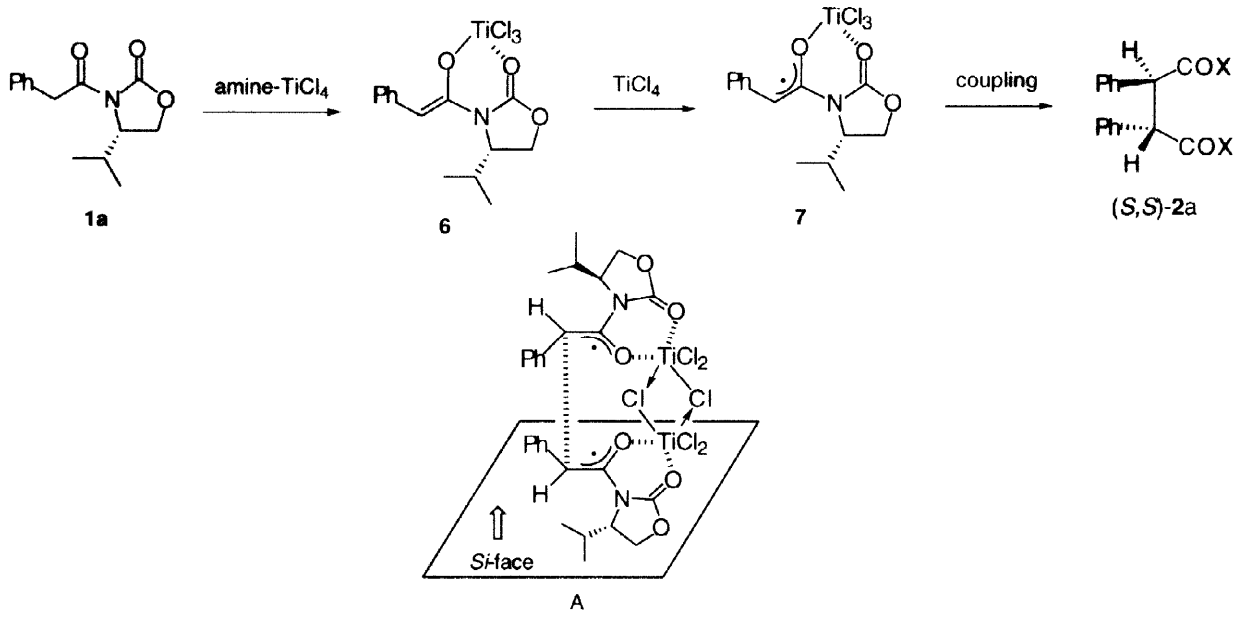
(3)

4

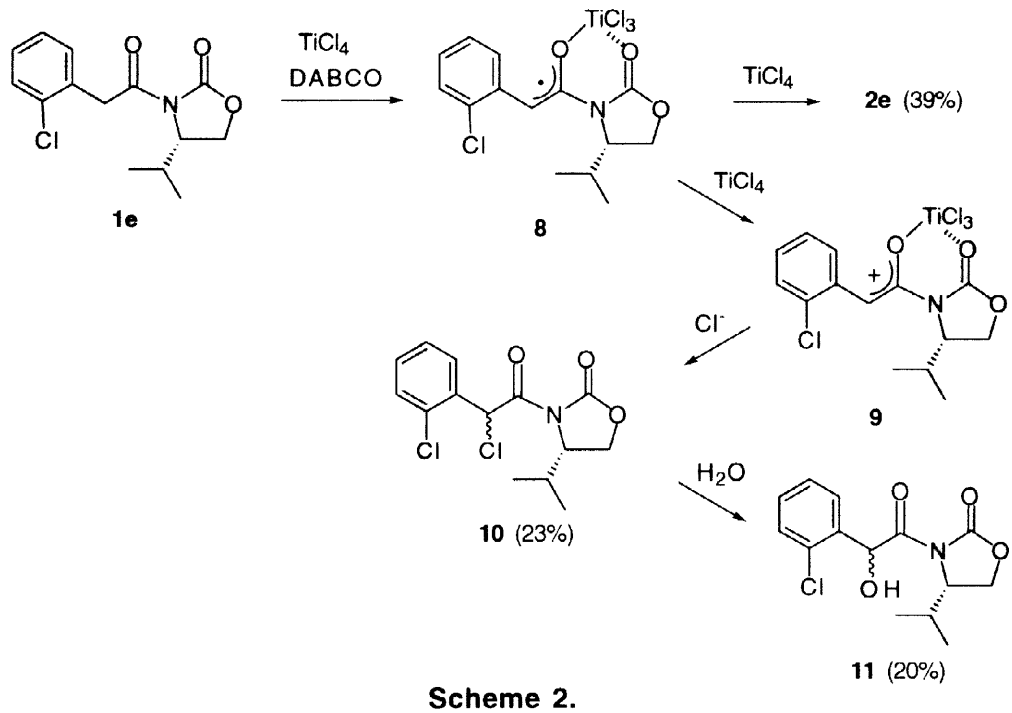
5 48 % dl : meso = 65 : 35

Reaction Mechanism of Oxidative Coupling. The stereoselectivities observed in the oxidative coupling of **1** can be reasonably explained with a radical mechanism as shown in Scheme 1 for **1a**. It has been reported that treatment of 3-acyl-2-oxazolidone with amine-$TiCl_4$ affords Ti-chelated Z-enolate.[9] In the reaction of **1a** with amine-$TiCl_4$, the Ti-chelated Z-enolate **6** is formed initially and then oxidized with Ti(IV) to generate a radical intermediate **7**. A para-substitution of an electron withdrawing group on the aromatic ring inhibits this electron transfer process. The radicals **7** then couple at the less hindered side (Si face), as depicted in transition state A, to give (*S,S*)-**2a** stereospecifically. An ortho-substitution on the aromatic ring inhibits this radical

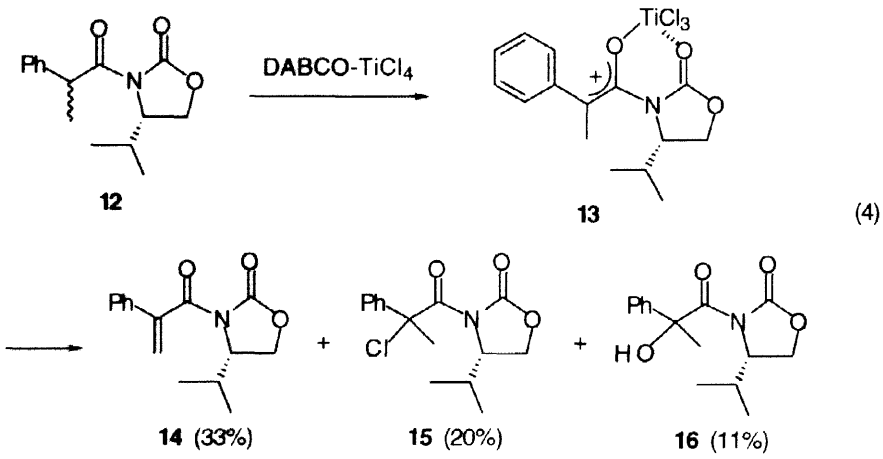
coupling process. As shown in Scheme 2 for **1e**, the radical intermediate **8** is further oxidized to a cation **9** and reacts with chlorine anion to give α-chlorinated product **10**. α-Hydroxylated product **11** was formed from **10** by work-up with water. The reaction of 3-(2-phenylpropionyl)-2-oxazolidone **12** with DABCO-$TiCl_4$ afforded α,β-unsaturated product **14**, α-chlorinated product **15**, and α-hydroxylated product **16**, and no coupling product was detected (eq 4). This result also suggests the formation of a cationic intermediate **13**.



