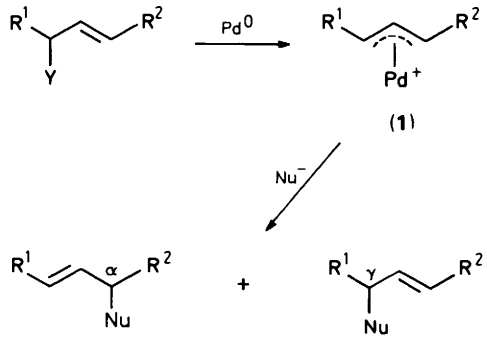
Regioselective and Stereospecific Palladium(0)-catalyzed Reactions of 4-Chloroacetoxyalk-2-enoic Esters with Carbon and Nitrogen Nucleophiles

Rikuhei Tanikaga,* Tuo Xiao Jun, and Aritsune Kaji
Department of Chemistry, Faculty of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto 606, Japan

In the presence of a palladium(0) catalyst, treatment of 4-chloroacetoxyalk-2-enoic esters with carbon or nitrogen nucleophiles leads to the regioselective substitution at the 4-position. The reactions of optically active esters, prepared from an optically active phenylsulphinylacetic ester and aldehydes, take place with retention of configuration, and those of (*E*)- and (*Z*)-esters are not accompanied by the complete geometrical isomerization. The palladium(0)-catalyzed reactions of these esters are assumed to proceed through unsymmetrical π-allyl complexes.

The functionalization of α,β-unsaturated esters at the γ-position is a reaction with great synthetic potential. For example, γ-hydroxy- or γ-amino-α,β-unsaturated esters can be readily converted into lactones[1] or lactams.[2] However, little is known about methods for achieving regio- or stereo-selective γ-functionalization. Halogenation at the γ-position, followed by reaction with nucleophiles, is limited by lack of regioselectivity.[3] Although the alkylation of copper ester dienoates derived from α,β-unsaturated esters takes place at the γ-position, the reaction of dienoate anions in general occurs at the α-position with high selectivity.[4] Previously we reported a useful method for preparing γ-hydroxy-α,β-unsaturated ester (4-hydroxyalk-2-enoic ester).[5] Unfortunately treatment of their methanesulphonate esters with nucleophiles gives a mixture of α- and γ-substituted products.

The reaction of π-allylpalladium complexes with a variety of nucleophiles is of great synthetic value.[6–9] While nucleophilic substitution for palladium complexes (**1**; $R^1 \neq R^2$) occurs at both α- and γ-positions, the introduction of an electron-withdrawing group at the conjugated position is expected to improve regioselectivity in the reaction.[10–13] In a previous communication we reported the regioselective palladium(0)-catalyzed amination of γ-chloroacetoxy-α,β-unsaturated esters (4-chloroacetoxyalk-2-enoic esters; $R^2 = CO_2R^3$, Y = $OCOCH_2Cl$),[2] and here we wish to elucidate regioselectivity and stereospecificity in the reaction of the palladium complexes derived from α,β-unsaturated esters bearing a leaving group Y at the γ-position (Scheme 1).



Scheme 1.

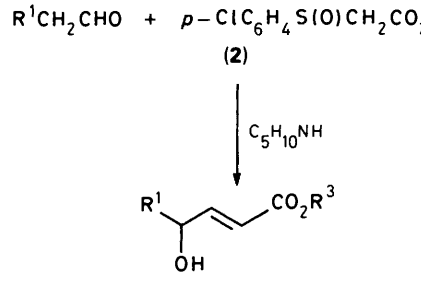
Results and Discussion

Simple treatment of aldehydes and methyl *p*-chlorophenylsulphinylacetate (**2a**; R^3 = Me) with piperidine yielded methyl (2*E*)-4-hydroxyalk-2-enoates (γ-hydroxy-α,β-unsaturated esters) (**3**).[5] By use of enantiomerically pure t-butyl (R_s)-*p*-chlorophenylsulphinylacetate (*R*)-(**2**; R^3 = Bu^t), t-butyl (2*E*,4*R*)-4-hydroxyhex-2-enoate (*R*)-(**3c**), and t-butyl (2*E*,4*R*)-4-hydroxydec-2-enoate (*R*)-(**3d**) were obtained from butanal and octanal, respectively (Scheme 2). During this procedure, the Knoevenagel reaction, a double-bond migration, and a sulphoxide–sulphenate [2,3] sigmatropic rearrangement must occur successively, and the final stage would accompany a lowering of enantiomeric excess (e.e.).[14,15] Addition of camphorsulphonic acid[15] was found to be effective for the stereospecific sigmatropic rearrangement, though not explicable. Some results are shown in Table 1.

Table 1. Preparation of (*R*)-(**3c**) and (*R*)-(**3d**).

R^1	Piperidine (equiv.)	CSA[a] (equiv.)	Yield[b] (%)	%E.e.[c]	$[\alpha]_{365}^{23}$
Et	1.2	0	95	45	−30.0°
Et	1.2	0.5	95	45	−30.8°
Et	5.0	2.0	94	54	−35.7°
$Me(CH_2)_5$	5.0	2.0	93	63	−30.6°

[a] (1*R*)-(−)-10-Camphorsulphonic acid.[15] [b] Isolated yield. [c] Determined by HPLC after converting (*R*)-(**3**) into (*R*)-(−)-MTPA ester.



	R^1	R^3
(**3a**)	Et	Me
(**3b**)	$Me(CH_2)_5$	Me
(*R*)-(**3c**)	Et	Bu^t
(*R*)-(**3d**)	$Me(CH_2)_5$	Bu^t

Scheme 2.

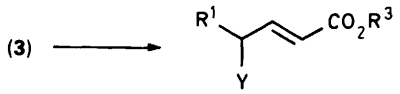
Alcohols (**3**) were readily converted into γ-substituted α,β-unsaturated esters (**4**)–(**8**) by treatment with chloroacetyl

Table 2. Pd^0-Catalyzed reactions of compounds (4)–(7).[a]

Y	R^1	NuH	Temp. (°C)	Time (min)	(9)	Yield[b] (%)
$OCOCH_2Cl$	Et	$CH_2(CO_2Et)_2$	20	60	(9a)	79
OCOMe	Et	$CH_2(CO_2Et)_2$	20	120	(9a)	50
$OCOCF_3$	Et	$CH_2(CO_2Et)_2$	20	60	(9a)	70
OCO_2Et	Et	$CH_2(CO_2Et)_2$	20	120	(9a)	73
OCO_2Et	Et	$CH_2(CO_2Et)_2$	20	120	(9a)	11[c]
$OCOCH_2Cl$	Et	$CH_2(CO_2Et)_2$	75	5	(9a)	84
$OCOCH_2Cl$	Et	$CH(Bu)(CO_2Et)_2$	75	5	(9b)	63
$OCOCH_2Cl$	Et	$CH_2(COMe)(CO_2Me)$	75	5	(9c)	87
$OCOCH_2Cl$	Et	$CH_2(CN)_2$	75	5	(9d)	73
$OCOCH_2Cl$	$Me(CH_2)_5$	$CH_2(CO_2Et)_2$	20	60	(9e)	83
$OCOCH_2Cl$	$Me(CH_2)_5$	$CH_2(CO_2Et)_2$	75	5	(9e)	80
$OCOCH_2Cl$	$Me(CH_2)_5$	$CH_2(COMe)(CO_2Me)$	75	5	(9f)	67
$OCOCH_2Cl$	$Me(CH_2)_5$	$CH_2(CN)_2$	75	5	(9g)	53

[a] (4)-(7) (1 equiv.), NuH (1.2 equiv.), NaH (1.2 equiv.), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.03 equiv.), Ph_3P (0.06 equiv.), THF–toluene. [b] Isolated yield. [c] In the absence of NaH.

chloride, acetyl chloride, trifluoroacetic anhydride, and ethyl chloroformate in the presence of pyridine and/or 4-dimethylaminopyridine (DMAP) (Scheme 3).



