The Palladium-Catalyzed Asymmetric α-Allylations of Carbonyl Compounds with Chiral Allyl Esters via Enamines and Imines[1,2]

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A novel and excellent method for asymmetric α-allylation of carbonyl compounds via their chiral enamines or imines bearing allyl esters has been developed. Readily available chiral allyl esters having chirality at the α-position of the ester carbonyl group, such as (*S*)-proline and other (*S*)-α-amino acid allyl esters, have been found to serve as good asymmetric allylating reagents in palladium-catalyzed reactions of the chiral enamines and imines derived from them. The use of (*S*)-proline or (*S*)-valine allyl esters as the amino parts in the enamines or imines provided the highest optical yields of the corresponding α-allyl carbonyl compounds. A mechanism for asymmetric induction is proposed based on the stereochemical results obtained.

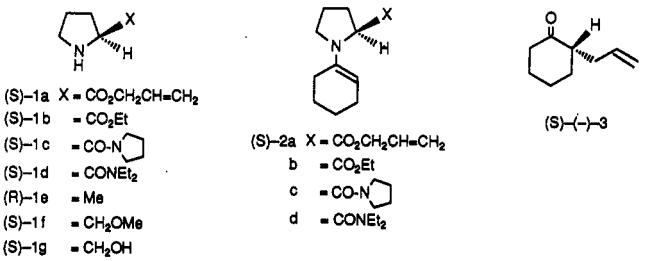
Introduction

In recent years, transition metal-catalyzed reactions[3] have made markedly rapid progress in organic synthesis and have been applied to the synthesis of many kinds of valuable, complex organic molecules such as alkaloids, terpenoids, steroids, and other natural products. Recent progress in palladium chemistry has revealed that palladium-catalyzed reactions, especially those involving π-allylpalladium complexes, are an excellent way to form new carbon–carbon bonds.[4] Upon treatment with palladium(0) catalysts, allylic acetates are transformed into π-allylpalladium complexes, which react readily with carbonucleophiles to form new carbon–carbon bonds.

In recent palladium chemistry, much interest has been focused on the stereochemistry of palladium-catalyzed allylations[5] with various kinds of chiral sources such as chiral phosphine ligands,[6] chiral allylic sulfinates,[7] and chiral allylic alcohols.[8] Previously, we developed a new method for the transfer of chirality from chiral sulfur atoms to carbons via thermal or palladium-catalyzed rearrangements of chiral allylic sulfinates to sulfones.[7] The palladium-catalyzed reactions of chiral allylic sulfinates led to facile conversion of the sulfinates into chiral allylic sulfones. This result indicates that the chirality of the π-allylpalladium complexes, determined by the starting chiral sulfinates, directed the formation of the new chiral carbon–sulfur bond in the allylic sulfones. This reaction is the first example of a palladium-catalyzed asymmetric allylation with an allylating reagent having chirality in the anionic counterpart. We now report a novel and excellent method for asymmetric allylations with chiral allyl esters.

In our recent work, we have been studying esters having chirality at the α-position of the ester carbonyl group,[2,9] such as (*S*)-proline allyl ester and other (*S*)-α-amino acid allyl esters. We chose the enamine or imine systems derived from (*S*)-proline allyl ester and other (*S*)-α-amino acid allyl esters since the conformation of the molecule must be fixed in order for the enantioselectivity in the palladium-catalyzed allylations to develop.

Chart 1



Stereochemical Results

Chiral enamine (*S*)-**2a**, derived from (*S*)-proline allyl ester (**1**) and cyclohexanone, was treated with allyl acetate in the presence of $Pd(PPh_3)_4$ (0.10 equiv) and PPh_3 (0.40 equiv) in refluxing THF, DME, benzene, or chloroform. Subsequent acidic hydrolysis (in 10% aqueous acetic acid–sodium acetate–benzene at rt) gave (*S*)-(−)-2-allylcyclohexanone (**3**)[2a,10,11b] in excellent optical yield (see Table I). In refluxing chloroform, the new asymmetric center was formed at the α-position of the ketone with high enantioselectivity (≥98% ee).

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(2) For preliminary reports of this work see (a) Hiroi, K.; Suya, K.; Sato, S. *J. Chem. Soc., Chem. Commun.* **1986**, 469. (b) Hiroi, K.; Abe, J.; Suya, K.; Sato, S. *Tetrahedron Lett.* **1989**, 1543. (c) Hiroi, K.; Abe, J. *Heterocycles* **1990**, *30*, 283. (d) Hiroi, K.; Koyama, T.; Anzai, K. *Chem. Lett.* **1990**, 235.

(3) Paerson, A. J. *Metallo-organic Chemistry*; John Wiley & Sons: New York, 1985. *Advance in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; Jai Press: London, England, 1989; Vol. I.

(4) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. Tuji, J. *Tetrahedron* **1986**, *42*, 4361. Tuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140.

(5) Hiroi, K. *Tohoku Yakka Daigaku Kenkyu Nempo* **1984**, *31*, 1.

(6) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649. Fiaud, J. C.; Hibon de Gournay, A.; Larcheveque, M.; Kagan, H. B. *J. Organomet. Chem.* **1978**, *154*, 175. Hayashi, T.; Kanehira, K.; Tuchiya, H.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1162. Yamamoto, K.; Tsuji, J. *Tetrahedron Lett.* **1982**, 3089.

(7) Hiroi, K.; Kitayama, R.; Sato, S. *J. Chem. Soc., Chem. Commun.* **1984**, 303. *Chem. Lett.* **1984**, 929. Hiroi, K.; Makino, K. *Chem. Lett.* **1986**, 617. Hiroi, K. *Yuki Gosei Kyokai Shi* **1986**, *44*, 907.

(8) Trost, B. M.; Schmuff, N. R. *Tetrahedron Lett.* **1981**, 2999. Hayashi, T.; Hagihara, T.; Koshino, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767. Hayshi, T.; Konishi, M.; Kumada, K. *J. Chem. Soc., Chem. Commun.* **1984**, 107.

(9) Hiroi, K.; Maezuru, K.; Kimura, M.; Ito, N. *Chem. Lett.* **1989**, 1751.

(10) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081.

(11) (a) Yamada, S.; Hiroi, K.; Achiwa, K. *Tetrahedron Lett.* **1969**, 4233. (b) Hiroi, K.; Achiwa, K.; Yamada, S. *Chem. Pharm. Bull.* **1972**, *20*, 246. (c) Kitamoto, M.; Hiroi, K.; Terashima, S.; Yamada, S. *Ibid.* **1974**, *22*, 459.

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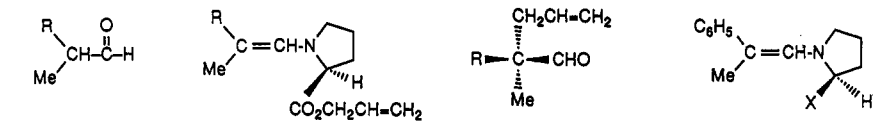
Table 1. Asymmetric Synthesis of (S)-(−)-2-Allylcyclohexanone (3) by Palladium-Catalyzed Allylation of Chiral Enamines 2a–d

enamine	allylating reagent	reaction conditions for allylation[a] solvent	reaction temp (°C)	reaction time (h)	product (S)-3 yield (%)	$[\alpha]_D$ (MeOH), deg	ee (%)[b]
2a	–	THF	66	20	40	−13.8	87
2a	–	$CHCl_3$	61	22	47	−15.8	>98
2a	–	DME	82	20	31	−12.7	80
2a	–	C_6H_6	80	17	42	−11.0	70
2a	–	CH_3CN	82	22	36	−8.4	53
2b	A	THF	66	20	48	−5.5	35
2b	A	THF	40	24	36	−6.4	41
2b	A	THF	rt	20	26	−9.6	61
2b	A	THF	0	50	32	−10.2	65
2b	A	C_6H_6	80	20	26	−2.4	15
2b	B	C_6H_6	80	16	37[c] (4)[e]	−6.3	40
2b	B	C_6H_6	80	20	46[d] (10)[e]	−4.4	28
2c	A	THF	66	20	33	−10.6	67
2d	A	THF	66	22	30	−11.0	70

[a] Enamines 2a–d were allowed to react with or without allylating reagents (A = allyl acetate, B = allyl phenyl ether) (2.0 equiv) in the presence of $Pd(PPh_3)_4$ (0.15 equiv) and PPh_3 (0.66 equiv). [b] The ee (%) was determined on the basis of the reported maximum optical rotation of (S)-(−)-3 ($[\alpha]_D$ −15.8° (MeOH)).[10] [c] Palladium(II) acetate (0.15 equiv) was used instead of $Pd(PPh_3)_4$. [d] Bis(benzonitrile)palladium(II) chloride (0.15 equiv) was used instead of $Pd(PPh_3)_4$. [e] Yields of 2,6-diallylcyclohexanone are listed in parentheses.

Chart 2



The intermolecular allylations of (S)-2b–d[11] (derived from (S)-proline ethyl ester (1b), (S)-proline pyrrolidine amide (1c), and (S)-proline diethylamide (1d), respectively) with various allylating agents were examined in the presence of palladium catalysts. The allylation of (S)-2b with allyl phenoxide was performed in refluxing benzene for 16 h in the presence of $Pd(OAc)_2$ (0.15 equiv) and PPh_3 (0.66 equiv). Subsequent acidic hydrolysis gave (S)-(−)-3 with 40% ee in 37% yield as well as 2,6-diallylcyclohexanone (4% yield).[12] When the same reaction was carried out with bis(benzonitrile)palladium(II) chloride [$Pd(C_6H_5CN)_2Cl_2$] (0.15 equiv) and PPh_3 (0.66 equiv) in refluxing benzene for 20 h, (S)-(−)-3 with 28% ee was obtained in 46% yield along with 10% of 2,6-diallylcyclohexanone.

The reaction of (S)-2b–d with allyl acetate was investigated with the $Pd(PPh_3)_4$ (0.10 equiv)–PPh_3 (0.40 equiv) catalyst in THF or benzene under various conditions, and the results are summarized in Table I. The degree of asymmetric induction increased as the temperature decreased. The reaction of enamine (S)-2d with allyl acetate catalyzed by $Pd(PPh_3)_4$–PPh_3 in refluxing THF for 20 h resulted in the highest optical yield (70%) of (S)-(−)-3.

The optical yields obtained in this palladium-catalyzed allylation were much higher than those obtained in normal alkylation with allyl halides without catalysts,[11] presumably because of the greater steric bulk of the Pd-activated allylating reagents. Furthermore, much higher asymmetric induction was observed in the allylation of chiral allyl ester enamine (S)-2a, as described earlier.