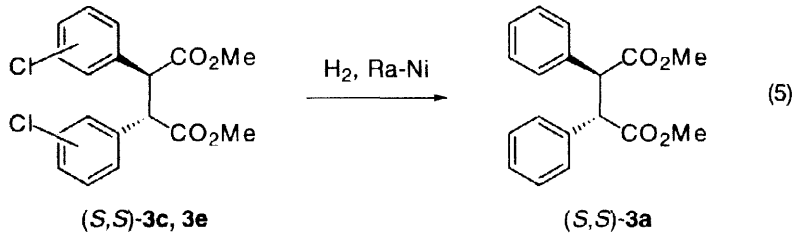
Scheme 1.



Scheme 2.



Synthesis of Optically Active 2,3-Diarylsuccinic Acids. The conversion of dimers **2** to 2,3-diarylsuccinic acids was easily achieved in good yields by the reported method.[10] In order to facilitate the purification, the acids were isolated as dimethyl esters **3** (Table 3). The absolute stereoconfiguration and ee (>98%) of dimethyl (2*S*,3*S*)- and (2*R*,3*R*)-2,3-diphenylsuccinates (**3a**) were determined by measurement of their optical rotations[5a] and ^{1}H NMR analyses with Eu(hfc)$_3$. Chloro substituted 2,3-diphenylsuccinates **3c** and **3e** were converted by catalytic hydrogenolysis to **3a**, and hence their configurations were assigned to be (2*S*,3*S*) (eq 5). Although the stereoconfigurations of **3b** and **3f-h** could not be confirmed, they were assumed to be (2*S*,3*S*) from the data of **3a**, **3c**, and **3e**. These results show that the present oxidative coupling provides a useful synthetic methodology from arylacetic acids to enantiomerically pure 2,3-diarylsuccinic acids. As an example of preparative scale synthesis, 10 g of **1a** was converted to 2.3 g of (2*S*,3*S*)-diphenylsuccinic acid in 48% total yield using recrystallization for isolation method.

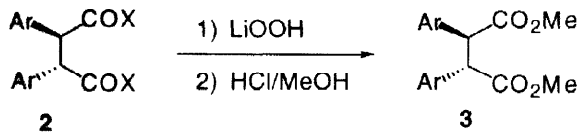


CONCLUSION

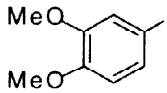
Asymmetric synthesis of a variety of optically pure 2,3-diarylsuccinic acids was achieved by stereospecific dimerization of chiral 3-(arylacetyl)-2-oxazolidones **1** with amine-TiCl4 and following hydrolysis of the resulting dimers. However, the oxidative dimerization was considerably hindered by an electron withdrawing group on the aromatic ring of **1**. Steric hindrance by an ortho-substituent also inhibited the dimerization.

The amine-TiCl4 combination was not effective for dimerization of 3-alkanoyl-2-oxazolidones other than **1**. Investigations for the stereoselective dimerization of other chiral alkanoic acid derivatives are in progress.

Table 3. Hydrolysis of Dimers 2 to 3



2 3

run	2	Ar	% yield of 3[a]	
1	**2a**	Ph	(*S,S*)-**3a**	81
2	**2i**	Ph	(*S,S*)-**3a**	70
3	**2j**	Ph	(*S,S*)-**3a**	67
4	**2k**	Ph	(*R,R*)-**3a**	82
5	**2l**	Ph	(*R,R*)-**3a**	78
6	**2b**	*p*-$MeOC_6H_4$	(*S,S*)-**3b**	89
7	**2c**	*p*-ClC_6H_4	(*S,S*)-**3c**	89
8	**2e**	*o*-ClC_6H_4	(*S,S*)-**3e**	51
9	**2f**	1-Naphthyl	(*S,S*)-**3f**	60
10	**2g**	2-Naphthyl	(*S,S*)-**3g**	81
11	**2h**		(*S,S*)-**3h**	64

a) Isolated yields.

EXPERIMENTAL SECTION

General: IR spectra were recorded with a Shimadzu FTIR-8100 infrared spectrometer. ^1H and ^{13}C NMR spectra were measured with a JEOL GX-270 spectrometer with tetramethylsilane (TMS) as an internal standard. Optical rotations were recorded with a Jasco DIP-360 digital polarimeter. Column chromatography was performed on silica gel 60 (Merck). Dichloromethane was distilled from P_2O_5, then CaH_2, and dried over molecular sieves 4A.

Starting Materials: Optically active 3-acyl-2-oxazolidones were prepared by treatment of optically active 2-oxazolidones with n-BuLi and acyl chlorides successively in THF at -70 °C.[11,12] The products were purified by column chromatography on silica gel or recrystallization from hexane-ethyl acetate.

(*S*)-4-Isopropyl-3-(phenylacetyl)-2-oxazolidone (1a): *Rf* 0.18 (hexane-ethyl acetate, 5:1); $[\alpha]^{20}_D$ +77.6 (*c* 2.05, $CHCl_3$); IR (neat) 1765, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (d, 3 H, *J* = 6.9 Hz), 0.87 (d, 3 H, *J* = 7.0 Hz), 2.23-2.37 (m, 1 H), 4.11-4.38 (m, 5 H), 7.20-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.22 (q), 17.60 (q), 28.00 (d), 41.33 (t), 58.36 (d), 63.14 (t), 127.20 (d), 128.57 (d), 129.72 (d), 133.81 (s), 154.13 (s), 171.35 (s). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93.; N, 5.66. Found: C, 67.91; H, 7.03; N, 5.49.

(*S*)-4-Isopropyl-3-(4-methoxyphenylacetyl)-2-oxazolidone (1b): *Rf* 0.50 (hexane-ethyl acetate, 2:1); mp 91-92 °C; $[\alpha]^{20}_D$ +69.8 (*c* 1.30, $CHCl_3$); IR (KBr) 1762, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (d, 3 H, *J* = 6.8 Hz), 0.88 (d, 3 H, *J* = 6.8 Hz), 2.27-2.41 (m, 1 H), 3.79 (s, 3 H), 4.11-4.34 (m, 4 H), 4.39-4.46 (m, 1 H), 6.82-6.89 (m, 2 H), 7.20-7.27 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.48 (q), 17.81 (q), 28.19 (d), 40.57 (t), 55.16 (d),

58.44 (q), 63.19 (t), 113.87 (d), 125.72 (s), 130.61 (d), 153.92 (s), 158.67 (s), 171.45 (s). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.95; H, 6.97; N, 4.88.