	Y	R^1	R^3
(4a)	$OCOCH_2Cl$	Et	Me
(4b)	$OCOCH_2Cl$	$Me(CH_2)_5$	Me
(5a)	OCOMe	Et	Me
(6a)	$OCOCF_3$	Et	Me
(7a)	OCO_2Et	Et	Me
(8a)	$OCOCH_2Cl$	Et	Bu^t
(8b)	$OCOCH_2Cl$	$Me(CH_2)_5$	Bu^t

Scheme 3.

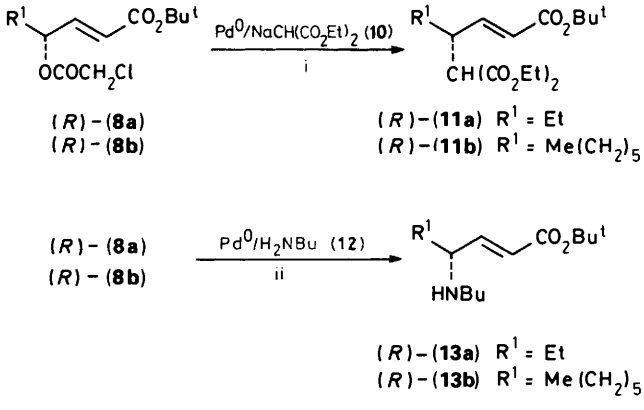
In the presence of a catalytic amount of $Pd_2(dba)_3\cdot CHCl_3$ (dba = dibenzylidene acetone),[16] (4)–(7) were treated with some carbon nucleophiles such as diethyl sodiomalonate to produce γ-substituted α,β-unsaturated esters (9) (Scheme 4). TLC, HPLC, and NMR showed that no α-substituted products nor (*Z*)-isomers were formed. Although allylic acetates are widely used for generation of π-allylpalladium complexes, the acetate (5a) was rather unreactive probably because the introduction of an electron-withdrawing group at the conjugated position would lower the reactivity toward a palladium catalyst. On the other hand, the reaction of (4a) or (6a) containing a better leaving group took place with satisfactory results. Competitive reaction of diethyl sodiomalonate toward a CF_3CO carbonyl group giving the starting alcohol as found in amination[2] was not serious. Without NaH, only allylic carbonate reacted to afford the product in 11% yield probably owing to the formation of the basic ^-OEt.[9] High yields and regioselectivity were obtained for reactions of malonate-type anions, but the attempted reaction with weak nucleophiles such as enamines resulted in a recovery of starting materials. These results are summarized in Table 2.

Scheme 4. *Reagents:* $[Pd_2(dba)_3]\cdot CHCl_3$, Ph_3P, NuH, NaH.

Asymmetric synthesis is a topic of considerable current interest, and a number of methods for syntheses of chiral alcohols in high e.e. have been reported. Therefore, it is synthetically important to carry out the transformation of an allylic CH–OH group into an allylic CH–N or CH–C group without a lowering of e.e. From a mechanistic point of view, it is interesting to elucidate the stereochemistry of the regioselective Pd^0-catalyzed reaction.

Chiral alcohols (*R*)-(3c) and (*R*)-(3d), prepared in moderate e.e. as described above, were converted into t-butyl (2*E*,4*R*)-4-chloroacetoxyhex-2-enoate [(*R*)-(8a)] and t-butyl (2*E*,4*R*)-4-chloroacetoxydec-2-enoate [(*R*)-(8b)] in high yields, without a lowering of e.e. The Pd^0-catalyzed reaction of (*R*)-(8a) or (*R*)-(8b) with diethyl sodiomalonate (10) lead to the carbon–carbon bond formation to give (*R*)-(11a) or (*R*)-(11b). Similar treatment with butylamine (12)[2] afforded the amines (*R*)-(13a) and (*R*)-(13b) (Scheme 5). The e.e. of (*R*)-(11) was determined by ^1H NMR analysis using the chiral shift reagent, tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(tfc)$_3$]. Determination of the e.e. of (*R*)-(13) was achieved by conversion with 3,5-dinitrobenzoyl chloride into the corresponding amide, and HPLC analysis using a chiral column, Chiralcel OD. These results are shown in Table 3.

The highly regioselective and stereospecific amination in benzene may provide a valuable synthetic route from (3) to γ-lactams.[2] Upon treatment of (*R*)-(8a) with (10) in benzene the starting material was recovered unchanged presumably because (10) was insoluble in the solvent.

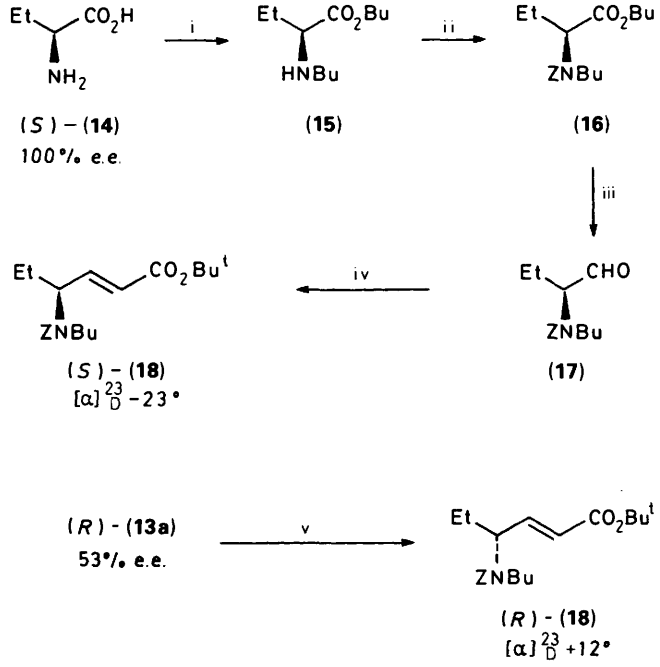


Scheme 5. *Reaction conditions:* i, 20 °C, 20 min; ii, 75 °C, 5 min.