Chiral enamine (S)-5a, obtained by azeotropic dehydration of (S)-1a and 2-phenylpropanal (4a) in refluxing benzene for 4 h, was treated with $Pd(PPh_3)_4$ (0.15 equiv) in the presence of PPh_3 (0.66 equiv) in THF, DME, or benzene. Subsequent acidic hydrolysis (heated in 10% aqueous hydrochloric acid for 1 h) provided (R)-(−)-2-methyl-2-phenyl-4-pentenal (6a).[2b,13] The yields and ees of the products are summarized in Table 2. The reaction in THF at rt gave the highest optical yield (90%) of (R)-(−)-6a. The reactions of (S)-5a catalyzed by bis(di-

Table 2. Palladium-Catalyzed Allylations of Chiral Enamine (S)-5a[a]

solvent	reaction temp (°C)	reaction time (h)	(R)-(−)-6a $[\alpha]_D$ (MeOH)	ee (%)[d]	yield (%)
THF	66	19	−22.8° (c 2.8, 23 °C)	76	85
THF	40	19	−30.2° (c 1.0, 23 °C)	80	71
THF	rt	45	−34.2° (c 1.0, 21 °C)	90	43
THF	66	19	−6.6° (c 2.8, 24 °C)	17	79[b]
THF	40	19	−10.7° (c 2.9, 24 °C)	28	60[b]
THF	rt	45	−13.0° (c 2.5, 20 °C)	34	45[b]
THF	66	19	−2.4° (c 3.2, 20 °C)	6	88[b,c]
THF	40	19	−5.2° (c 1.2, 24 °C)	14	70[b,c]
THF	rt	45	−8.3° (c 1.0, 23 °C)	22	32[b,c]
C_6H_6	80	19	−25.9° (c 1.0, 22 °C)	68	50
C_6H_6	80	19	−5.8° (c 1.3, 23 °C)	15	54[b]
DME	82	19	−19.7° (c 1.3, 22 °C)	52	68
DME	66	19	−30.0° (c 1.0, 24 °C)	79	72
DME	82	19	−5.2° (c 1.2, 24 °C)	14	69[b]
toluene	110	19	−3.4° (c 1.4, 24 °C)	9	19[b]

[a] The reactions were carried out in the presence of $Pd(PPh_3)_4$ (0.2 equiv)–PPh_3 (0.4 equiv) and hydrolyzed by heating in 10% aqueous HCl–benzene for 1 h. [b] The reactions were carried out in the presence of $Pd(dba)_2$ (0.2 equiv). [c] The reactions were carried out in the presence of 1,2-bis(diphenylphosphino)ethane (0.4 equiv). [d] The ee (%) of 6a was determined by NMR spectral analysis using a shift reagent [Eu(hfc)$_3$] and from the optical rotation of optically pure (R)-(−)-6a: $[\alpha]_D$ −38.0° (MeOH).

(12) Tsuji, J.; Takahashi, H.; Morikawa, M. *Kogyo Kagaku Zasshi* **1966**, *69*, 920. Onoue, H.; Moritani, I.; Murahashi, S. *Tetrahedron Lett.* **1973**, *14*, 121. Hirao, T.; Enda, J.; Ohshiro, T.; Agawa, T. *Ibid.* **1981**, *22*, 3079.

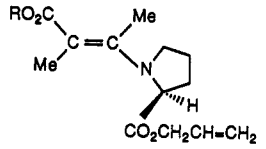
(13) (a) James, B. R.; Young, C. G. *J. Organomet. Chem.* **1985**, *285*, 321. (b) Hayashi, T.; Kayashi, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113.

Table 3. Palladium-Catalyzed Asymmetric Allylations of Chiral Aldehyde Enamines (*S*)-7a–d[a]

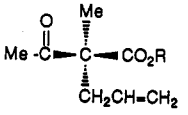
enamine 7	reaction temp (°C)	reaction time (h)	$[\alpha]_D$ (MeOH) of 6a (abs confign)	ee (%) of 6a[b]	yield (%) of 6a
7a	66	19	+1.0° (*c* 3.9, 23 °C) (*S*)	3	88
7a	40	19	+3.3° (*c* 2.8, 24 °C) (*S*)	9	80
7a	rt	45	+5.3° (*c* 2.4, 25 °C) (*S*)	15	69
7b	40	19	+2.0° (*c* 1.0, 21 °C) (*S*)	5	79
7b	rt	45	+2.6° (*c* 2.3, 21 °C) (*S*)	7	60
7c	40	19	+2.5° (*c* 2.4, 24 °C) (*S*)	7	72
7c	rt	45	+6.0° (*c* 1.3, 24 °C) (*S*)	16	62
7d	66	19	−9.5° (*c* 1.2, 23 °C) (*R*)	25	88
7d	40	19	−12.7° (*c* 1.0, 23 °C) (*R*)	33	83
7d	rt	45	−15.9° (*c* 1.1, 24 °C) (*R*)	42	67

[a] The reactions of (*S*)-7a–d with allyl acetate (2.0 equiv) were carried out in the presence of $Pd(PPh_3)_4$ (0.2 equiv)–PPh_3 (0.4 equiv) in THF followed by hydrolysis with 10% aqueous HCl–benzene for 1 h. [b] The ee of 6a was determined by NMR spectral analysis using a shift reagent [Eu(hfc)$_3$] and calculated on the basis of the optical rotation of optically pure (*S*)-(+)-6a: $[\alpha]_D$ +38.0° (MeOH).

Chart 3



(S)-8a R = Et
b = t-Bu



(S)-(−)-9a R = Et
b = t-Bu

benzylideneacetone)palladium [Pd(dba)$_2$] were much less enantioselective than those catalyzed by the $Pd(PPh_3)_4$–PPh_3 catalyst (see Table II).

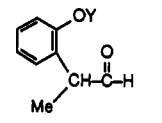
The absolute configuration of the newly created asymmetric carbon was determined by chemical correlation of aldehyde (*R*)-(−)-6a to (*R*)-(−)-2-methyl-2-phenylpentanoic acid of known absolute configuration[14] by a sequence involving reduction of (−)-6a with diimide followed by oxidation with chromic acid. The ee of (*R*)-(−)-6a was confirmed by NMR spectral analysis with a shift reagent [tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III), Eu(hfc)$_3$]. A sample of chiral aldehyde (*R*)-(−)-6a having an optical rotation of $[\alpha]_D$ −18.3° (MeOH) was determined to exhibit 48% ee from the NMR with the shift reagent. Therefore, optically pure (*R*)-(−)-6a was calculated to have an optical rotation of $[\alpha]_D$ −38.0° (MeOH), and the ee of aldehyde 6a produced under other reaction conditions was based on this value (see Table II). Chiral aldehyde (*R*)-(−)-6a ($[\alpha]_D$ − 18.3° (MeOH)) showed an optical rotation of $[\alpha]_D$ −33.8° in a chloroform solution, which is consistent with the value reported previously.[13b]

Allylations of other chiral enamines (*S*)-7a–c (derived from (*S*)-proline ethyl ester (1b), (*R*)-2-methylpyrrolidine (1e), and (*S*)-2-(methoxymethyl)pyrrolidine (1f), respectively) were carried out in THF at rt with the same palladium catalyst and allyl acetate to give (*S*)-(+)-6a with an absolute configuration opposite that obtained from the (*S*)-proline allyl ester enamine, as expected, with lower ee. In particular, the palladium-catalyzed reaction of the (*S*)-prolinol enamine 7d with allyl acetate gave an 84% yield of (*R*)-(−)-6a with 42% ee. The results are summarized in Table III.

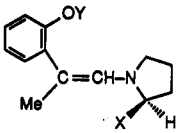
The reactions of chiral aldehyde–enamines (*S*)-5b,c, derived from (*S*)-1a and 4b,c, produced optically active

(14) Calas, M.; Calas, B.; Giral, L. *Bull. Soc. Chim. Fr.* **1976**, 857.

Chart 4

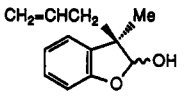


10a Y = H
b = $CH_2CH{=}CH_2$
c = $CO_2CH_2CH{=}CH_2$

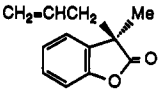


(S)-11a Y = H
b = $CH_2CH{=}CH_2$
c = $CO_2CH_2CH{=}CH_2$
d = H
e = H
f = $CH_2CH{=}CH_2$

X = CO_2Et
= CO_2Et
= CO_2Et
= $CO_2CH_2CH{=}CH_2$
= CH_2PPh_2
= CH_2PPh_2



(R)-12



(R)-(+)-13

α-allyl aldehydes (*R*)-(+)-2-[(4-*tert*-butylphenyl)methyl]-2-methyl-4-pentenal (6b, 91% ee) and (*S*)-(−)-2-ethyl-2-methyl-4-pentenal (6c, 57% ee), respectively. The results are summarized in Table IV. The absolute configuration of the new chiral centers was deduced on the basis of the mechanistic pathway that will be described later.

This method was applied to the asymmetric allylation of a β-keto ester. The palladium-catalyzed reactions of chiral enamines (*S*)-8a,b (derived from ethyl and *tert*-butyl 2-methylacetoacetate, respectively, and (*S*)-1a) with allyl acetate were carried out in the presence of $Pd(PPh_3)_4$ and PPh_3 under the conditions listed in Table V and yielded ethyl and *tert*-butyl (*S*)-(−)-2-allyl-2-methylacetoacetate (9a[15] and 9b). The highest optical yield (84%) was observed upon treatment of (*S*)-8b with $Pd(PPh_3)_4$ in THF at rt.

In addition to the (*S*)-proline allyl ester enamine method, we have studied the allylation of chiral enamines that incorporate the allylating functionality at the ortho-position of the phenyl group in 4a.[2c]

Upon treatment with $Pd(PPh_3)_4$ or $Pd(dba)_2$–PPh_3 in THF at 40 °C or 66 °C for 19 h, chiral enamines (*S*)-11b,c underwent an intramolecular allylation to give α-allyl hemiacetal 12, oxidation of which with chromic acid produced optically active lactone (*S*)-(−)-13 with 14–48% ee. The intermolecular asymmetric allylation provided slightly lower enantioselectivity; the palladium-catalyzed reaction of (*S*)-11a, derived from (*S*)-1b and 10a, with allyl acetate in THF at 40 °C or 66 °C for 19 h, followed by hydrolysis and oxidation, gave (*S*)-(−)-13 with 28 or 10% ee, respectively. However, the intramolecular allylation of (*S*)-proline allyl ester enamine 11d, derived from (*S*)-1a and 10a, demonstrated a higher enantioselectivity. The palladium-catalyzed reaction of (*S*)-11d at rt, 40 °C or 66 °C, followed by hydrolysis and oxidation, produced (*R*)-(+)-13 in a good yield with 84, 43, or 23% ee, respectively. Similarly, chiral enamine (*S*)-11e, derived from (*S*)-2-[(diphenylphosphino)methyl]pyrrolidine (possessing a phosphine ligand at the chiral site),[1,16] provided (*R*)-(+)-13 with 29, 18, or 6% ee upon treatment with allyl acetate in THF at rt, 40 °C, or 60 °C, respectively, in the presence of $Pd(PPh_3)_4$ (after hydrolysis and oxidation). The palladium-catalyzed reaction of (*S*)-11f by means of the same process gave (*R*)-(+)-13 with slightly higher ee.

