Stereochemistry of the Asymmetric Carbopalladation of Allenes Followed by Nucleophilic Substitution Reactions with Carbo- and Aminonucleophiles

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The stereochemistry of the asymmetric palladium-catalyzed reaction of allenes with iodobenzene followed by nucleophilic substitution reaction with sodium malonate and *N*-methylbenzylamine is described. On the basis of the absolute configuration of the product and the stereochemical result of a similar reaction of a chiral allene, the mechanism of the above asymmetric reactions is discussed.

Key words allene; palladium catalyst; chiral ligand; carbonucleophile; aminonucleophile

An allene functionality has received much interest for introducing a three-carbon unit in organic synthesis,[1—5] especially as a good chiral regulator with the axial chirality in asymmetric synthesis.[6,7] The axial chirality has received much attention for the stereochemical characteristics, and many methodologies of the asymmetric synthesis of allenes with the axial chirality have been reported so far.[8] Currently, the use of the allene functionality in transition metal-catalyzed reactions has become of great importance from the synthetic and theoretical points of view with regard to the chemical characteristics associated with the axial chirality.[9—12] Therefore, an allene with the axial chirality might be a synthetically useful chiral director for the elaboration of chiral complex organic molecules in asymmetric synthesis with metal catalysts. For the approach to chiral allenes, however, few synthetically useful methodology has been devised so far by asymmetric synthesis, especially with catalytic versions,[13—17] despite the efforts to access chiral allenes that were made by many investigators.

We describe in this report asymmetric 1,2-functionalization of an allenyl olefin *via* carbopalladation with chiral phosphine ligands.[18] The palladium-assisted asymmetric direct 1,2-functionalization of an allene was realized with the assistance of chiral ligands[19,20]; an allenyl compound was reacted with iodobenzene in the presence of a palladium(0) catalyst *via* carbopalladation of the allene with the resulting Ph–Pd–I species to provide a π–allylpalladium complex, which was followed by the nucleophilic substitution with a nucleophile such as malonate enolate giving an α,β-functionalized olefin derivative.[21—26]

For an asymmetric version of the above palladium-catalyzed reaction, initially, we tried the above palladium-catalyzed asymmetric reaction with chiral phosphine ligands using a readily available racemic allene.

One point of importance on which we should focus our attention in this planning is whether the reaction proceeds with or without stereospecificity. If the reaction of each enantiomeric allene proceeds with complete stereospecificity, the above reaction will provide a racemic product, since a racemic allene is used. If the interconversion between π–allylpalladium complexes **4a**, **b** coordinated by chiral phosphine ligands *via* carbocationic intermediates **3a**—**c** might be possible, the enantiomeric excess of the product **5** will depend on the relative thermodynamic stabilities of **4a**, **b**.

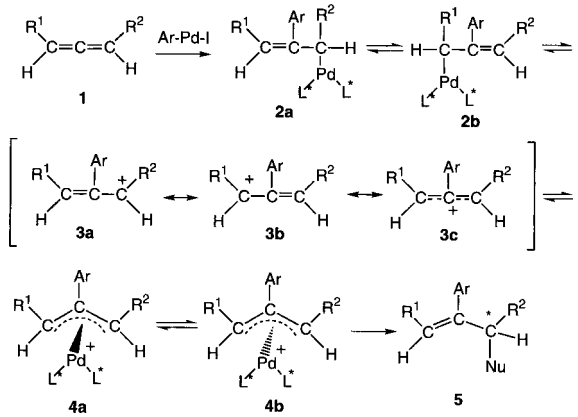

Chart 1

Results and Discussion

The Palladium-Catalyzed Intermolecular Asymmetric Reactions of an Allene with a Carbonucleophile Using Chiral Phosphine Ligands The palladium-catalyzed asymmetric reactions of a racemic allene, (±)-**6**, with iodobenzene (**7**) and a nucleophile (malonate carbanion (**8**)) were studied by using (4*R*,5*R*)-(−)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane ((−)-DIOP), (4*R*,5*R*)-(+)-4,5-bis[bis(4′-methoxy-3′,5′-dimethylphenyl)phosphinomethyl]-2,2-dimethyl-1,3-dioxolane [(+)-MOD-DIOP] or (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(*S*)-BINAP] as a chiral ligand. The reactions of (±)-**6** with **7** (1.5 eq) and lithium or sodium malonate (**8a**, **b**) were carried out in the presence of $Pd(dba)_2$ (0.04 eq) and chiral phosphine ligands (0.04 eq) such as described above in THF, DME, or DMSO at room temperature, 40, or 66 °C to give (*S*)-**9**. The geometry of the olefin in the product **9** was determined as *Z* configuration by the observation of the NOE between the olefinic hydrogen and the methyl group and the hydrogen at the chiral carbon center in the NMR spectral analysis. The enantiomeric excess of the product **9** was determined by HPLC analysis with Chiralcel OD.

The effects of solvent, reaction temperature, and base were examined in the palladium-catalyzed reactions of (±)-**6** with iodobenzene and dimethyl malonate using (*S*)-(−)-BINAP as a chiral ligand. Dramatic solvent effects on the enantioselectivity were observed. Use of DMSO as solvent at higher re-

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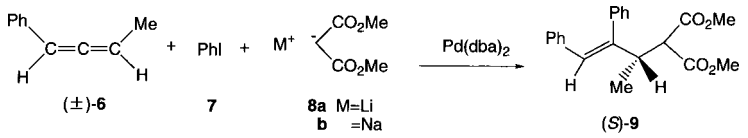

Chart 2

Table 1. Asymmetric Induction in the Carbopalladation of Allenes Using Chiral Phosphine Ligand ((*S*)-(−)-BINAP)[a]

Solvent	Base	Reaction temp. (°C)	Reaction time (h)	Yield of **9** (%)	e.e. of (*S*)-**9**[b] (%)
THF	NaH	40	24	23	50
THF	NaH	66	18	33	88
THF	*sec*-BuLi	40	24	20	72
THF	*sec*-BuLi	66	18	34	37
DME	NaH	40	24	31	53
DME	NaH	66	18	64	69
DMSO	NaH	r.t.	43	11	85
DMSO	NaH	40	24	42	96
DMSO	NaH	66	18	75	89
DMSO	*sec*-BuLi	40	24	48	65
DMSO	*sec*-BuLi	66	18	69	66

a) The reactions of (±)-**6** with **7** (1.5 eq) and **8** (1.2 eq) (the carbanion was prepared by treating with NaH or *sec*-BuLi (1.3 eq)) were carried out in the presence of $Pd(dba)_2$ (0.04 eq) and (*S*)-BINAP (0.04 eq). *b*) The e.e. of the product **9** was determined by HPLC analysis with chiralcel OD.