Table 3. Pd^0-Catalyzed reaction of (*R*)-(**8a**) or (*R*)-(**8b**)[a] with (**10**) or (**12**)[b].

Product	Solvent	Yield (%)[c]	%E.e.[d]
(*R*)-(**11a**)	Toluene/THF	82	45
(*R*)-(**11a**)	Benzene	0	—
(*R*)-(**11b**)	Toluene/THF	84	52
(*R*)-(**13a**)	Toluene	79	40
(*R*)-(**13a**)	Benzene	76	53
(*R*)-(**13b**)	Toluene	83	53
(*R*)-(**13b**)	Benzene	73	61

[a] E.e.'s of starting materials (*R*)-(**8a**) and (*R*)-(**8b**) were 54 and 63%, respectively. [b] (**8**) (1 equiv.), (**10**) (1.2 equiv.) or (**12**) (2 equiv.), $[Pd_2(dba)_3]$·$CHCl_3$ (0.03 equiv.), Ph_3P (0.06 equiv.). [c] Isolated yield. [d] See text.



Scheme 6. *Reagents:* i, BuBr, DBU; ii, $ClCO_2CH_2Ph$ (ZCl), Et_3N; iii, DIBAL-H; iv, $(Pr^iO)_2P(O)CH_2CO_2Bu^t$, NaH; v, ZCl, Et_3N.

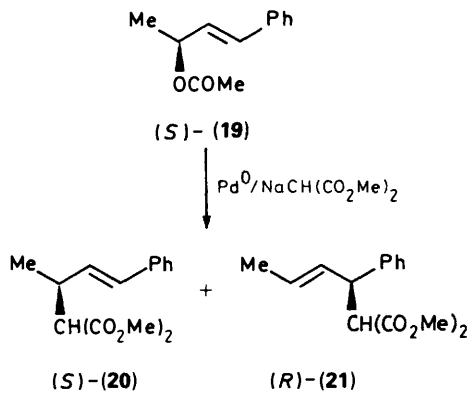
The absolute configuration of (*R*)-(**13a**) was determined by comparison with the amine [(*S*)-(**18a**)] independently synthesized from enantiomerically pure (2*S*)-2-aminobutanoic acid [(*S*)-(**14**)] (Scheme 6). The reaction using (**12**) was found to proceed with retention of configuration, and this finding suggests that the attacks by a palladium catalyst and (**12**), respectively, may occur with inversion. Similarly, the Pd^0-catalyzed reaction of (1*E*,3*S*)-3-acetoxy-1-phenylbut-1-ene (*S*)-(**19**) with sodium methyl malonate is known to take place with retention of configuration resulting in the formation of a mixture of the γ- and α-substituted products (*S*)-(**20**) and (*R*)-(**21**) (Scheme 7).[17] Thus, in analogy with these reactions, the reaction of (*R*)-(**8**) with (**10**) is assumed to occur with retention of configuration.

Since the Pd^0-catalyzed reaction in general takes place by way of a π-allylpalladium complex intermediate, the same products are obtained from (*S*)-(**19**) and (1*S*,2*E*)-1-acetoxy-1-phenylbut-2-ene.[17] It seemed of interest to evaluate the extent of the *E*-*Z* isomerization during the Pd^0-catalyzed reaction of (**4**), in which a nucleophile attacks the γ-position only. Unfortunately, it was very difficult to synthesize the (*Z*)-isomer of (**4**), and thus, we prepared methyl (2*E*)- and (2*Z*)-4-chloroacetoxy-3-methylbut-2-enoates (*E*)-(**22**) and (*Z*)-(**22**) in the following way. Treatment of 1-chloroacetoxypropan-2-one and methyl (diethoxyphosphonyl)acetate with NaH afforded (*E*)-(**22**) and (*Z*)-(**22**) in 1.3:1.0 ratio. Each isomer was isolated by use of preparative HPLC. Assignment of (**22**) was based on the downfield shift of a Me group *cis* to a CO_2Me function.

Table 4. Pd^0-Catalyzed reactions of (*E*)-(**22**) and (*Z*)-(**22**) with (**10**)[a].

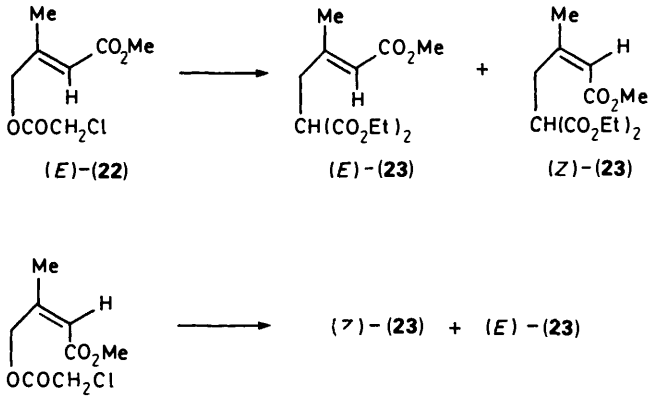
Substrate	Product (23) Yield[b](%)	(*E*):(*Z*) Ratio[c]
(*E*)-(**22**)	96	85:15
(*Z*)-(**22**)	91	32:68

[a] (**22**) (1 equiv.), $CH_2(CO_2Et)_2$ (1.2 equiv.), NaH (1.2 equiv.), $[Pd_2(dba)_3]$·$CHCl_3$ (0.03 equiv.), Ph_3P (0.06 equiv.), THF–toluene, 20 °C, 10 min. [b] Yields are for the isolated total products. [c] Determined by ^1H NMR.



Scheme 7.

The reactions of (*E*)-(**22**) and (*Z*)-(**22**) with sodium diethyl malonate were carried out in the presence of $[Pd_2(dba)_3]$·$CHCl_3$ at 20 °C, and the results are summarized in Table 4 (Scheme 8).

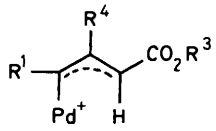


Scheme 8. *Reagents:* $[Pd_2(dba)_3]$·$CHCl_3$, $CH_2(CO_2Et)_2$, NaH.

The chemical yields were excellent, and the stereochemistry of the product was assigned on the basis of the chemical shift of a Me group (see above). Interestingly, the initial geometry was retained to some extent, and no α-substituted product was detected.

Hayashi reported that (*S*)-(**19**) and (1*Z*,3*R*)-3-acetoxy-1-phenylbut-1-ene reacted with sodium methyl malonate to afford γ- and α-substituted *E*-products in the same 90:10 ratio, and the results were explained by the σ-π-σ rearrangement mechanism through an allylic σ-complex.[17-19] The present findings suggest that in the Pd^0-catalyzed reaction of the allylic compound

containing an electron-withdrawing group the mechanism may be somewhat different from the one above. The regiospecific reactivity may be associated with an unsymmetrical π-complex (**24**) similar to a σ one where a σ-structure is favoured by the conjugation between a C=C bond and a CO_2R^3 group, and the σ-π-σ rearrangement is slightly slower than the nucleophilic attack of the malonate anion.