(15) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718.
(16) Hiroi, K.; Abe, J. *Tetrahedron Lett.* **1990**, *31*, 3623. *Chem. Pharm. Bull.* **1991**, *39*, 616.

Table 4. Palladium-Catalyzed Asymmetric Allylation of (*S*)-Proline Allyl Ester Aldehyde Enamines (*S*)-5b,c[a]

enamine 5	reaction temp (°C)	reaction time (h)	product	$[\alpha]_D$ (MeOH) of 6b,c	ee (%) of 6b,c[b]	yield (%) of 6b,c[c]
5b	66	19	(*R*)-**6b**	+1.7° (*c* 3.0, 25 °C)	31	39 (83)
5b	40	19	(*R*)-**6b**	+4.2° (*c* 3.0, 26 °C)	46	46 (71)
5b	rt	45	(*R*)-**6b**	+5.0° (*c* 1.2, 27 °C)	91	26 (86)
5c	66	19	(*S*)-**6c**	−4.3° (*c* 1.2, 26 °C)	19	42 (82)
5c	40	19	(*S*)-**6c**	−8.1° (*c* 2.1, 25 °C)	37	25 (88)
5c	rt	45	(*S*)-**6c**	−12.6° (*c* 1.0, 25 °C)	57	21 (84)

[a] The reactions were carried out in the presence of $Pd(PPh_3)_4$ (0.2 equiv)–PPh_3 (0.4 equiv) in THF followed by hydrolysis with 10% aqueous HCl–benzene for 1 h. [b] The ees of **6b,c** were determined by NMR spectral analysis using a shift reagent [Eu(hfc)$_3$] and calculated on the basis of the optical rotation of optically pure (*R*)-(+)-**6b**: $[\alpha]_D$ +5.5° (MeOH), (*S*)-(−)-**6c**: $[\alpha]_D$ −22.1° (MeOH). [c] The corrected yields based on the recovered starting materials are listed in parentheses.

Table 5. Palladium-Catalyzed Asymmetric Allylation of (*S*)-8a,b[a]

enamine 8	solvent	reaction temp (°C)	reaction time (h)	$[\alpha]_D$ ($CHCl_3$)	(*S*)-(−)-**9** ee (%)[b]	yield (%)
8a	THF	66	19	−4.7° (*c* 1.9, 28 °C)	21	79
8a	THF	40	19	−12.8° (*c* 1.3, 25 °C)	43	64
8a	THF	rt	45	−18.7° (*c* 1.5, 25 °C)	66	45
8a	DME	82	19	−3.0° (*c* 1.4, 23 °C)	10	84
8a	C_6H_6	80	19	−2.5° (*c* 1.0, 22 °C)	8	79
8a	$CHCl_3$	63	19	−3.8° (*c* 1.3, 22 °C)	13	69
8a	CH_3CN	82	19	−3.2° (*c* 2.1, 24 °C)	11	72
8b	THF	66	19	−10.9° (*c* 1.2, 24 °C)	48	72
8b	THF	40	19	−16.3° (*c* 1.0, 20 °C)	72	49
8b	THF	rt	45	−19.1° (*c* 1.5, 25 °C)	84	26
8b	DME	82	19	−8.4° (*c* 1.4, 24 °C)	37	82
8b	C_6H_6	80	19	−7.7° (*c* 1.2, 23 °C)	34	74
8b	$CHCl_3$	63	19	−10.2° (*c* 1.2, 23 °C)	45	68
8b	CH_3CN	82	19	−7.3° (*c* 2.1, 24 °C)	32	81

[a] The reactions were carried out in the presence of $Pd(PPh_3)_4$ (0.2 equiv)–PPh_3 (0.4 equiv). [b] Calculated on the basis of the optical rotation of optically pure (*S*)-(−)-**8a**: $[\alpha]_D$ −29.7° ($CHCl_3$), and (*S*)-(−)-**8b**: $[\alpha]_D$ −22.7° ($CHCl_3$).

Table 6. Palladium-Catalyzed Asymmetric Allylation of (*S*)-11a–f[a]

enamine 11	reaction temp (°C)	reaction time (h)	$[\alpha]_D$ (MeOH) of 13	ee (%) of 13[d]	yield (%) of 13
11a	66	19	−1.4° (c 1.0, 18 °C)	10	77[b]
11a	40	19	−4.0° (c 1.1, 27 °C)	28	49[b]
11b	66	19	−2.6° (c 3.5, 28 °C)	18	49
11b	40	19	−4.5° (c 20, 28 °C)	31	37
11c	66	19	−3.8° (c 0.8, 28 °C)	27	80
11c	40	19	−5.0° (c 1.2, 28 °C)	35	63
11c	rt	45	−6.8° (c 1.2, 27 °C)	48	40
11d	66	19	+3.3° (c 1.6, 28 °C)	23	69
11d	40	19	+6.0° (c 1.5, 27 °C)	43	50
11d	rt	45	+11.0° (c 1.0, 28 °C)	84	30
11e	66	19	+0.8° (c 1.0, 20 °C)	6	35[b,c]
11e	40	19	+2.5° (c 1.3, 20 °C)	18	31[b,c]
11e	rt	45	+4.1° (c 1.7, 17 °C)	29	27[b,c]
11f	66	19	+1.4° (c 2.1, 29 °C)	10	47[c]
11f	40	19	+4.0° (c 0.8, 27 °C)	28	24[c]

[a] The reactions were carried out in THF in the presence of $Pd(PPh_3)_4$ (0.2 equiv)–PPh_3 (0.4 equiv). [b] Allyl acetate (2.0 equiv) was used as an allylating reagent. [c] The reactions were carried out without PPh_3. [d] The ee of **13** was determined by NMR spectral analysis with a shift reagent [Eu(hfc)$_3$] and calculated on the basis of the optical rotation of optically pure (*R*)-(−)-**13**: $[\alpha]_D$ −14.1° (MeOH).

These results are summarized in Table VI. The absolute configuration of **13** was deduced on the basis of the mechanistic pathways of the reactions of (*S*)-**11a,d**, which are similar to those of (*S*)-**5a** and (*S*)-**7a**, which will be described later.

This method was applicable to chiral imine systems derived from optically active α-amino acid allyl esters.[2d] Chiral imines (*S*)-**16a–e** were obtained quantitatively by azeotropic dehydration of 2-(*p*-toluenesulfenyl)cyclohexanone (**15**) and (*S*)-α-amino acid allyl esters **14a–e** in refluxing benzene for 6 h with a Dean–Stark apparatus.

Treatment of the imines (*S*)-**16a–e** with $Pd(PPh_3)_4$–PPh_3 in THF, DME, or benzene and subsequent hydrolysis with 10% aqueous hydrochloric acid (refluxed for 1.5 h) produced (*R*)-(+)-2-allyl-2-(*p*-toluenesulfenyl)cyclohexanone (**17**) with high ee in good yields. The reaction conditions and the results are summarized in Table VII. Among the chiral α-amino acid allyl esters examined, (*S*)-valine allyl ester (**14d**) gave the highest optical yield (87%) of (*R*)-(+)-**17**.

Table 7. Palladium-Catalyzed Asymmetric Allylations of Chiral Imines (*S*)-16a–e and 18a–e[a]

imines 16 or 18	product	$[\alpha]_D$ (MeOH), deg	product ee (%)[b]	yield (%)[c]
16a	(*R*)-**17**	+104.1	41	23 (85)
16b	(*R*)-**17**	+165.7	65	26 (85)
16c	(*R*)-**17**	+96.4	38	38 (79)
16d	(*R*)-**17**	+223.2	87	27 (81)
16e	(*R*)-**17**	+195.6	77	31 (80)
18a	(*R*)-**6a**	−5.4	14	33 (80)
18b	(*R*)-**6a**	−23.4	62	29 (77)
18c	(*R*)-**6a**	−19.4	51	38 (85)
18d	(*R*)-**6a**	−37.5	99	30 (82)
18e	(*R*)-**6a**	−30.9	82	26 (89)

[a] The imines (*S*)-**16a–e** and **18a–e** were treated with $Pd(PPh_3)_4$ (0.15 equiv)–PPh_3 (0.66 equiv) in refluxing THF for 18 h, followed by refluxing in 10% aqueous HCl–benzene for 1–1.5 h, to afford (*R*)-(+)-**17** and (*R*)-(−)-**6a**. [b] The ee was determined by NMR spectral analysis using a shift reagent [Eu(hfc)$_3$] and calculated on the basis of the optical rotation of optically pure (*R*)-(+)-**17**: $[\alpha]_D$ +255.4° (EtOH), and (*R*)-(−)-**6a**: $[\alpha]_D$ −38.0° (MeOH). [c] The corrected yields based on the recovered starting materials are listed in parentheses.

The optical yields of product **17** were calculated by NMR spectral analysis with a shift reagent [Eu(hfc)$_3$]. The absolute configuration of the newly created chiral carbon in **17** was determined by applying the Octant rule in the circular dichroism spectrum.

The palladium-catalyzed reactions of chiral imines (*S*)-**18a–e**, prepared from **4a** and (*S*)-**14a–e**, were carried out in refluxing THF for 18 h in the presence of $Pd(PPh_3)_4$ and PPh_3. Subsequent acidic hydrolysis gave (*R*)-(−)-**6a** in good yields. The results are summarized in Table VII.