Table 2. Asymmetric Induction in the Carbopalladation of Allene Using Chiral Phosphine Ligands[a]

Ligands	Solvent	Reaction temp. (°C)	Reaction time (h)	Yield of **9** (%)	e.e. of (*S*)-**9**[b] (%)
(−)-DIOP	THF	40	24	22	47
(−)-DIOP	THF	66	18	43	56
(−)-DIOP	DME	40	24	35	71
(−)-DIOP	DME	66	18	54	53
(−)-DIOP	DMSO	40	24	32	67
(−)-DIOP	DMSO	66	18	76	80
(+)-MOD-DIOP	THF	40	24	45	50
(+)-MOD-DIOP	THF	66	18	50	36
(+)-MOD-DIOP	DME	40	24	53	36
(+)-MOD-DIOP	DME	66	18	75	67
(+)-MOD-DIOP	DMSO	40	24	56	89
(+)-MOD-DIOP	DMSO	66	18	89	95
(*R*)-(*S*)-PPFOMe	THF	40	24	41	59
(*R*)-(*S*)-PPFOMe	THF	66	18	36	56
(*R*)-(*S*)-PPFOMe	DME	40	24	43	59
(*R*)-(*S*)-PPFOMe	DME	66	18	54	72
(*R*)-(*S*)-PPFOMe	DMSO	40	24	72	78
(*R*)-(*S*)-PPFOMe	DMSO	66	18	76	80
(*R*)-(*S*)-BPPFOAc	THF	40	24	21	72
(*R*)-(*S*)-BPPFOAc	THF	66	18	51	68
(*R*)-(*S*)-BPPFOAc	DME	40	24	30	48
(*R*)-(*S*)-BPPFOAc	DME	66	18	75	65
(*R*)-(*S*)-BPPFOAc	DMSO	40	24	85	85
(*R*)-(*S*)-BPPFOAc	DMSO	66	18	89	95

a) The reactions of (±)-**6** with **7** (1.5 eq) and **8** (1.2 eq) (the carbanion was prepared by treating with NaH (1.3 eq)), were carried out in the presence of $Pd(dba)_2$ (0.04 eq) and chiral ligands (0.04 eq). *b*) The e.e. of the product **9** was determined by HPLC analysis with chiralcel OD.

action temperature (66 °C) resulted in the highest chemical and optical yields of (*S*)-**9**, as listed in Table 1. With sodium hydride as a base, higher enantionselectivity was obtained than that with *sec*-BuLi. In the reactions using (*S*)-(−)-BINAP as a ligand, the highest enantioselectivity (96%) was provided by the reaction at 40 °C in DMSO using sodium hydride as a base.

Studies on the palladium-catalyzed reaction with other chiral phosphines were conducted using sodium hydride as a base, and the results obtained are summarized in Table 2. The palladium-catalyzed asymmetric reactions of (±)-**6** with iodobenzene and sodium dimethyl malonate were carried out in the presence of $Pd(dba)_2$ (0.04 eq) using chiral phosphine ligands (0.04 eq) such as (−)-DIOP, (+)-MOD-DIOP, (−)-(*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyl methyl ether [(*R*)-(*S*)-PPFOMe], and (*R*)-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl acetate [(*R*)-(*S*)-BPPFOAc],[27] providing (*S*)-**9** with considerably high e.e. With these ligands, severe solvent effects were also observed; the reaction in DMSO at 66 °C generally provided high enantioselectivities (80—95%). Particularly, the reactions of (±)-**6** with **7** and **8** in DMSO at 66 °C using (+)-MOD-DIOP and (*R*)-(*S*)-BPPFOAc produced (*S*)-**9** with high e.e. (95% e.e.) in high chemical yields (89%). It should be noted that the starting allene **6** recovered before the reaction completed remained still racemic. This fact indicates that the asymmetric induction in the above-mentioned carbopalladation reaction does not stem from a kinetic resolution.

The absolute configuration of the newly created asymmetric carbon center in the aforementioned asymmetric synthesis was determined by the chemical correlation to a known compound as follows. The oxidative cleavage of the carbon–carbon double bond of (−)-**9** with OsO_4–$NaIO_4$ followed by Baeyer–Villiger oxidation of **10** with CF_3CO_3H and hydrolytic decarboxylation of **11** gave (*S*)-(−)-**12** of known absolute configuration.[28,29] Accordingly, the absolute configuration of the product **9** obtained above was determined as (*S*)-(−).

This palladium-catalyzed reaction was applied to a chiral allene system (Chart 4). A chiral allene (*R*)-**6** (100% e.e.), prepared by the known method *via* the stereospecific nucleophilic substitution of (*S*)-1-methylpropargyl methanesulfonate with phenylmagnesium bromide-$CuCl_2$,[30] was reacted with **7** (1.5 eq) and **8b** (1.2 eq) in the presence of $Pd(dba)_2$ (0.04 eq) and dppe (0.04 eq) under reflux in THF for 18 h to produce (*S*)-**9** with complete stereospecificity, which was confirmed by HPLC analysis. Thus, we can certainly conclude that the palladium-catalyzed reaction of a chiral allene ((*R*)-**6**) with iodobenzene and sodium malonate as a nucleophile proceeds with complete stereospecificity.

The Palladium-Catalyzed Asymmetric Reactions of an Allene with Iodobenzenes Bearing Nucleophilic Parts Successively, much interest has been placed on the palladium-catalyzed intramolecular reactions of allenes with reagents bearing both iodophenyl groups and nucleophilic parts in the molecules,[31—33] using chiral phosphine ligands.

The reactions of **6** with an iodobenzene compound possessing a carbonucleophilic part were studied. The palladium-catalyzed reactions of (±)-**6** with dimethyl (2-iodoben-

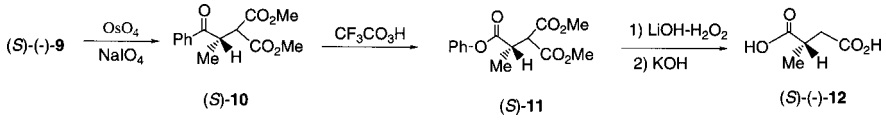

Chart 3

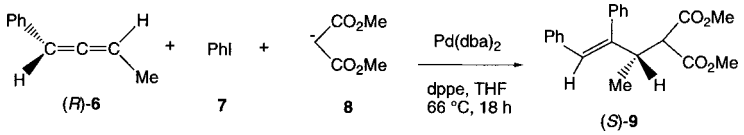

Chart 4

zyl)propanedioate (**13**) sodium enolate (generated by treating with NaH) were carried out under heating in the presence of $Pd(dba)_2$ (0.05 eq) and chiral phosphine ligands (0.10 eq) to give a cyclized product, a tetraline derivative **14**. The geometry of the olefinic parts in **14** was established as *Z* by the NOE observation between both the hydrogen and the methyl groups at the C_3 chiral center and the olefin hydrogen in **14** in the NMR spectral analysis.

The asymmetric palladium-catalyzed reactions of (±)-**6** with **13** were studied using chiral phosphine. The reactions of (±)-**6** with **13** (sodium enolate generated by treatment with NaH) were carried under reflux in THF for 18 h in the presence of $Pd(dba)_2$ (0.05 eq) and a chiral ligand ((*S*)-BINAP, (4*R*,5*R*)-(−)-DIOP, (4*R*,5*R*)-(+)-MOD-DIOP, or (*S*)-(*R*)-BPPFOAc) (0.1 eq) to give no cyclized product with recovery of the starting materials. Use of chiral ferrocenyl phosphines as ligands, however, in the above reactions gave **14** with very low enantioselectivities. The palladium-catalyzed reactions of (±)-**6** with sodium enolate of **13** using (*R*)-(*S*)-PPFOMe as a ligand were conducted in refluxing THF or in DME at 70 °C for 18 h to give (*R*)-**14** in 45 or 44% yield with 5 or 10% e.e., respectively. Use of (*S*)-(*R*)-PPFA or (*S*)-(−)-*N*,*N*-dimethyl-1-ferrocenylethylamine as a ligand in the above reactions under reflux in THF for 18 h gave (*R*)-**14** in 23 or 41% yield with 10 or 7% e.e., respectively. The enantiomeric excess of the product **14** was determined by HPLC analysis with SUMICHIRAL OA-3100 (isopropanol–hexane 1 : 500).