(**24**)

Unfortunately, a similar attempt using butylamine was unsuccessful because of considerable isomerization of a double bond at the elevated temperature (75 °C).

Experimental

^{1}H NMR spectra were recorded with a JEOL PS-100 (100 MHz) or a JEOL-FX-400 (400 MHz) spectrometer using tetramethylsilane as internal standard and $CDCl_3$ as solvent. IR spectra were taken on a Hitachi 215 spectrometer, and mass spectra on a JEOL JMX-DX-300 instrument. Optical rotation was determined with a JASCO DIP-181 polarimeter. HPLC analyses were carried out with a Shimadzu LC-6A or a Hitachi L-6000 system containing a ODS, a PYE[20] or a chiral cellulose (Daicel Chiralcel OD) column. Preparative HPLC was carried out on a Shimadzu LC-8A system with a silanol column (Shimpack PREP-SIL, 50 mm × 250 mm). Column chromatography was performed with Wakogel 200 silica gel, and TLC with Merck silica gel 60 F_{254}.

Chloroacetyl chloride, diethyl malonate, butylamine, and other commercially available reagents were purified by distillation. Toluene and benzene were distilled from calcium hydride and stored over 4 Å molecular sieves. THF was freshly distilled from calcium hydride before use. Methyl (2*E*)-4-hydroxyalk-2-enoates (**3**),[5] t-butyl (R_S)-*p*-chlorophenylsulphinylacetate (*R*)-(**2**),[14] and tris(dibenzylideneacetone) dipalladium(chloroform) [$Pd_2(dba)_3$·$CHCl_3$][16] were prepared by the methods previously reported.

t-Butyl (2*E*,4*R*)-4-*Hydroxyhex*-2-*enoate* (*R*)-(**3c**) *and t-Butyl* (2*E*,4*R*)-4-*Hydroxydec*-2-*enoate* (*R*)-(**3d**).—The sulphoxide (*R*)-(**2**) (10 mmol), piperidine (50 mmol), and (1*R*)-(−)-camphor-10-sulphonic acid (CSA) (20 mmol) were mixed in MeCN (150 ml) at 0 °C, and then butanal (12 mmol) was added. Mixing was continued for 24 h at room temperature. After having removed the solvent, column chromatography on silica gel with hexane–EtOAc (4:1, v/v) gave (*R*)-(**3c**) as a liquid in 94% yield, $[\alpha]_{365}^{23}$ −35.7° (*c* 0.9 in MeOH) (54% e.e.); ν_{max} 1 170, 1 660, and 1 720 cm^{-1} (C=O); δ_H 0.97 (3 H, t, *J* 7 Hz, Me), 1.49 (9 H, s, CMe_3), 1.62 (2 H, m, CH_2), 2.17 (1 H, br s, OH), 4.20 (1 H, q, *J* 6 Hz, CH), 5.94 (1 H, d, *J* 16 Hz, =CH), and 6.82 (1 H, dd, *J* 16 and 6 Hz, CH=).

A solution of (*R*)-(**3c**) (1 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MTPA-Cl] (1 mmol), and 4-dimethylaminopyridine (DMAP) (2.4 mmol) in CH_2Cl_2 (20 ml) was stirred for 2 h at 0 °C. It was then worked up and the product subjected to preparative TLC on silica gel to give a quantitative yield of the (+)-MTPA ester of (*R*)-(**3c**) with 54% e.e. (by ^{1}H NMR analysis).

Similar treatment of (*R*)-(**2**) with octanal gave (*R*)-(**3d**) as a liquid in 93% yield, $[\alpha]_{365}^{23}$ −30.6° (*c* 1.3 in MeOH) (63% e.e.); ν_{max} 1 160, 1 660, and 1 720 cm^{-1} (C=O); δ_H 0.88 (3 H, t, *J* 7 Hz, Me), 1.10–1.40 (8 H, m, CH_2), 2.10 (1 H, br s, OH), 4.20 (1 H, q, *J* 6 Hz, CH), 5.85 (1 H, d, *J* 16 Hz, =CH), and 6.72 (1 H, dd, *J* 16 and 6 Hz, CH=).

The γ-*Substituted* α,β-*Unsaturated Esters* (**4**)–(**7**), *and* (**8**).—To a stirred solution of (**3a**) (10 mmol), pyridine (20 mmol), and DMAP (2 mmol) in THF (50 ml) at 0 °C was added dropwise chloroacetyl chloride (12 mmol) in THF (10 ml). The resulting solution was stirred for 15 min at 0 °C and then poured into water and extracted with EtOAc. The organic layer was washed successively with aqueous $NaHCO_3$, dilute hydrochloric acid, and water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on a silica-gel column eluting hexane–EtOAc (4:1, v/v) to give methyl (2*E*)-4-chloroacetoxyhex-2-enoate (**4a**) as a liquid in 90% yield, ν_{max} 1 170, 1 660, and 1 720 cm^{-1} (C=O); δ_H 0.92 (3 H, t, *J* 7 Hz, Me), 1.74 (2 H, dq, *J* 6 and 7 Hz, CH_2), 3.73 (3 H, s, OMe), 4.08 (2 H, s, CH_2Cl), 5.39 (1 H, q, *J* 6 Hz, CH), 5.97 (1 H, d, *J* 16 Hz, =CH), and 6.81 (1 H, dd, *J* 16 and 6 Hz, CH=).

By applying the same procedure to (**3b**), (*R*)-(**3c**), and (*R*)-(**3d**), the following esters were obtained as liquids in 89, 90, and 88% yields, respectively.

Methyl (2*E*)-4-chloroacetoxydec-2-enoate (**4b**): ν_{max} 1 160, 1 650, and 1 720 cm^{-1} (C=O); δ_H 0.88 (3 H, t, *J* 7 Hz, Me), 1.23–1.38 (8 H, m, CH_2), 1.72 (2 H, m, CH_2), 3.75 (3 H, s, OMe), 4.09 (2 H, s, CH_2Cl), 5.46 (1 H, q, *J* 6 Hz, CH), 5.99 (1 H, d, *J* 16 Hz, =CH), and 6.84 (1 H, dd, *J* 16 and 6 Hz).

t-Butyl (2*E*,4*R*)-4-chloroacetoxyhex-2-enoate (*R*)-(**8a**): $[\alpha]_{365}^{23}$ +61.2° (*c* 1.4 in MeOH) (54% e.e.); ν_{max} 1 330, 1 660, and 1 740 cm^{-1} (C=O); δ_H 0.95 (3 H, t, *J* 7 Hz, Me), 1.49 (9 H, s, CMe_3), 1.74 (2 H, dq, *J* 6 and 7 Hz, CH_2), 4.09 (2 H, s, CH_2Cl), 5.40 (1 H, q, *J* 6 Hz, CH), 5.90 (1 H, d, *J* 16 Hz, =CH), and 6.71 (1 H, dd, *J* 16 and 6 Hz, CH=).

t-Butyl (2*E*,4*R*)-4-chloroacetoxydec-2-enoate (*R*)-(**8b**): $[\alpha]_{365}^{23}$ +46.6° (*c* 1.3 in MeOH) (63% e.e.); ν_{max} 1 300, 1 660, 1 730 cm^{-1} (C=O); δ_H 0.88 (3 H, t, *J* 7 Hz, Me), 1.23–1.38 (8 H, m, CH_2), 1.48 (9 H, s, CMe_3), 1.70 (2 H, m, CH_2), 4.09 (2 H, s, CH_2Cl), 5.45 (1 H, q, *J* 6 Hz, CH), 5.89 (1 H, d, *J* 16 Hz, =CH), and 6.72 (1 H, dd, *J* 16 and 6 Hz, CH=).