Chart 5

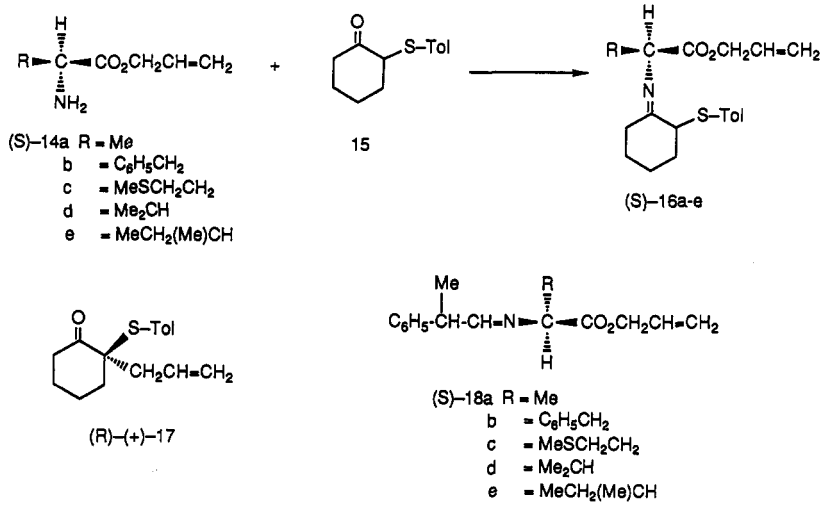
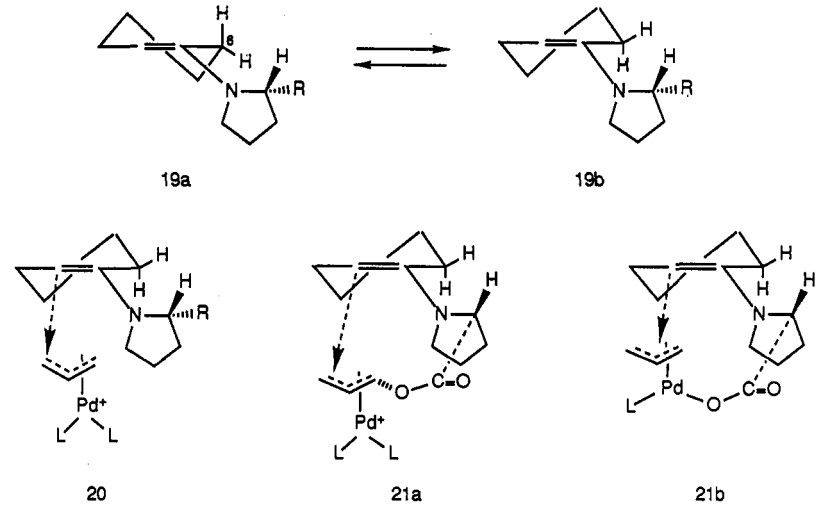


Chart 6



It should be pointed out that an excellent optical yield (99%) was observed in the case of (*S*)-valine allyl ester imine (*S*)-**18d**.

Based on the stereochemical results obtained, plausible mechanisms for these palladium-catalyzed asymmetric allylations are presented. From the standpoint of the conformational analyses of the cyclohexanone enamines, conformer **19b** would be preferred to **19a** because of the existence of the $A^{1,3}$ strain between the chiral part (*R*) and the equatorial hydrogen at **6c** in **19a**.[11b] Therefore, in the palladium-catalyzed reactions of chiral enamines (*S*)-**2b–d** with allyl acetate, axial allylation of **19b** by the π-allylpalladium complex would occur preferentially, as depicted in **20**, to furnish (*S*)-**3**.

In the case of the (*S*)-proline allyl ester enamine ((*S*)-**2a**), the intramolecular allylation via transition state **21** would occur to give (*S*)-**3**. This stereochemical control provided by the intramolecular allyl ester in (*S*)-**2a** resulted in a higher enantioselectivity for **2a** than for (*S*)-**2b–d**. In order to determine the bases of the regiochemical discrimination between the α- and γ-carbons of the allyl group in (*S*)-**2a**, we studied the palladium-catalyzed reaction of chiral enamine (*S*)-**27**, derived from (*S*)-proline, 1,1-dideuterioallyl ester (**26b**). Deuterated allyl ester (*S*)-**26b** was prepared as follows. Michael adduct **22** of phenylselenenyl anion and methyl acrylate was reduced with lithium aluminum deuteride to give 3-(phenylselenenyl)-1,1-dideuteriopropanol (**23**). Esterification of (*S*)-*N*-(*tert*-butoxycarbonyl)proline (**24**) with **23** followed by oxidative elimination of the selenyl group in (*S*)-**25** and debutoxycarbonylation of (*S*)-**26a** with TFA produced (*S*)-**26b**. The palladium-catalyzed reaction of chiral enamine (*S*)-**27** gave a 1:1 mixture of (*S*)-**28a** and (*S*)-**28b**. Thus, the α- and γ-carbons of the allyl group in (*S*)-**2a** could not be discriminated in the palladium-catalyzed reactions. This lack of discrimination means that the α- and γ-carbons of the allyl group are chemically equivalent in the palladium-catalyzed reaction, and, therefore, that the reaction proceeds via chiral π-allylpalladium complex **21b** rather than **21a**.

Allylation of the β-carbons of enamines (*S*)-**7a–c** by the Pd-activated allylating species would occur from the back side of the chiral centers in enamine **29c**, which is the most preferred conformer in the conformational equilibriums of **29a–c** (**29b,c** are preferred over **29a** because of the severe steric interaction between the amino moieties and the phenyl group (R^1) in **29a**) because the steric interaction between the chiral part and the methyl group in **29b** is more severe than that with the hydrogen atom (R^2) in **29c**.

In (*S*)-proline allyl ester enamines (*S*)-**5a–c** and (*S*)-**8a,b**, however, intramolecular allylation via transition state **30** would occur to give (*R*)-**6a,b**, (*S*)-**6c**, and (*S*)-**9a,b**.

It should also be noted that the palladium-catalyzed

Chart 7

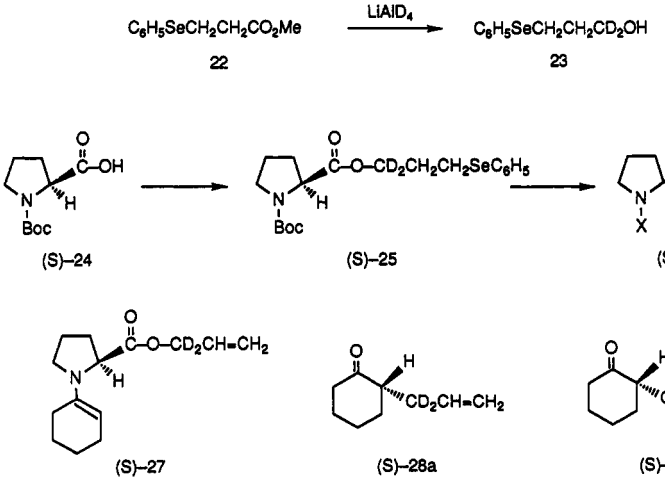


Chart 8

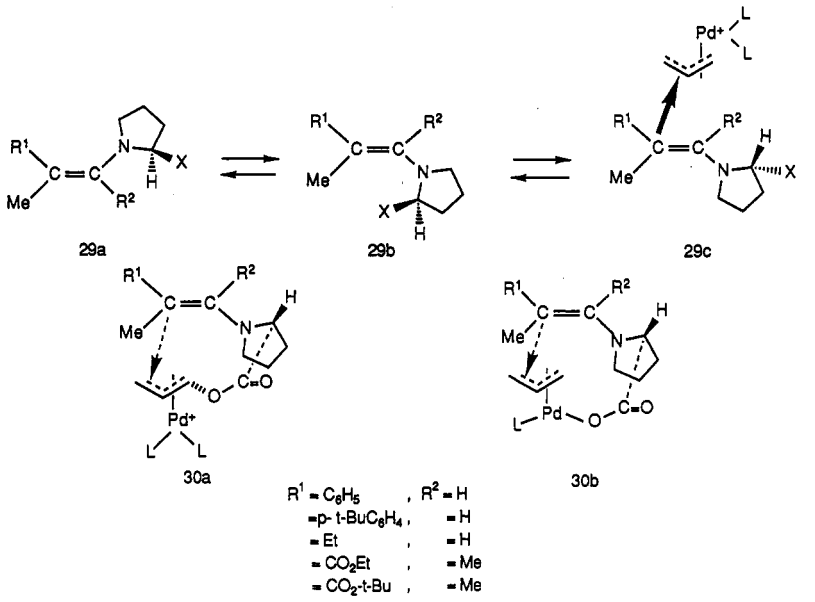


Table 8. Palladium-Catalyzed Allylation of (*S*)-Proline 1,1-Dideuterioallyl Ester Enamine[a]

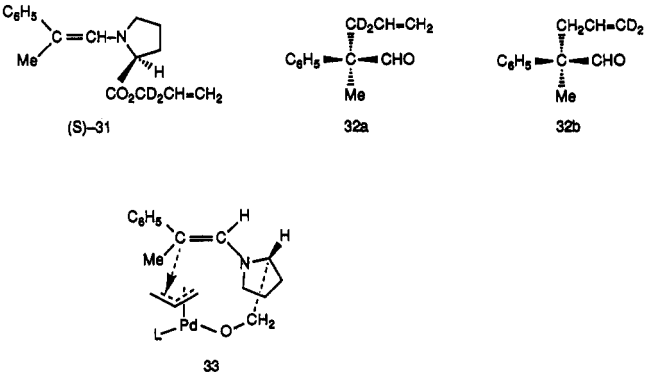
enamine	reaction temp (°C)	reaction time (h)	product	yield (%)
(*S*)-**27**	66	19	(*S*)-**28**	47
(*S*)-**31**	66	19	(*S*)-**32**	57
(*S*)-**31**	40	19	(*S*)-**32**	48
(*S*)-**31**	rt	45	(*S*)-**32**	35

[a] The enamine (*S*)-**27** or (*S*)-**31** was treated with $Pd(PPh_3)_4$ (0.1 equiv)–PPh_3 (0.4 equiv) in THF under the conditions listed in this table. Subsequent hydrolysis with AcONa–AcOH–H_2O–benzene (for (*S*)-**27** or 10% aqueous HCl–benzene (for (*S*)-**31**) gave a 1:1 mixture of (*S*)-**28a** and **28b**, or (*S*)-**32a** and **32b**. The product ratios were calculated by the NMR analysis of the products.

reaction of chiral enamine (*S*)-**31**, obtained from **4a** and (*S*)-**26b**, afforded a 1:1 mixture of **32a** and **32b**. Therefore, in the same way described earlier for the cyclohexanone enamine system ((*S*)-**2a**), the palladium-catalyzed reaction of the (*S*)-proline allyl ester enamines would proceed through transition state **30b**, involving coordination of the palladium catalyst with the carboxylate, rather than **30a**.

The reaction of (*S*)-prolinol enamine (*S*)-**7d** with allyl acetate would occur (presumably by an intramolecular-like allylation mechanism) via transition state **33**, in which

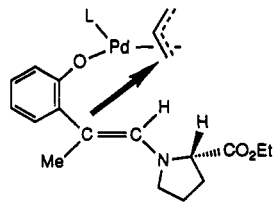
Chart 9



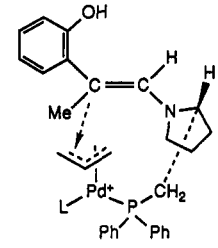
the palladium catalyst is coordinated with the oxygen atom of the hydroxy group in (*S*)-**7d**, to yield (*R*)-(−)-**6a** with the same absolute configuration as **6a** obtained from (*S*)-**5a**.