The intramolecular reactions of a chiral allene (*R*)-**6** (100% e.e.) with a carbonucleophile were examined (Table 3).[34] The palladium-catalyzed reaction of an optically pure allene ((*R*)-**6**) with sodium enolate of **13** (generated by treating with NaH) was carried out in refluxing THF in the presence of $Pd(dba)_2$ (0.05 eq) and 1,1′-bis(diphenylphosphino)-ferrocene (dppf) (0.10 eq) to give (*R*)-**14** with 50% e.e. The reactions with other phosphine ligands provided (*R*)-**14** with lower e.e. The increase of the chemical yield was observed without phosphine ligands, as shown in Table 3. The absolute configuration of the product **14** was deduced by the mechanism proposed on the basis of the results of the intermolecular reaction, which will be discussed later. The results obtained under other reaction conditions are summarized in Table 3.

Similarly, the palladium-catalyzed reaction of an allene ((±)-**6**) with 2-bromobenzylamine (**15**) was carried out in refluxing THF in the presence of $Pd(dba)_2$ (0.05 eq) and triphenylphosphine (PPh_3) (0.10 eq) using NaH (1.5 eq) as a base,

Chart 5

Table 3. The Palladium-Catalyzed Asymmetric Reactions of Chiral Allene (*R*)-**6** with (2-Iodobenzyl)propanedioate (**13**)[a]

Solvent	Ligand	Yield (%) of (*R*)-**14**[b]	e.e. (%) of (*R*)-**14**[c]
THF	—	59	15
THF	PPh_3	20 (30)	44
THF	dppf	12 (20)	50
DME	—	88	11
DME	PPh_3	28 (56)	30
DME	dppb	11 (17)	30
DME	dpppentane	7 (12)	17
DME	dppf	30 (48)[d]	34

a) The reactions of (*R*)-**6** (1.1 eq) with enolate of **13** (1 eq) (the carbanion was prepared by treating with NaH (1.1 eq)), were carried out under reflux for 18 h in the presence of $Pd(dba)_2$ (0.1 eq) and ligands (0.2 eq). *b*) The corrected yields based on the recovered starting material are given in parentheses. *c*) The enantiomeric excess of the product (*R*)-**14** was determined by HPLC analysis with SUMICHIRAL OA-3100. *d*) Reacted in the presence of $Pd(dba)_2$ (0.05 eq) and dppf (0.1 eq).

giving products **17a** and **18a**, by carbopalladation followed by the intramolecular nucleophilic substitution in **16**, which were identified as the corresponding acetamides **17b** (6% yield from **6**) and **18b** (21% yield from **6**).

In contrast, the palladium-catalyzed reactions of an allene **6** with *N*-methyl-2-iodobenzylamine (**19**) provided a cyclized product, a tetrahydroisoquinoline compound **20**, by carbopalladation of the carbon–carbon double bond of the allene followed by intramolecular nucleophilic substitution reaction. The geometry of the olefinic part in **20** was established as *E* by the NOE observation between both the hydrogen and the methyl groups at the C_3 chiral center and the phenyl group in **20** in the NMR spectral analysis.

The palladium-catalyzed reaction of an optically pure allene ((*R*)-**6**) with **19** was carried out under the same reaction conditions as described above to afford optically active cyclized product, (*S*)-**20**, with slightly low e.e., along with the recovered starting materials (about 30%). The absolute configuration of the product **20** was deduced on the basis of the stereochemical reaction path proposed by us, which will be discussed later. The e.e. of the product **20** was determined by HPLC analysis with SUMICHIRAL OA-4800. The stereo-

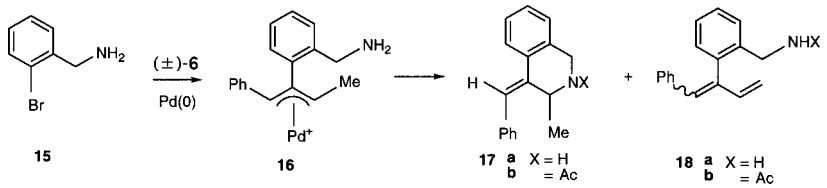

Chart 6

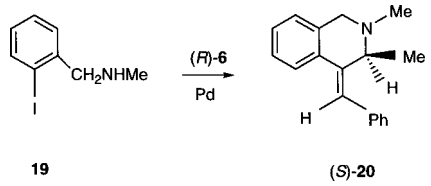

Chart 7

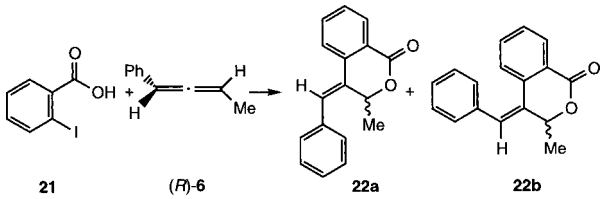

Chart 8

Table 4. The Palladium-Catalyzed Asymmetric Reactions of Chiral Allene (*R*)-**6** with *N*-Methyl-2-iodobenzylamine (**19**)[a]

Solvent	Base	Yield (%) of (*S*)-**20**[b]	e.e. (%) of (*S*)-**20**[c]
THF	—	9	56
THF	Et_3N	18	46
THF	NaH	6	44
MeCN	—	9	14
MeCN	Et_3N	24	13
DME	—	8	31
DME	Et_3N	30	28
DME	NaH	6	30

a) The reactions of (*R*)-**6** (1.1 eq) with **19** (1 eq) were carried out umder reflux for 12 h in the presence of $Pd(dba)_2$ (0.05 eq) and PPh_3 (0.1 eq). *b*) The enantiomeric excess of the product (*S*)-**20** was determined by HPLC analysis with SUMICHIRAL OA-4800.

Table 5. Palladium-Catalyzed Reactions of Chiral Allene (*R*)-**6** with 2-Iodobenzoic Acid (**21**)[a]

Ligand	Total Yield (%) of **22a** and **22b**	Ratio (%) of **22a** to **22b** **22a** : **22b**[b]	e.e (%) of **22a**[c]	e.e (%) of **22b**[c]
PPh_3	79	70 : 30	5	—
dppe	67	80 : 20	5	4
dppb	68	82 : 18	6	—
dpphexane	80	79 : 21	4	—

a) The reactions of (*R*)-**6** (1.1 eq) with **21** (1.0 eq) were carried out at 70 °C in MeCN for 18 h in the presence of $Pd(PPh_3)_4$ (0.05 eq), ligands (0.1 eq), K_2CO_3 (4.0 eq), and Ag_2CO_3 (0.05 eq). *b*) The product ratio was determined by ^{1}H-NMR analysis. *c*) The enantiomeric excess of the products **22a**, **b** was determined by HPLC analysis with Chiralpak AD.

specificity in the transformation of (*R*)-**6** into **20** was obtained on the basis of the e.e. of the product **20**, and is summarized in Table 4. The reactions of (*R*)-**6** with **19** under heating in toluene or DMF provided (±)-**20**; the chirality of the allene was almost completely lost under the reaction conditions.