Similar treatment of (**3a**) with acetyl chloride in the place of chloroacetyl chloride produced methyl (2*E*)-4-acetoxyhex-2-enoate (**5a**) as a liquid in 87% yield, ν_{max} 1 230, 1 650, and 1 720 cm^{-1} (C=O); δ_H 0.90 (3 H, t, *J* 7 Hz, Me), 1.72 (2 H, m, CH_2), 2.04 (3 H, s, COMe), 3.70 (3 H, s, OMe), 5.34 (1 H, m, CH), 5.90 (1 H, d, *J* 16 Hz, =CH), and 6.80 (1 H, dd, *J* 16 and 6 Hz, CH=).

Upon similar treatment of (**3a**) with ethyl chloroformate methyl (2*E*)-4-ethoxycarbonyloxyhex-2-enoate (**7a**) was prepared as a liquid in 76% yield, ν_{max} 1 260, 1 650, and 1 730 cm^{-1} (C=O); δ_H 1.00 (3 H, t, *J* 7 Hz, Me), 1.32 (3 H, t, *J* 7 Hz, Me), 1.75 (2 H, m, CH_2), 3.78 (3 H, s, OMe), 4.22 (2 H, q, *J* 7 Hz, OCH_2), 5.18 (1 H, m, CH), 6.00 (1 H, d, *J* 16 Hz, =CH), and 6.85 (1 H, dd, *J* 16 and 6 Hz, CH=).

To a stirred solution of (**3a**) (15 mmol) in CH_2Cl_2 (30 ml) at 0 °C was added trifluoroacetic anhydride (18 mmol). After being stirred for 1 h, the solution was washed with water, aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated to dryness. Distillation (b.p. 54 °C/0.9 mmHg) of the residue gave methyl (2*E*)-*trifluoroacetoxyhex*-2-*enoate* (**6a**) as a liquid (66%); ν_{max} 1 170, 1 660, 1 720, and 1 780 cm^{-1} (C=O); δ_H 0.94 (3 H, t, *J* 7 Hz, Me), 1.80 (2 H, m, CH_2), 3.74 (3 H, s, OMe), 5.50 (1 H, m, CH), 5.98 (1 H, d, *J* 16 Hz, =CH), and 6.84 (1 H, dd, *J* 16 and 6 Hz, CH=).

Pd^0-*Catalyzed Reactions of* (**4**)–(**7**) *with Carbon Nucleophiles*.—To a suspension of [$Pd_2(dba)_3$]·$CHCl_3$ (0.15 mmol), Ph_3P (0.3 mmol), and (**4a**) (5 mmol) in toluene (25 ml) at 20 °C with stirring under argon atmosphere was added diethyl sodiomalonate (**10**) which was prepared separately by dropping diethyl malonate (6 mmol) into a suspension of NaH (6 mmol)

in THF (25 ml). After being stirred for 1 h, the mixture was washed with brine, dried ($MgSO_4$), and evaporated. The residue was subjected to column chromatography on silica gel with hexane–EtOAc (4:1, v/v) and afforded *diethyl* [(1*R*)-1-(2-*methoxycarbonylvinyl*)*propyl*]*malonate* (**9a**) as a liquid in 79% yield, ν_{max} 1 650 and 1 720 cm^{-1} (C=O); δ_H 0.88 (3 H, t, *J* 7 Hz, Me), 1.24 (3 H, t, *J* 7 Hz, Me), 1.24 (3 H, t, *J* 7 Hz, Me), 1.24 (1 H, dq, *J* 4 and 7 Hz, CH_2), 1.61 (1 H dq, *J* 4 and 7 Hz, CH_2), 2.86 (1 H, dq, *J* 9 and 4 Hz, CH), 3.43 (1 H, d, *J* 4 Hz, CH), 3.72 (3 H, s, OMe), 4.15 (2 H, q, *J* 7 Hz, OCH_2), 4.20 (2 H, q, *J* 7 Hz, OCH_2), 5.87 (1 H, d, *J* 16 Hz, =CH), and 6.80 (1 H, dd, *J* 16 and 9 Hz, CH=) (Found: C, 58.9; H, 7.8. $C_{14}H_{22}O_6$ requires C, 58.7; H, 7.7%).

Similar treatment of (**4**)–(**7**) with other carbon nucleophiles under the conditions (reaction temperature and time) as shown in Table 2 resulted in the formation of the following γ-substituted products (**9**).

Diethyl butyl[1-(2-*methoxycarbonylvinyl*)*propyl*]*malonate* (**9b**): ν_{max} 1 650 and 1 720 cm^{-1} (C=O); δ_H 0.85 (3 H, t, *J* 7 Hz, Me), 0.87 (3 H, t, *J* 7 Hz, Me), 1.23–1.30 (4 H, m, CH_2), 1.26 (3 H, t, *J* 7 Hz, Me), 1.29 (3 H, t, *J* 7 Hz, Me), 1.75–1.85 (4 H, m, CH_2), 2.65 (1 H, dt, *J* 10 and 2 Hz, CH), 3.70 (3 H, s, OMe), 4.20 (2 H, q, *J* 7 Hz, OCH_2), 4.22 (2 H, q, *J* 7 Hz, OCH_2), 5.85 (1 H, d, *J* 16 Hz, =CH), and 6.76 (1 H, dd, *J* 16 and 10 Hz, CH=) (Found: C, 63.2; H, 8.8. $C_{18}H_{30}O_6$ requires C, 63.1; H, 8.8%).

Methyl 2-*acetyl*-3-(2-*methoxycarbonylvinyl*)*pentanoate* (**9c**): ν_{max} 1 650 and 1 720 cm^{-1} (C=O); δ_H 0.87 (3 H, t, *J* 7 Hz, Me), 1.37 (1 H, m, CH_2), 1.55 (1 H, m, CH_2), 2.18 and 2.24 (3 H, s, COMe), 2.90 (1 H, dq, *J* 9 and 4 Hz, CH), 3.56 and 3.58 (1 H, d, *J* 9 Hz, CH), 3.69 and 3.75 (3 H, s, OMe), 3.72 and 3.73 (3 H, s, OMe), 5.86 and 5.88 (1 H, d, *J* 16 Hz, =CH), and 6.68 and 6.74 (1 H, dd, *J* 16 and 9 Hz, CH=) (Found: C, 59.2; H, 7.5. $C_{12}H_{18}O_5$ requires C, 59.5; H, 7.5%).