Rather low optical yields were observed in the palladium-catalyzed reactions of (*S*)-**11a–f**. The palladium-catalyzed allylation of (*S*)-**11b,c** would presumably occur intramolecularly from the back side of the ester group via π-allylpalladium complex **34**, in which the Pd is coordinated with the oxygen atom of the phenol part. This mode

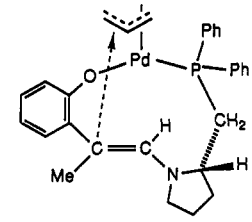
Chart 10



34

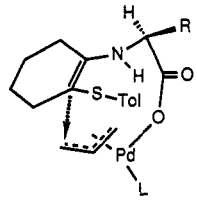


35

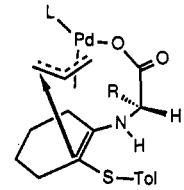


36

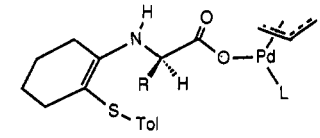
Chart 11



37a



37b



37c

of attack resulted in a slight increase in the degree of asymmetric induction for (*S*)-**13** compared with that obtained from the intermolecular reaction of (*S*)-**11a**. On the other hand, intramolecular allylation of (*S*)-**11d** from the direction of the ester group gave (*R*)-**13** with a higher optical yield. Similarly, the reactions of enamines (*S*)-**11e,f** proceeded through intermediary π-allylpalladium complexes **35** and **36**, in which the Pd was coordinated intramolecularly with the phosphine ligand in the chiral amino part, to afford (*R*)-**13**.[16]

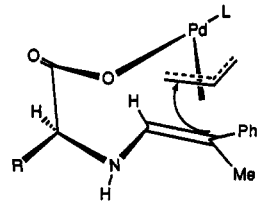
The mechanism for asymmetric allylation of chiral imines is presented as follows. Upon treatment with palladium catalysts, imine (*S*)-**16** undergoes intramolecular allylation via enamine **37**, which bears the π-allylpalladium carboxylate function. The conformationally stable enamine generated from (*S*)-**16** has a *syn*-configuration between the nitrogen–hydrogen bond and the *p*-toluenesulfenyl group, as depicted in **37a,b**, since the other conformational isomer, **37c**, has a rather severe steric interaction between the *p*-toluenesulfenyl group and the alkyl part of the amino acid. However, conformational isomer **37b** also has a severe steric interaction between the cyclohexane ring and the alkyl (R) group. Therefore, the allylation would occur preferentially via the conformationally most stable intermediate, **37a**, from the re face, giving (*R*)-(+)-**17** with high optical yields. The stereochemistry in the allylation of the aldehyde-imine (*S*)-**18** can be rationalized in a similar way.

Of the two intermediate π-allylpalladium carboxylates **38a** and **38b** of the stable (*E*)-enamine generated from imine (*S*)-**18** (the amino group is *anti* to the phenyl group and the nitrogen–hydrogen bond is *syn* to the methyl substituent), **38a** would be preferable to **38b** because of the existence of a severe steric interaction between the substituent R and the olefinic hydrogen atom of the enamine part in **38b**. Therefore, the allylation would occur preferentially via **38a** to give (*R*)-(−)-**6a** with high optical yield.

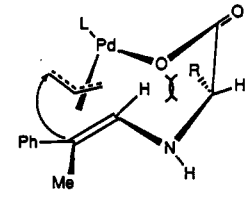
Conclusions

As discussed above, chiral allyl esters are readily available and potentially useful reagents for palladium-catalyzed asymmetric allylations. The palladium-catalyzed reactions of chiral enamines and imines derived from (*S*)-proline allyl ester and (*S*)-valine allyl ester demonstrate extremely good potential for asymmetric α-allylations of carbonyl compounds.

Chart 12



38a



38b

The use of chiral allyl esters in palladium-catalyzed reactions of enamines and imines allows an intramolecular allylation via π-allylpalladium complexes coordinated with the carboxylates originating from the chiral allyl esters to provide high enantioselectivity. Intermolecular, direct allylations of the chiral enamines with allylating reagents produced α-allyl carbonyl compounds of the opposite absolute configuration with slightly lower ee. Therefore, we can control the stereochemistry of the product by selecting the (*S*)-proline allyl ester enamine systems or other chiral enamines.

Furthermore, we can predict the stereochemistry of the products from the mechanistic pathway, depending on the chiral model used. Thus, this novel method provides a simple and highly efficient entry into synthetically valuable optically active α-allyl carbonyl compounds.

Experimental Section

Melting points are uncorrected. Thin-layer and preparative thick-layer plates (preparative TLC) were made of Merck Silica gel 60 PF-254 activated by drying at 140 °C for 3.5 h. Columns for flash chromatography were made of Merck Silica gel 60. Infrared (IR) spectra were determined in the indicated solvent at 270 MHz with TMS as an internal standard. Electron impact mass spectra were obtained at an ionization voltage of 70 eV. Optical rotations were measured at 589 nm in a 1-mL cell at 25 °C.

Synthesis of Chiral Amino Acid Allyl Ester. General Procedure. A catalytic amount of concentrated sulfuric acid was added to a solution of amino acid ((*S*)-proline, (*S*)-alanine, (*S*)-phenylalanine, (*S*)-methionine, (*S*)-valine, or (*S*)-isoleucine) (0.023 mol) in 14 mL of allyl alcohol at 0 °C. The reaction mixture was refluxed for 18 h and then concentrated *in vacuo*. The residual oil was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with saturated aqueous NaCl and saturated aqueous $NaHCO_3$, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to distillation under reduced pressure to give an α-amino acid allyl ester.

(*S*)-Proline Allyl Ester (1a): bp 120 °C (4 Torr); 64% yield; $[\alpha]_D$ −38.3° (*c* 3.1, $CHCl_3$); IR 1745 (C=O), 1645 (C=C); ^1H NMR ($CDCl_3$) δ 1.61–2.09 (4H, m), 2.77–3.03 (2H, m), 3.67–3.72 (2H, m), 4.51–4.54 (2H, *J* = 6 Hz), 5.12–5.26 (2H, m), 5.75–5.90 (1H, m). (*S*)-*N*-Acetylproline Allyl Ester: MS *m/z* 197 (M^+); HRMS 197.1078 (calcd for $C_{10}H_{15}O_3N$: 197.1052).

(*S*)-Alanine Allyl Ester (14a): bp 100 °C (7 Torr); 31% yield; $[\alpha]_D$ +1.6° (*c* 3.7, $CHCl_3$); IR 1720 (C=O), 1625 (C=C); ^1H NMR ($CDCl_3$) δ 1.13–1.69 (5H, m), 3.54–3.62 (1H, m), 4.60–4.63 (2H, m), 5.22–5.36 (2H, m), 5.91–6.00 (1H, m); MS *m/z* 129 (M^+); HRMS 129.0788 (calcd for $C_6H_{11}O_2N$: 129.0790).

(*S*)-Phenylalanine Allyl Ester (14b): bp 120 °C (8 Torr); 44% yield; $[\alpha]_D$ −1.0° (*c* 5.0, $CHCl_3$); IR 1740 (C=O), 1610 (aromatic); ^1H NMR ($CDCl_3$) δ 1.54 (2H, s), 2.84–3.13 (2H, m), 3.73–3.77 (1H, m), 4.60–4.62 (2H, m), 5.21–5.34 (2H, m), 5.81–5.96 (1H, m), 7.16–7.33 (5H, m); MS *m/z* 205 (M^+); HRMS 205.1094 (calcd for $C_{12}H_{15}O_2N$: 205.1102).

(*S*)-Methionine Allyl Ester (14c): bp 135 °C (8 Torr); 42% yield; $[\alpha]_D$ −3.0° (*c* 7.4, $CHCl_3$); IR 1730 (C=O), 1640 (C=C), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.55 (2H, s), 1.74–2.04 (2H, m), 2.08 (3H, s), 2.57–2.63 (2H, m), 3.56–3.61 (1H, q), 4.60–4.61 (2H, m), 5.20–5.34 (2H, m), 5.82–5.95 (1H, m); MS *m/z* 189 (M^+); HRMS 189.0807 (calcd for $C_8H_{15}O_2NS$: 189.0823).

(*S*)-Valine Allyl Ester (14d): bp 130 °C (5 Torr); 42% yield; $[\alpha]_D$ +21.3° (*c* 5.1, $CHCl_3$); IR 1730 (C=O), 1640 (C=C), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 0.88–0.98 (6H, m), 1.51 (2H, s), 1.97–2.09 (1H, m), 3.29–3.31 (1H, m), 4.59–4.62 (2H, m), 5.21–5.36 (2H, m), 5.84–5.98 (1H, m); MS *m/z* 158 (M^+); HRMS 158.1164 (calcd for $C_8H_{16}O_2N$: 158.1181).

(*S*)-Isoleucine Allyl Ester (14e): bp 120 °C (8 Torr); 58% yield; $[\alpha]_D$ +24.1° (*c* 4.4, $CHCl_3$); IR 1730 (C=O), 1640 (C=C); ^1H NMR ($CDCl_3$) δ 0.87–0.95 (6H, m), 1.14–1.50 (2H, m), 1.53 (2H, s), 1.73–1.77 (1H, m), 3.35–3.37 (1H, d), 4.59–4.63 (2H, m), 5.21–5.36 (2H, m), 5.84–5.97 (1H, m); MS *m/z* 171 (M^+); HRMS 171.1261 (calcd for $C_9H_{17}O_2N$: 171.1260).

Palladium-Catalyzed Allylation of Chiral Enamines. General Procedure for Palladium-Catalyzed Reactions of (*S*)-Proline Allyl Ester Enamines. A solution of (*S*)-**1a** (50 mg, 0.322 mmol) and a ketone (cyclohexanone or ethyl and *tert*-butyl 2-methylacetoacetate) (0.322 mmol)[1,16] or an aldehyde (2-phenylpropanal (**4a**), 3-(4-*tert*-butylphenyl)isobutanal (**4b**), 2-methylbutanal (**4c**), or 2-(2-hydroxyphenyl)propanal (**10a**)) in 10 mL of benzene was refluxed for 4 h with a Dean–Stark apparatus. The solution was concentrated *in vacuo* to give the corresponding aldehyde- or keto-enamine.