3-(4-Chlorophenylacetyl)-(*S*)-4-isopropyl-2-oxazolidone (1c): *Rf* 0.55 (hexane-ethyl acetate, 2:1); mp 86-87 °C ; $[\alpha]^{20}_D$ +65.4 (c 1.34, $CHCl_3$); IR (KBr) 1785, 1766, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (d, 3 H, *J* = 7.0 Hz), 0.88 (d, 3 H, *J* = 7.0 Hz), 2.26-2.47 (m, 1 H), 4.14-4.39 (m, 4 H), 4.39-4.52 (m, 1 H), 7.21-7.41 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.51 (q), 17.85 (q), 28.28 (d), 40.83 (t), 58.51 (d), 63.35 (t), 128.60 (d), 131.02 (d), 132.17 (s), 133.04 (s), 153.89 (s), 170.65 (s). Anal. Calcd for $C_{14}H_{16}NO_3Cl$: C, 59.68; H, 5.72; N, 4.97; Cl, 12.58. Found: C, 59.74; H, 5.78; N, 4.88; Cl, 12.37.

(*S*)-4-Isopropyl-3-(4-trifluoromethylphenylacetyl)-2-oxazolidone (1d): *Rf* 0.60 (hexane-ethyl acetate, 2:1); mp 94-95 °C (recryst. from hexane-ethyl acetate, 2:1); $[\alpha]^{20}_D$ +67.8 (c 1.13, $CHCl_3$); IR (KBr) 1787, 1772 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (d, 3 H, *J* = 6.8 Hz), 0.89 (d, 3 H, *J* = 6.8 Hz), 2.23-2.51 (m, 1 H), 4.13-4.79 (m, 5 H), 7.38-7.50 (m, 2 H), 7.50-7.72 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.43 (q), 17.71 (q), 28.23 (d), 41.26 (t), 58.49 (d), 63.34 (t), 125.33 (d), 130.03 (d), 137.71 (s), 153.92 (s), 170.18 (s). Anal. Calcd for $C_{15}H_{16}NO_3F_3$: C, 57.14; H, 5.12; N, 4.44; F, 18.08. Found: C, 57.32; H, 5.27; N, 4.29; F, 17.83.

3-(2-Chlorophenylacetyl)-(*S*)-4-isopropyl-2-oxazolidone (1e): *Rf* 0.50 (hexane-ethyl acetate, 2:1); $[\alpha]^{20}_D$ +71.5 (c 1.20, $CHCl_3$); IR (neat) 1774, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, 3 H, *J* = 7.3 Hz), 0.92 (d, 3 H, *J* = 7.0 Hz), 2.30-2.57 (m, 1 H), 4.15-4.43 (m, 3 H), 4.43-4.71 (m, 2 H), 7.05-7.33 (m, 3 H), 7.33-7.61 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.57 (q), 17.66 (q), 28.19 (d), 40.38 (t), 58.44 (d), 63.49 (t), 126.75 (d), 128.61 (d), 129.24 (d), 131.64 (d), 132.33 (s), 134.53 (s), 154.07 (s), 169.69 (s). Anal. Calcd for $C_{14}H_{16}NO_3Cl$: C, 59.68; H, 5.72; N, 4.97; Cl, 12.58. Found: C, 59.80; H, 5.85; N, 4.94; Cl, 12.34.

(*S*)-4-Isopropyl-3-(1-naphthylacetyl)-2-oxazolidone (1f): *Rf* 0.40 (hexane-ethyl acetate, 2:1); $[\alpha]^{20}_D$ +75.1 (c 1.26, $CHCl_3$); IR (neat) 1769, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, 3 H, *J* = 7.0 Hz), 0.87 (d, 3 H, *J* = 7.0 Hz), 2.21-2.45 (m, 1 H), 4.23 (dd, 1 H, *J* = 3.5, 8.5 Hz), 4.31 (t, 1 H, *J* = 8.5 Hz), 4.56 (dt, 1 H, *J* = 3.5, 8.5 Hz), 4.66 (d, 1 H, *J* = 16.9 Hz), 4,84 (d, 1 H, *J* = 16.9 Hz), 7.31-7.67 (m, 4 H), 7.67-8.21 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.52 (q), 17.76 (q), 28.19 (d), 39.10 (t), 58.54 (d), 63.34 (t), 123.71 (d), 125.33 (d), 125.62 (d), 126.16 (d), 128.02 (d), 128.70 (d), 130.42 (s), 132.23 (s), 133.75 (s), 154.21 (s), 170.86 (s). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44.; N, 4.71. Found: C, 72.58; H, 6.55; N, 4.46.

(*S*)-4-Isopropyl-3-(2-naphthylacetyl)-2-oxazolidone (1g): *Rf* 0.55 (hexane-ethyl acetate, 2:1); mp 82-83 °C; $[\alpha]^{20}_D$ +74.7 (c 1.08, $CHCl_3$); IR (KBr) 1758, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (d, 3 H, *J* = 7.3 Hz), 0.87 (d, 3 H, *J* = 6.8 Hz), 2.26-2.49 (m, 1 H), 4.08-4.33 (m, 2 H), 4.33-4.77 (m, 3 H), 7.26-7.63 (m, 3 H), 7.63-8.42 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.45 (q), 17.74 (q), 28.16 (d), 41.64 (t), 58.46 (d), 63.18 (t), 125.67 (d), 125.95 (d), 127.51 (d), 127.62 (d), 127.97 (d), 128.32 (d), 131.20 (s), 132.41 (s), 133.33 (s), 153.89 (s), 170.99 (s). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44.; N, 4.71. Found: C, 72.76; H, 6.45; N, 4.62.

(*S*)-3-(3,4-dimethoxyphenylacetyl)-4-Isopropyl-2-oxazolidone (1h): *Rf* 0.3 (hexane-ethyl acetate, 2:1); $[\alpha]^{20}_D$ +69.9 (c 1.14, $CHCl_3$); IR (neat) 1770, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (d, 3 H, *J* = 6.8 Hz), 0.88 (d, 3 H, *J* = 7.3 Hz), 2.37-2.42 (m, 1 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.10-4.39 (m, 4 H), 4.39-4.50 (m, 1 H), 6.75-6.98 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.28 (q), 17.51 (q), 27.99 (d), 40.62 (t), 55.51 (q), 58.15 (d), 63.00 (t), 110.93 (d), 112.60 (d), 121.56 (d), 125.96 (s), 147.85 (s), 148.53 (s), 153.68 (s), 171.01 (s). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89.; N, 4.56. Found: C, 62.43; H, 6.96; N, 4.48.