[1-(2-*Methoxycarbonylvinyl*)*propyl*]*malononitrile* (**9d**): ν_{max} 2 450 (CN), 1 710, and 1 650 cm^{-1} (C=O); δ_H 1.00 (3 H, t, *J* 7 Hz, Me), 1.73 (1 H, dq, *J* 4 and 7 Hz, CH_2), 1.86 (1 H, dq, *J* 4 and 7 Hz, CH_2), 2.74 (1 H, dq, *J* 9 and 4 Hz, CH), 3.79 (3 H, s, OMe), 3.80 (1 H, d, *J* 4 Hz, CH), 6.10 (1 H, d, *J* 16 Hz, =CH), and 6.73 (1 H, dd, *J* 16 and 9 Hz, CH=) (Found: C, 62.3; H, 6.3; N, 16.8. $C_{10}H_{12}N_2O_2$ requires C, 62.5; H, 6.3; N, 16.7%).

Diethyl [1-(2-*methoxycarbonylvinyl*)*heptyl*]*malonate* (**9e**): ν_{max} 1 650 and 1 720 cm^{-1} (C=O); δ_H 0.87 (3 H, t, *J* 7 Hz, Me), 1.21–1.35 (8 H, m, CH_2), 1.25 (3 H, t, *J* 7 Hz, Me), 1.28 (3 H, t, *J* 7 Hz, Me), 1.45 (2 H, m, CH_2), 2.91 (1 H, dq, *J* 9 and 4 Hz, CH), 3.40 (2 H, d, *J* 9 Hz, CH), 3.72 (3 H, s, OMe), 4.15 (2 H, q, *J* 7 Hz, OCH_2), 4.21 (2 H, q, *J* 7 Hz, OCH_2), 5.87 (1 H, d, *J* 16 Hz, =CH), and 6.80 (1 H, dd, *J* 16 and 8 Hz, CH) (Found: C, 63.0; H, 8.9. $C_{18}H_{30}O_6$ requires C, 63.1; H, 8.8%).

Methyl 2-*acetyl*-3-(2-*methoxycarbonylvinyl*)*nonanoate* (**9f**): ν_{max} 1 660 and 1 730 cm^{-1} (C=O); δ_H 0.90 (3 H, t, *J* 7 Hz, Me), 1.23–1.38 (8 H, m, CH_2), 1.45 (2 H, m, CH_2), 2.18 and 2.24 (3 H, s, COMe), 2.97 (1 H, dq, *J* 9 and 3 Hz, CH), 3.52 and 3.54 (1 H, d, *J* 9 Hz, CH), 3.68 and 3.75 (3 H, s, OMe), 3.72 and 3.73 (3 H, s, OMe), 5.83 and 5.87 (1 H, d, *J* 16 Hz, =CH), and 6.69 and 6.73 (1 H, dd, *J* 16 and 9 Hz, CH=) (Found: C, 64.3; H, 8.8. $C_{16}H_{26}O_5$ requires C, 64.4; H, 8.8%).

[1-(2-*Methoxycarbonylvinyl*)*heptyl*]*malononitrile* (**9g**): ν_{max} 1 660, 1 720 (C=O), and 2 250 cm^{-1} (CN); δ_H 0.88 (3 H, t, *J* 7 Hz, Me), 1.24–1.33 (8 H, m, CH_2), 1.66 (1 H, m, CH_2), 1.77 (1 H, m, CH_2), 2.82 (1 H, dq, *J* 9 and 4 Hz, CH), 3.78 (3 H, s, OMe), 3.85 (1 H, d, *J* 4 Hz, CH), 6.08 (1 H, d, *J* 16 Hz, =CH), and 6.75 (1 H, dd, *J* 16 and 9 Hz, CH=) (Found: C, 67.5; H, 8.0; N, 11.4. $C_{14}H_{20}N_2O_2$ requires C, 67.7; H, 8.12; N, 11.3%).

Pd^0-*Catalyzed Reaction of* (*R*)-(**8a**) *or* (*R*)-(**8b**) *with Sodium Diethyl Malonate* (**10**).—In a manner similar to that described above, treatment of (*R*)-(**8a**) or (*R*)-(**8b**) (1 mmol) with (**10**) (1.2 mmol) yielded *diethyl* [(1*R*)-1-(2-*t-butoxycarbonylvinyl*)-*propyl*]*malonate* (*R*)-(**11a**) or *diethyl* [(1*R*)-1-(2-*t-butoxycarbonylvinyl*)*heptyl*]*malonate* (*R*)-(**11b**) as a liquid in 82 or 84% yield. Their e.e.'s were determined by ^1H NMR analysis in the presence of [Eu(TFC)$_3$].

(*R*)-(**11a**): $[\alpha]_D^{23}$ +7.1° (*c* 0.71 in MeOH) (45% e.e.); ν_{max} 1 660 and 1 740 cm^{-1} (C=O); δ_H 0.88 (3 H, t, *J* 7 Hz, Me), 1.23 (3 H, t, *J* 7 Hz, Me), 1.27 (3 H, t, *J* 7 Hz, Me), 1.42 (1 H, dq, *J* 4 and 7 Hz, CH_2), 1.47 (9 H, s, CMe_3), 1.61 (1 H, dq, *J* 4 and 7 Hz, CH_2), 2.84 (1 H, dq, *J* 4 and 9 Hz, CH), 3.40 (1 H, d, *J* 9 Hz, CH), 4.15 (2 H, q, *J* 7 Hz, OCH_2), 4.20 (2 H, q, *J* 7 Hz, OCH_2), 5.79 (1 H, d, *J* 16 Hz, =CH), and 6.67 (1 H, dd, *J* 16 and 9 Hz, CH=) (Found: C, 61.9; H, 8.6. $C_{17}H_{28}O_6$ requires C, 62.2; H, 8.6%).

(*R*)-(**11b**): $[\alpha]_D^{23}$ +4.7° (*c* 6.0 in MeOH) (52% e.e.); ν_{max} 1 640 and 1 720 cm^{-1} (C=O); δ_H 0.87 (3 H, t, *J* 7 Hz, Me), 1.23 (3 H, t, *J* 7 Hz, Me), 1.27 (3 H, t, *J* 7 Hz, Me), 1.19–1.28 (8 H, m, CH_2), 1.47 (9 H, s, CMe_3), 1.49 (2 H, m, CH_2), 2.90 (1 H, dq, *J* 4 and 9 Hz, CH), 3.38 (1 H, d, *J* 9 Hz, CH), 4.15 (2 H, q, *J* 7 Hz, OCH_2), 4.20 (2 H, q, *J* 7 Hz, OCH_2), 5.78 (1 H, d, *J* 16 Hz, =CH), and 6.66 (1 H, dd, *J* 16 and 9 Hz, CH=) (Found: C, 71.9; 10.6. $C_{21}H_{36}O_6$ requires C, 71.5; H, 10.3%).