A mixture of the enamine (0.322 mmol) obtained above in 10 mL of solvent was stirred under N_2 in the presence of $Pd(PPh_3)_4$ (0.10–0.20 equiv), $Pd(OAc)_2$, or $Pd(C_6H_5CN)_2Cl$ (0.15 equiv) and PPh_3 (0.40 or 0.66 equiv) or (diphenylphosphino)ethane at the indicated temperature for the time described in Tables I, II, and IV–VI. The reaction mixture was treated with 10% aqueous HCl (2.5 mL)–benzene (2.5 mL) under reflux for 1 h (for **5a–c** or **11d**) or with AcONa (496 mg)–AcOH (1.2 mL)–H_2O (6.0 mL)–benzene (7.0 mL) at rt for 1 h (for **2a** or **8a,b**). The reaction mixture was diluted with ether. The ethereal solution was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC to give the corresponding α-allyl carbonyl compound: (*S*)-(−)-2-allylcyclohexanone (**3**) (ether–hexane, 1:5),[11b] ethyl or *tert*-butyl (*S*)-(−)-2-allyl-2-methylacetatoacetate (**9a**) (ether–hexane, 1:5)[15] or (**9b**) (ether–hexane, 1:3),[1] (*R*)-(−)-2-methyl-2-phenyl-4-pentenal (**6a**) (benzene–hexane, 1:2), (*R*)-(+)-2-[(4-*tert*-butylphenyl)methyl]-2-methyl-4-pentenal (**6b**) (isopropyl ether–hexane, 1:3),[1] (*S*)-(−)-2-methyl-2-ethyl-4-pentenal (**6c**) (isopropyl ether–hexane, 1:5).[1] The yields, the optical rotations, and the ees of the products are summarized in Table I, II, and IV–VI.

(*R*)-(−)-6a: IR 1725 (CHO), 1645 (C=C), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.44 (3H, s), 2.63–2.68 (2H, m, *J* = 6 Hz), 5.00–5.09 (2H, m), 5.47–5.62 (1H, m), 7.23–7.41 (5H, m), 9.52 (1H, s); MS *m/z* 174 (M^+); HRMS 174.1061 (calcd for $C_{12}H_{14}O$: 174.1045).

(*S*)-(−)-9b: IR 1745, 1725 (C=O); ^1H NMR ($CDCl_3$) δ 1.16 (3H, s), 1.38 (9H, s), 2.07 (3H, s), 2.31–2.56 (2H, m, *J* = 4 Hz), 4.94–5.06 (2H, m), 5.44–5.66 (1H, m); MS *m/z* 212 (M^+); HRMS 212.1445 (calcd for $C_{12}H_{20}O_3$: 212.1431).

General Procedure for Palladium-Catalyzed Allylations of Chiral Enamines (*S*)-2a–d or (*S*)-7a–d with Allyl Acetate or Phenoxide. A solution of cyclohexanone (44 mg, 0.447 mmol) or **4a** (60 mg, 0.447 mmol) and a chiral amine ((*S*)-proline ethyl ester (**1b**),[17] (*S*)-proline pyrrolidine amide (**1c**),[17] (*S*)-proline diethylamide (**1d**),[17] (*S*)-2-methylpyrrolidine (**1e**),[18] (*S*)-2-(methoxymethyl)pyrrolidine (**1f**),[19] or (*S*)-prolinol (**1g**)[20]) (0.447 mmol) in 10 mL of benzene was refluxed for 4 h with a Dean–Stark apparatus. The solution was concentrated *in vacuo* to give the corresponding keto- or aldehyde-enamine ((*S*)-**2a–d** or (*S*)-**7a–d**). A mixture of the enamine ((*S*)-**2a–d** or (*S*)-**7a–d**) (0.447 mmol) obtained above and allyl acetate or allyl phenoxide (2.0 equiv) in 10 mL of THF was stirred under N_2 in the presence of $Pd(PPh_3)_4$ (163 mg, 0.090 mmol) and PPh_3 (47 mg, 0.179 mmol) at the indicated temperature for the time shown in Table III. The reaction mixture was treated with 10% aqueous HCl (2.5 mL)–benzene (2.5 mL) under reflux for 1 h. The reaction mixture was diluted with ether. The ethereal solution was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC to give (*S*)-**3** (ether–hexane, 1:5) or (*R*)-(−)- or (*S*)-(+)-**6a** (benzene–hexane, 1:2). The yields, the optical rotations, and the ees of the products are summarized in Table III.

Chemical Correlation of (−)-6a with (*R*)-(−)-2-Methyl-2-phenylpentanoic Acid. Hydrazine monohydrate (955 mg, 19.080 mmol) was added to a solution of (−)-**6a** (83 mg, 0.477 mmol, $[\alpha]_D$ −13.5° (*c* 2.2, MeOH) in 2 mL of dioxane at rt, and then saturated aqueous $CuSO_4$ (0.1 mL) and acetic acid (0.1 mL) were added. A suspension of sodium metaperiodate (1.0 g, 4.770 mmol) in 2 mL of H_2O was added to the reaction mixture at 0 °C, and the resulting mixture was stirred at rt for 19 h. The reaction mixture was diluted with ether. The ethereal solution was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo* to give 2-methyl-2-phenylpentanol (474 mg) [IR 3450 (OH), 1600 (aromatic)].

Jones reagent (0.5 mL) was added to a solution of the 2-methyl-2-phenylpentanol obtained above in 2 mL of acetone at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then quenched with isopropyl alcohol. The reaction mixture was concentrated *in vacuo*, and ether was added to the residue. The suspension was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The aqueous layers were combined and acidified with concentrated HCl. The acidic aqueous layer was extracted with ether. The ethereal solution was washed with saturated aqueous NaCl and dried over anhyd Na_2SO_4. The solution was concentrated *in vacuo* to give (*R*)-(−)-2-methyl-2-phenylpentanoic acid[14] (44 mg, 54% yield): $[\alpha]_D$ −14.0° (*c* 1.21, MeOH); IR 3100 (OH), 1700 (CO_2H), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 0.88–0.93 (3H, t, 7 Hz), 1.28–1.15 (2H, m), 1.56 (3H, s), 1.89–2.03 (2H, m), 7.30–7.39 (5H, m), 11.28–11.49 (1H, m); MS *m/z*: 192 (M^+); HRMS 192.1150 (calcd for $C_{12}H_{14}O_3$: 192.1150).

Asymmetric Synthesis of 3-Allyl-3-methyl-2,3-dihydro-2-benzofuran-2-one (13). Methyl (2-Hydroxyphenyl)acetate. A solution of (2-hydroxyphenyl)acetic acid (5.0 g, 0.330

(17) Yamada, S.; Otani, G. *Tetrahedron* **1969**, *10*, 4237. Nagasawa, K.; Takahashi, H.; Hiroi, K.; Yamada, S. *Ibid.* **1975**, *95*, 46.
(18) Paquette, L. A.; Freeman, J. P.; Maiorana, S. *Tetrahedron* **1971**, *27*, 2599.
(19) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *122*, 2933.
(20) Karrer, P.; Naik, A. R. *Helv. Chem. Acta* **1948**, *31*, 1617.
(21) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887; Timms, G. H.; Wildsmith, E. *Tetrahedron Lett.* **1971**, *12*, 195.

mol) in 50 mL of methanol was refluxed for 16 h in the presence of a catalytic amount of concd sulfuric acid. The reaction mixture was concentrated *in vacuo*. Ether was added to the residue, and the solution was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by recrystallization from hexane to give methyl (2-hydroxylphenyl)acetate (5.5 g, 92% yield) as colorless plates with mp 64 °C: IR 3450 (OH), 1735 (ester), 1600 (aromatic); ^1H NMR (CCl_4) δ 3.53 (2H, s), 3.63 (3H, s), 6.60–7.60 (4H, m); MS *m/z* 166 (M^+); HRMS 166.0618 (calcd for $C_9H_{10}O_3$: 166.0630).

Methyl (2-Allyloxyphenyl)acetate. A solution of methyl (2-hydroxyphenyl)acetate (1.0 g, 6.024 mmol) and allyl bromide (1.6 mL, 18.042 mmol) was stirred at rt for 16 h in the presence of K_2CO_3 (1.7 g, 12.048 mmol). The reaction mixture was filtered, and the precipitates were washed with ether. The filtrates were combined and concentrated *in vacuo*. The residual oil was dissolved with ether. The solution was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether:hexane, 1:2) to give methyl [2-(allyloxy)phenyl]acetate (1.0 g, 84% yield): IR 2870 (ether), 1740 (C=O), 1645 (C=C), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 3.72 (2H, s), 3.73 (3H, s), 4.53–4.61 (2H, d, *J* = 5 Hz), 5.28–5.50 (2H, m), 6.00–6.14 (1H, m), 6.83–7.70 (4H, m); MS *m/z* 206 (M^+); HRMS 206.0738 (calcd for $C_{12}H_{14}O_3$: 206.0742).

Methyl [2-(Tetrahydropyranyloxy)phenyl]acetate. A catalytic amount of phosphorus oxychloride was added to a mixture of 2,3-dihydropyran (4.7 mL, 0.052 mol) and methyl (2-hydroxyphenyl)acetate (7.2 g, 0.034 mol) in 50 mL of THF at 0 °C. The reaction mixture was stirred at 0 °C for 6 h and then diluted with ether. The solution was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to flash column chromatography (ether–hexane, 1:2) to give methyl [2-(tetrahydropyranyloxy)phenyl]acetate (9.9 g, 88% yield): IR 1740 (C=O), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.46–1.99 (6H, m), 3.33–3.88 (2H, m), 3.58 (2H, s), 3.61 (3H, s), 5.37–5.39 (1H, t), 6.84–7.18 (4H, m); MS *m/z* 250 (M^+); HRMS 250.1199 (calcd for $C_{14}H_{18}O_4$: 250.1205).

Methyl 2-[2-(Allyloxy)phenyl]propionate and Methyl 2-[2-(Tetrahydropyranyloxy)phenyl]propionate. A solution of methyl [2-(allyloxy)phenyl]acetate (2.6 g, 0.013 mol) in 5 mL of THF was added to a −78 °C solution of LDA (prepared from diisopropylamine (2.0 mL, 0.013 mol) and BuLi (1.5 N hexane solution, 6.0 mL, 0.013 mol)). The whole was stirred at −78 °C for 1.5 h. Methyl iodide (1.6 mL, 0.026 mol) was added to the above mixture at −78 °C, and the reaction mixture was stirred at −78 °C for 6 h. The reaction mixture was diluted with ether, washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether–hexane 1:3) to give methyl 2-[2-(allyloxy)phenyl]propionate (2.6 g, 97% yield). Methylation of methyl 2-[2-(tetrahydropyranyloxy)phenyl]acetate (2.4 g, 0.011 mol) was carried out under the same conditions to give methyl 2-[2-(tetrahydropyranyloxy)phenyl]propionate (preparative TLC, ether–hexane 1:2, 2.5 g, 98% yield).