A palladium-catalyzed carboxylation of an allene provides a lactone. Reactions of a chiral allene, (*R*)-**6**, with **21** were carried out at 70 °C in acetonitrile for 18 h in the presence of $Pd(PPh_3)_4$ (0.05 eq), a phosphine ligand (0.1 eq), K_2CO_3 (4.0 eq), and Ag_2CO_3 (0.05 eq) to give lactones **22a**, **b** in fairly good chemical yields. The product ratio was determined by ^{1}H-NMR analysis. The enantiomeric excess of the products **22a**, **b** was determined by HPLC analysis with chialpak AD. The results are summarized in Table 5. The preference of (*E*)-isomer **22a** to (*Z*)-**22b** (4 : 1 ratio) was observed. The structure of the products was determined by NOE observation between the hydrogen and the methyl groups at the stereogenic center and the phenyl group in **22a**, or the vinylic hydrogen in **22b** in the NMR spectral analysis. Use of dpphexane as a ligand produced the lactones **22a**, **b** in the highest yield (80%). However, chirality of the starting allene could not be retained under these palladium-catalyzed reaction conditions.

The intramolecular nucleophilic reaction of an allene with an alcohol under palladium-catalyzed reaction conditions provides a heterocycle. Reactions of (*R*)-**6** (100% e.e.) with

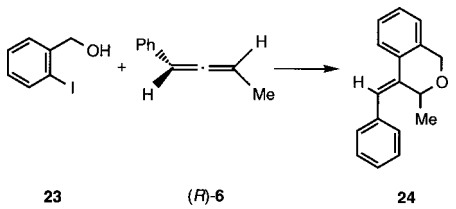

Chart 9

Table 6. Palladium-Catalyzed Reactions of Chiral Allene (*R*)-**6** with 2-Iodobenzyl Alcohol (**23**)[a]

Solvent	Reaction temp. (°C)	Base	Yield (%) of **24**
THF	66	Na_2CO_3	43
THF	66	K_2CO_3	48
MeCN	82	K_2CO_3	53
DME	85	K_2CO_3	59
DMF	60	K_2CO_3	7

a) The reactions of (*R*)-**6** (1.1 eq) with **23** (1.0 eq) were carried out for 12 h in the presence of $Pd(OAc)_2$ (0.05 eq), PPh_3 (0.1 eq), base (5.0 eq), and *n*-Bu_4NCl (1.0 eq).

23 were carried out under heating in THF, MeCN, DME, or DMF for 12 h in the presence of $Pd(OAc)_2$ (0.05 eq), PPh_3 (0.1 eq), Na_2CO_3 or K_2CO_3 (5.0 eq), and *n*-Bu_4NCl (1.0 eq) to give **24** in moderate chemical yields as shown in Table 6. However, the chirality of the allene was completely lost in these reactions.

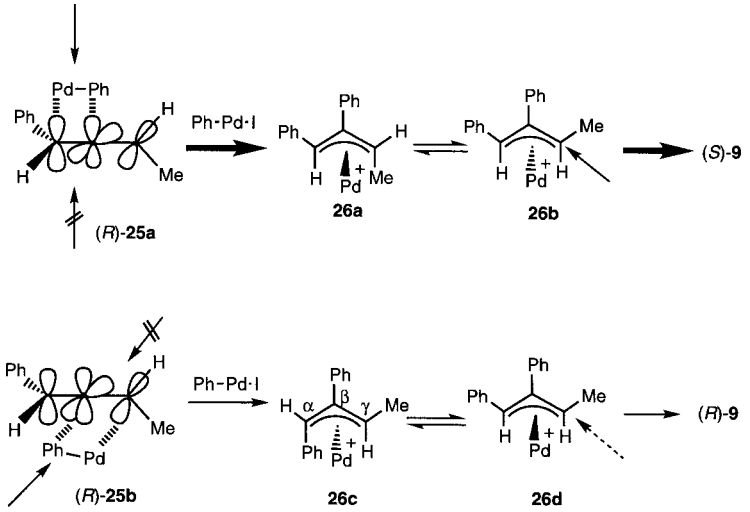

Chart 10

The almost complete loss of the chirality of the allene in the aforementioned lactonization and the etherification is rationalized by the existence of equilibrium between the products and the corresponding π–allylpalladium complexes under the palladium-catalyzed reaction conditions.

The Mechanism of the Palladium-Catalyzed Asymmetric Reactions of an Allene The stereochemistry of the aforementioned completely-stereospecific palladium-catalyzed reaction of a chiral allene (*R*)-**6** with sodium malonate is rationalized as follows. If the carbopalladation at the methyl-substituted carbon–carbon double bond (MeCH=C) site in (*R*)-**25b** would occur preferentially from the sterically less crowded hydrogen side due to the steric interference of the phenyl group at the α site of the allene, a π–allylpalladium complex **26c** would be formed. However, the complex **26c** has the steric hindrance of $A^{1,3}$ strain between the phenyl (α) and the hydrogen (γ) groups. Therefore, **26c** would be transformed to the conformationally more preferred π–allylpalladium complex **26d** with retention of the configuration, to which the nucleophilic substitution of malonate enolate from the back side of the palladium catalyst in the intermediate **26d** provides (*R*)-**9**. This explanation is in conflict with our result obtained.

The carbopalladation of (*R*)-**6** with Ph–Pd–I at the phenyl substituted carbon–carbon double bond (Ph–CH=C) site in (*R*)-**25a** would occur preferentially from the sterically less crowded upward hydrogen side at the γ carbon to form sterically rather preferred π–allylpalladium complex **26a** which would isomerize to the more stable π–allyl system **26b** with retention of the chirality of the π–allylpalladium **26a** induced by the starting chiral allene. The nucleophilic substitution of **26a** or **26b** with malonate enolate from the back of the palladium catalyst produces (*S*)-**9**. Based on the results obtained, the latter reaction path to (*S*)-**9** is preferred, since **26c** has rather severe $A^{1,3}$ strain between the phenyl ring and the hydrogen group. Thus, we are able to rationalize the stereochemical outcome obtained in this explanation.

On the basis of the stereochemical result of the reaction of (*R*)-**1** mentioned above, the mechanism of the asymmetric induction in the carbonpalladation of the racemic allene with chiral phosphine ligands is discussed as follows. The result

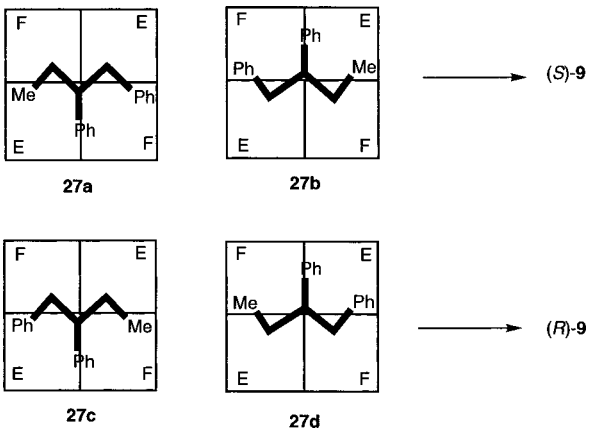

Chart 11

of the aforementioned reaction of (*R*)-**6** using dppe as a ligand (Chart 4) indicates that the palladium-catalyzed reaction of (±)-**6** with chiral phosphine ligands should generate a sterically preferred stable (less reactive) π–allylpalladium intermediate, presumably *via* diastereomeric equilibrium, which has a chiral environment induced by chiral phosphine ligands. In the case of chiral ligands, (*S*)-BINAP, (−)-DIOP, and (+)-MOD-DIOP, having the same chiral environment, the sterically preferred π–allylpalladium complex **27a** and **27b** would be preferentially formed, in the four possible isomers **27a**—**d** (depicted as a face group site as *F* and an edge group site as *E*), owing to the existence of the large phenyl group in the sterically less crowded face (*F*) side, and reacted with the nucleophile from the back side of the palladium catalyst to give (*S*)-**9**.