(*S*)-4-Isobutyl-3-(phenylacetyl)-2-oxazolidone (1i): *Rf* 0.35 (hexane-ethyl acetate, 5:1); $[\alpha]^{20}_D$ +96.2 (c 1.81, $CHCl_3$); IR (neat) 1765, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, 6 H, *J* = 5.9 Hz), 1.34-1.67 (m, 2 H), 1.67-1.89 (m, 1 H), 4.11 (dd, 1 H, J = 2.4, 8.6 Hz), 4.26 (s, 2 H), 4.37 (t, 1 H, *J* = 8.6 Hz), 4.43-4.55 (m, 1 H), 7.11-7.60 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.28 (q), 23.19 (q), 24.51 (d), 41.01 (t), 41.31 (t), 52.96 (d), 67.35 (t), 126.84 (d), 128.26 (d), 129.44 (d), 133.50 (s), 153.38 (s), 170.67 (s). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33.; N, 5.36. Found: C, 68.70; H, 7.19; N, 5.08.

(*S*)-4-Benzyl-3-(phenylacetyl)-2-oxazolidone (1j): *Rf* 0.60 (hexane-ethyl acetate, 2:1); mp 71 °C; $[\alpha]^{20}_D$ +75.7 (c 1.31, $CHCl_3$); IR (KBr) 1772, 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76 (dd, 1 H, *J* = 9.5, 13.2 Hz), 3.27 (dd, 1 H, *J* = 3.2, 13.2 Hz), 4.12-4.25 (m, 2 H), 4.26 (d, 1 H, *J* = 15.4 Hz), 4.35 (d, 1 H, *J* = 15.4 Hz), 4.62-4.77 (m, 1 H), 7.09-7.19 (m, 2 H), 7.23-7.44(m, 8 H); ^{13}C NMR ($CDCl_3$) δ 37.55 (t), 41.41 (t), 55.17 (d), 66.00 (t), 127.11 (d), 128.43 (d), 128.78 (d), 129.30 (d), 129.70 (d), 133.44 (s), 135.00 (s), 153.25 (s), 171.05 (s). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.22; H, 5.69; N, 4.70.

(*R*)-4-Phenyl-3-(phenylacetyl)-2-oxazolidone (1k): *Rf* 0.53 (hexane-ethyl acetate, 2:1); mp 67-69 °C; $[\alpha]^{20}_D$ -83 (*c* 1.1, $CHCl_3$); IR (KBr) 1765, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.22-4.33 (m, 3 H), 4.69 (t, 1 H, *J* = 8.8

Hz), 5.43 (dd, 1 H, J = 3.9, 8.8 Hz), 7.18-7.38 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 41.26 (t), 57.31 (d), 69.56 (t), 125.60 (d), 126.83 (d), 128.15 (d), 128.72 (d), 129.41 (d), 133.12 (s), 138.66 (s), 153.40 (s), 170.18 (s). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37.; N, 4.98. Found: C, 72.64; H, 5.37; N, 4.90.

(*R*)-4-methyl-(*S*)-5-phenyl-3-(phenylacetyl)-2-oxazolidone (11): *Rf* 0.45 (hexane-ethyl acetate, 5:1); mp 99-101 °C; $[\alpha]^{20}_D$+16.3 (c 1.40, $CHCl_3$); IR (KBr) 1768, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3 H, J = 7.0 Hz), 4.28 (d, 1 H, J = 15.4 Hz), 4.34 (d, 1 H, J = 15.4 Hz), 4.76 (dq, 1 H, J = 7.0, 7.3 Hz), 5.66 (d, 1 H, J = 7.0 Hz), 7.08-7.72 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 14.40 (q), 41.64 (t), 54.88 (d), 78.90 (d), 125.61 (d), 127.11 (d), 128.49 (d), 128.60 (d), 128.72 (d), 129.58 (d), 133.21 (s), 133.56 (s), 152.91 (s), 170.82 (s). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.30; H, 5.86; N, 4.61.

3-(Phenylacetyl)-2-oxazolidone (4): *Rf* 0.40 (hexane-ethyl acetate, 2:1); mp 66-67 °C; IR (KBr) 1767, 1692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.95 (t, 2 H, J = 8.0 Hz), 4.23-4.40 (m, 4 H), 7.22-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 40.93 (t), 42.53 (t), 61.86 (t), 127.05 (d), 128.39 (d), 129.59 (d), 133.45 (s), 153.40 (s), 171.09 (s). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.36; H, 5.41; N, 6.77.

(*S*)-4-Isopropyl-3-(2-phenylpropionyl)-2-oxazolidone (12) (diastereomer A): *Rf* 0.30 (hexane-ethyl acetate, 5:1); ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3 H, J = 7.0 Hz), 0.92 (d, 3 H, J = 6.8 Hz), 1.52 (d, 3 H, J = 7.3 Hz), 2.29-2.66 (m, 1 H), 3.97-4.25 (m, 2 H), 4.25-4.47 (m, 1 H), 5.15 (q, 1 H, J = 7.0 Hz), 7.04-7.71 (m, 5 H).

12 (diastereomer B): *Rf* 0.35 (hexane-ethyl acetate, 5:1); $[\alpha]^{20}_D$ -19.0 (c 1.15, $CHCl_3$); IR (neat) 1764, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.45 (d, 3 H, J = 6.8 Hz), 0.80 (d, 3 H, J = 7.0 Hz), 1.47 (d, 3 H, J = 7.0 Hz), 2.07-2.28 (m, 1 H), 4.10 (dd, 1 H, J = 3.6, 8.6 Hz), 4.24 (t, 1 H, J = 8.6 Hz), 4.49(dt, 1 H, J = 3.6, 8.6 Hz), 5.14 (q, 1 H, J = 7.0 Hz), 7.01-7.64 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.89 (q), 17.56 (q), 18.49 (q), 27.74 (d), 43.17 (d), 57.86 (t), 62.70 (t), 126.94 (d), 127.87 (d), 128.36 (d), 140.31 (s), 153.28 (s), 174.24 (s). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33.; N, 5.36. Found: C, 68.72; H, 7.40; N, 5.19.

Oxidative coupling of 1 with amine-$TiCl_4$. To an ice-cooled solution of **1** (1.0 mmol) in dry dichloromethane (5 mL) was added $TiCl_4$ (0.28 mL, 2.5 mmol) and an amine (2.0 mmol) successively under N_2. The dark blue solution was stirred at 25 °C for 24-48 h until almost all of **1** was consumed (checked by TLC). The mixture was diluted with 1 M HCl (20 mL) and extracted with CH_2Cl_2 (3 X 10 mL). In the reaction of **1h**, the crude product was refluxed with CH3I (0.25 mL, 4.0 mmol) and K_2CO_3 (0.55g, 4.0 mmol) in acetone (10 mL) for 6 h and then filtered. The product was isolated by column chromatography on silica gel (hexane-ethyl acetate). The isolated dimer **2** seemed to be practically a single stereoisomer (>98%) on the basis of ^{1}H NMR analysis and could be further purified by recrystallization from hexane-ethyl acetate.