Pd^0-*Catalyzed Reaction of* (*R*)-(**8a**) *or* (*R*)-(**8b**) *with Butylamine*.—To a suspension of [$Pd_2(dba)_3$]·$CHCl_3$ (0.03 mmol) and Ph_3P (0.06 mmol) in toluene (20 ml) at 75 °C with stirring under argon atmosphere were added (*R*)-(**8a**) (1 mmol) and butylamine (2 mmol). After being stirred for 10 min, the mixture was poured into water and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. Preparative TLC on silica gel of the residue gave *N-butyl*-(1*R*)-1-(2-*t-butoxycarbonylvinyl*)*heptylamine* (*R*)-(**13a**) as a liquid (79%),$[\alpha]_D^{23}$ +1.9° (*c* 0.70 in MeOH) (40% e.e.); ν_{max} 1 150 and 1 710 cm^{-1} (C=O); δ_H 0.89 (3 H, t, *J* 7 Hz, Me), 0.91 (3 H, t, *J* 7 Hz, Me), 1.08–1.60 (7 H, m, CH_2 and NH), 1.49 (9 H, s, CMe_3), 2.47 (1 H, m, CH_2), 2.57 (1 H, m, CH_2), 3.40 (1 H, q, *J* 7 Hz, CH), 5.80 (1 H, d, *J* 16 Hz, =CH), and 6.61 (1 H, dd, *J* 16 and 7 Hz, CH=) (Found: C, 69.4; H, 11.2: N, 5.9. $C_{14}H_{27}NO_2$ requires C, 69.7; H, 11.3; N, 5.8%).

To a solution of (*R*)-(**13a**) (0.5 mmol) and 3,5-dinitrobenzoyl chloride (0.75 mmol) in CH_2Cl_2 (10 ml) at 0 °C was added pyridine (0.75 mmol), and the resulting solution was stirred for 2 h at room temperature. The mixture was poured into water and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), and, after removal of the solvent, chromatography of the residue on a silica-gel column afforded the corresponding amide as a liquid (96%). The enantiomers were separated by HPLC with use of a chiral cellulose column (Chiralcel OD), eluting with hexane–Pr^iOH (9:1 v/v); ν_{max} 1 160, 1 170 (C=O), and 1 550 cm^{-1} (NO_2); δ_H 0.07–1.40 (6 H, m), 1.20–2.00 (6 H, m), 1.50 (9 H, s), 3.31 (2 H, m), 4.11 (1 H, m), 5.84 (1 H, m), 6.84 (1 H, m), 8.56 (2 H, s), and 9.07 (1 H, s).

Similarly, *N-butyl*-(1*R*)-1-(2-*t-butoxycarbonylvinyl*)*heptylamine* (*R*)-(**13b**) was obtained as a liquid (83%) $[\alpha]^{23}$ +1.5° (*c* 0.5 in MeOH) (53% e.e.); ν_{max} 1 160 and 1 710 cm^{-1} (C=O); δ_H 0.7–1.0 (6 H, m, Me), 1.10–1.65 (15 H, m, CH_2 and NH), 1.50 (9 H, s, CMe_3), 2.50 (2 H, m, CH_2), 3.45 (1 H, q, *J* 7 Hz, CH), 5.85 (1 H, d, *J* 16 Hz, =CH), and 6.65 (1 H, dd, *J* 16 and 7 Hz, CH=) (Found: C, 72.9; H, 12.1; N, 4.8. $C_{18}H_{35}O_2N$ requires C, 72.7; H, 11.9; N, 4.7%).

The amide of (*R*)-(**13b**): ν_{max} 1 160 and 1 710 (C=O), and 1 550 cm^{-1} (NO_2); δ_H 0.76–1.15 (6 H, m), 1.25–2.00 (14 H, m), 1.51 (9 H, s), 3.31 (2 H, m), 4.10 (1 H, m), 5.84 (1 H, m), 6.85 (1 H, m), 8.56 (2 H, s), and 9.08 (1 H, s).

t-Butyl (2*E*,4*S*)- *and t-Butyl* (2*E*,4*R*)-4-[(N-*Benzyloxycarbonyl*-N-*butyl*)*amino*]*hex*-2-*enoates* [(*S*)-(**18**) and (*R*)-(**18**)].—To a solution of (2*S*)-2-aminobutanoic acid (*S*)-(**14**) (8 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (16 mmol) in benzene (50 ml) at room temperature was added 1-bromobutane (16 mmol), and the resultant mixture was refluxed for 2 h. After

cooling, the mixture was diluted with diethyl ether (50 ml), and the precipitate was filtered off and washed with diethyl ether. The filtrate and the washing were combined, washed with water, dried (Na_2SO_4), and evaporated to dryness. Purification by column chromatography on silica gel with hexane–EtOAc (3:1,v/v) afforded butyl (2*S*)-2-(butylamino)butanoate (**15**) as a liquid (42%), $[\alpha]_D^{23}$ −10.1° (*c* 0.89 in $CHCl_3$); ν_{max} 1 740 (C=O) and 3 300 cm^{-1} (NH); δ_H 0.90 (3 H, t, *J* 7 Hz, Me), 0.93 (3 H, t, *J* 7 Hz, Me), 0.95 (3 H, t, *J* 7 Hz, Me), 1.26–1.54 (6 H, m, CH_2), 1.60–1.70 (4 H, m, CH_2), 1.81 (1 H, br s, NH), 2.47 (1 H, m, NCH_2), 2.58 (1 H, m, NCH_2), 3.16 (1 H, t, *J* 7 Hz, CH), and 4.14 (2 H, t, *J* 7 Hz, OCH_2); *m/z* 215 (M^+, 0.5%) and 114 (M^+–CO_2Bu).

To a solution of (**15**) (2.5 mmol) and Et_3N (5.5 mmol) in CH_2Cl_2 (30 ml) with vigorous stirring at 0 °C was added benzyl chloroformate (3.5 mmol). After being stirred for 2 h, the reaction mixture was washed with water, extracted with EtOAc, and the extract dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel to give butyl (2*S*)-2-[*N*-(benzyloxycarbonyl)-*N*-butylamino]butanoate (**16**) as a liquid (86%), $[\alpha]_D^{23}$ −35.6° (*c* 1.1 in $CHCl_3$); ν_{max} 1 710 and 1 740 cm^{-1} (C=O); δ_H 0.87–0.96 (9 H, m, Me), 1.22–1.42 (4 H, m, CH_2), 1.43–1.65 (4 H, m, CH_2), 1.80 (1 H, m, CH_2), 2.05 (1 H, m, CH_2), 3.20 (1 H, m, CH), 3.40 (1 H, m, NCH_2), 4.00 (1 H, m, NCH_2), 4.10 (1 H, m, OCH_2), 5.14 (2 H, s, OCH_2), and 7.25–7.39 (5 H, m, Ph).