Methyl 2-[2-(Allyloxy)phenyl]propionate: IR 1740 (C=O), 1645 (C=C), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.51, 1.53 (3H, d, *J* = 7 Hz), 3.69 (3H, s), 4.06–4.14 (1H, q, *J* = 6 Hz), 4.58–4.60 (2H, d, *J* = 4 Hz), 5.28–5.49 (2H, m), 6.00–6.12 (1H, m), 6.88–7.30 (4H, m); MS *m/z* 220 (M^+); HRMS 220.1079 (calcd for $C_{13}H_{16}O_3$: 220.1098).

Methyl 2-[2-(Tetrahydropyranyloxy)phenyl]propionate: IR 1740 (C=O), 1645 (C=C), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.40–1.45 (3H, dd), 1.45–2.10 (6H, m), 3.59 (3H, s), 3.69–4.89 (3H, m), 5.35–5.40 (1H, m), 6.60–7.33 (4H, m); MS *m/z* 264 (M^+); HRMS 264.1382 (calcd for $C_{15}H_{20}O_4$: 264.1362).

Synthesis of 2-[2-(Allyloxy)- or 2-(Tetrahydropyranyloxy)phenyl]propanol. Lithium aluminum hydride (496 mg, 0.013 mol) was added to a solution of methyl 2-[2-(allyloxy)phenyl]propionate (2.4 g, 0.010 mol) in 30 mL of THF cooled to 0 °C. The reaction mixture was stirred at rt for 16 h and then quenched with H_2O (1.1 mL) and 10% aqueous NaOH (0.6 mL). The mixture was diluted with ether and then refluxed for 1 h. The precipitates were filtered and washed with ether. The filtrates were combined and concentrated *in vacuo*. The product was subjected to preparative TLC (ether–hexane 1:2) to give 2-[2-(allyloxy)phenyl]propanol (1.8 g, 86% yield). 2-[2-(Tetrahydropyranyloxy)phenyl]propanol (preparative TLC, ether–hexane 1:2, 1.9 g, 92% yield) was prepared from methyl [2-(tetrahydropyranyloxy)phenyl]propionate (2.3 g) under the same conditions described above.

2-[2-(Allyloxy)phenyl]propanol: IR 3350 (OH), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.33, 1.35 (3H, d, *J* = 7 Hz), 1.67 (1H, br s), 3.73–3.86 (2H, m), 4.60–4.63 (2H, d, *J* = 6 Hz), 5.31–5.52 (1H, m), 6.91–7.31 (4H, m); MS *m/z* 192 (M^+); HRMS 192.1124 (calcd for $C_{12}H_{16}O_2$: 192.1149).

2-[2-(Tetrahydropyranyloxy)phenyl]propanol: IR 3400 (OH), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.19–1.22 (3H, dd), 1.54–1.99 (6H, m), 3.34–3.86 (3H, m), 5.22–5.38 (1H, m), 6.87–7.18 (4H, m); MS *m/z* 236 (M^+); HRMS 236.1435 (calcd for $C_{14}H_{20}O_3$: 236.1412).

Synthesis of 2-[2-(Allyloxy)phenyl]propanal (10b) and 2-[2-(Tetrahydropyranyloxy)phenyl]propanal. A solution of 2-[2-(allyloxy)phenyl]propanol (1.3 g, 0.008 mol) in 20 mL of dichloromethane was added to a solution of pyridinium chlorochromate (2.7 g, 0.013 mol) in 30 mL of dichloromethane. The reaction mixture was stirred at rt for 3 h and then concentrated *in vacuo*. Ether was added to the residue. The resulting suspension was filtered through silica gel, and the precipitates were washed with ether. The filtrates were combined and concentrated *in vacuo*. The residual oil was diluted under reduced pressure to give **10b** (1.1 g, 62% yield). 2-[2-(Tetrahydropyranyloxy)phenyl]propanal (1.1 g, 85% yield) was prepared from the corresponding alcohol (1.6 g) under the same conditions described above.

10b: bp 180 °C (4 Torr); IR 1740 (CHO), 1645 (C=C), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.54, 1.56 (3H, d, *J* = 6 Hz), 3.99–4.07 (1H, q), 4.68–4.71 (2H, d, *J* = 7 Hz), 5.38–5.56 (2H, m), 6.09–6.23 (1H, m), 7.03–7.43 (4H, m), 9.84 (1H, s); MS *m/z* 190 (M^+); HRMS 190.0979 (calcd for $C_{10}H_{12}O_2$: 190.0993).

2-[2-(Tetrahydropyranyloxy)phenyl]propanal: bp 200 °C (4 Torr); IR 1760 (CHO), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.33–1.55 (3H, dd, *J* = 7.7 Hz), 1.72–1.88 (6H, m), 3.34–3.86 (3H, m), 5.22–5.38 (1H, t), 6.87–7.18 (4H, m), 9.64, 9.67 (1H, d); MS *m/z* 234 (M^+); HRMS 234.1233 (calcd for $C_{14}H_{14}O_3$: 234.1256).

2-(2-Hydroxyphenyl)propanal (10a). A solution of 2-[2-(tetrahydropyranyloxy)phenyl]propanal (1.0 g, 0.004 mol) in 20 mL of methanol was stirred at rt for 16 h in the presence of a catalytic amount of *p*-toluenesulfonic acid. The solution was concentrated *in vacuo*. The crude product was subjected to distillation under reduced pressure to give **10a** (638 mg, quantitative yield); IR 3300 (OH), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.33, 1.35 (3H, d, *J* = 6 Hz), 2.30 (1H, br s), 3.24–3.47 (1H, m), 5.60 (1H, m), 6.70–7.80 (4H, m); MS *m/z* 150 (M^+); HRMS 150.0813 (calcd for $C_9H_{10}O_2$: 150.0798).

2-[2-[[(Allyloxy)carbonyl]oxy]phenyl]propanal (10c). Allyl chloroformate (0.7 mL, 6.379 mmol) was added to a solution of 2-(2-hydroxyphenyl)propanal (638 mg, 4.253 mmol) and triethylamine (0.8 mL, 6.379 mmol) in 20 mL of THF at 0 °C. The reaction mixture was stirred at rt for 16 h. The precipitates were filtered and washed with ether. The filtrates were combined and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether–hexane, 1:2) to give **10c** (856 mg, 86% yield); IR 1740, 1720 (C=O), 1645 (C=C), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.32, 1.35 (3H, d, *J* = 6 Hz), 3.71–3.79 (1H, q), 4.65–4.68 (2H, d, *J* = 7 Hz), 5.24–5.40 (2H, m), 5.85–5.99 (1H, m), 7.10–7.31 (4H, m), 9.59 (1H, d); MS *m/z* 234 (M^+); HRMS 234.0871 (calcd for $C_{13}H_{13}O_4$: 234.0891).

General Procedure for Palladium-Catalyzed Allylations of Chiral 2-(2-Hydroxy- or 2-Alkoxyphenyl)propanal Enamine. Synthesis of Chiral Enamines (11a–f). A solution of **10a** (50 mg, 0.333 mmol) and a chiral amine ((*S*)-**1a,b** or 2-[(diphenylphosphino)methyl]pyrrolidine[1]) (0.333 mmol) in 10 mL of benzene was refluxed for 4 h with a Dean–Stark apparatus. The solution was concentrated *in vacuo* to give the corresponding chiral enamine ((*S*)-**11a,d,e**) (0.333 mmol). The reaction of **10b** (50 mg, 0.263 mmol) or **10c** (50 mg, 0.214 mmol) with (*S*)-**1b** or 2-[(diphenylphosphino)methyl]pyrrolidine (1.0 equiv) was car-

ried out under the same conditions to lead to chiral enamine (*S*)-**11b,f** or (*S*)-**11c**.

Palladium-Catalyzed Allylation of (*S*)-11a,e. A solution of enamine (*S*)-**11a** (0.333 mmol) and allyl acetate (67 mg, 0.666 mmol) in 10 mL of THF was stirred under N_2 in the presence of $Pd(PPh_3)_4$ (77 mg, 0.067 mmol) and PPh_3 (35 mg, 0.133 mmol) at the indicated temperature for the time shown in Table VI. The reaction mixture was treated with a mixture of 10% aqueous HCl (2.5 mL)–benzene (2.5 mL) under reflux for 1 h. The reaction mixture was diluted with ether. The ethereal solution was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether–hexane, 1:2) to give 3-allyl-3-methyl-2,3-dihydrobenzofuran-2-ol (**12**): IR 3400 (OH), 1620 (C=C), 1580 (aromatic); ^1H NMR (CCl_4) δ 1.23 (3H, J = 6 Hz), 2.13–2.56 (2H, m), 3.23 (1H, br s), 4.70–6.13 (4H, m), 6.70–7.30 (4 H, m); MS m/z 190 (M^+); HRMS 190.0984 (calcd for $C_{12}H_{14}O_2$: 190.0993).

Jones reagent (0.3 mL) was added to a solution of **12** (48 mg) obtained above in 2 mL of acetone at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then quenched with isopropyl alcohol. The reaction mixture was concentrated *in vacuo*, and ether was added to the residue. The suspension was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried over anhyd Na_2SO_4. The solution was concentrated *in vacuo*, and the crude product was subjected to preparative TLC (ether–hexane 1:2) to give (–)-**13** (47 mg, quantitative yield): IR 1800 (C=O), 1620 (C=C), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.46 (3H, s), 2.49–2.53 (2H, m, J = 6 Hz), 4.93–5.01 (2H, m), 5.23–5.50 (1H, m), 7.01–7.25 (4H, m); MS m/z 188 (M^+) HRMS 188.0816 (calcd for $C_{12}H_{12}O_2$: 188.0837).

The ees of the product are summarized in Table VI. When the same sequence was applied to (*S*)-**11e** (0.333 mmol) under the conditions without triphenylphosphine, (+)-**13** was obtained. The yields, the optical rotations, and the ees of the products are summarized in Table VI.

Palladium-Catalyzed Allylation of (*S*)-11b–d and (*S*)-11f. A solution of (*S*)-**11b** (0.263 mmol) in 10 mL of THF was stirred under N_2 in the presence of $Pd(PPh_3)_4$ (61 mg, 0.053 mmol) and PPh_3 (28 mg, 0.105 mmol) at the indicated temperature for the time described in Table IV. The reaction mixture was treated with 10% aqueous HCl (2.5 mL)–benzene (2.5 mL) under reflux for 1 h. The reaction mixture was diluted with ether. The ethereal solution was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether–hexane 1:2) to give **12** (49 mg). Jones oxidation of acetal **12** obtained above was carried out in the same way described above to afford (–)-**13** (48 mg, quantitative yield). The ees of the products are summarized in Table IV. When the same sequence was applied to (*S*)-**10c** (0.214 mmol) or (*S*)-**10d** (0.236 mmol) under the same conditions, (–)-**13** or (+)-**13** was obtained. Reaction of (*S*)-**11f** was carried out without triphenylphosphine and led to (+)-**13**. The yields, the optical rotations, and the ees of the products are summarized in Table IV.