(*S,S*)-**2a**: *Rf* 0.56 (hexane-ethyl acetate, 5:1); mp 208-209 °C; $[\alpha]^{20}_D$ +338 (*c* 1.03, $CHCl_3$); IR (KBr) 1782, 1692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 6 H, J = 7.1 Hz), 0.98 (d, 6 H, J = 7.0 Hz), 2.30-2.50 (m, 2 H), 4.02-4.19 (m, 4 H), 4.30-4.40 (m, 2 H), 5.68 (s, 2 H), 7.04-7.16 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 14.07 (q), 17.60 (q), 27.72 (d), 53.80 (d), 58.72 (d), 62.58 (t), 127.48 (d), 128.17 (d), 129.40 (d), 134.83 (s), 153.10 (s), 173.66 (s). Anal. Calcd for $C_{28}H_{32}N_2O_6$: C, 68.28; H, 6.55; N, 5.69. Found: C, 68.42; H, 6.59; N, 5.66.

(*S,S*)-**2b**: *Rf* 0.30 (hexane-ethyl acetate, 2:1); mp 254-255 °C; $[\alpha]^{20}_D$ +398 (c 1.25, $CHCl_3$); IR (KBr) 1772, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 6 H, J = 7.0 Hz), 0.96 (d, 6 H, J = 6.8 Hz), 2.27-2.41 (m, 2 H), 3.71 (s, 6 H), 4.03-4.18 (m, 4 H), 4.26-4.36 (m, 2 H), 5.59 (s, 2 H), 6.54-6.78 (m, 4 H), 6.90-7.11 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.28 (q), 17.76 (q), 27.94 (d), 53.01 (d), 54.97 (q), 58.79 (d), 62.65 (t), 113.48 (d), 126.84 (s), 130.32 (d), 152.89 (s), 158.72 (s), 173.75 (s). Anal. Calcd for $C_{30}H_{36}N_2O_8$: C, 65.20; H, 6.57; N, 5.07. Found: C, 65.28; H, 6.60; N, 5.01

(*S,S*)-**2c**: *Rf* 0.55 (hexane-ethyl acetate, 2:1); mp 217-218 °C; $[\alpha]^{20}_D$ +418 (c 1.06, $CHCl_3$); IR (KBr) 1773, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 6 H, J = 7.0 Hz), 0.96 (d, 6 H, J = 7.0 Hz), 2.30-2.45 (m, 2 H), 4.05-4.25 (m, 4 H), 4.24-4.40 (m, 2 H), 5.62 (s, 2 H), 6.97-7.08 (m, 4 H), 7.08-7.23 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.23 (q), 17.71 (q), 27.94 (d), 53.16 (d), 58.79 (d), 62.80 (t), 128.41 (d), 130.57 (d), 133.01 (s), 133.45 (s), 152.89 (s), 172.77 (s). Anal. Calcd for $C_{28}H_{30}N_2O_6Cl_2$: C, 59.90; H, 5.39; N, 4.99; Cl, 12.63. Found: C, 59.97; H, 5.41; N, 4.87; Cl, 12.49.

(*S,S*)-**2e**: *Rf* 0.40 (hexane-ethyl acetate, 2:1); mp 284-285 °C; $[\alpha]^{20}_D$ +438 (c 1.05, $CHCl_3$); IR , (KBr) 1767, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, 6 H, J = 7.3 Hz), 1.00 (d, 6 H, J = 6.8 Hz), 2.33-2.50 (m, 2 H), 4.07-4.20 (m, 4 H), 4.35-4.44 (m, 2 H), 6.02 (s, 2 H), 7.08-7.16 (m, 8 H), 7.36-7.47 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.38 (q), 17.81 (q), 27.99 (d), 50.61 (d), 58.98 (d), 62.95 (t), 126.40 (d), 128.75 (d), 129.73 (d), 130.52 (d), 131.69 (s), 136.05 (s), 152.65 (s), 172.72 (s). Anal. Calcd for $C_{28}H_{30}N_2O_6Cl_2$: C, 59.90; H, 5.39; N, 4.99; Cl, 12.63. Found: C, 59.95; H, 5.32; N, 4.93; Cl, 12.55.

10 (50:50 mixture of two diastereomers): *Rf* 0.55 (hexane-ethyl acetate, 2:1); IR , (KBr) 1775, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (d, 1.5 H, J = 7.0 Hz), 0.92 (d, 1.5 H, J = 7.5 Hz), 0.95 (d, 1.5 H, J = 7.0 Hz), 0.96 (d, 1.5 H, J = 7.0 Hz), 2.36-2.54 (m, 1 H), 4.22-4.41 (m, 2 H), 4.46-4.56 (m, 1 H), 7.15 (s, 0.5 H), 7.18 (s, 0.5 H), 7.30-7.46 (m, 3 H), 7.58-7.65 (m, 0.5 H), 7.68-7.73 (m, 0.5 H); ^{13}C NMR ($CDCl_3$) δ 14.43 (q), 14.62 (q), 17.71 (q), 17.81 (q), 28.04 (d), 28.14 (d), 54.04 (d), 54.58 (d), 58.74 (d), 58.98 (d), 63.49 (t), 63.63 (t), 127.19 (d), 129.39 (d), 129.68 (d), 129.88 (d), 130.22 (d), 132.82 (s), 133.21 (s), 133.50 (s), 152.89 (s), 166.85 (s), 166.99 (s). Anal. Calcd for $C_{14}H_{15}NO_3Cl_2$: C, 53.18; H, 4.78; N, 4.43; Cl, 22.43. Found: C, 53.06; H, 4.80; N, 4.29; Cl, 22.26.

11 (could not be separated from **1e**): *Rf* 0.50 (hexane-ethyl acetate, 2:1); ^1H NMR ($CDCl_3$) δ 0.94 (d, 3 H, *J* = 7.0 Hz), 0.95 (d, 3 H, *J* = 7.3 Hz), 2.30-2.57 (m, 1 H), 4.26-4.43 (m, 2 H), 4.45-4.54 (m, 1 H), 6.26 (br s, 1 H), 7.23-7.35 (m, 2 H), 7.37-7.49 (m, 2 H).