To a stirred solution of (**16**) (2 mmol) in toluene (30 ml) at −50 °C, 1.5M Bu_2^iAlH (DIBAL-H) solution in toluene (3 ml) was added dropwise under an argon atmosphere. The resulting mixture was stirred for an additional 20 min, quenched with dilute hydrochloric acid, and allowed to warm to 0 °C. The organic phase was separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated to dryness below 40 °C. Column chromatography of the residue on silica gel with hexane–EtOAc (3:1, v/v) gave (2*S*)-2-[*N*-(benzyloxycarbonyl)-*N*-butylamino]butanal (**17**) as a liquid (70%), $[\alpha]_D^{23}$ −76.9° (*c* 0.83 in $CHCl_3$); ν_{max} 1 700 and 1 740 cm^{-1} (C=O); δ_H 0.87–1.10 (6 H, m, Me), 1.30 (2 H, m, CH_2), 1.50 (2 H, m, CH_2), 1.75 (1 H, m, CH_2), 2.07 (1 H, m, CH_2), 3.10 (1 H, m, CH), 3.50 (1 H, m, NCH_2), 3.74 (1 H, m, NCH_2), 5.16 (2 H, s, OCH_2), and 7.26–9.50 (5 H, m, Ph).

Under an argon atmosphere, a solution of t-butyl di-isopropyloxyphosphonylacetate[21] (1 mmol) in dry THF (5 ml) was added dropwise to a slurry of NaH (1 mmol) in dry THF (30 ml) with stirring at room temperature. After the mixture had been stirred for 1 h, compound (**17**) (1 mmol) was added, and stirring was continued for an additional 20 min. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. Chromatography of the residue on a silica-gel column using hexane–EtOAc (4:1, v/v) generated (*S*)-(**18**) as a liquid in 87% yield, $[\alpha]_D^{23}$ −23.0° (*c* 0.52 in $CHCl_3$); ν_{max} 1 660 and 1 710 cm^{-1} (C=O); δ_H 0.82–0.96 (6 H, m, Me), 1.25 (2 H, m, CH_2), 1.48 (9 H, s, CMe_3), 1.49 (2 H, m, CH_2), 1.71 (2 H, m, CH_2), 3.10 (2 H, m, NCH_2), 4.14 (1 H, m, CH), 5.14 (2 H, s, OCH_2), 5.75 (1 H, d, *J* 16 Hz, =CH), 6.80 (1 H, dd, *J* 16 and 6 Hz, CH=), and 7.34 (5 H, m, Ph) (Found: C, 70.5; H, 8.9; N, 3.8. $C_{22}H_{33}NO_4$ requires C, 70.4; H, 8.9; N, 3.7%).

A solution of (*R*)-(**13a**) (1 mmol; 53% e.e.), Et_3N (2.2 mmol), and benzyl chloroformate (1.5 mmol) in CH_2Cl_2 (20 ml) was refluxed for 2 h. After cooling the reaction mixture was washed with water, dried ($MgSO_4$), and evaporated. The residue was subjected to column chromatography on silica gel with hexane–EtOAc (4:1, v/v), to give (*R*)-(**18**) as a liquid (54%), $[\alpha]_D^{23}$ +12.4° (*c* 0.54 in $CHCl_3$); ν_{max} and δ_H were same as in (*S*)-(**18**).

Methyl (2E)-4-(*Chloroacetoxy*)-3-*methylbut*-2-*enoate* (*E*)-(**22**) *and Methyl* (2Z)-4-(*Chloroacetoxy*)-3-*methylbut*-2-*enoate* (*Z*)-(**22**).—According to the procedure described in the preparation of (**4a**), 1-hydroxypropan-2-one was treated with chloroacetyl chloride to yield 1-chloroacetoxypropan-2-one (**25**). To a suspension of NaH (11 mmol) in THF (50 ml) at room temperature under an argon atmosphere was added slowly methyl (diethoxyphosphonyl)acetate (11 mmol) and compound (**25**) (10 mmol). The resulting mixture was refluxed for 2 h, cooled, and poured into water. The aqueous phase was extracted with EtOAc, and the combined organic phases were dried ($MgSO_4$), and evaporated. Column chromatography of the residue on silica gel gave a mixture of (*E*)-(**22**) and (*Z*)-(**22**) (31%). The *E*:*Z* ratio was determined as 1.3:1.0 by HPLC analysis. These two isomers were isolated by preparative HPLC with a silanol column (50 mm × 250 mm), eluting hexane–Pr^iOH (95:5, v/v), at a 50 ml/min flow rate.

(*E*)-(**22**): liquid; ν_{max} 1 250, 1 670, and 1 740 cm^{-1} (C=O); δ_H 2.16 (3 H, s, Me), 3.72 (3 H, s, OMe), 4.13 (2 H, s, CH_2Cl), 4.69 (2 H, s, OCH_2), and 5.89 (1 H, s, CH) (Found: C, 46.3; H, 5.3. $C_8H_{11}ClO_4$ requires C, 46.5:H, 5.3%).

(*Z*)-(**22**): liquid; ν_{max} 1 250, 1 670, and 1 740 cm^{-1} (C=O); δ_H 1.94 (3 H, s, Me), 3.71 (3 H, s, OMe), 4.10 (2 H, s, CH_2Cl), 5.35 (2 H, s, OCH_2), and 5.82 (1 H, s, CH).

Pd^0-*Catalyzed Reactions of* (E)-(**22**) *and* (Z)-(**22**) *with Diethyl Sodiomalonate*.—The reactions were carried out in a flow of argon at 20 °C for 10 min. In a manner similar to that described in the reaction giving (**9**), (*E*)-(**22**) was converted into a *E*/*Z* mixture of *diethyl* [*2-methyl-3-(methoxycarbonyl)prop-2-enyl*]*malonate* (*E*)-(**23**) and (*Z*)-(**23**)] (*E*:*Z* = 85:15) in 74% yield. Similarly, (*Z*)-(**22**) was converted into a mixture of (*E*)-(**23**) and (*Z*)-(**23**) (*E*:*Z* = 32:68) in 69% yield. The *E*:*Z* ratio was determined by HPLC and NMR analyses. These isomers were separated by preparative HPLC as described above.

(*E*)-(**23**): liquid; ν_{max} 1 250, 1 650, and 1 740 cm^{-1} (C=O); δ_H 1.26 (6 H, t, *J* 7 Hz, Me), 2.18 (3 H, s, Me), 2.74 (2 H, d, *J* 7 Hz, CH_2), 3.59 (1 H, t, *J* 7 Hz, CH), 3.68 (3 H, s, OMe), 4.20 (4 H, q, *J* 7 Hz, OCH_2), and 5.70 (1 H, s, =CH) (Found: C, 57.0; H, 7.6. $C_{13}H_{20}O_6$ requires C, 57.3; H, 7.4%).

(*Z*)-(**23**): liquid; ν_{max} 1 240, 1 650, and 1 740 cm^{-1} (C=O); δ_H 1.26 (6 H, t, *J* 7 Hz, Me), 1.91 (3 H, s, Me), 3.19 (2 H, d, *J* 7 Hz, CH_2), 3.60 (1 H, t, *J* 7 Hz, CH), 3.68 (3 H, s, OMe), 4.19 (4 H, q, *J* 7 Hz, OCH_3), and 5.76 (1 H, s, =CH).

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