The mechanism of the carbopalladation of a chiral allene with **13** and the subsequent intramolecular nucleophilic substitutions can be deduced on the basis of the stereochemistry of the similar reaction proceeding with the intermolecular nucleophilic substitution, which was mentioned earlier. As mentioned earlier, the absolute configuration of the product **14** by the palladium-catalyzed reaction of (*R*)-**6** with **13** is deduced as (*R*)-configuration, which is rationalized as follows. The initially-formed aromatic palladium iodide would

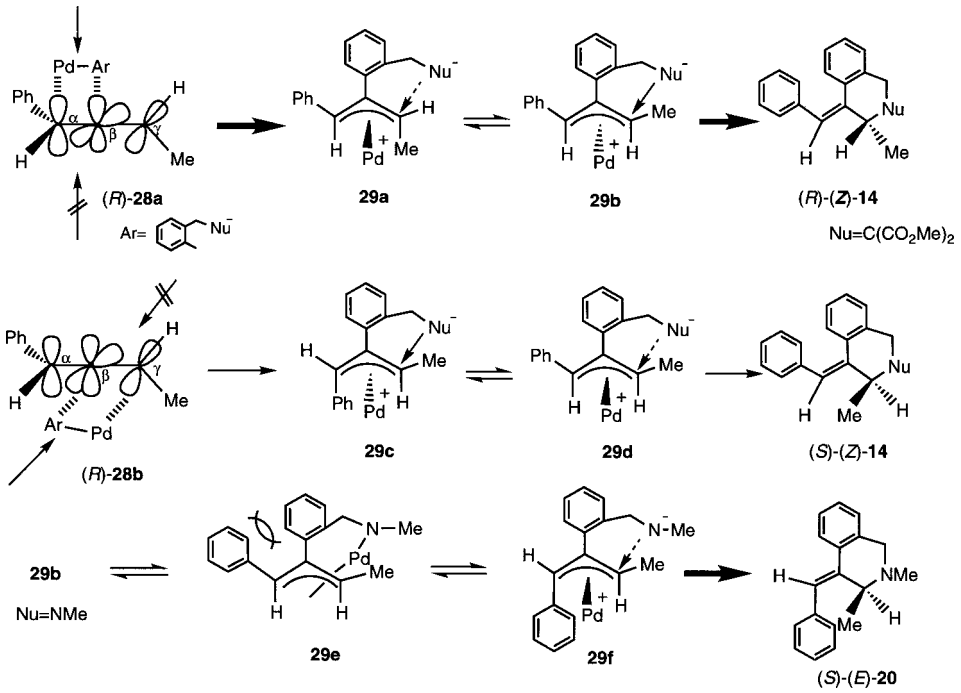

Chart 12

attack the phenyl-substituted carbon–carbon double bond (Ph–CH=C) preferentially from the upward hydrogen (Cγ) side in (*R*)-**8a** due to the steric interference by the methyl group at Cγ, as **28a** in Chart 12, to give a rather stable π–allylpalladium complex (**29a**) which would be converted at equilibrium into the more stable π–allyl isomer (**29b**). The intramolecular nucleophilic substitution in **29a** and/or **29b** from the back side of the palladium catalyst occurs at the sterically less-crowded part (Cγ) to produce (*R*)-**14**.

Similarly, in the reaction with the methyl-substituted carbon–carbon double bond (Me–C=C) in (*R*)-**6**, the aromatic palladium iodide would access to the double bond preferentially from the front hydrogen (Cα) side as **28b**, due to the steric interruption by the phenyl group at the back side, to yield a π–allylpalladium complex (**29c**), which has rather severe $A^{1,3}$ strain between the phenyl (Cα) and the hydrogen (Cγ) groups in the allyl system and accordingly would be equilibrated into the more stable π–allylpalladium complex (**29d**). The intramolecular nucleophile reacts at the sterically favored Cγ position from the back side of the palladium catalyst in **29d** to give (*S*)-**14**.

In contrast to the aforementioned intermolecular palladium-catalyzed reactions, the rather low stereospecifity in the intramolecular ones indicates that both of the two pathways described above might proceed rather competitively, presumably providing preferably (*R*)-**14** owing to the steric reasons, the favorable formation of **29a** in preference to **29c** due to the rather severe $A^{1,3}$ strain between the phenyl and the hydrogen groups in **29c**, and the preferred *syn* geometry of the phenyl group with the orientation of the parallel conformation of the two phenyl rings in **29a**.

The great difference in the geometry of the olefins between products (**14**) and (**20**) is rationalized as follows. The carbonucleophile reacts at the allylic site (Cγ) in the π–allylpalladium complex, rather immediately before the complete

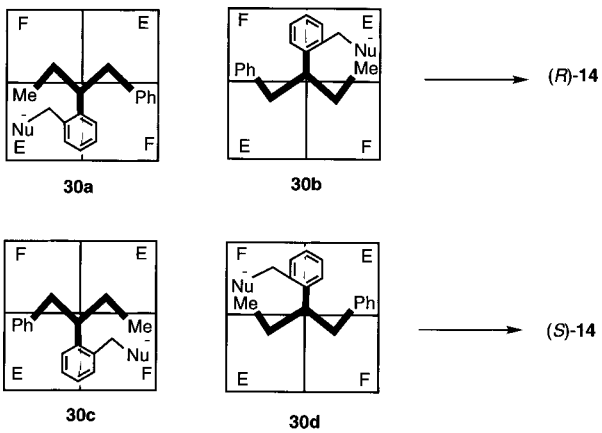

Chart 13

equilibration is attained in allylic system, at the initial stage of the formation of the stable π–allyl isomer (**29a**) because of the considerably high reactivity of the nucleophilic center. However, since the nitrogen anion is a slightly less reactive species, the π–allylpalladium complex would be converted at equilibrium. The preferential transformation of (*Z*)-isomer (**29b**) into (*E*)-isomer (**29f**) at equilibrium would stem from the steric interference between the two phenyl groups in the transition state for the intramolecular amination, presumably *via* **29e** by coordination of the amino group to the palladium catalyst. The subsequent amination would occur from the back side of the palladium in **29f** in the normal way with inversion of the configuration[35—37] to furnish (*S*)-(*E*)-**20**.

The aforementioned low enantioselectivity in the palladium-catalyzed reactions of (±)-**6** with sodium enolate of **13** using chiral ferrocenyl phosphine ligands is rationalized as follows. Intermediary π–allylpalladium complexes **30a**—**d** with chiral environment are formed by coordination of the

chiral phosphines employed. Intramolecular nucleophilic substitutions from the back side of the palladium catalysts in **30a**, **b** or **30c**, **d** give (*S*)- or (*R*)-**14**, respectively. Existence of severe steric interference between the nucleophilic part and an edge (E) side in **30a**, **b**, and the phenyl group and the E in **30c**, **d** as shown in Chart 12 provides small difference in conformational preference between **30a**—**d**, which results in low enantioselectivity of the product.