(*S,S*)-**2f**: *Rf* 0.40 (hexane-ethyl acetate, 2:1); mp 298-299 °C; $[\alpha]^{20}_D$ +496 (c 1.00, $CHCl_3$); IR (KBr) 1770, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 6 H, *J* = 6.8 Hz), 1.06 (d, 6 H, *J* = 6.5 Hz), 2.40-2.66 (m, 2 H), 3.99-4.20 (m, 4 H), 4.37-4.55 (m, 2 H), 6.50 (s, 2 H), 6.70-6.86 (m, 2 H), 6.86-7.03 (m, 2 H), 7.20-7.38 (m, 6 H), 7.38-7.50 (m, 2 H), 7.66-7.79 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.52 (q), 17.90 (q), 28.19 (d), 50.02 (d), 59.08 (d), 62.85 (t), 123.47 (d), 124.40 (d), 124.69 (d), 126.99 (d), 128.22 (d), 132.08 (s), 133.06 (s), 152.99 (s), 174.09 (s). Anal. Calcd for $C_{36}H_{36}N_2O_6$: C, 72.95; H, 6.12; N, 4.73. Found: C, 72.98; H, 6.13; N, 4.68.

(*S,S*)-**2g**: *Rf* 0.55 (hexane-ethyl acetate, 2:1); mp 228-230 °C; $[\alpha]^{20}_D$ +569 (c 1.00, $CDCl_3$); IR (KBr) 1765, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, 6 H, *J* = 6.8 Hz), 1.02 (d, 6 H, *J* = 6.8 Hz), 2.32-2.63 (m, 2 H), 3.76-4.25 (m, 4 H), 4.25-4.65 (m, 2 H), 6.02 (s, 2 H), 6.86-8.11 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 14.34 (q), 17.79 (q), 27.99 (d), 53.96 (d), 58.86 (d), 62.66 (t), 125.72 (d), 127.34 (d), 127.68 (d), 127.80 (d), 128.09 (d), 132.35 (s), 132.52 (s), 132.98 (s), 152.97 (s), 173.53 (s). Anal. Calcd for $C_{36}H_{36}N_2O_6$: C, 72.95; H, 6.12; N, 4.73. Found: C, 72.86; H, 6.20; N, 4.61.

(*S,S*)-**2h**: *Rf* 0.40 (hexane-ethyl acetate, 1:1); mp 235-236 °C; $[\alpha]^{20}_D$ +400 (c 1.00, $CDCl_3$); IR (KBr) 1769, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 6 H, *J* = 6.8 Hz), 0.97 (d, 6 H, *J* = 7.3 Hz), 2.25-2.54 (m, 2 H), 3.71 (s, 6 H), 3.79 (s, 6 H), 4.06-4.22 (m, 4 H), 4.28-4.42 (m, 2 H), 5.60 (s, 2 H), 6.44-6.85 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 14.40 (q), 17.85 (q), 28.05 (d), 53.39 (d), 55.69 (q), 58.92 (d), 62.77 (t), 110.69 (d), 112.36 (d), 121.64 (d), 127.39 (s), 148.47 (s), 153.02 (s), 173.76 (s). Anal. Calcd for $C_{32}H_{40}N_2O_{10}$: C, 62.73; H, 6.58; N, 4.57. Found: C, 62.75; H, 6.59; N, 4.50.

(*S,S*)-**2i**: *Rf* 0.20 (hexane-ethyl acetate, 5:1); mp 178-180 °C; $[\alpha]^{20}_D$ +348 (c 1.02, $CHCl_3$); IR (KBr) 1768, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 6 H, *J* = 6.5 Hz), 1.01 (d, 6 H, *J* = 6.5 Hz), 1.54-1.72 (m, 4 H), 1.72-1.85 (m, 2 H), 4.04 (dd, 2 H, *J* = 2.3, 8.3 Hz), 4.18 (t, 2 H, *J* = 8.3 Hz), 4.35-4.48 (m, 2 H), 5.54 (s, 2 H), 6.98-7.07 (m, 4 H), 7.07-7.17 (m, 4 H), 7.26 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.42 (q), 23.55 (q), 24.59 (d), 40.83 (t), 53.21 (d), 53.96 (d), 66.98 (t), 127.22 (d), 127.97 (d), 129.18 (d), 134.82 (s), 152.39 (s), 172.95 (s). Anal. Calcd for $C_{30}H_{36}N_2O_6$: C, 69.21; H, 6.97; N, 5.38. Found: C, 69.30; H, 7.05; N, 5.19.

(*S,S*)-**2j**: *Rf* 0.50 (hexane-ethyl acetate, 2:1); mp 103-105 °C; $[\alpha]^{20}_D$ +337.0 (c 1.46, $CHCl_3$); IR (KBr) 1770, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.92 (dd, 2 H, *J* = 8.9, 13.5 Hz), 3.24 (dd, 2 H, *J* = 3.2, 13.5 Hz), 3.90-4.23 (m, 4 H), 4.55-4.72 (m, 2 H), 5.70 (s, 2 H), 6.90-7.20 (m, 10 H), 7.20-7.90 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 37.20 (t), 53.96 (d), 55.23 (d), 65.31 (t), 127.05 (d), 127.34 (d), 128.03 (d), 128.72 (d), 129.18 (d), 129.35 (d), 134.65 (s), 134.94 (s), 152.22 (s), 173.47 (s). Anal. Calcd for $C_{36}H_{32}N_2O_6$: C, 73.45; H, 5.48; N, 4.76. Found: C, 73.62; H, 5.58; N, 4.64.

(*R,R*)-**2k**: *Rf* 0.44 (hexane-ethyl acetate, 2:1); mp 94-96 °C; $[\alpha]^{20}_D$ -488 (*c* 1.00, $CHCl_3$); IR (KBr) 1784, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (dd, 2 H, *J* = 2.4, 8.4 Hz), 4.42 (t, 2 H, *J* = 8.4 Hz), 5.33 (dd, 2 H, J = 2.4, 8.4 Hz), 5.68 (s, 2 H), 6.94-7.19 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 53.87 (d), 57.46 (d), 70.08 (t), 124.42 (d), 127.70 (d), 128.32 (d), 129.09 (d), 129.42 (d), 135.05 (s), 138.41 (s), 152.86 (s), 172.73 (s). Anal. Calcd for $C_{34}H_{28}N_2O_6$: C, 72.85; H, 5.03; N, 5.00. Found: C, 72.62; H, 4.69; N, 4.89.

(*R,R*)-**2l**: *Rf* 0.30 (hexane-ethyl acetate, 5:1); mp 130-132 °C; $[\alpha]^{20}_D$ -197 (c 1.46, $CHCl_3$); IR (KBr) 1772, 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, 6 H, *J* = 6.5 Hz), 4.55-4.81 (m, 2 H), 5.48 (d, 2 H, *J* = 7.0 Hz), 5.69 (s, 2 H), 6.97-7.86 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 14.04 (q), 54.14 (d), 55.07 (d), 78.47 (d), 125.62 (d), 127.48 (d), 128.26 (d), 128.61 (d), 129.29 (d), 133.21 (s), 134.87 (s), 151.96 (s), 173.41 (s). Anal. Calcd for $C_{36}H_{32}N_2O_6$: C, 73.45; H, 5.48; N, 4.76. Found: C, 73.67; H, 5.54; N, 4.58.