Palladium-Catalyzed Allylation of Chiral Imines. (*R*)-(+)-2-Allyl-2-(*p*-toluenesulfenyl)cyclohexanone (17) and (*R*)-(–)-6a. General Procedure: A solution of 2-(*p*-toluenesulfenyl)cyclohexanone (**15**)[21] (100 mg, 0.460 mmol) or **4a** (62 mg, 0.460 mmol) and (*S*)-**14a–e** (0.460 mmol) in 20 mL of benzene was refluxed for 6 h (for the ketone) or 4 h (for the aldehyde) with a Dean–Stark apparatus. The solution was concentrated *in vacuo* to give chiral keto- or aldehyde-imine ((*S*)-**16a–e** or (*S*)-**18a–e**) (0.460 mmol).

A solution of (*S*)-**16a–e** or (*S*)-**18a–e** (0.460 mmol) obtained above in 10 mL of THF was stirred under N_2 in the presence of $Pd(PPh_3)_4$ (79 mg, 0.070 mmol) and PPh_3 (79 mg, 0.300 mmol) at the indicated temperature for the time described in Table VII. The reaction mixture was treated with 10% aqueous HCl (3.0 mL)–benzene (5.0 mL) under reflux for 1.5 h. The reaction mixture was diluted with ether. The ethereal solution was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether–hexane 1:5, for the ketone, or benzene–hexane 1:2, for the aldehyde) to give (*S*)-(+)-**17** or (*R*)-(–)-**6a**. The yields, the optical rotations, and the ees of the products are summarized in Table VII.

(*R*)-(+)-**17**: IR 1710, 1640 (C=O), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.10–2.48 (8H, m), 2.25 (3H, s), 3.23–3.41 (2H, m), 4.93–5.04 (2H, m), 5.69–5.84 (1H, m), 7.00–7.18 (4H, m); MS m/z 260 (M^+); HRMS 260.1201 (calcd for $C_{16}H_{20}OS$: 260.1235); $[\alpha]_D$ +164.8° (*c* 2.3, MeOH); CD (MeOH) $[\theta]_{307.5}$ +4936.

Synthesis of (*S*)-Proline 1,1-Dideuterioallyl Ester (26b). Methyl 3-(Phenylselenenyl)propionate (22). Sodium borohydride (250 mg, 0.007 mol) was added to a solution of diphenyl diselenide (861 mg, 0.003 mol) in 20 mL of methanol at 0 °C over a period of 20 min, and then methyl acrylate (0.5 mL, 0.006 mol) was added. The reaction mixture was stirred at rt for 3 h. The solution was concentrated *in vacuo*. The residual oil was dissolved with ether. The solution was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (benzene–hexane 1:2) to give **22** (2.4 g, 80% yield): IR 1740 (C=O), 1580 (aromatic); ^1H NMR ($CDCl_3$) δ 2.30–3.30 (4H, m), 3.56 (3H, s), 6.83–7.63 (5H, m); MS m/z 243 (M^+); HRMS 243.9146 (calcd for $C_{10}H_{12}O_2Se$: 243.9120).

1,1-Dideuterio-3-(phenylselenenyl)propanol (23). Lithium aluminum deuteride (842 mg, 0.020 mmol) was added to a solution of **22** (4.6 g, 0.017 mol) in 40 mL of ether cooled to 0 °C. The reaction mixture was stirred at 0 °C for 16 h and then quenched with H_2O (3.2 mL) and 10% aqueous NaOH (2.4 mL). The mixture was diluted with ether and then refluxed for 1 h. The precipitates were filtered and washed with ether. The filtrates were combined and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether–hexane 1:2) to give **23** (3.4 g, 94% yield): IR 3400 (OH), 2200, 2100 (CD_2), 1580 (aromatic); ^1H NMR ($CDCl_3$) δ 1.53 (1H, br s), 1.90–1.96 (2H, t, J = 7 Hz), 3.00–3.03 (2H, t, J = 7 Hz), 6.96–7.63 (5H, m); MS m/z 217 (M^+); HRMS 217.7687 (calcd for $C_9H_{10}OSeD_2$: 217.7673).

(*S*)-*N*-(*tert*-Butoxycarbonyl)proline 1,2-Dideuterio-3-(phenylselenenyl)propyl Ester (25). Ethyl chlorocarbonate (0.5 mL, 0.005 mol) was added to a solution of (*S*)-*N*-(*tert*-butoxycarbonyl)proline (**24**) (1.0 g, 0.005 mol) and triethylamine (0.7 mL, 0.010 mol) in 50 mL of THF at 0 °C. The reaction mixture was stirred at 0 °C for 4 h. The precipitates were filtered, and the filtrate was concentrated *in vacuo* to give (*S*)-*N*-(*tert*-butoxycarbonyl)proline ethyl carbonate (1.3 g) [IR 1820, 1760 (carbonate), 1700 (C=O)].

Compound **23** (1.2 g, 0.060 mol) was added to a solution of the carbonate (1.3 g, 0.005 mol) obtained above and pyridine (0.5 mL, 0.006 mol) in 30 mL of THF at 0 °C. The reaction mixture was stirred at 0 °C for 16 h and then diluted with ether. The solution was washed with 10% aqueous HCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether–hexane 1:2) to give **25** (1.8 g, 90% yield): $[\alpha]_D$ –47.2° (*c* 2.0, $CHCl_3$); IR 2200, 2100 (CD_2), 1740, 1690 (C=O), 1580 (aromatic); ^1H NMR ($CDCl_3$) δ 1.41–1.58 (9H, s), 1.85–2.18 (6H, m), 2.89–2.98 (2H, m), 3.39–3.51 (2H, m), 4.15–4.21 (1H, m), 7.47–7.51 (5H, m); MS m/z 415 (M^+); HRMS 415.1208 (calcd for $C_{19}H_{25}O_4SeD_2N$: 415.1231).

(*S*)-*N*-(*tert*-Butoxycarbonyl)proline 1,1-Dideuterioallyl Ester (26a). Aqueous hydrogen peroxide (70%) (2.7 mL, 0.006 mol) was added to a suspension of **25** (2.3 g, 0.006 mol) and anhyd magnesium sulfate (1.5 g) in 30 mL of THF, and the mixture was stirred at rt for 16 h. The precipitates were filtered and washed with ether. The filtrates were combined and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether–hexane, 1:2) to give **26a** (1.3 g, 93% yield): $[\alpha]_D$ –53.3° (*c* 4.3, $CHCl_3$); IR 2250, 2150 (CD_2), 1740, 1700 (C=O), 1650 (C=C); ^1H NMR ($CDCl_3$) δ 1.43 (9H, s), 1.60–2.20 (4H, m), 3.40–3.54 (2H, m), 4.13–4.38 (1H, m), 5.21–5.36 (2H, m), 5.86–5.96 (1H, m); MS m/z 329 (M^+); HRMS 329.1577 (calcd for $C_{19}H_{19}O_4D_2N$: 329.1596).

(*S*)-Proline 1,1-Dideuterioallyl Ester (26b). Compound **26a** (1.3 g, 0.005 mol) was dissolved in 10 mL of freshly distilled TFA at 0 °C, and the solution was stirred for 2 h. The solution was concentrated *in vacuo* to leave (*S*)-proline 1,1-dideuterioallyl ester trifluoroacetic acid salt. The salt was dissolved in 30 mL of $CHCl_3$, and Na_2CO_3 was added. The mixture was stirred for 10 min and then diluted with $CHCl_3$. The solution was washed

with saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to distillation under reduced pressure to give **26b** (400 mg, 60% yield): bp 120 °C (4 Torr); $[\alpha]_D$ −38.5° (*c* 1.3, $CHCl_3$); IR 2175, 2075 (CD_2), 1735 (C=O), 1645 (C=C); ^1H NMR (CCl_4) δ 1.05–2.46 (4H, m), 2.76–3.04 (2H, m), 3.34–3.96 (2H, m), 5.03–6.46 (3H, m); MS *m/z* 157 (M^+); HRMS 157.1068 (calcd for $C_8H_{11}O_2D_2N$: 157.1072).

Palladium-Catalyzed Reaction of (*S*)-Proline 1,1-Dideuterioallyl Ester Enamines. General Procedure: A solution of **26b** (77 mg, 0.478 mmol) and cyclohexanone or 2-phenylpropanal (0.487 mmol) in 10 mL of benzene was refluxed for 4 h with a Dean–Stark apparatus. The solution was concentrated *in vacuo* to give keto- or aldehyde-enamine ((*S*)-**27** or (*S*)-**31**). A solution of (*S*)-**27** or (*S*)-**31** (0.478 mol) in 10 mL of THF was stirred under N_2 in the presence of $Pd(PPh_3)_4$ (56 mg, 0.049 mmol) and PPh_3 (51 mg, 0.195 mmol) under reflux for 20 h (for (*S*)-**27**), or at rt (45 h), 40 °C, or 66 °C (19 h) (for (*S*)-**31**).

The reaction mixture was treated with AcONa (496 mg)–AcOH (1.2 mL)–H_2O (6.0 mL)–benzene (7.0 mL) at rt (for the ketone) or 10% aqueous HCl (2.5 mL)–benzene (2.5 mL) (for the aldehyde) under reflux for 1 h. The reaction mixture was diluted with ether. The ethereal solution was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC to give α-allyl carbonyl compounds 2-(1,1- or 3,3-dideuterioallyl)cyclohexanone (**28a,b**; ether–hexane, 1:5; 40% yield) or 3,3- or 5,5-dideuterio-2-methyl-2-phenyl-4-pentanal (**32a,b**; benzene–hexane, 1:2; 35, 48, or 57% yield).

28: IR 2200, 2100 (CD_2), 1720 (C=O), 1650 (C=C); ^1H NMR ($CDCl_3$) δ 1.07–2.54 (9H, m), 3.33–3.44 (2H, m), 4.90–4.98 (1.5H, m), 5.64–5.74 (1H, m); MS *m/z* 140 (M^+); HRMS 140.1178 (calcd for $C_9H_{12}OD_2$: 140.1200).

32: IR 2180, 2080 (CD_2), 1725 (CHO), 1645 (C=C), 1600 (aromatic); ^1H NMR ($CDCl_3$) δ 1.44 (3H, s), 2.63–2.68 (2H, d, *J* = 6 Hz), 5.00–5.09 (1.5H, m), 5.64–5.74 (1H, m), 7.23–7.41 (5H, s), 9.52 (1H, s); MS *m/z* 176 (M^+); exact mass determination 176.1775 (calcd for $C_{12}H_{12}OD_2$: 176.1762).

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Supplementary Material Available: Copies of the ^1H NMR spectra of all compounds (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.