Thus, it should be concluded the palladium-catalyzed asymmetric reaction of (±)-**6** with iodobenzene and nucleophile (malonate carbanion) in DMSO at 66 °C using chiral phosphine ligands provides a direct 1,2-functionalized compound with extremely high enantioselectivity, presumably *via* a sterically preferred stable π–allylpalladium intermediate in diastereomeric equilibrium by the effect of chiral phosphine ligands and the reaction conditions employed. In contrast to this result, however, it should be remarkably attractive that a similar reaction of the chiral allene using an achiral phosphine ligand proceeded with complete enantiospecificity.

The palladium-catalyzed synthetic methods with chiral allenes *via* asymmetric carbopalladation followed by intramolecular nucleophlic substitutions provided a facile entry to chiral carbocycles and heterocycles with slightly low enantiospecificity.

Experimental

Infrared (IR) spectra were obtained in the indicated state with a JASCO DR-81 fourier-transform IR spectrometer. NMR spectra were determined in the indicated solvent with a JEOL EX-270 high-resolution NMR spectrometer; chemical shifts are given in ppm from tetramethylsilane as an internal standard. Splitting patterns are designated as s: singlet, d: doublet, q: quartet, m: multiplet. Mass spectra were taken on a JEOL JMS-DX 303/JMA-DA 5000 system. High performance liquid chromatography (HPLC) was performed with a Tosoh UV-8010 CCPM. Optical rotations were measured with a JASCO DIP-370 polarimeter. Flash column chromatography was performed with Merck Silica gel 60 (230—400 mesh). Thin layer or thick layer plates (preparative TLC) were made of Merck Silica gel 60PF-254 activated by drying at 140 °C for 3.5 h.

The Palladium-Catalyzed Intermolecular Asymmetric Reactions of an Allene with a Carbonucleophile Using Chiral Phosphine Ligands. General Procedure A 15 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing sodium hydride (NaH) (29 mg, 0.60 mmol, 50% oil dispersion) was flushed with argon and maintained under a positive pressure of argon. THF (1 ml) was added to the flask and a solution of dimethyl malonate (73 mg, 0.55 mmol) in THF (1 ml) was added at 0 °C. The mixture was stirred at room temperature for 30 min.

Another 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing $Pd(dba)_2$ (10.6 mg, 0.018 mmol) and (*S*)-BINAP (5.75 mg, 0.018 mmol) was flushed with argon and maintained under a positive pressure of argon. To the above flask THF (1 ml) was added and the mixture was stirred for 30 min. A solution of iodobenzene (**7**) (141 mg, 0.69 mmol) in THF (1 ml) was next added and the mixture was stirred for 30 min. Then, a solution of (±)-1-phenyl-1,2-butadiene (**6**) (60 mg, 0.46 mmol) in THF (1 ml) was further added and the reaction mixture was stirred for 30 min. This solution was added to the above solution and the reaction mixture was heated under reflux for 18 h. The reaction mixture was diluted with ether, and the solution was washed with a saturated aqueous NH_4Cl and a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was submitted to preparative TLC (ether–hexane 1 : 2) to give dimethyl (*S*)-(−)-(1,2-diphenyl-1-buten-3-yl)propanedioate (**9**) (51 mg, 33% yield, 88% e.e.).

The e.e. of the product **9** was determined by HPLC analysis with Chiralcel OD (*i*-propanol–hexane 1 : 20). The results obtained under other reaction conditions are summarized in Tables 1 and 2.

(*S*)-**9**: $[\alpha]_D$ −9.7° (*c*=3.29, $CHCl_3$, 22 °C). IR (cm^{-1}): 1750, 1730 (ester), 1590 (aromatic). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.18 (3H, d, *J*=6.76 Hz, CH_3), 2.45—3.68 (1H, m, C<u>H</u>CH_3), 3.60 (1H, d, *J*=10.23 Hz, C<u>H</u>$(CO_2CH_3)_2$), 3.67, 3.73 (6H, s, s, $C(CO_2CH_3)_2$), 6.48 (1H, s, HC=C), 6.81—7.42 (10H, m, 2×C_6H_5). MS *m*/*z*: 338 (M^+). Exact mass determination: 338.15180 (Calcd $C_{21}H_{22}O_4$: 338.1511).

Determination of the Absolute Configuration of 9 by Chemical Correlation. Oxidative Cleavage of (−)-9 A 1.57 N THF solution (0.3 ml) of OsO_4, and $NaIO_4$ (458 mg, 2.14 mmol) were added to a solution of (−)-**9** (361 mg, 1.07 mmol, 83% e.e.) in ether (2 ml)–H_2O (2 ml), and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with ether, and the solution was washed with a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was submitted to preparative TLC (ether–hexane 1 : 2) to give dimethyl (*S*)-(1-benzoylethyl)propanedioate (**10**) (200 mg, 71% yield).

(*S*)-**10**: IR (cm^{-1}): 1750, 1735 (ester), 1680 (C=O), 1590 (aromatic). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.20 (3H, d, *J*=6 Hz, CH_3), 3.67, 3.82 (6H, s, s, $C(CO_2CH_3)_2$), 3.87—4.50 (2H, m, C<u>H</u>C<u>H</u>$_3$C<u>H</u>), 7.35—8.23 (5H, m, C_6H_5). MS *m*/*z*: 264(M^+). Exact mass determination: 264.09980 (Calcd $C_{14}H_{16}O_5$: 264.096).

Baeyer–Villiger Oxidation of (*S*)-10 *m*-Chloroperbenzoic acid (394 mg, 1.827 mmol) was added to a solution of CF_3CO_2H (0.12 ml, 1.568 mmol) in CH_2Cl_2 (1.2 ml), and the solution was stirred at room temperature for 6 h. A solution of (*S*)-**10** (138 mg, 0.522 mmol) obtained above in CH_2Cl_2 (0.8 ml) was added and the reaction mixture was stirred for 48 h. The reaction mixture was diluted with ether, and the mixture was washed with a 2 N-NaOH aqueous solution and a saturated aqueous NaCl, and concentrated under reduced pressure to give dimethyl (*S*)-[1-(phenyloxycarbonyl)-ethyl]propanedioate (**11**) (108 mg, 74% yield).

(*S*)-**11**: IR (cm^{-1}): 1740, 1750 (ester), 1590 (aromatic). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.39 (3H, d, *J*=7.25 Hz, CH_3), 3.37—3.49 (1H, m, C<u>H</u>CH_3), 3.77, 3.79 (6H, s, s, $C(CO_2CH_3)_2$), 3.82 (1H, d, *J*=9.40 Hz, C<u>H</u>$(CO_2CH_3)_2$), 7.10—7.40 (5H, m, C_6H_5). MS *m*/*z*: 280 (M^+). Exact mass determination: 280.09470 (Calcd $C_{14}H_{16}O_6$: 280.0922).

Hydrolysis of (*S*)-11 A 30% aqueous H_2O_2 solution (0.27 ml) and an aqueous solution (0.5 ml) of $LiOH\cdot H_2O$ (59 mg, 1.4 mmol) were added to a solution of (*S*)-**11** (65 mg, 0.23 mmol) obtained above in THF (1.5 ml), and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with $Na_2SO_3\cdot 5H_2O$ (570 mg, 2.3 mmol) and the reaction solution was concentrated under reduced pressure. An aqueous solution of the residue was acidified with 10% aqueous HCl and extracted with ether. The ether extract was extracted with a saturated aqueous $NaHCO_3$. The aqueous $NaHCO_3$ solution was acidified with 10% aqueous HCl, and the separated oil was extracted with ether and ethyl acetate. The organic layers were combined and washed with a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was submitted to a hydrolysis reaction without further purification.