5 (*dl:meso* = 65:35 mixture): *Rf* 0.15 (hexane-ethyl acetate, 1:1); ^1H NMR ($CDCl_3$) δ 3.57-4.45 (m, 8 H), 5.61 (s, 1.3 H), 6.19 (s, 0.7 H), 7.02-7.16 (m, 6.5 H), 7.23-7.37 (m, 2.1 H), 7.59-7.65 (m, 1.4 H). Recrystallization

of the mixture from ethyl acetate gave pure *dl*-**5**: mp 250-251 °C; IR (KBr) 1778, 1696, 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82-4.45 (m, 8 H), 5.61 (s, 2 H), 7.02-7.16 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 42.57 (t), 53.38 (d), 61.70 (d), 127.41 (d), 128.10 (d), 129.26 (d), 129.48 (d), 134.61 (s), 152.49 (s), 173.48 (s). Anal. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.74; H, 4.97; N, 6.73.

14: *Rf* 0.50 (hexane-ethyl acetate, 2:1); IR (neat) 1792, 1770, 1732, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3 H, *J* = 7.0 Hz), 0.98 (d, 3 H, *J* = 7.3 Hz), 2.46-2.61 (m, 1 H), 4.16-4.33 (m, 2 H), 4.51-4.60 (m, 1 H), 5.50 (s, 1 H), 5.77 (s, 1 H), 7.27-7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.62 (q), 17.90 (q), 28.23 (d), 58.20 (d), 63.19 (t), 117.10 (t), 126.06 (d), 128.36 (d), 128.46 (d), 135.61 (s), 144.42 (s), 152.50 (s), 169.29 (s); MS (EI) *m/z* 259 (M^+). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.50; H, 6.66; N, 5.32.

15 (50:50 mixture of two diastereomers): *Rf* 0.85 (hexane-ethyl acetate, 2:1); IR (neat) 1800, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 1.5 H, *J* = 6.5 Hz), 0.87 (d, 1.5 H, *J* = 6.5 Hz), 1.01 (d, 1.5 H, *J* = 6.5 Hz), 1.02 (d, 1.5 H, *J* = 6.5 Hz), 1.94 (s, 3 H), 2.20-2.37 (m, 1 H), 3.77-3.96 (m, 2 H), 4.12-4.25 (m, 1 H), 7.30-7.60 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 19.81 (q), 25.00 (q), 25.20 (q), 28.92 (d), 41.85 (t), 60.94 (d), 61.38 (d), 85.03 (s), 85.28 (s), 124.59 (d), 128.85 (d), 129.05 (d), 136.39 (s), 154.31 (s), 174.53 (s), 174.63 (s). Anal. Calcd for $C_{15}H_{18}NO_3Cl$: C, 60.91; H, 6.13; N, 4.74; Cl, 11.99; MS (EI) *m/z* 295 (M^+). Found: C, 60.97; H, 6.19; N, 4.65; Cl, 11.70.

16 (77:23 mixture of two diastereomers): *Rf* 0.45 (hexane-ethyl acetate, 2:1), IR (KBr) 3580, 1800, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (d, 0.7 H, *J* = 7.3 Hz), 0.82 (d, 2.3 H, *J* = 6.8 Hz), 1.01 (d, 0.7 H, *J* = 6.8 Hz), 1.02 (d, 2.3 H, *J* = 7.0 Hz), 1.93 (s, 3 H), 2.25-2.58 (m, 2 H), 3.69-3.95 (m, 2 H), 4.00-4.15 (m, 1 H), 7.32-7.48 (m, 3 H), 7.48-7.65 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.57 (q), 25.00 (q), 26.52 (d), 26.67 (q), 60.65 (t), 60.79 (t), 61.53 (d), 61.77 (d), 85.13 (s), 124.44 (d), 128.80 (d), 129.05 (d), 136.34 (s), 155.19 (s), 175.32 (s); MS (EI) *m/z* 277 (M^+). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.03; H, 6.95; N, 4.90.

Hydrogenolysis of 2c and 2e. A suspension of **2c** or **2e** (0.5 mmol) with Ra-Ni (ca. 0.5 g) in EtOH (10 mL) was stirred under H_2 (1 atm) at 25 °C for 12 h. After filtration and evaporation of the mixture, the product was isolated by column chromatography on silica gel and assigned to be (*S,S*)-**2a** .

Hydrolysis of 2. To an ice cooled solution of **2** (1 mmol) in THF (4 mL) and H_2O (1 mL) was added $LiOH•H_2O$ (4 mmol) and 30% H_2O_2 (1 mL) successively. The mixture was stirred for 24 h at room temperature and then quenched with 1.5 M Na_2SO_3 (4 mL) at 0 °C. After addition of 1 M HCl (10 mL), the mixture was extracted with CH_2Cl_2. The crude diacid was dissolved in sat. HCl-MeOH and the solution was stirred for 12 h at room temperature. After removal of the solvent, dimethyl ester **3** and starting optically active 2-oxazolidone (60-80 % recovery) were isolated by column chromatography on silica gel.

(*S,S*)-**3a**: *Rf* 0.45 (hexane-ethyl acetate, 5:1); mp 165-166 °C (lit.[5a] 165-166 °C); $[\alpha]^{20}_D$ +342 (*c* 1.25, acetone) (lit.[5a] +341.9); ^1H NMR ($CDCl_3$) δ 3.69 (s, 6 H), 4.25 (s, 2 H), 6.98-7.08 (m, 4 H), 7.10-7.18 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 52.25 (q), 54.54 (d), 127.55 (d), 128.42 (d), 128.57 (d), 135.87 (s), 173.89 (s).

(*R,R*)-**3a**: mp 164-165 °C (lit.[5a] 165-166 °C); $[\alpha]^{20}_D$ -340 (*c* 1.15, acetone) (lit.[5a] -342.1).

(*S,S*)-**3b**: *Rf* 0.50 (hexane-ethyl acetate, 2:1); $[\alpha]^{20}_D$ +377 (c 1.00, $CHCl_3$); IR (neat) 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54-3.90 (m, 12 H), 4.16 (s, 2 H), 6.54-6.77 (m, 4 H), 6.81-7.03 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 52.18 (q), 53.79 (d), 54.97 (q), 113.97 (d), 127.68 (s), 129.29 (d), 158.72 (s), 173.85 (s). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 67.01; H, 6.20.

(*S,S*)-**3c**: *Rf* 0.35 (hexane-ethyl acetate, 5:1); mp 119-120 °C; $[\alpha]^{20}_D$ +391 (c 1.10, $CHCl_3$); IR (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, 6 H), 4.20 (s, 2 H), 6.85-7.05 (m, 4 H), 7.05-7.21 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 52.57 (q), 53.84 (d), 128.85 (d), 129.59 (d), 133.60 (s), 133.80 (s), 172.97 (s). Anal. Calcd for $C_{18}H_{16}O_4Cl_2$: C, 58.87; H, 4.39; Cl, 19.31. Found: C, 58.86; H, 4.42; Cl, 19.25.