A reaction mixture of the crude product obtained above and a 20% KOH/MeOH solution (2 ml) was stirred at room temperature for 8 h. The reaction solution was concentrated under reduced pressure, and an aqueous solution of the residue was washed with ether, and then acidified with 10% aqueous HCl. The separated oil was extracted with ether. The ether solution was washed with a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give (*S*)-(−)-methyl succinic acid (**12**)[28] (17.3 mg, 90% yield).

(*S*)-(−)-**12**: IR (cm^{-1}): 3400, 1700 (CO_2H). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.32 (3H, d, *J*=7.258 Hz, CH_3), 3.69—3.79 (1H, m, CH), 4.02 (2H, d, *J*=8.743 Hz, CH_2), 5.03 (2H, bs, 2(CO_2H)). MS *m*/*z*: 132 (M^+). Exact mass determination: 132.04230 (Calcd $C_5H_8O_4$: 132.04226). $[\alpha]_D$ −11.4° (*c*= 0.63, EtOH, 22 °C).

The Palladium-Catalyzed Intramolecular Asymmetric Reactions of an Allene Using Chiral Phosphine Ligands. General Procedure A 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing sodium hydride (NaH) (32 mg, 0.677 mmol, 50% oil dispersion) was flushed with argon and maintained under a positive pressure of argon. THF (1 ml) was added to the flask and a solution of dimethyl (2-iodobenzyl)propanedioate (**13**) (214 mg, 0.615 mmol) in THF (2 ml) was added at 0 °C. The mixture was stirred at room temperature for 30 min.

Another 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing $Pd(dba)_2$ (14.1 mg, 0.025mmol) and (*S*)-(*R*)-PPFOMe (36.9 mg, 0.062 mmol) was flushed with argon and maintained under a positive pressure of argon. To the above flask THF (1 ml) was added and the mixture was stirred for 40 min. This solution was added to the above solution and the reaction mixture was stirred for 30 min. Then, a solution of **6** (80 mg, 0.615 mmol) in THF (1 ml) was further added and the reaction mixture was heated under reflux for 18 h. The reaction mixture was diluted with ether, and the solution was washed with a 10% aqueous HCl, a saturated aqueous $NaHCO_3$, and a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was submit-

ted to preparative TLC (ether–hexane 1 : 2) to give dimethyl 4-benzylidene-3-methyl-1,2,3,4-tetrahydronaphthalene-2,2-dicarboxylate (**14**) (97 mg, 45% yield, 5% e.e.). With (*S*)-(*R*)-PPFOMe as a ligand: yield 44%, 10% e.e. (at 70 °C in DME 18 h); (*S*)-(*R*)-PPFA: yield 23%, 10% e.e. (reflux in THF, 18 h); (*S*)-*N*,*N*-dimethyl-1-ferrocenylethylamine: yield 41%, 7% e.e. (reflux in THF, 18 h).

The e.e. of the product (*R*)-**14** obtained was determined by HPLC analysis with SUMICHIRAL OA-3100 (*i*-propanol–hexane 1 : 500; flow rate: 0.5 ml/min; retention time: 17.1, 18.6 min).

14: IR (cm^{-1}): 1735 (ester), 1610, 1590 (aromatic). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.12 (3H, d, J=6.76 Hz, $CHC\underline{H}_3$), 3.39—3.60 (1H, m, $C\underline{H}CH_3$), 3.65, 3.72 (2H, d, d, J=7.25, 7.25 Hz, $C\underline{H}_2C(CO_2CH_3)$), 3.62, 3.79 (6H, s, s, $C(CO_2CH_3)_2$), 6.55 (1H, s, CH=C), 6.80—7.83 (9H, m, aromatic H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 15.21, 31.04, 39.40, 43.4, 51.5, 52.6, 52.7, 53.0, 124.9, 126.5, 126.7, 127.6, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.9, 129.9, 130.5, 139.7. MS *m*/*z*: 350 (M^+). Exact mass determination: 350.1503 (Calcd $C_{22}H_{22}O_4$: 350.1503).

The Palladium-Catalyzed Asymmetric Reaction of a Chiral Allene, (*R*)-6, with 13. General Procedure A 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing sodium hydride (NaH) (29 mg, 0.594 mmol, 50% oil dispersion) was flushed with argon and maintained under a positive pressure of argon. THF (1 ml) was added to the flask and a solution of **13** (214 mg, 0.615mmol) in THF (2 ml) was added at 0 °C. The mixture was stirred at room temperature for 30 min.

Another 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing $Pd(dba)_2$ (14.1 mg, 0.025 mmol) and dppf (30 mg, 0.054 mmol) was flushed with argon and maintained under a positive pressure of argon. To the above flask THF (1 ml) was added and the mixture was stirred for 40 min. This solution was added to the above solution and the reaction mixture was stirred for 30 min. Then, a solution of (*R*)-**6** (80 mg, 0.615 mmol) in THF (1 ml) was further added and the reaction mixture was heated under reflux for 18 h. The reaction mixture was diluted with ether, and the solution was washed with a 10% aqueous HCl, a saturated aqueous $NaHCO_3$, and a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was submitted to preparative TLC (ether–hexane 1 : 2) to give (*R*)-(**14**) (38 mg, 12% yield, 50% e.e.). The results obtained with other phosphine ligands are summarized in Table 3.

The Palladium-Catalyzed Reactions of (±)-6 with 2-Bromobenzylamine (15) A 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing sodium hydride (NaH) (32 mg, 0.677 mmol, 50% oil dispersion) was flushed with argon and maintained under a positive pressure of argon. THF (2 ml) was added to the flask and a solution of **15** (115 mg, 0.60 mmol) in THF (2 ml) was added at 0 °C. The mixture was stirred at room temperature for 30 min.

Another 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing $Pd(dba)_2$ (17.0 mg, 0.03 mmol) and PPh_3 (16 mg, 0.06 mmol) was flushed with argon and maintained under a positive pressure of argon. To the above flask THF (1.5 ml) was added and the mixture was stirred for 40 min. This solution was added to the above solution and the reaction mixture was stirred for 30 min. Then, a solution of (±)-**6** (80 mg, 0.615 mmol) in THF (1 ml) was further added and the reaction mixture was heated under reflux for 18 h. The reaction mixture was diluted with ether and filtered. The filtrate was concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (7 ml) was added at 0 °C a solution of acetic anhydride (78 mg, 0.78 mmol), Et_3N (0.2 ml, 0.78 mmol), and a catalytic amount of 4-(dimethylamino)pyridine in CH_2Cl_2 (1 ml) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ether, and the solution was washed with a saturated aqueous $NaHCO_3$ and a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was submitted to preparative TLC (ether) to give (*E*)-2-acetyl-4-benzylidene-3-methyl-1,2,3,4-tetrahydroisoquinoline (**17b**) (10 mg, 6% yield) and *N*-[2-(1-phenyl-1,3-butadien-2-yl)benzyl]acetamide (**18b**) (35 mg, 21% yield).

17b: IR (cm^{-1}): 1630, 1640 (amide), 1600 (aromatic). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.23 (3H, d, J=2.16 Hz, $NCHC\underline{H}_3$), 2.02 (3H, s, $COCH_3$), 4.52 (2H, d, J=4.32 Hz, CH_2N), 6.60 (1H, s, C=CH), 7.11—7.56 (9H, m, aromatic H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 23.29, 53.02, 58.02, 77.23, 125.49, 126.01, 126.49, 127.13, 127.33, 127.79, 128.15, 128.24, 128.38, 128.95, 129.14, 129.26, 130.59, 132.81. MS *m*/*z*: 277(M^+). Exact mass determination: 277.14670 (Calcd $C_{19}H_{19}NO$: 277.1490).