(*S,S*)-**3e**: *Rf* 0.45 (hexane-ethyl acetate, 5:1); mp 152-153 °C; $[\alpha]^{20}_D$ +305 (c 0.76, $CHCl_3$); IR (KBr) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (s, 6 H), 5.08 (s, 2 H), 6.95-7.21 (m, 6 H), 7.31-7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 49.10 (d), 52.61 (q), 126.73 (d), 128.78 (d), 129.55 (d, 2c), 133.04 (s), 134.42 (s), 172.89 (s). Anal. Calcd for $C_{18}H_{16}O_4Cl_2$: C, 58.87; H, 4.39; Cl, 19.31. Found: C, 58.90; H, 4.41; Cl, 19.17.

(*S,S*)-**3f**: *Rf* 0.30 (hexane-ethyl acetate, 5:1); mp 211-212 °C; $[\alpha]^{20}_D$ +259 (c 0.75, $CHCl_3$); IR (KBr) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, 6 H), 5.49 (br s, 2 H), 6.96-7.81 (m, 12 H), 7.87-8.29 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 46.0-49.0 (br d), 52.49 (q), 123.12 (d), 124.84 (d), 125.28 (d), 125.96 (d), 128.02 (d), 128.51 (d), 131.64 (s), 133.65 (s), 174.24 (s). Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57. Found: C, 78.35; H, 5.59.

(*S,S*)-**3g**: *Rf* 0.60 (hexane-ethyl acetate, 2:1); mp 148-150 °C; $[\alpha]^{20}_D$ +480 (c 1.01, $CHCl_3$); IR (KBr) 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 6 H), 4.59 (s, 2 H), 7.12-7.26 (m, 2 H), 7.28-7.42 (m, 4 H), 7.52-7.72 (m, 8

H); ^{13}C NMR ($CDCl_3$) δ 52.41 (q), 54.60 (d), 125.84 (d), 125.95 (d), 127.39 (d), 127.57 (d), 127.68 (d), 128.20 (d), 132.52 (s), 132.92 (s), 133.10 (s), 173.58 (s). Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57. Found: C, 78.32; H, 5.60.

(*S,S*)-**3h**: *Rf* 0.20 (hexane-ethyl acetate, 2:1); $[\alpha]^{20}_D$ +291 (c 2.40, $CHCl_3$); IR (KBr) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (s, 6 H), 3.73 (s, 6 H), 3.79 (s, 6 H), 4.14 (s, 2 H), 6.62- (d, 2 H, *J* = 2.4 Hz), 6.55 (dd, 2 H, *J* = 2.4, 7.8 Hz), 6.64 (d, 2 H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 52.27 (q), 54.28 (d), 55.70 (q), 110.93 (d), 111.13 (d), 120.72 (d), 128.02 (s), 148.24 (s), 148.68 (s), 173.75 (s). Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.28; H, 7.41.

Preparative scale synthesis of (2*S*,3*S*)-diphenylsuccinic acid. To an ice-cooled solution of **1a** (10 g, 40 mmol) in dry dichloromethane (100 mL) was added $TiCl_4$ (11 mL, 100 mmol) and an DMAP (9.8 g, 80 mmol) successively under N_2. The dark blue solution was stirred at 25 °C for 36 h. The mixture was diluted with 1 M HCl (200 mL) and extracted with CH_2Cl_2 (2 X 100 mL). The crude product was recrystallized from hexane-ethyl acetate (2:1) to give 5.8 g of **2a**. To an ice cooled solution of the obtained **2a** (5.8 g, 12 mmol) in THF (40 mL) and H_2O (10 mL) was added $LiOH{\cdot}H_2O$ (2.1 g, 50 mmol) and 30% H_2O_2 (10 mL) successively. The mixture was stirred for 24 h at room temperature and then quenched with 1.5 M Na_2SO_3 (60 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (3 X 50 mL) in order to remove (4*S*)-isopropyl-2-oxazolidone. The water layer was acidfied (pH = <2) by 6 M HCl and then extracted with CH_2Cl_2 (3 X 50 mL). After removal of the solvent, the residual white solid was recrystallized from water to give 2.3 g of (2*S*,3*S*)-diphenylsuccinic acid (48% yield from **1a**): mp 179 °C (lit.[5a] 179-180 °C), $[\alpha]^{15}_D$ +369 (c 1.40, EtOH) (lit.[5a] +369.5).

REFERENCES AND NOTES

1. (a) Kofron, W. G.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 2085. (b) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605. (c) Brocksom, T. J.; Petragnani, N.; Rodrigues, R.; LaScala Teixeira, H. *Synthesis* **1975**, 396. (d) Tokuda, M.; Shigei, T.; Itoh, M. *Chem. Lett.* **1975**, 621. (e) Inaba, S.; Ojima, I. *Tetrahedron Lett.* **1977**, 2009. (f) Chung, S. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1983**, *48*, 1125. (g) Ojima, I.; Brandstadter, S. M.; Donovan, R. J. *Chem. Lett.* **1992**, 1591.
2. Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809.
3. (a) Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969. (b) Tamaru, Y.;
4. (a) Naemura, K.; Komatsu, M.; Adachi, K.; Chikamatsu, H. *J. Chem. Soc., Chem. Commun.* **1986**, 1675. (b) Krause, H.; Sailer, C. *J. Organomet. Chem.* **1992**, *423*, 271.
5. (a) Wren, H.; Still, C. J. *J. Chem. Soc.* **1915**, 444, 1449. (b) Krause, H. W.; Meinicke, C. *J. Prakt. Chem.* **1985**, *6*, 1023.
6. (a) Porter, N. A.; Su, Q.; Harp, J. J.; Rosenstein, I. J.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 4457. (b) Langer, T.; Illich, M.; Helmchen.; *Tetrahedron Lett.* **1995**, *36*, 4409. (c) Studer, A.; Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1185.
7. Kise, N.; Tokioka, K.; Aoyama, Y.; Matsumura, Y. *J. Org. Chem.*, **1995**, *60*, 1100.
8. The crude product of **2a** was confirmed to be practically a single stereoisomer of (*S,S*)-**2a** (>98%) by ^1H NMR and HPLC analyses using the authentic diastereomers (*R,S*)-**2a** and (*R,R*)-**2a**.[7]
9. (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. (b) Evans, D. A.; Urpí, F.; Sommers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (c) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
10. Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.
11. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Gage, J. G.; Evans D. A. *Organic Synthesis*; Wiley: New York, 1993; Vol. VIII, p 339.
12. Recently, an alternative method for *N*-acylation of 2-oxazolidones with triethylamine and catalytic amount of DMAP has been reported: Ager, D. J.; Allen, D. R.; Schaad, D. R. *Synthesis* **1996**, 1283.