18b: IR (cm^{-1}): 1630, 1640 (amide), 1590 (aromatic). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.00 (3H, s, $COCH_3$), 4.46—4.48 (2H, m, CH_2N), 6.40 (1H, m, NHCO), 7.10—7.66 (10H, m, C=CH, aromatic H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 23.13, 43.64, 43.80, 123.64, 127.65, 127.78, 128.37, 128.54, 128.60, 129.06, 130.26, 131.63, 131.88, 131.93, 132.07, 132.69, 133.16, 137.33, 138.28. MS *m*/*z*: 277(M^+). Exact mass determination: 277.14670 (Calcd $C_{19}H_{19}NO$: 277.1469).

Palladium-Catalyzed Reactions of (*R*)-6 with *N*-Methyl-2-iodobenzylamine (19). General Procedure A 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing $Pd(dba)_2$ (12.0 mg, 0.02 mmol) and PPh_3 (11 mg, 0.04 mmol) was flushed with argon and maintained under a positive pressure of argon. To the above flask THF (1 ml) was added and the mixture was stirred for 30 min. A solution of **19** (100 mg, 0.40 mmol) in THF (5 ml) was added and the mixture was stirred at room temperature for 30 min. Then, a solution of (*R*)-**6** (58 mg, 0.45 mmol) and Et_3N (0.08 mmol) in THF (1 ml) was further added and the reaction mixture was heated under reflux for 12 h. The reaction mixture was diluted with ether and filtered. The filtrate was concentrated under reduced pressure. The residue was submitted to preparative TLC (ether–hexane 1 : 1) to give (*S*)-(*E*)-4-benzylidene-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**20**) (18 mg, 18% yield, 46% e.e.). The e.e. of (*S*)-**20** obtained was determined by HPLC analysis with SUMICHIRAL OA-4800 (*n*-hexane–THF–MeOH–trifluoroacetic acid 60 : 38 : 2 : 0.2); flow: 0.5 ml/min, retention time: 55, 64 min.

The results obtained under other reaction conditions with other phosphine ligands are summarized in Table 4.

(*S*)-**20**: IR (cm^{-1}): 1590 (aromatic). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.270 (3H, d, J=6.76 Hz, $CHC\underline{H}_3$), 2.35 (3H, s, NCH_3), 3.64—4.12 (3H, m, $C\underline{H}_2NC\underline{H}CH_3$), 7.05—7.68 (10H, m, CH=C, aromatic H). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 0.00, 13.88, 42.49, 50.72, 54.25, 124.30, 124.80, 126.52, 126.6, 126.8, 127.51, 128.3, 128.82, 132.78, 133.16, 137.34, 137.5. MS *m*/*z*: 249 (M^+). Exact mass determination: 249.1517 (Calcd $C_{18}H_{19}N$: 249.1513).

The Palladium-Catalyzed Intramolecular Carboxylations of an Allene, (*R*)-6, with 2-Iodobenzoic Acid (21). General Procedure A 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing $Pd(PPh_3)_4$ (17.0 mg, 0.03 mmol), PPh_3 (17 mg, 0.067 mmol), **21** (32 mg, 0.121 mmol), K_2CO_3 (334 mg, 2.42 mmol), and silver carbonate (8 mg, 0.03 mmol) was flushed with argon and maintained under a positive pressure of argon. To the above flask CH_3CN (5 ml) was added and the mixture was stirred for 30 min. A solution of (*R*)-**6** (87 mg, 0.67 mmol) in CH_3CN (4 ml) was added and the reaction mixture was heated under reflux for 18 h. The reaction mixture was diluted with ether and filtered through silica gel. The filtrate was concentrated under reduced pressure. The residue was submitted to preparative TLC (ethyl acetate–hexane 1 : 4) to give 4-benzylidene-3-methyl-1-oxo-1,2,3,4-tetrahydro-2-oxanaphthalene (**22a**, **b**) (119 mg, 79% yield). The product ratio of **22a**, **b** was determined by ^{1}H-NMR analysis. The results obtained are summarized in Table 5.

(*E*)-**22a**: IR (cm^{-1}): 1600 (aromatic). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.62 (3H, d, J=1 Hz, CH_3), 5.16 (1H, q, J=1 Hz, OCH), 6.82—8.16 (10H, m, C_6H_4, C_6H_5CH). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 14.78, 82.56, 116.10, 123.94, 126.58, 126.85, 127.25, 128.37, 128.52, 128.57, 129.34, 130.30, 130.38, 134.19, 13.73, 137.34, 138.97. MS *m*/*z*: 250(M^+). Exact mass determination: 250.0970 (Calcd $C_{17}H_{14}O_2$: 250.0994).

(*Z*)-**22b**: IR (cm^{-1}): 1600 (aromatic). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.61 (3H, d, J=1 Hz, CH_3), 5.74 (1H, q, J=1 Hz, OCH), 6.82—8.16 (10H, m, C_6H_4, C_6H_5CH). MS *m*/*z*: 250 (M^+). Exact mass determination: 250.1003 (Calcd $C_{17}H_{14}O_2$: 250.0994).

HPLC: CHIRALPAK AD (*i*-propanol–hexane 1 : 20); flow: 0.5 ml/min; retention time: 24, 27 (*E*), 38, 41 (*Z*) min.

The Palladium-Catalyzed Reactions of an Allene, (*R*)-6, with 2-Iodobenzyl Alcohol (23). General Procedure A 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing $Pd(OAc)_2$ (14.0 mg, 0.064 mol), PPh_3 (34 mg, 0.128 mmol), **23** (150 mg, 0.64 mmol), Na_2CO_3 (340 mg, 3.21 mmol), and tetra-*n*-butylammonium chloride (178 mg, 0.64 mmol) was flushed with argon and maintained under a positive pressure of argon. To the above flask THF (4 ml) was added and the mixture was stirred for 30 min. A solution of (*R*)-**6** (92 mg, 0.71 mmol) in THF (6 ml) was added and the reaction mixture was heated under reflux for 12 h. The reaction mixture was diluted with ether, and the solution was washed with a saturated aqueous NH_4Cl and a saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was submitted to preparative TLC (ethyl acetate–hexane 1 : 20) to give (*E*)-4-benzylidene-3-methyl-1,2,3,4-tetrahydro-2-oxanaphthalene (**24**) (65 mg, 43% yield).

The results obtained are summarized in Table 6.

24: IR (cm^{-1}): 1600 (aromatic). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.46 (3H, d, J=6.4 Hz, CH_3), 4.46 (1H, dt, J=6.4, 1.2 Hz, OCH), 4.87 (2H, s, OCH_2), 6.54 (1H, s, C=CH), 6.86—7.41 (9H, m, aromatic). ^{13}C-NMR (67.8 MHz,

$CDCl_3$) δ: 19.11, 66.39, 74.45, 123.82, 123.99, 125.47, 126.71, 126.89, 126.94, 127.28, 127.37, 128.10, 128.24, 128.52, 128.61, 128.72, 129.00. MS *m*/*z*: 236(M^+). Exact mass determination: 236.1218 (Calcd $C_{17}H_{16}O$: 236.1201).

HPLC: CHIRALPAK AD (*i*-propanol–hexane 1 : 100); flow: 0.5 ml/min; retention time: 12, 13 min.

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